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Synthesis of New Artemisinin Analogues from Artemisinic Acid Modified at C-3 and C-13 and Their Antimalarial Activity

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Artemisinic acid (**2**) was modified through allylic oxidation at C-3 or conjugate addition at C-13 to afford 12 methyl artemisinate derivatives (**4**−**15**). Photooxidation of the derivatives yielded eight new artemisinin analogues, including 13-cyanoartemisinin (**16**), 13-methoxycarbonyl artemisinin (**17**), 13-methoxyartemisinin (**18**), 13-ethylsulfonylartemisinin (**19**), 13-nitromethylartemisinin (**20**), 13-(1-nitroethyl)artemisinin (**21**), (3*R*)-3-hydroxyartemisinin (**22**), and (3*R*)-3-acetoxyartemisinin (**23**). Among the analogues, only compound **20** had antimalarial activity comparable to artemisinin (**1**).

Malaria, an epidemic disease, has been the major cause of death in tropical regions of the world since the prehistoric age, and new strains of drug-resistant *Plasmodium falciparum* are causing substantial deterioration in clinical situations.[1] Chinese researchers reported on an antimalarial compound, artemisinin (**1**), which is currently established as a clinically important drug against chloroquine-resistant strains of *P. falciparum*.[1] Recently, the activity was attributed to the disrupted hemoglobin catabolism and heme detoxification systems in the parasite.[2] Artemisinin, at the molecular level, was found to generate a carbon-centered free radical intermediate in the parasite on interaction with heme-iron by opening the endoperoxide functionality of the molecule.[3,4]

The biological activity and the challenging structure of artemisinin have prompted extensive synthetic efforts to disclose analogues that have more potency and better pharmacokinetic properties compared to the parent molecule, while retaining its biologically crucial endoperoxide functionality.[5] In parallel with the efforts on the total synthesis of artemisinin (**1**) via several routes,[6] a semisynthetic approach from artemisinic acid has recently gained attention due to the simplicity in promoting the conversion into artemisinin and its abundance in the plant compared to artemisinin.[7,8]

Modifications to artemisinic acid would therefore present the possibility of more versatile structures because it would withstand harsher reaction conditions than artemisinin. Furthermore, artemisinic acid (**2**) has more functional groups available for chemical derivatization than artemisinin. As the first attempt to this approach, Kim et al. reported that a cyclopropyl analogue of artemisinic acid (**2**) could be photooxidized to afford the corresponding artemisinin.[9] Acton et al. have also prepared several artemisinin analogues through a similar strategy via modification of artemisitene, a didehydro derivative of artemisinin.[10] A semisynthesis of (3*S*)-3-hydroxyartemisinin was also reported in a similar line of thinking with the authors.[11]

Chemically, the C-11−C-13 double bond of artemisinic acid is very reactive to the Michael-type reactions. Furthermore, these chemical modifications are not likely to interfere with the subsequent photooxidation to form artemisinin derivatives.[23−25] Derivatization of the C-3 site of **2** can also produce important C-3-derivatized artemisinins, which could enhance the knowledge regarding the action mechanism of artemisinin (**1**).[12] We have thus chosen this approach to synthesize artemisinin analogues exploiting the facile modification of the C-11−C-13 double bond and the allylic C-3 position. The in vitro bioactivity of the prepared compounds against chloroquine-resistant *Plasmodium* strains is also reported.

Results and Discussion

Artemisinic acid (**2**) was first methylated quantitatively with CH_2N_2 to protect the carboxyl group. When a large excess of CH_2N_2 is used, cycloaddition into the C-11−C-13 double bond also occurs, and the resulting cyclic diazo compound was utilized in the preparation of a cyclopropane derivative.[9] This methylation was more effective and easier than the published method employing methyl *p*-toluenesulfonate.[13]

Conjugate addition and allylic oxidation reactions were carried out with methyl artemisinate (**3**), and the resulting derivatives are presented, with their ^{13}C NMR spectral data, in Table 1 in the Supporting Information. Hydrocyanation of **3** with KCN in AcOH resulted in methyl 13-cyano-11-hydroartemisinate (**4**) in 50% yield. Addition of the nitrile group was established by the resonances at δ 2.80 (H-11) and 2.58 (H-13) from ^1H NMR spectrum and the ν_{max} of 2225 cm^{-1} (C≡N stretching) from the IR spectrum. This reaction resulted in two diastereomeric 11*R*- and 11*S*-compounds (2.3:1). Conjugate additions of methyl artemisininate at C-11−C-13 usually proceed with the addition of the hydrogen atom to the *si*-face at C-11 to yield 11*R*-diasteomers in higher yields than the corresponding 11*S* isomers, because the 11*R*-form is more stable than the 11*S*-form.[9] The H-5 resonance of the isomers appeared at 5.04 (11*R*) and at 5.20 ppm (11*S*). Subsequent photooxygenation of the C-11-derivatized artemisinate resulted in only the (11*R*)-artemisinin analogue.

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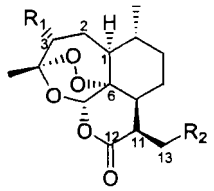
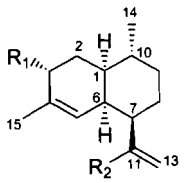
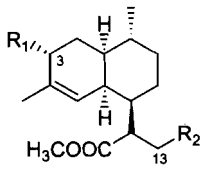


1. R_1 = H R_2 = H
16. R_1 = H R_2 = CN
17. R_1 = H R_2 = $COOCH_3$
18. R_1 = H R_2 = OCH_3
19. R_1 = H R_2 = $SO_2CH_2CH_3$
20. R_1 = H R_2 = CH_2NO_2
21. R_1 = H R_2 = $CH(CH_3)NO_2$
22. R_1 = OH R_2 = H
23. R_1 = OAc R_2 = H





2. R_1 = H R_2 = COOH
3. R_1 = H R_2 = $COOCH_3$
12. R_1 = OH R_2 = $COOCH_3$
13. R_1 = OAc R_2 = $COOCH_3$

4. R_1 = H R_2 = CN
5. R_1 = H R_2 = COOH
6. R_1 = H R_2 = $COOCH_3$
7. R_1 = H R_2 = OCH_3
8. R_1 = H R_2 = SCH_2CH_3
9. R_1 = H R_2 = $SO_2CH_2CH_3$
10. R_1 = H R_2 = CH_2NO_2
11. R_1 = H R_2 = $CH(CH_3)NO_2$
14. R_1 = OH R_2 = H
15. R_1 = OAc R_2 = H

The diastereomeric mixture of **4** was hydrolyzed with NaOH in ethylene glycol to obtain methyl 13-carboxy-11-hydroartemisinate (**5**) in 80% yield, and the crude hydrolysate was esterified with CH_3I to give methyl 11-hydro-13-methoxycarbonylartemisinate (**6**) in 75% yield. When 2 M NH_3 in CH_3OH solution was added to **3** in the presence of a catalytic amount of CH_3ONa, methyl 11-hydro-13-methoxyartemisinate (**7**) was formed with 60% yield.

Methyl 13-ethylthio-11-hydroartemisinate (**8**, 100% yield) was synthesized through ethanethiol treatment under a nitrogen atmosphere, with CH_3ONa as a catalyst. The diastereomeric ratio was 2:1 with preference for 11*R*. Methyl 13-ethylsulfonyl-11-hydroartemisinate (**9**, 75% yield) was prepared from **8** through treatment with H_2O_2 under WO_3 catalysis.

The addition of nitromethane to the terminal double bond of **3** was carried out with *t*-BuOK as the catalyst for this Michael-type reaction. Formation of methyl 11-hydro-13-nitromethylartemisinate (**10**, 45% yield) was confirmed through NMR and HRMS spectral analyses. The presence of a nitro group was further established by N=O stretching bands (1556, 1374 cm^{-1}) in the IR spectrum. The reaction with nitroethane yielded methyl (11*R*)-11-hydro-13-(1-nitroethyl)artemisinate (**11**) as the sole product, which was confirmed by the single H-5 signal at δ 5.09. This preference for the 11*R*-isomer was presumably due to the bulkiness of the additional methyl group.

An artemisinin analogue derivatized at C-3 could be important in establishing the metabolism and the action mechanism of artemisinin (**1**). Posner et al. reported on the H_{proR}-3 abstraction by Fe^{2+} during the pharmacological activation of artemisinin in *Plasmodium*.[12] Therefore, should their proposition hold, substitution of H_{proR}-3 with other functional groups could significantly modify the efficacy of the drug against *Plasmodium* and should be more informative than the substitution at H_{proS}-3 reported by Acton.[11] Sharpless allylic oxidation was used to substitute H_{proR}-3 with a hydroxy group, resulting in the synthesis of the allylic alcohol **12** (78% yield).[14] The assignment of configuration at C-3 was deduced as 3*R* through the examination of J_{H2-H3} in the ^1H NMR spectrum and the comparison of the spectral data with those of the literature.[11,15] Methyl (3*R*)-3-acetoxyartemisinate (**13**, 96% yield) was prepared through the reaction with acetic anhydride in pyridine. The derivatized compounds at C-3 were hydrogenated using Acton's method[8] to prepare methyl (3*R*)-11,13-dihydro-3-hydroxyartemisinate (**14**) and (3*R*)-3-acetoxy-11,13-dihydroartemisinate (**15**) with the neutral workup procedure. The reported acidic workup[8] yielded several byproducts, thus resulting in a lower yield of **15**. Confirmation of the configuration at C-11 was not possible in **15** owing to the unresolved proton signals of H-7, H-11, and H-13.

Syntheses of the artemisinin analogues from the artemisinic acid derivatives were carried out through the method of Haynes[7] or Acton[8] with modifications in reaction temperature and time. Their ^{13}C NMR spectral data are shown in Table 2 in the Supporting Information. Time required for the oxidation with artemisinic acid derivatives, as revealed by monitoring the disappearance of the starting material using TLC, was different from compound to compound. This may reflect the quenching and scavenging capacities of the newly introduced functional groups at C-3 and C-13. For example, because the amino group is a well-known scavenger of $^1O_2$,[16] the amine derivatives required longer photooxygenation time.

The isolated yield of 13-cyanoartemisinin (**16**) was 5% from starting material **4**. Conversion of the initial hydroperoxide adduct into **16** was slow, requiring several weeks. The endo-peroxide structure was elucidated through a combination of IR (1109, 880, 827 cm^{-1}), mass, and ^1H and ^{13}C NMR spectroscopies, and the correlation of the protons was checked through $^1H-^1H$ COSY and HETCOR. The chirality at C-11 was confirmed as *R* through the comparison of its coupling constant, J_{H7-H11} = 5.2 Hz, with artemisinin. The (11*S*)-diastereomer of **4** was not converted to the corresponding artemisinin analogue, but part of it was reisolated from the reaction product. In the photooxidation of methyl 13-carboxy-11-hydroartemisinate (**5**), no desired artemisinin analogue was obtained using either Haynes' or Acton's methods.[7,8] It was interpreted that the singlet oxygen adduct of methyl 13-carboxy-11-hydroartemisinate (**5**) was so unstable that the putative hydroperoxide intermediate led to several unidentified byproducts, other than the expected 13-carboxyartemisinin. The presence of the electron-withdrawing carboxyl group may have interfered with the electrophilic triplet oxygen oxidation, as reported by Jung.[17] Thus, further derivatization of **5** to methyl 11-hydro-13-methoxycarbonylartemisinate (**6**) was carried out to obtain the corresponding artemisinin analogue, 13-methoxycarbonylartemisinin (**17**), in a low yield of 4.3%. Predominant formation of a diketone, methyl 11-hydro-13-methoxycarbonylartemisinate, during photooxidation and its mechanistic implication were reported elsewhere.[18]

The close structural relationship of 13-methoxyartemisinin (**18**) and 13-ethylsulfonylartemisinin (**19**) to artemisinin (**1**) was clearly demonstrated through a comparison of the ^{13}C NMR spectra of the three compounds (Table 2, Supporting Information). Oxidation of the nitro compounds (**10**, **11**) afforded 13-nitromethylartemisinin (**20**) and 13-

Table 1. In Vitro Antimalarial Activity of Artemisinin (**1**) and Its Derivatives against *P. falciparum* Strains D6 (Sierra Leone) and W2 (Indochina)[a]

compound	IC_{50} (ng/mL) D6	W2
artemisinin (**1**)	0.5	0.2
chloroquine	4.9	66.4
quinine	19.6	102
mefloquine	6.3	3.6
11-cyclopropylidenylartemisinin[20]	6.2	4.3
13-cyanoartemisinin (**16**)	18.4	8.4
13-methoxycarbonylartemisinin (**17**)	46	33
13-methoxyartemisinin (**18**)	75	59
13-ethylsulfonylartemisinin (**19**)	>500	>500
13-nitromethylartemisinin (**20**)	0.68	0.26
13-(1-nitroethyl)artemisinin (**21**)	12.8	3.86
(3*R*)-3-acetoxyartemisinin (**23**)	11.1	2.07

[a] Activities of compounds **1**, **16**–**21**, and **23** against KB were >20 000 ng/mL.

(1-nitroethyl)artemisinin (**21**). The photooxygenation of methyl (3*R*)-11,13-dihydro-3-hydroxyartemisinate (**14**) and methyl (3*R*)-3-acetoxy-11,13-dihydroartemisinate (**15**) and the subsequent acid-catalyzed rearrangement occurred at very slow rates, the rearrangement requiring one month at room temperature to obtain enough **22** (7.7% yield) and **23** (3.1% yield) for spectral analyses.

The antimalarial activity of 13-nitromethylartemisinin (**20**) was comparable to that of artemisinin (**1**) among the prepared analogues (Table 1), but 13-(1-nitroethyl)artemisinin (**21**) was about 20-fold less active, indicating that the activity was very sensitive to the bulkiness of the side chain. Activities of the remaining synthesized derivatives were inferior to that of artemisinin. Interestingly, compound **20** showed activity against the vinblastine-resistant KB-V cell-line with IC_{50} values of 5.1 and 5.4 ng/mL, with or without vinblastine, respectively. The antiplasmodial activity of the (3*R*)-acetoxy derivative (**23**) was lower than that of artemisinin, reflecting the importance of proton abstraction for the action of artemisinin.[3,4] However, the activity was still better than that of quinine, signifying that abstraction of the acetoxy group is efficient enough to substitute for $H_{pro\text{-}R}$-3 loss. The activities of (3*S*)-[8] and (3*R*)-3-hydroxyartemisinin are yet to be determined to fully understand the effect of stereospecific substitution with a hydroxy moiety at C-3.

Experimental Section

General Experimental Procedures. Melting points were determined using a Meltemp apparatus (Laboratory Devices, Holliston, MA). NMR spectra were obtained on a Bruker AC80, JEOL JNM-GSXN 400, or Bruker ARX-400 spectrometer. The GC–MS was operated on an HP 5980II GC-HP 5988 MS in the EI or CI mode, and an SPB-5 (30 m × 0.25 mm × 0.25 μm) column was used. Direct mass and IR spectra were obtained using a VG 70VS2Q spectrometer and a Perkin-Elmer 1710 FT-IR spectrometer, respectively. MMX calculations were carried out using PCMODEL (Serena Software, Bloomington, IN). To obtain the energy-minimized structures, the subroutines MMX and RANDOMIZ were used. PMR was used to calculate the coupling constants of the vicinal protons. Column chromatography for the separation of the photooxidation products was routinely used employing a hexane–acetone solvent system. VLC was also used when necessary, applying the same solvent system as column chromatography.[19] Artemisinic acid (**2**) was isolated, following the reported method, from *A. annua* L., which has been maintained at the garden of Seoul National University.[20] Its purity was checked through the measurement of melting point (131 °C) and NMR spectroscopy. ^{13}C NMR data of compounds **1**–**23** are presented in Tables 1 and 2 (Supporting Information).

Antimalarial Bioassay. The in vitro antimalarial activity against two strains of *Plasmodium falciparum* was determined against the chloroquine-resistant W2 and chloroquine-sensitive D6 strains as described elsewhere.[21] Cytotoxicity against the KB cell-line was also assessed to estimate the selectivity.

Syntheses. Methyl artemisinate (**3**) was prepared through methylation of artemisinic acid (**2**) using CH_2N_2. Conjugate addition of cyanide yielded 13-cyano-11-hydroartemisinate (**4**), and subsequent alkaline hydrolysis yielded methyl and methyl 13-carboxy-11-hydroartemisinate (**5**). Methanolysis of the cyanide (**4**) resulted in the formation of methyl 11-hydro-13-methoxycarbonylartemisinate (**6**). Reaction of the ester (**3**) and methoxide yielded methyl 11-hydro-13-methoxyartemisiniate (**7**) through conjugate addition.[22] Similar conjugate addition of ethyl sulfide produced methyl 13-ethylthio-11-hydroartemisinate (**8**),[23] and methyl 13-ethylsulfonyl-11-hydroartemisinate (**9**) was prepared through subsequent oxidation of **8** by H_2O_2.[24] Methyl 11-hydromethylartemisinate (**10**) and methyl 11-hydro-13-(1-nitroethyl)artemisinate (**11**) were obtained through the reaction of **3** with corresponding nitroalkanes in the presence of potassium metal.[25] The Sharpless oxidation[14] successfully introduced a hydroxy group at C-3 to produce methyl (3*R*)-3-hydroxyartemisinate (**12**), and subsequent acetylation of **12** yielded methyl (3*R*)-acetoxyartemisinate (**13**).[26] Reduction of the C-11–C-13 double bond of **12** and **13** by $NaBH_4$ yielded the dihydro compounds **14** and **15** suitable for subsequent reaction with singlet oxygen, respectively.[8] Photooxygenation of the artemisinic acid derivatives **4**–**15** was performed either through Haynes' or Acton's method[7,8] to yield the artemisinin derivatives **16**–**23**, respectively. Detailed synthetic procedures are given in the Supporting Information.

Methyl artemisinate (3): ^1H NMR ($CDCl_3$, 80 MHz) δ 6.28 (1H, s, H-12), 5.43 (1H, s, H-13), 4.99 (1H, br s, H-5), 3.73 (3H, s, 12-$COOCH_3$), 2.73 (1H, m, H-7), 2.54 (1H, br s, H-6), 1.59 (3H, s, CH_3-15), 0.89 (3H, d, J = 6 Hz, CH_3-14); EIMS (70 eV, rel int) *m/z* 248 ($[M]^+$, 37), 121 (100).

Methyl 13-cyano-11-hydroartemisinate (4): Only the spectra of the 11*R* major product are presented here. ^1H NMR ($CDCl_3$, 80 MHz): δ 5.04 (1H, br s, H-5), 3.78 (3H, s, 12-$COOCH_3$), 2.80 (1H, m, H-11), 2.58 (2H, d, J = 10.4 Hz, H-13), 2.40 (1H, br s, H-6), 1.55 (3H, s, H-15), 0.86 (3H, d, J = 5.5 Hz, H-14); EIMS (70 eV, rel int) *m/z* 275 ($[M]^+$, 3), 162 (100), 147 (20), 121 (10), 105 (11), 91 (16).

Methyl 13-carboxy-11-hydroartemisinate (5): Only the spectra of the major product are presented: IR (KBr) ν_{max} 3200 (O–H stretching), 1734 (C=O stretching), 1686 (C=O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.83 (1H, br s, COOH), 5.37 (1H, s, H-5), 3.74 (3H, s, 12-$COOCH_3$), 2.85 (1H, m, H-11), 2.70 (2H, s, H-13), 2.40 (1H, br s, H-6), 1.64 (3H, s, H-15), 0.88 (3H, d, J = 5.0 Hz, H-14); EIMS (70 eV, rel int) *m/z* 294 ($[M]^+$, 23), 276 ($[M - H_2O]^+$, 36), 249 ($[M - COOH]^+$, 19), 162 (100), 147 (76), 107 (46), 91 (83).

Methyl 11-hydro-13-methoxycarbonylartemisinate (6): Only the spectra of the major product are presented: IR (KBr) ν_{max} 1740 (C=O stretching), 1438 (C=C stretching), 1260 (C–O stretching), 1165 (C–O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.04 (1H, s, H-5), 3.61 (3H, s, 12-$COOCH_3$), 3.56 (3H, s, 16-$COOCH_3$), 2.87 (1H, m, H-11), 2.52 (2H, d, J = 7 Hz, H-13), 2.33 (1H, br s, H-6), 1.63 (3H, s, H-15), 0.87 (3H, d, J = 6.5 Hz, H-14); EIMS (70 eV, rel int) *m/z* 308 ($[M]^+$, 10), 277 ($[M - OCH_3]^+$, 19), 249 ($[M - COOCH_3]^+$, 11), 162 (98), 146 (100), 114 (39), 107 (15), 91 (17); HREIMS (70 eV) *m/z* 308.1987 (obsd), 308.1988 (calcd for $C_{18}H_{28}O_4$).

Methyl 11-hydro-13-methoxyartemisinate (7): IR (KBr) ν_{max} 1740 (C=O stretching), 1436 (C=C stretching), 1165 (C–O stretching), 1115 (C–O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.23 (1H, s, H-5), 3.72 (3H, s, 12-$COOCH_3$), 3.63 (2H, m, H-13), 3.32 (3H, s, OCH_3), 2.82 (1H, m, H-11), 2.48 (1H, br s, H-6), 1.62 (1H, m, H-9), 1.53 (3H, s, H-15), 1.18 (1H, m, H-8), 1.04 (1H, m, H-8), 0.89 (3H, d, J = 6.5 Hz, H-14), 0.86 (1H, m, H-9); EIMS (70 eV, rel int) *m/z* 280 ($[M]^+$, 20), 248 ($[M - OCH_3]^+$, 29), 217 (17), 162 (100), 147 (98), 119 (87), 105 (72),

91 (60); HREIMS (70 eV) *m/z* 280.2018 (obsd), 280.2038 (calcd for $C_{17}H_{28}O_3$).

Methyl 13-ethylthio-11-hydroartemisinate (8): Only the spectra of the major product are presented: IR (KBr) ν_{max} 1739 (C=O stretching), 1420 (C=C stretching), 1145 (C−O stretching), 690 (C−S stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.04 (1H, s, H-5), 3.63 (3H, s, 12-$COOCH_3$), 2.46 (2H, q, J = 7.4 Hz, SCH_2CH_3), 2.41 (1H, br s, H-6), 1.62 (3H, s, H-15), 1.61 (1H, m, H-10), 1.22 (3H, t, J = 7.4 Hz, SCH_2CH_3), 0.89 (1H, m, H-9), 1.02 (1H, m, H-10), 0.83 (3H, d, J = 6.5 Hz, H-14); EIMS (70 eV, rel int) *m/z* 310 ([M]$^+$, 20), 295 ([M − CH_3]$^+$, 4), 281 ([M − C_2H_5]$^+$, 3), 279 ([M − OCH_3]$^+$, 4), 248 (7), 162 (100), 147 (20), 119 (8), 105 (9); HREIMS (70 eV) *m/z* 310.1984 (obsd), 310.1967 (calcd for $C_{18}H_{30}O_2S$).

Methyl 13-ethylsulfonyl-11-hydroartemisinate (9): Only the spectra of the major product are presented: mp 155−161 °C; $[\alpha]^7_D$ +29.17° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 1739 (C=O stretching) 1305 (S=O stretching), 1126 (S=O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.22 (1H, s, H-5), 3.73 (3H, s, 12-$COOCH_3$), 2.98 (2H, q, J = 7.5 Hz, SOOCH_2CH_3), 1.62 (3H, s, H-15), 1.41 (3H, t, J = 7.5 Hz, $SOOCH_2CH_3$), 0.83 (3H, d, J = 6.5 Hz, H-14); CIMS (CH_4, rel int) *m/z* 343 ([M + H]$^+$, 100), 311 (88), 283 (20), 162 (19).

Methyl 11-hydro-13-nitromethylartemisinate (10): IR (KBr) ν_{max} 1723 (C=O stretching), 1556 (N=O stretching), 1374 (N=O stretching), 1168 (C−O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 5.10 (1H, s, H-5), 4.36 (2H, m, CH_2NO_2), 3.72 (3H, s, 12-$COOCH_3$), 2.6 (1H, tdd, J = 11, 4, 2 Hz, H-7), 2.5 (1H, br s, H-6), 2.45 (1H, ddd, J = 14, 8, 4 Hz, H-13), 2.13 (2H, m, H-11, H-13), 2.0−1.8 (3H, m, H-2, H-3), 1.7−1.5 (5H, m, H-2, H-9, H-15), 1.46 (1H, m, H-1), 1.45 (1H, m, H-10), 1.25 (2H, m, H-8), 0.96 (1H, m, H-9), 0.87 (3H, d, J = 6.5 Hz, H-14); EIMS (70 eV, rel int) *m/z* 309 ([M]$^+$, 0.93), 274 (34), 261 (10), 162(100), 147 (32), 121 (17), 105 (22); HRCIMS (CH_4) *m/z* 310.2033 (obsd for [M + H]$^+$), 310.2018 (calcd for $C_{17}H_{28}O_4N$).

Methyl 11-hydro-13-(1-nitroethyl)artemisinate (11): IR (KBr) ν_{max} 1727.7, 1552.4, 1358.8, 1168.2 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 5.09 (1H, s, H-5), 4.45 (2H, qt, J = 6.7, 2.5 Hz, H-16), 3.72 (3H, s, 12-$COOCH_3$), 2.5 (2H, m, H-6, H-7), 2.4 (1H, ddd, J = 14.5, 10.5, 3.5 Hz, H-13), 2.0−1.75 (5H, m, H-2, H-3, H-11), 1.83 (1H, ddd, J = 14.5, 11.0, 3.0 Hz, H-13), 1.66 (3H, s, CH_3-15), 1.60 (1H, m, H-9), 1.55 (1H, d, J = 6.7 Hz, H-17), 1.45 (1H, m, H-10), 1.35−1.2 (2H, m, H-1, H-8), 1.11 (1H, ddd, J = 24.8, 12.4, 3.2 Hz, H-8), 0.90 (1H, ddd, J = 25.9, 12.7, 3.7 Hz, H-9), 0.87 (3H, d, J = 6.6 Hz, CH_3-14); HRCIMS *m/z* 324.2199 (obsd for [M + H]$^+$), 324.2175 (calcd for $C_{18}H_{30}O_4N$).

Methyl (3*R*)-3-hydroxyartemisinate (12): IR (KBr) ν_{max} 3201 (O−H stretching), 1721 (C=O stretching), 1627 (C=C stretching), 1436 (O−H bending), 1320 (O−H bending), 1044 (C−O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 6.30 (1H, s, H-13), 5.46 (1H, s, H-13), 5.13 (1H, s, H-5), 4.08 (1H, dd, J = 10.4, 4.9 Hz, H-3), 3.76 (3H, s, 12-$COOCH_3$), 2.68 (1H, s, H-7), 2.67 (1H, s, H-6), 2.41 (1H, ddd, J = 13.3, 4.9, 3.5 Hz, H_{proR}-2), 1.72 (3H, s, H-15), 1.70 (1H, m, H-9), 1.60 (1H, m, H-1), 1.48 (1H, ddd, J = 13.3, 10.4, 3.2 Hz, H_{proS}-2), 1.38 (1H, m, H-10), 1.35 (2H, m, H-8), 1.04 (1H, dd, J = 12.6, 3.4 Hz, H-9), 0.96 (3H, d, J = 6.5 Hz, H-14); EIMS (70 eV, rel int) *m/z* 264 ([M]$^+$, 2.2), 246 ([M − H_2O]$^+$, 100), 214 (50), 186 (78), 159 (66), 131 (52), 119 (100), 105 (65); HREIMS (70 eV) *m/z* 264.1709 (obsd), 264.1725 (calcd for $C_{16}H_{24}O_3$).

Methyl (3*R*)-3-acetoxyartemisinate (13): IR (KBr) ν_{max} 1737 (C=O stretching), 1717 (C=O stretching), 1626 (C=C stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 6.31 (1H, s, H-13), 5.47 (1H, s, H-13), 5.34 (1H, br t, H-3), 5.24 (1H, s, H-5), 3.75 (3H, s, 12-$COOCH_3$), 2.70 (1H, s, H-7), 2.68 (1H, s, H-6), 2.38 (1H, m, H-2), 2.06 (3H, s, CH_3COO−), 1.73 (1H, dd, J = 13.0, 3.0 Hz, H-9), 1.60 (1H, m, H-1), 1.58 (3H, s, H-15), 1.55 (1H, m, H-2), 1.44 (2H, m, H-8, H-10), 1.34 (1H, m, H-8), 1.04 (1H, dd, J = 12.8, 3.5 Hz, H-9), 0.98 (3H, d, J = 6.5 Hz, H-14); HRCIMS (CH_4) *m/z* 307.1911 (obsd for [M + H]$^+$), 307.1909 (calcd for $C_{18}H_{27}O_4$).

Methyl (3*R*)-11,13-dihydro-3-hydroxyartemisinate (14): Methyl (3*R*)-11,13-dihydro-3-hydroxyartemisinate (**14**) always contained an impurity, which prevented spectroscopic analyses. However, the synthesis of **14** was apparent since the corresponding artemisinin was subsequently synthesized from **14**.

Methyl (3*R*)-3-acetoxy-11,13-dihydroartemisinate (15): IR (KBr) ν_{max} 1737 (C=O stretching), 1732 (C=O stretching) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (1H, s, H-3), 5.31 (1H, s, H-5), 3.67 (3H, s, 12-$COOCH_3$), 2.62 (1H, br s, H-6), 2.51 (1H, m, H-11), 2.38 (1H, m, H-2), 2.07 (3H, s, CH_3COO), 1.7−1.4 (8H, m, H-1, H-2, H-7, H-9, H-10, H-15), 1.29 (2H, m, H-8), 1.15 (3H, d, J = 6.5 Hz, H-13), 1.04 (1H, m, H-9), 0.95 (3H, d, J = 6 Hz, H-14); HRCIMS (CH_4) *m/z* 309.2084 (obsd for [M + H]$^+$), 309.2066 (calcd for $C_{18}H_{29}O_4$).

13-Cyanoartemisinin (16): IR (neat) ν_{max} 2905, 2225 (C≡N stretching), 1730 (C=O stretching), 1186, 1109, 889, 827 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.00 (1H, s, H-5), 3.70 (1H, ddd, J = 10.8, 5.2, 5.1 Hz, H-11), 3.10 (1H, dd, J = 17.2, 10.8 Hz, H-13), 2.50 (1H, dd, J = 17.2, 5.1 Hz, H-13), 2.45 (1H, m, H-3), 2.18 (1H, m, H-7), 2.15 (1H, m, H-3), 2.07 (1H, m, H-2), 1.85 (1H, m, H-8, H-9), 1.50 (2H, m, H-1 and H-10), 1.48 (1H, m, H-2), 1.47 (3H, s, H-15), 1.20 (1H, m, H-9), 1.17 (1H, m, H-8), 1.04 (3H, d, J = 5.9 Hz, H-14); CIMS (CH_4) *m/z* 308 ([M + H]$^+$, 100), 307 ([M]$^+$, 4), 290 ([M + H − H_2O]$^+$, 73), 276 ([M + H − O_3]$^+$, 9), 248 (75).

13-Methoxycarbonylartemisinin (17): $[\alpha]^7_D$ −54.05° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 1730 (C=O stretching), 1104 (C−O stretching), 1120, 880, 837 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (1H, s, H-5), 3.91 (1H, m, H-11), 3.72 (3H, s, 12-$COOCH_3$), 2.99 (1H, dd, J = 16.4, 6.8 Hz, H-13), 2.43 (1H, m, H-3), 2.36 (1H, dd, J = 16.4, 8.5 Hz, H-13), 2.05 (1H, m, H-3), 1.95 (1H, m, H-7), 1.91 (1H, m, H-2), 1.71 (1H, m, H-8), 1.69 (1H, m, H-9), 1.58 (1H, m, H-2), 1.47 (3H, s, H-15), 1.43 (2H, m, H-1, H-10), 1.21 (1H, m, H-8), 1.16 (1H, m, H-9), 1.03 (3H, d, J = 5.9 Hz, H-14); CIMS (CH_4, rel int) *m/z* 341 ([M + H]$^+$, 100), 340 ([M]$^+$, 4), 322 ([M + H − H_2O]$^+$, 73), 291 (45); HRCIMS (CH_4) *m/z* 341.1587 (obsd for [M + H]$^+$), 341.1600 (calcd for $C_{17}H_{25}O_7$).

13-Methoxyartemisinin (18): mp 100−104 °C; $[\alpha]^7_D$ +82.38° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 1730 (C=O stretching), 1188, 1104 (C−O stretching), 1113, 889, 834 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 5.83 (1H, s, H-5), 3.81 (1H, dd, J = 9.1, 4.3 Hz, H-13), 3.53 (1H, dd, J = 10.2, 4.3 Hz, H-13), 3.51 (1H, m, H-11), 3.26 (3H, s, OCH_3), 2.35 (1H, m, H-3), 1.98 (1H, m, H-3), 1.95 (1H, m, H-7), 1.91 (1H, m, H-2), 1.81 (1H, m, H-8), 1.79 (1H, m, H-9), 1.38 (2H, m, H-1, H-10), 1.36 (3H, s, H-15), 1.35 (1H, m, H-2), 1.09 (1H, m, H-8), 1.05 (1H, m, H-9), 0.92 (3H, d, J = 3.7, H-14); CIMS (CH_4, rel int) *m/z* 313 ([M + H]$^+$, 100), 312 ([M]$^+$, 4), 295 ([M + H − H_2O]$^+$, 73), 267 ([M + H − O_3]$^+$, 9.16), 265 (14); HRCIMS (CH_4) *m/z* 313.1648 (obsd for [M + H]$^+$), 313.1651 (calcd for $C_{16}H_{25}O_6$).

13-Ethylsulfonylartemisinin (19): mp 169−172 °C; $[\alpha]^7_D$ +35.73° (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 1735 (C=O stretching), 1325 (SO_2 asymmetric stretching), 1136 (SO_2 symmetric stretching), 1115, 879, 840 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (1H, s, H-5), 4.06 (1H, ddd, J = 10.2, 5.0, 4.2 Hz, H-11), 3.81 (1H, dd, J = 14.6, 4.2 Hz, H-13), 3.11 (2H, q, J = 7.4 Hz, $SO_2CH_2CH_3$), 3.00 (1H, dd, J = 14.6, 5.0 Hz, H-13), 2.31 (1H, m, H-3), 1.46 (3H, s, H-15), 2.06 (1H, m, H-3), 1.44 (3H, t, J = 7.4 Hz, $SO_2CH_2CH_3$), 1.01 (3H, d, J = 5.9 Hz, H-14); CIMS (CH_4, rel int) *m/z* 403 ([M + C_2H_5]$^+$, 17), 375 ([M + H]$^+$, 56), 315 (100), 281 (26), 221 (60); HRCIMS (CH_4) *m/z* 375.1402 (obsd for [M + H]$^+$), 375.1399 (calcd for $C_{17}H_{26}SO_7$).

13-Nitromethylartemisinin (20): IR (KBr) ν_{max} 1734 (C=O stretching), 1551 (N=O stretching), 1388 (N=O stretching), 1116, 883, 835 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.89 (1H, s, H-5), 4.83 (1H, ddd, J = 14, 7.3, 7.3 Hz, H-16), 4.63 (1H, ddd, J = 14, 7.9, 5.9 Hz, H-16), 3.35 (1H, ddd, J = 9.3, 5.0, 4.6 Hz, H-11), 2.45 (2H, m, H-2, H-13), 2.09 (1H, m, H-2), 2.05 (2H, m, H-3, H-13), 1.86 (2H, m, H-7, H-8), 1.83 (1H, m, H-9), 1.49 (1H, m, H-2), 1.45 (3H, s, H-15), 1.43 (1H, m, H-1), 1.14 (2H, m H-8, H-9), 1.02 (3H, d, J = 3.8 Hz, H-14); CIMS (CH_4, rel int) *m/z* 342 ([M + H]$^+$, 68), 324 (80), 296 (96), 282 (100), 249 (55); HRCIMS (CH_4) *m/z* 342.1555 (obsd for [M + H]$^+$), 342.1553 (calcd for $C_{16}H_{24}O_7N$).

13-(1-Nitroethyl)artemisinin (21): IR (KBr) ν_{max} 1735.2, 1553.7, 1385.2, 1115, 883.2, 831.9 cm^{-1}; ^1H NMR ($CDCl_3$, 400

MHz), δ 5.87 (1H, s, H-5), 5.04 (1H, qt, J = 7, 3.3 Hz, H-16), 3.30 (1H, dt, J = 9, 4.5 Hz, H-11), 2.43 (1H, dt, J = 14, 3.5 Hz, H-3), 2.04 (1H, m, H-3), 2.03(1H, m, H-13), 2,0.0 (1H, m, H-2), 1.83 (1H, m, H-8), 1.81 (1H, m, H-7), 1.78 (1H, m, H-9), 1.61 (3H, d, J = 7 Hz, H-17), 1.45 (3H, s, CH_3-15), 1.44 (1H, m, H-10), 1.41 (1H, m, H-2), 1.13 (1H, m, H-8), 1.10 (1H, m, H-9), 1.01 (3H, d, J = 6.0 Hz, CH_3-14); CIMS (CH_4, rel int) *m/z* 356 ($[M + H]^+$, 57), 340 ($[M - CH_3]^+$, 39.3), 310 (100); HRCIMS (CH_4) *m/z* 356.1718 (obsd for $[M + H]^+$), 356.1709 (calcd for $C_{17}H_{26}O_7N$).

(3*R*)-3-Hydroxyartemisinin (22): IR (KBr) ν_{max} 3468 (O–H stretching), 1747 (C=O stretching), 1148, 882, 826 (peroxide) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.75 (1H, s, H-5), 4.01 (1H, br s, H-3), 3.30 (1H, dq, J = 7.3, 5.4 Hz, H-11), 2.16 (1H, ddd, J = 14.7, 6.8, 2.7 Hz, H-2), 1.84 (1H, m, H-8), 1.79–1.72 (3H, m, H-2, H-7, H-9), 1.54 (1H, ddd, J = 11, 11, 6.8 Hz, H-1), 1.45 (3H, s, H-15), 1.39 (1H, m, H-10), 1.16 (3H, d, J = 7.3 Hz, H-13), 1.03 (2H, m, H-8, H-9), 0.94 (3H, d, J = 6.3 Hz, H-14); CIMS (CH_4, rel int) *m/z* 299 ($[M + H]^+$, 20), 281 ($[M + H - H_2O]^+$, 51), 239 (100), 207 (83).

(3*R*)-3-Acetoxyartemisinin (23): ^1H NMR ($CDCl_3$, 400 MHz) δ 5.87 (1H, s, H-5), 5.21 (1H, dd, J = 11.5, 6.5 Hz, H-3), 3.40 (1H, m, H-11), 2.13 (3H, s, CH_3COO–), 1.95–1.5 (5H, m, H-2, H-7, H-8, H-9), 1.45 (3H, s, H-15), 1.42 (1H, m, H-10), 1.21 (3H, d, J = 7 Hz, H-13), 1.17 (2H, m, H-1, H-8), 1.05 (1H, m, H-9), 0.99 (3H, d, J = 6 Hz, H-14); CIMS (CH_4, rel int) *m/z* 341 ($[M + H]^+$, 35), 281 ($[M - C_2H_3O_2]^+$, 75), 249 (100), 221 (64).

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Supporting Information Available: Detailed synthetic procedures and tables showing the ^{13}C NMR data of compounds **1**–**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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