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ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 5247–5253
Bioorganic & Medicinal Chemistry

Electronically stabilized versions of the antimalarial acetal trioxanes artemether and artesunate

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Received 25 January 2008; revised 27 February 2008; accepted 3 March 2008
Available online 6 March 2008

Dedicated to E.J. Corey with admiration and respect on the happy occasion of his 80th birthday in 2008.

Abstract—From 9-substituted DHA, several new artemisinin-derived C-10 acetal ethers and esters were prepared with either a 9-fluoro or a 9-sulfonyl substituent. The very strong inductive electron-withdrawing C-9 substituent is shown to retard considerably C-10 ionization (acid-promoted etherification) of 9-fluoro-DHA and 9-sulfonyl-DHA.

1. Introduction

The effectiveness of quinoline-based antimalarials is being compromised seriously by the widespread resistance of malaria parasites to these drugs.[1] A traditional Chinese folk remedy for malaria has led to the isolation and identification of the 1,2,4-trioxane artemisinin (**1**), and subsequently to the synthesis of fast-acting semisynthetic derivatives (Fig. 1) such as dihydroartemisinin (DHA, **2**), artemether (**3**), and sodium artesunate (**4**).[2] The World Health Organization has recommended, and most countries where malaria is endemic have adopted, the use of artemisinin combination therapy (ACT) for fast and reliable cure for malaria-infected people.[3] One practical shortcoming of C-10 acetals such as **3** and **4** is the rapid but undesirable hydrolysis of their C-10 acetal functionality into the corresponding parent C-10 hemiacetal DHA which is reported to be toxic.[4,5]

Such C-10 acetal to C-10 hemiacetal hydrolysis after oral administration is likely due to the acidic environment of the human stomach. We thought that attaching a strongly electron-withdrawing group (EWG) at C-9 would inductively disfavor carbocation formation at C-10 (Fig. 2) and thus would electronically stabilize any C-10 ether or ester derivative **5** thereby making it a longer-lived and possibly better antimalarial. Related

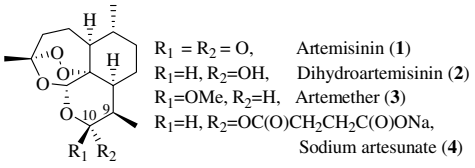

Figure 1. Artemisinin and semisynthetic derivatives.

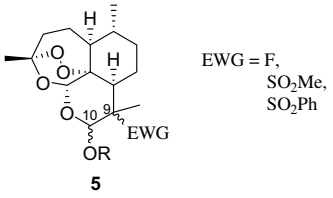

Figure 2. 9-Substituted artemisinin derivatives.

work in this area has involved C-10 *p*-substituted phenoxy derivatives[6] and C-10 sulfonamides,[5] as well as the incorporation of a trifluoromethyl group at C-10.[7]

Herein are the results of a new study using 9-fluoro and 9-sulfonyl groups to retard acid-promoted etherification via rate-determining ionization of the C-10 OH group in hemiacetal DHA (**2**). Although C-9 heteroatom systems are known,[8–10] 9-fluoro and 9-sulfonyl substituents have not been reported and were chosen due to their very powerful inductive electron-withdrawing ability.[11]

Keywords: Artemisinin; Artemether; Sodium artesunate; Antimalarial.
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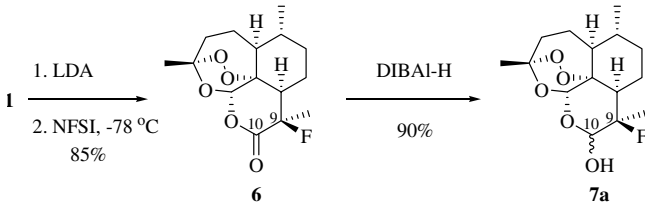
doi:10.1016/j.bmc.2008.03.010



Scheme 1. 9-Fluoroartemisinin and 9-fluoro-DHA.

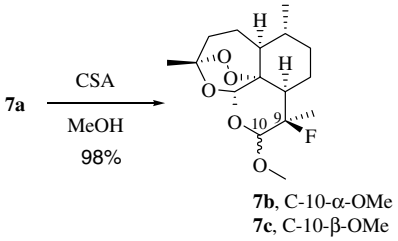
2. Results and discussion

2.1. Fluoro derivatives

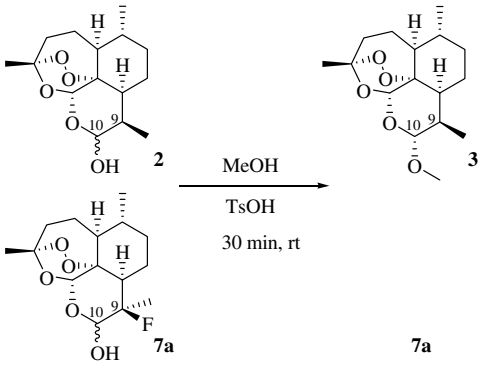
The synthesis of 9-fluoroartemisinin (**6**) was accomplished by reacting the lithium enolate of **1** with the electrophilic fluorinating reagent *N*-fluorobenzenesulfonimide (NFSI) in 85% yield. The attachment of the fluorine atom was exclusive to the β-face of artemisinin, as evident from X-ray crystal analysis. Attempts to fluorinate **1** on the α-face using smaller reagents (Selectfluor or *N*-fluoropyridinium triflate) or by using NFSI at elevated temperatures did not lead to the desired diastereomer. Reduction of **6** using diisobutylaluminium hydride (DIBAl-H) cleanly afforded 9-fluoro-DHA (**7a**) in 90% yield (Scheme 1).

In an attempt to synthesize the fluoro analog of artemether (**3**), hemiacetal **7a** was treated with camphorsulfonic acid (CSA) in methanol. Unlike the rapid formation of artemether (**3**) using the same procedure,[12] the formation of **7b** and **7c** was sluggish (**7b**/**7c** = 2:1, 98% yield at 60% conversion), reinforcing our hypothesis that the 9-fluorine atom disfavors carbocation formation at C-10 (Scheme 2).

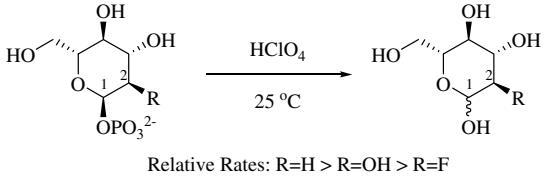
A competition etherification experiment was performed at room temperature using 1 equivalent of DHA (**2**), 1 equivalent of 9-fluoro-DHA (**7a**) and 0.5 equivalent of methanol in $CDCl_3$ solvent in an NMR tube with a catalytic amount of *p*-toluenesulfonic acid (Scheme 3). After only 1 min, a small amount of artemether (**3**) (singlet at δ 3.43 ppm) was seen in the ^1H NMR spectrum. After 0.5 h, all the methanol was consumed, as determined by ^1H NMR spectroscopy. The ratio of methyl ether products **3**:**7b** was at least 50:1 based on a ^1H NMR standard.[13] This result confirmed that the fluorine atom does in fact function to retard C-10 carbocation formation. A similar observation was made during the hydrolysis of C-10 trifluoromethyl artemether versus the hydrolysis of artemether itself.[7] The authors noted a 60-fold lowering of the hydrolysis rate by the incorporation of the C-10-CF_3 group, which acts to disfavor carbocation formation at C-10.[7]



Scheme 2. 9-Fluoroartemether.



Scheme 3. Competition experiment.



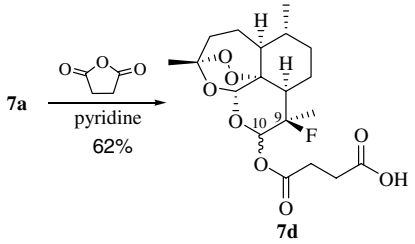
Scheme 4. Acid-catalyzed hydrolysis of sugar systems.

This result is also in agreement with work done on 2-substituted α-D-glucopyranosyl phosphate systems.[14–16] A series of analogs were prepared and subjected to acid-catalyzed hydrolysis. It was found that the relative rates followed the order 2-deoxy > 2-hydroxy > 2-deoxy-2-fluoro (Scheme 4). The fluorine atom adjacent to the anomeric center acts to inductively withdraw electron density, affecting both the equilibrium constant for protonation as well as destabilizing a developing carbocation at C-1.[15]

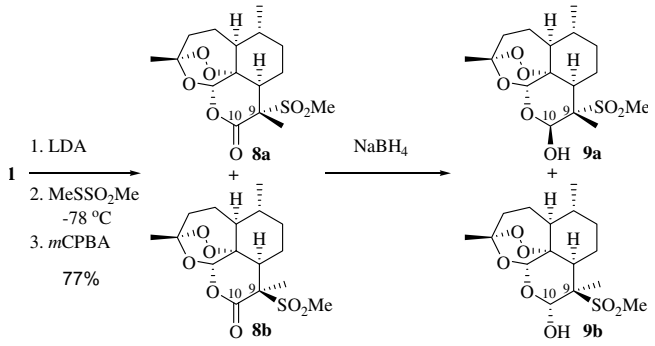
Wanting to synthesize the 9-fluoro derivative of sodium artesunate (**4**) for biological testing, **7a** was treated with succinic anhydride in pyridine to afford, after aqueous acidic work-up, 9-fluoroartesunic acid (**7d**) in 62% yield (Scheme 5) as an inseparable mixture of C-10 diastereomers (C-10 α/β = 14:1).

2.2. Sulfonyl derivatives

The synthesis of 9-methanesulfonylartemisinin (**8**) began with the reaction of the lithium enolate of **1** with *S*-methyl methanethiosulfonate affording a mixture of diastereomers. The crude sulfide products were oxidized directly in the presence of *m*-chloroperoxybenzoic acid (*m*CPBA)



Scheme 5. 9-Fluoroartesunic acid.



Scheme 6. 9-Methanesulfonyl systems.

to give 9-methanesulfonylartemesinin (9-SO_2Me α/β = 1:2) in 77% yield. The pair of diastereomers **8a** and **8b** was easily separable by column chromatography and identified by X-ray crystallography. These lactones were separately reduced with sodium borohydride ($NaBH_4$) to give α-9-SO_2Me-DHA (**9a**) in 85% yield and β-9-SO_2Me-DHA (**9b**) in 87% yield (Scheme 6).

The reduction from **8a** to **9a** and from **8b** to **9b** proceeded stereospecifically; in each case only one lactol product was formed. This result is most likely due to the unzipping and rezipping of the lactol, under basic conditions, to form the more thermodynamically stable product.[17] In an effort to synthesize the methanesulfonyl analog of artemether (**3**), lactols **9a** and **9b** were each treated with an equimolar amount of CSA in methanol at room temperature. After 2 days, no reaction occurred even when subsequently heated to reflux for 30 h. These results suggest that carbocation formation at C-10 is exceptionally retarded when a methanesulfonyl group is present at C-9. Indeed, the inductive electron-withdrawing ability of a sulfonyl group is known to be considerably greater than that of a fluorine atom.[11]

To avoid the aforementioned toxicity associated with DHA (**2**), a series of electronically stabilized C-10 esters were synthesized for biological testing. Based on recent reports that optimal antimalarial oral efficacy was achieved with trioxanes of relatively high lipophilicity ($\log P = 8$)[18,19] we prepared 10-stearoyl (**9c**) and 10-*p*-decylbenzoyl (**9d**) esters (Fig. 3).

In order to maintain the high lipophilicity of these molecules while at the same time reducing the aliphatic chain length, it was necessary to substitute the 9-methanesulfonyl group with a 9-benzenesulfonyl group.[20] The preparation of **10a** followed a similar sequence to that of **9b**, affording a separable 12:1 mixture of diastereomers in 51% yield. The major lactol **10a** was treated

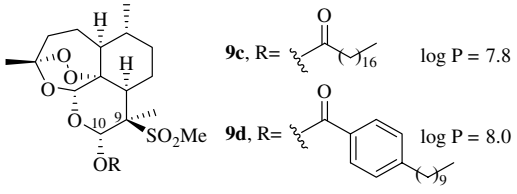
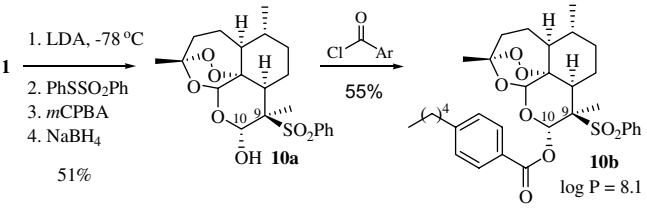


Figure 3. 9-Methanesulfonyl 10-esters.



Scheme 7. 9-Benzenesulfonyl *p*-pentylbenzoate ester.

with *p*-pentylbenzoyl chloride to give analog **10b** in 55% yield and as a single diastereomer (Scheme 7).

3. Conclusion

Several 9-substituted artemisinin analogs have been prepared. The incorporation of the strongly inductive electron-withdrawing fluoro and sulfonyl groups led to compounds in which the formation of the C-10 carbocation was retarded. A competition experiment between DHA (**2**) and 9-fluoro-DHA (**7a**) solidified this claim, as acid-promoted etherification was at least 50 times slower for the formation of 9-fluoroartemether (**7b** and **7c**) than for the formation of artemether (**3**). When the fluoro substituent was replaced by a methanesulfonyl group, etherification was not observed at all even under forcing conditions presumably due to the instability of the C-10 carbocation. It was plausible to expect, therefore, that the formation of the toxic 9-substituted-DHA via in vivo hydrolysis of the corresponding orally-administered ether and ester derivatives would be suppressed due to the electron-withdrawing groups at C-9. Disappointingly, however, the 9-fluoroartemethers **7b** and **7c** and 9-fluoroartesunic acid (**7d**) as well as 9-sulfonyl benzoates **9d** and **10b** were not strongly antimalarial upon oral administration to rodents. As compared with our recently reported antimalarials which upon oral administration to mice at a 1 × 30 mg/kg dose, typically prolong survival up to 11 days post infection[21] these 9-fluoro and 9-sulfonyl derivatives did not prolong mouse survival past 7 days, which is the typical lifespan of malaria-infected mice receiving no treatment at all.[21] This lack of antimalarial activity in our analogs, however, may be due to changes in lipophilicity, transport, and/or metabolism rather than to only the increased hydrolytic stability of these new 9-substituted trioxanes. Alternatively, the lack of activity may be due to the orientation of the C-9-α-methyl group,[22] which is on the non-natural α-face of artemisinin. This orientation may inhibit one of the two known radical pathways of artemisinin metabolism.[23–25] Our attempts to synthesize 9-α-fluoroartemisinin have not afforded promising results.

4. Experimental

4.1. General

All reactions were performed in oven dried glassware, and stirred under an atmosphere of ultra high purity Argon. The tetrahydrofuran used was distilled from sodium/benzophenone, and the dichloromethane was

distilled from calcium hydride. All other reagents were used as received from commercial suppliers, unless otherwise noted. Analytical TLC analysis was conducted on precoated glass-backed silica gel plates (Merck Kieselgel 60 F_{254}, 250 μ thickness) and visualized with *p*-anisaldehyde or $KMnO_4$ stains. Column chromatography was preformed using flash silica gel (particle size 230–400 mesh). Yields reported are for pure products (>95% based on their chromatographic and spectroscopic homogeneity), and are unoptimized. NMR spectra were obtained on a Bruker-400 spectrometer, operating at 400 MHz for ^1H, and 100 MHz for ^{13}C. Chemical shifts are reported in ppm (δ) and are referenced to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra were obtained using fast atom bombardment in the positive ion mode on a VG Instruments VG70S or electrospray ionization in the positive ion mode on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source. IR spectra were carried out on a Bruker Vector 22 spectrometer from liquid films. $[\alpha]_D$ values were recorded in $CHCl_3$ on a Jasco P-1010 polarimeter. log *P* values were calculated by using MarvinSketch and a calculator plug-in by ChemAxon Kft.

4.2. Synthesis of 9-fluoroartemesinin (6)

A 25 mL roundbottom flash was charged with ^{n}BuLi (1.33 mL, 1.6 M, 2.1 mmol) and diluted with THF (5 mL) before being cooled to −10 °C. Diisopropylamine (0.37 mL, 2.7 mmol) was added to the solution dropwise, and allowed to stir for 10 min before cooling to −78 °C. Artemisinin (0.500 g, 1.8 mmol) dissolved in THF (5 mL) was added via cannula, and allowed to stir for 1 h before adding NFSI (1.68 g, 5.3 mmol). After 60 min, the reaction was quenched with H_2O, washed with a saturated aqueous solution of citric acid, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (10% ethyl acetate, 90% hexanes) to give **6** (0.452 g, 85%) as an amorphous white solid. $[\alpha]_D^{25}$ 84.2 (*c* 0.005, $CDCl_3$); IR (neat) ν_{max} 3000, 2973, 2964, 2928, 2883, 2856, 1755, 1457, 1376, 1232, 1205, 1124, 1033, 979, 871 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 2.43–2.36 (m, 1H), 2.16–1.96 (m, 4H), 1.873–1.871 (m, 1H), 1.810–1.808 (m, 2H), 1.78–1.77 (m, 1H), 1.49–1.37 (m, 7H), 1.28–1.24 (m, 1H), 1.08–1.04 (m, 1H), 0.99 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.3, 105.5, 94.3, 91.9, 90.1, 80.92, 80.86, 50.7, 50.6, 50.0, 49.8, 37.5, 35.9, 33.1, 33.08, 27.5, 27.3, 25.0, 24.6, 23.6, 23.5, 19.7; HRMS (FAB, M+1) calcd 301.14513 for $C_{15}H_{22}FO_5$, found 301.14336.

4.3. Synthesis of 9-fluoro-DHA (7a)

A 15 mL roundbottom flask was charged with **6** (0.150 g, 0.50 mmol), dissolved in CH_2Cl_2 (8 mL), and cooled to −78 °C. DIBAl-H (0.75 mL, 1.0 M, 0.75 mmol) was added dropwise over 5 min. After 2 h, the reaction was quenched with a saturated aqueous solution of Na_2SO_4, and filtered over Celite. The crude mother liquor was washed with a saturated aqueous solution of citric acid, followed by a saturated aqueous solution of $NaHCO_3$ dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give **7a** (0.136 g, 90%) as an amorphous white solid and a 1:1 mixture of inseparable isomers. $[\alpha]_D^{21}$ 69.8 (*c* 0.780, $CDCl_3$); IR (neat) ν_{max} 3446, 2949, 2931, 2858, 1457, 1385, 1159, 1122, 1023, 1005, 915, 869, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 5.42–5.37 (m, 2H), 5.16–5.14 (m, 1H), 3.79–3.77 (m, 1H), 3.57–3.53 (m, 1H), 2.37–2.23 (m, 2H), 2.07–1.84 (m, 9H), 1.71–1.64 (m, 3H), 1.61–1.50 (m, 5H), 1.47–1.22 (m, 13H), 1.00–0.94 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.5, 103.1, 94.7, 94.5, 93.9, 93.7, 92.9, 92.7, 91.5, 91.2, 89.1, 82.0, 81.9, 81.21, 81.17, 51.6, 51.47, 51.46, 50.44, 50.38, 50.22, 50.18, 37.23, 37.17, 36.3, 36.1, 33.59, 33.56, 33.45, 33.43, 26.0, 25.8, 25.6, 25.4, 24.3, 24.2, 23.9, 23.8, 23.0, 22.9, 20.1, 19.9, 19.8, 19.6; HRMS (FAB, M+1) calcd 325.14217 for $C_{15}H_{24}FO_5$, found 325.14169.

4.4. Synthesis of 9-fluoroartemethers (7b and 7c)

A 5 mL roundbottom flask was charged with **7a** (0.068 g, 0.22 mmol) and dissolved in methanol (1 mL). CSA (0.052 g, 0.22 mmol) and 6 4Å mol sieves were added, and the reaction was allowed to stir at room temperature for 48 h, at which point the reaction did not appear to be progressing any further by TLC analysis. The reaction was quenched with H_2O, washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude products were purified by silica gel chromatography (10% ethyl acetate, 90% hexanes) to afford **7b** (0.027 g, 38%), **7c** (0.015 g, 21%), and recovered **7a** (0.027 g, 38%). Major (**7b**): $[\alpha]_D^{21}$ 22.3 (*c* 0.825, $CDCl_3$); IR (neat) ν_{max} 2946, 2888, 2856, 1463, 1379, 1183, 1127, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (m, 1H), 4.68 (d, J = 3.2 Hz, 1H), 3.58 (s, 3H), 2.39–2.31 (m, 1H), 2.09–1.99 (2H), 1.95–1.87 (m, 2H), 1.72–1.67 (m, 5H), 1.51–1.22 (m, 6H), 1.05–0.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.5, 98.7, 98.4, 94.2, 92.5, 91.4, 82.02, 81.96, 57.4, 51.76, 51.75, 50.5, 50.3, 37.3, 36.2, 33.5, 25.5, 24.3, 23.1, 23.0, 20.5, 20.3, 20.2; HRMS (ESI, M+Na) calcd 285.15021 for $C_{16}H_{26}FO_5$, found 285.15023. Minor (**7c**): $[\alpha]_D^{21}$ 111.2 (*c* 0.525, $CDCl_3$); IR (neat) ν_{max} 2974, 2927, 2853, 1445, 1371, 1099, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (s, 1H), 4.75 (s, 1H), 3.53 (s, 3H), 2.34–2.29 (m, 1H), 2.06–1.87 (m, 5H), 1.71 (s, 1H), 1.67–1.62 (m, 3H), 1.58–1.20 (m, 6H), 0.96–0.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.0, 103.1, 102.8, 92.6, 90.7, 87.7, 81.93, 81.88, 77.2, 56.4, 52.4, 49.7, 49.4, 37.3, 36.4, 33.8, 27.1, 26.9, 25.7, 24.2, 23.9, 23.8, 20.2; HRMS (FAB, M+1) calcd 285.15021 for $C_{16}H_{26}FO_5$, found 285.15016.

4.5. Synthesis of 9-fluoroartesunic acid (7d)

A 10 mL roundbottom flask was charged with **7a** (0.025 g, 0.08 mmol) and dissolved in CH_2Cl_2 (2.5 mL). Pyridine (13 μL, 0.16 mmol) and dimethylaminopyridine (0.007 g, 0.6 mmol) were added neatly at room temperature. After 60 min, the reaction was quenched with H_2O, washed with a saturated aqueous solution of citric acid, followed by a saturated aqueous

solution of $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude products were purified by silica gel chromatography (50% ethyl acetate, 50% hexanes) to afford **7d** (0.018 g, 62%) as an inseparable 14:1 mixture of isomers at C-10. Major: $[\alpha]_D^{21}$ 34.3 (*c* 0.110, $CDCl_3$); IR (neat) ν_{max} 3338, 2927, 1752, 1706, 1445, 1379, 1146, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, $J = 4.0$ Hz, 1H), 5.48 (m, 1H), 2.80–2.69 (m, 4H), 2.38–2.30 (m, 1H), 2.09–1.86 (m, 4H), 1.75–1.67 (m, 4H), 1.55–1.23 (m, 8H), 1.06–0.83 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 104.6, 93.0, 91.9, 91.2, 89.2, 88.9, 81.8, 81.7, 51.7, 50.6, 50.4, 37.2, 36.1, 33.4, 28.9, 25.5, 24.1, 23.0, 22.9, 21.0, 20.8, 20.6, 20.1; HRMS (ESI, M+Na) calcd 425.15822 for $C_{19}H_{27}FO_8Na$, found 425.15848.

4.6. Synthesis of 9-methanesulfonylartemisinin (8a and 8b)

A 25 mL roundbottom flash was charged with ^{n}BuLi (1.25 mL, 1.6 M, 1.9 mmol) and diluted with THF (4 mL) before being cooled to −10 °C. Diisopropylamine (0.30 mL, 1.9 mmol) was added to the solution dropwise, and allowed to stir for 10 min before cooling to −78 °C. Artemisinin (0.500 g, 1.8 mmol) dissolved in THF (3 mL) was added via cannula, and allowed to stir for 1 h before adding *S*-methyl methanethiosufate (0.9 mL, 8.9 mmol). The crude sulfide product was oxidized without purification with *m*CPBA (1.5 g, 8.8 mmol) in CH_2Cl_2 for 16 h. The reaction was quenched with H_2O, washed with a saturated aqueous solution sodium bisulfite, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give the minor diastereomer **8a** and the major diastereomer **8b** in 77% yield (**8a/8b** = 1:2) as amorphous white solids. Minor (**8a**): $[\alpha]_D^{20}$ 174.1 (*c* 0.290, $CDCl_3$); IR (neat) ν_{max} 3019, 2986, 2956, 2944, 2863, 2846, 1759, 1350, 1246, 1165, 1045, 1001, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 1H), 3.13 (s, 1H), 2.75–2.71 (m, 1H), 2.39–2.31 (m, 1H), 2.13–2.05 (m, 1H), 1.97–1.85 (m, 1H), 1.78–1.72 (m, 3H), 1.71–1.41 (m, 6H), 1.39–1.24 (m, 4H), 1.16–1.01 (m, 3H), 0.99 (d, $J = 5.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 105.5, 94.7, 80.7, 68.1, 50.9, 42.3, 38.6, 36.9, 35.7, 33.6, 26.2, 25.4, 24.3, 19.6, 19.3; HRMS (FAB, M+1) calcd 361.13210 for $C_{16}H_{24}O_7S$, found 361.13088. Major (**8b**): $[\alpha]_D^{20}$ 38.9 (*c* 1.030, $CDCl_3$); IR (neat) ν_{max} 3019, 2986, 2956, 2944, 2863, 2846, 1759, 1350, 1246, 1165, 1045, 1001, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 3.10 (s, 1H), 2.71–2.67 (m, 1H), 2.35–2.27 (m, 1H), 2.20–2.16 (m, 1H), 1.96–1.85 (m, 1H), 1.76–1.68 (m, 3H), 1.67–1.40 (m, 6H), 1.39–1.24 (m, 4H), 1.16–1.01 (m, 2H), 0.99 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 105.4, 94.4, 81.8, 68.4, 50.5, 47.8, 39.3, 37.2, 35.5, 33.8, 26.3, 24.96, 24.93, 24.7, 19.5; HRMS (FAB, M+1) calcd 361.13210 for $C_{16}H_{24}O_7S$, found 361.13088.

4.7. Synthesis of 9-methanesulfonyl-DHA (9a)

A 100 mL roundbottom flask was charged with **8a** (0.142 g, 0.41 mmol), dissolved in MeOH (30 mL), and cooled to 0 °C. $NaBH_4$ (0.155 g, 4.11 mmol) was added slowly over 5 min. After 1 h, the reaction was quenched with a solution of 30% acetic acid in MeOH, and stirred for 15 min. The resultant solution was concentrated in vacuo, dissolved in CH_2Cl_2 (20 mL), and stirred with a solution of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (70% ethyl acetate, 30% hexanes) to give **9a** (0.126 g, 85%) as an amorphous white solid and a single diastereomer. $[\alpha]_D^{21}$ 217.2 (*c* 0.105, $CDCl_3$); IR (neat) ν_{max} 3435, 2923, 2918, 2896, 1498, 1355, 1233, 1160, 1036, 996, 906, 886 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.38 (s, 1H), 4.44 (br s, 1H), 2.99 (s, 1H), 2.52–2.29 (m, 2H), 2.05–1.80 (m, 3H), 1.66–1.62 (m, 1H), 1.56–1.00 (m, 13H), 0.93 (d, $J = 5.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.8, 89.9, 89.8, 80.7, 68.6, 51.9, 41.7, 38.3, 36.6, 36.2, 33.7, 27.1, 25.5, 24.2, 20.9, 19.6; HRMS (ESI, M+Na) calcd 385.12914 for $C_{16}H_{26}O_7S$, found 385.12901.

4.8. Synthesis of 9-methanesulfonyl-DHA (9b)

Prepared in the same manner as **9a** The crude product was purified by silica gel chromatography (70% ethyl acetate, 30% hexanes) to give **9b** (0.09 g, 87%) as an amorphous white solid and a single diastereomer. $[\alpha]_D^{21}$ 44.0 (*c* 0.173, $CDCl_3$); IR (neat) ν_{max} 3330, 2922, 2960, 1524, 1446, 1373, 1237, 1145, 1024, 1005, 920, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 5.42 (s, 1H), 4.61(br s, 1H), 3.06 (s, 1H), 2.52–2.47 (m, 1H), 2.38–2.30 (m, 1H), 2.21–2.15 (m, 1H), 2.02–1.75 (m, 5H), 1.70–0.80 (m, 14H) includes 0.92 (d, $J = 5.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.6, 91.2, 90.8, 81.2, 67.3, 52.1, 47.0, 41.9, 36.8, 36.1, 33.7, 25.7, 25.3, 24.5, 20.0, 15.0 HRMS (ESI, M+Na) calcd 385.12816 for $C_{16}H_{26}O_7S$, found 385.12811.

4.9. Synthesis of C-10-stearoyl ester 9c

A 25 mL roundbottom flask was charged with **9b** (0.102 g, 0.28 mmol), DMAP (0.03 g, 0.28 mmol), pyridine (1 mL), dissolved in CH_2Cl_2 (1 mL), and cooled to 0 °C. To the mixture was added stearoyl chloride (0.94 mL, 0.28 mmol) neat. After 2 h, the reaction was quenched with a solution of 10% HCl (10 mL) and CH_2Cl_2 (10 mL). The reaction mixture was washed with an aqueous solution of 50% citric acid, followed by a saturated aqueous solution of brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (20% ethyl acetate, 80% hexanes) to give **9c** (0.08 g, 48%) as an oil and a single diastereomer. $[\alpha]_D^{21}$ −74.5 (*c* 0.423, $CDCl_3$); IR (neat) ν_{max} 2956, 2965, 2892, 1759, 1475, 1355, 1233, 1115, 1026, 996, 905, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.50 (s, 1H), 2.94 (s, 1H), 2.60–2.40 (m, 2H), 2.38–2.33 (m, 3H), 2.30–2.15 (m, 1H), 2.10–0.80 (m, 51H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 104.4, 91.6, 88.7, 81.1, 65.9, 52.1, 47.2, 41.7, 36.6, 36.0, 34.0, 33.5, 31.8, 29.59, 29.56, 29.55, 29.54, 29.50, 29.48, 29.32, 29.26, 29.1, 28.98, 28.86, 25.5, 25.2, 24.3, 24.2, 22.6, 19.9, 15.7, 14.0; HRMS (ESI, M+Na) calcd 651.39011 for $C_{34}H_{60}O_8SNa$, found 651.38737.

4.10. Synthesis of 10-*p*-decylbenzoyl ester 9d

A 25 mL roundbottom flask was charged with **9b** (0.06 g, 0.16 mmol), DMAP (0.017 g, 0.28 mmol), pyridine (1 mL), dissolved in CH_2Cl_2 (1 mL), and cooled to 0 °C. To the mixture was added *p*-decylbenzoyl chloride (0.10 g, 0.16 mmol). After 2 h, the reaction was quenched with a solution of 10% HCl (10 mL) and CH_2Cl_2 (10 mL). The reaction mixture was washed with an aqueous solution of 50% citric acid followed by a saturated aqueous solution of brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give **9d** (0.07 g, 70%) as an oil and a single diastereomer. $[\alpha]_D^{21}$ 185.5 (*c* 0.425, $CDCl_3$); IR (neat) ν_{max} 2948, 2926, 2878, 1761, 1625, 1510, 1471, 1355, 1233, 1125, 1036, 979, 905, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 6.59 (s, 1H), 5.61 (s, 1H), 2.94 (s, 1H), 2.70–2.44 (m, 3H), 2.40–2.22 (m, 2H), 2.10–1.90 (m, 4H), 1.85–1.10 (m, 25H), 1.00–0.90 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 149.7, 130.0, 128.8, 126.3, 104.5, 91.7, 89.0, 81.3, 77.3, 66.4, 52.3, 47.5, 41.6, 36.8, 36.2, 36.1, 33.7, 31.9, 31.0, 29.6, 29.5, 29.4, 29.3, 28.2, 25.7, 25.3, 24.4, 22.6, 20.0, 14.0; HRMS (ESI, M+Na) calcd 629.31186 for $C_{34}H_{60}O_8SNa$, found 629.30985.

4.11. Synthesis of 9-benzenesulfonyl-DHA (10a)

A 25 mL roundbottom flash was charged with ^{n}BuLi (1.25 mL, 1.6 M, 1.9 mmol) and diluted with THF (4 mL) before being cooled to −10 °C. Diisopropylamine (0.30 mL, 1.9 mmol) was added to the solution dropwise, and allowed to stir for 10 min before cooling to −78 °C. Artemisinin (0.500 g, 1.8 mmol) dissolved in THF (3 mL) was added via cannula, and allowed to stir for 1 h before adding *S*-phenyl benzenethiosulfate (1.27 g, 5.1 mmol). After 1 h, the reaction was worked up, and the crude sulfide product was oxidized without purification with *m*CPBA (1.7 g, 9.8 mmol) in CH_2Cl_2 for 16 h. The reaction was quenched with H_2O, washed with a saturated aqueous solution sodium bisulfite, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give a pair of diastereomer products 9-phenylsulfoneartemisinin in ratio of 1:12. The major product, β-9-penylsulfoneartemisinin (0.150 g, 0.35 mmol), was placed in a 100 mL roundbottom flask, dissolved in MeOH (20 mL), and cooled to 0 °C. $NaBH_4$ (0.135 g, 3.55 mmol) was added slowly over 5 min. After 1.5 h, the reaction was quenched with a solution of 30% acetic acid in MeOH, and stirred for 15 min. The solution was concentrated in vacuo, dissolved in 20 mL of CH_2Cl_2, and stirred in a solution of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (70% ethyl acetate, 30% hexanes) to give **10a** (0.102 g, 68%) as an amorphous white solid and a single diastereomer. $[\alpha]_D^{21}$ 18.2 (*c* 0.011, $CDCl_3$); IR (neat) ν_{max} 3498, 2943, 2870, 1718, 1446, 1352, 1310, 1274, 1256, 1112, 907, 730, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8 Hz, 2H), 7.57 (m, 1H), 7.56 (t, J = 4 Hz, 2H), 5.67 (s, 1H), 5.47 (s, 1H), 2.82–2.79 (m, 1H), 2.39–2.30 (m, 3H), 2.03–1.92 (m, 3H), 1.81–1.66 (m, 3H), 1.60–1.15 (m, 8H), 1.10–0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 134.3, 133.3, 129.6, 104.5, 91.2, 81.5, 77.3, 69.0, 52.2, 47,9, 37.1, 36.1, 33.9, 25.9, 25.3, 24.6, 20.1, 16.3; HRMS (ESI, M+Na) calcd 447.14479 for $C_{21}H_{28}O_7S$, found 447.14371.

4.12. Synthesis of 10-*p*-pentylbenzoyl ester 10b

A 25 mL roundbottom flask was charged with **10a** (0.06 g, 0.16 mmol), DMAP (0.017 g, 0.28 mmol), pyridine (1 mL), dissolved in CH_2Cl_2 (1 mL), and cooled to 0 °C. To this mixture was added *p*-pentylbenzoyl chloride (0.045 g, 0.16 mmol) neatly. After 12 h, the reaction was quenched with an aqueous solution of 10% HCl (10 mL) and CH_2Cl_2 (10 mL), washed with an aqueous solution of 50% citric acid followed by saturated aqueous solution of brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (30% ethyl acetate, 70% hexanes) to give **10b** (0.05 g, 55%) as a white solid and a single diastereomer. $[\alpha]_D^{21}$ 11.5 (*c* 0.435, $CDCl_3$); IR (neat) ν_{max} 2955, 2943, 2823, 1758, 1655, 1625, 1510, 1505, 1466, 1342, 1256, 1125, 1040, 981, 910, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.20–7.10 (m, 4H), 6.73 (s, 1H), 5.63 (s, 1H), 2.88–2.84 (m, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.42–2.31 (m, 2H), 2.04–1.86 (m, 3H), 1.85–1.70 (m, 3H), 1.68–1.45 (m, 5H), 1.44–1.10 (m, 10H), 1.08–0.80 (m, 5H) includes 0.99 (d, J = 5.6 Hz) and 0.91 (t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 149.4, 138.8, 133.0, 130.9, 130.6, 128.4, 128.2, 126.3, 104.5, 91.4, 89.0, 81.5, 77.3, 68.1, 52.3, 48.2, 37.0, 36.2, 35.9, 33.9, 31.3, 30.8, 26.0, 25.3, 24.6, 22.4, 20.1, 17.7, 14.0; HRMS (ESI, M+Na) calcd 621.24926 for $C_{34}H_{60}O_8SNa$, found 621.2492.

Acknowledgments

This work was supported by the National Institutes of Health (Grant AI 34885). We thank Dr. Amy Sarjeant for X-ray crystal analysis and Dr. Phil Mortimer and Mrs. Susan Hatcher for mass analysis as well as Dr. Matthias Rottmann at the Swiss Tropical Institute for oral antimalarial testing in rodents.

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