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Antimalarial Artemisinin Analogs. Synthesis via Chemoselective C–C Bond Formation and Preliminary Biological Evaluation‡

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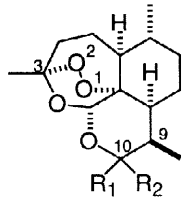
Abstract: The peroxide bond in artemisinin trioxane lactone (**1**) withstood exposure to lithiothiazole and to lithiobenzothiazole; nucleophilic addition of these powerful organometallic reagents to only the lactone carbonyl group was observed. Likewise, trioxane aldehyde **5** reacted with organolithium, Grignard, and phosphorus ylide nucleophiles exclusively *via* carbonyl addition. Also, trioxane ketone **7b** reacted with phenyllithium *via* only carbonyl addition. These chemoselective lactone, aldehyde, and ketone carbonyl addition reactions produced a series of new, enantiomerically pure, C-10 non-acetal derivatives of natural trioxane artemisinin having high *in vitro* antimalarial potencies.

Keywords: Chemoselective Carbonyl Additions, Peroxide Bond Stability, Antimalarial, Trioxanes, Artemisinin

Introduction

Globally, malaria is once again threatening mankind.[1] No vaccine to prevent malaria is available, and using quinoline derivatives (*e.g.* chloroquine) to cure people having malaria is becoming much less effective due to the parasites' rapidly increasing resistance to such standard drugs.[2] An ancient Chinese herbal remedy against malaria has led relatively recently to the discovery of a new class of endoperoxide antimalarial drugs: natural lactone trioxane artemisinin (qinghaosu, **1**) and semi-synthetic ether and ester derivatives of trioxane lactol dihydroartemisinin (**2**) are now used broadly and effectively in many areas of the world where malaria is endemic.[3] Various recent explorations of the fundamental organic chemistry of such peroxidic drugs have led to a surprising chemical generalization: the peroxide bond in such 1,2,4-trioxanes is often quite robust.[4-19] Herein we report the following new results: (1) evidence of chemical stability of such trioxanes even toward some highly reactive organometallic (*e.g.* organolithium) reagents; (2) application of chemoselective C–C bond formation to prepare various C-10 carbon-substituted analogs of 10-deoxoartemisinin; and (3) determination of the *in vitro* antimalarial potencies of eleven of these C-10 non-acetal artemisinin analogs.



1 $R_1 = R_2 = O$ (artemisinin)

2 $R_1 = OH$, $R_2 = H$ (dihydroartemisinin)

‡ Dedicated to the memory of Sir Derek Barton whose lifelong contributions to, and love of, organic chemistry inspired so many of us. He is sorely missed.

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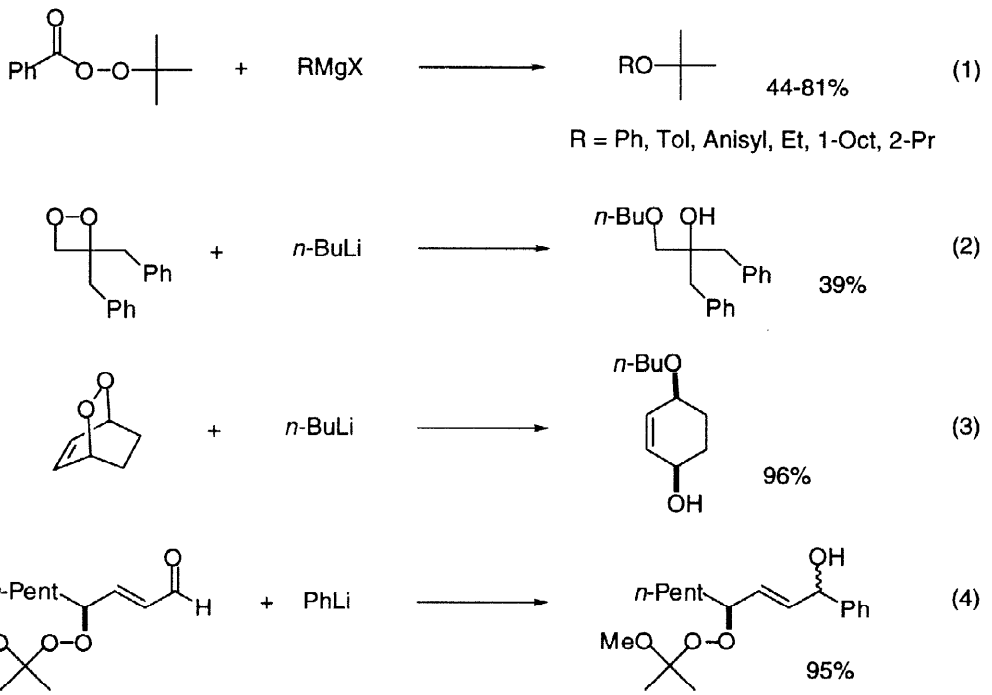
Results and Discussion

Heterolytic cleavage of the peroxide O–O bond *via* S_N2 attack of nucleophiles is well documented.[20,21] For example, *tert*-butyl ethers are conveniently prepared by Grignard nucleophilic attack on the O–O bond in *tert*-butyl peresters (eq. 1).[22] Also, 3,3-disubstituted-1,2-dioxetanes react with organolithium reagents primarily *via* S_N2 O–O bond cleavage (with regioselective attack at the sterically less encumbered O atom) to form β-hydroxy ethers (eq. 2),[23] and bicyclic endoperoxides likewise react with lithium and magnesium organometallics to produce O–O bond-cleaved hydroxy ethers (eq. 3).[24] When a dialkyl peroxide O–O bond is sterically hindered, then nucleophilic attack by a reactive organometallic reagent is made more difficult; an excellent example of this phenomenon leading to chemoselective nucleophilic addition of an organolithium reagent to the aldehyde carbonyl group in a peroxy aldehyde is shown in eq. 4.[25,26] 1,2,4-Trioxanes in the artemisinin family undergo peroxide O–O bond cleavage when exposed to dimethylcopperlithium and to trityllithium; in these two cases, however, single-electron-reductive cleavage of the peroxide bond is likely occurring.[27] Sodium borohydride chemoselectively reduces artemisinin (**1**) into its lactol (**2**), but more potent lithium aluminum hydride reduces both the lactone carbonyl group and the trioxane O–O bond.[28]

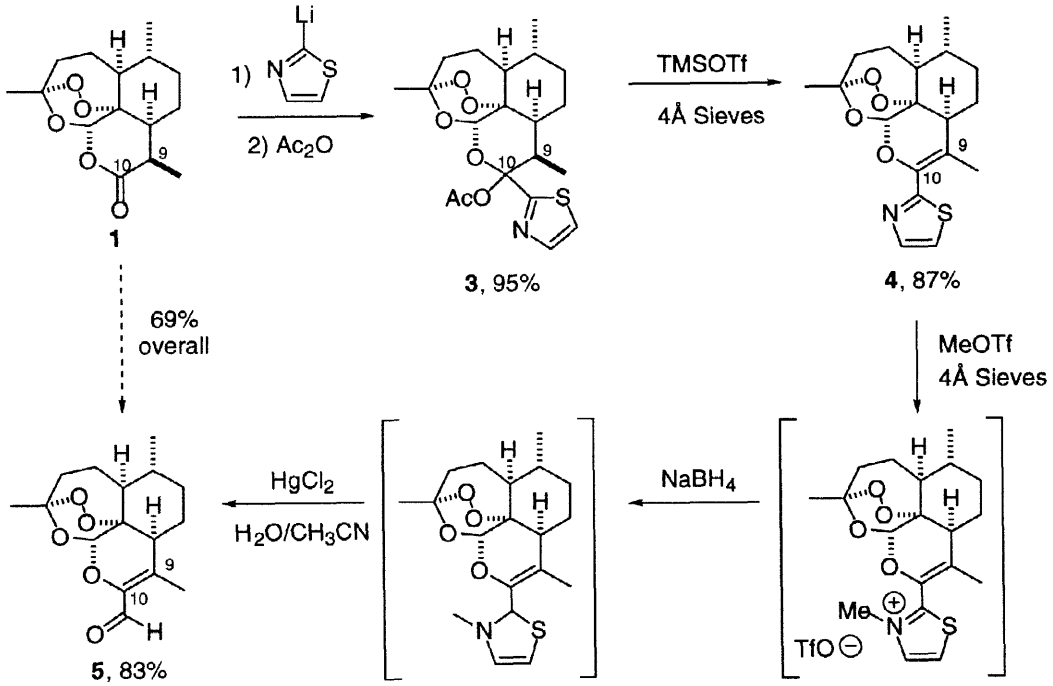


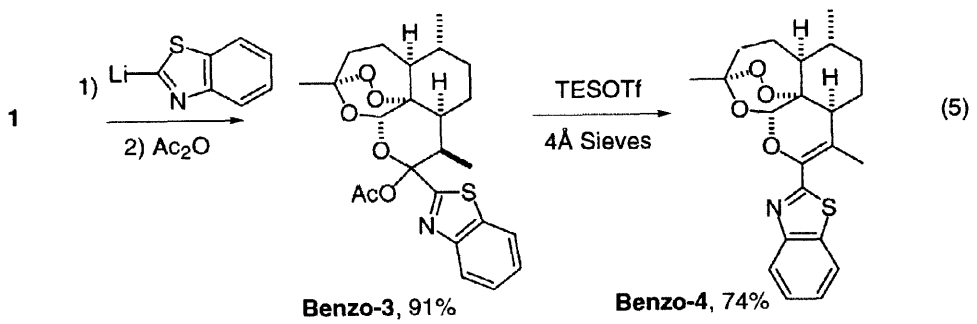
Based on these published precedents, it seemed that it would be very difficult to find any reactive organometallic reagents that would add chemoselectively to the lactone carbonyl group (less electrophilic than an aldehyde) of trioxane lactone artemisinin (**1**) without also cleaving the trioxane O–O bond. In fact, exposing artemisinin to 1.2 equivalent of phenyllithium in THF at -78 °C produced at least three major products (not characterized).

Based on reports from the Dondoni research group that 2-lithiothiazole adds easily at -65 °C to the carbonyl group of sugar lactones,[29,30] we treated trioxane lactone **1** (artemisinin) with this heteroaryllithium reagent (Scheme I). After *in situ* O-acetylation, thiazole carbonyl adduct **3** was isolated in 95% yield! Mass spectrometry confirmed that the trioxane unit was intact, thereby establishing that this new C–C

bond-forming reaction had occurred with very high chemoselectivity at C-10 of the artemisinin skeleton without rupturing the O–O bond in this trioxane. In contrast to experience with the corresponding tertiary acetate esters of sugar lactone thiazole addition products,[29] the acetate group in artemisinin thiazole acetate **3** could not be replaced by a hydrogen atom using triethylsilane as a reducing agent; trioxane thiazole acetate **3** reacted with triethylsilane and trimethylsilyl triflate (TMS-OTf)[29] to form only the corresponding elimination product 9,10-alkene **4**; this product **4** of overall acetic acid elimination from acetate **3** was formed in high yield also when acetate **3** was exposed to only TMS-OTf. A similar chemoselective result was obtained using lithiobenzothiazole as nucleophile (eq. 5). Interestingly, other heteroaryllithium reagents (*e.g.* 2-lithiothiophene, 2-lithiobenzoxazole) failed to react with artemisinin under conditions in which lithiothiazole and lithiobenzothiazole did react. Alkene thiazole **4** was N-methylated, reduced, and then hydrolyzed without purification of intermediates[30] to form 9,10-unsaturated C-10 aldehyde **5** (Scheme 1). The three separate steps in Scheme I allowed conversion of artemisinin (**1**) into trioxane 9-en-10-al **5** in 69% overall yield. This addition-elimination sequence overall represents addition of a formyl anion unit at C-10 of artemisinin followed by dehydration.

Scheme I.

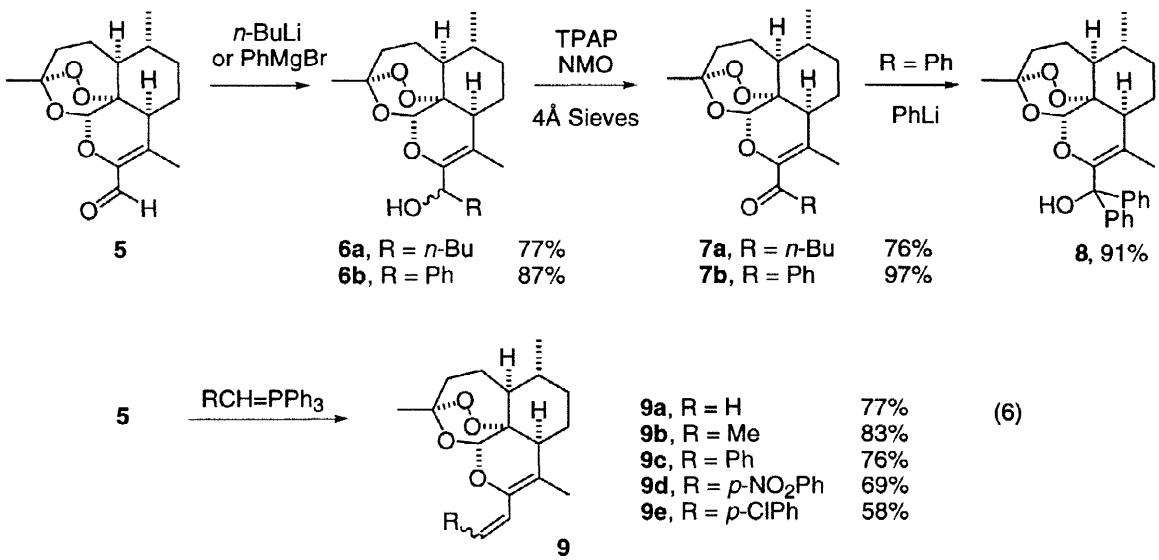




(5)

Demonstration of further high chemoselectivity in organometallic reaction with such artemisinin trioxane analogs was achieved by organometallic nucleophilic addition to the carbonyl group of enal **5** (Scheme II); organolithium nucleophiles added exclusively (and in some cases stereoselectively) to only the aldehyde carbonyl group of trioxane enal **5** to form allylic alcohols **6**, without rupturing the trioxane O–O bond. *n*-Butyllithium added to enal **5** to give a roughly 2:1 diastereomeric mixture of allylic alcohols **6**. Whereas phenyllithium added to aldehyde **5** to produce a 3.2:1.0 mixture of allylic alcohol diastereomers **6**, phenylmagnesium bromide formed the same benzylic alcohols **6** in a 7.6:1.0 ratio, presumably due to magnesium coordination also to one or more of the non-aldelydic oxygen atoms in polyoxygenated aldehyde **5**. When excess phenylmagnesium bromide was used, however, the peroxide O–O bond in trioxane alcohol **6b** underwent nuceophilic rupture. Oxidation of alcohols **6** with tetrapropylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO)[31] produced enones **7**. Phenyl enone **7b** reacted with phenyllithium exclusively *via* carbonyl addition to form tertiary alcohol trioxane **8**. Also, nucleophilic phosphonium ylides alkylidenated aldehyde **5** to form a mixture of geometric isomers of exocyclic alkenes **9** without cleaving the trioxane O–O bond (Scheme II). The *Z*- and *E*-geometric isomers of these exocyclic alkenes **9** were separated from each other chromatographically. In the case of **9** in which R = *p*-chlorophenyl, only the more soluble major isomer *Z*-**9e** remained in solution when a 1:1 mixture of the two isomers selectively precipitated out of solution from ethyl acetate/hexane solvent. Assignment of exocyclic alkene geometry was achieved reliably by ^{1}H NMR spectroscopy with the *E*-isomers having considerably larger vicinal H–H coupling constants than those of the corresponding *Z*-isomers.

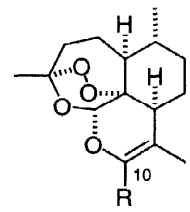
Scheme II.



Antimalarial testing *in vitro* against *Plasmodium falciparum* NF54 malaria parasites, according to our published protocol,[32] showed that C-9,10-unsaturated, C-10 carbon-substituted heteroaryl artemisinin analogs **4** and benzo-**4**, ketones **7**, tertiary alcohol **8** and exocyclic alkenes **9** are all similar to clinically used natural artemisinin (**1**) in antimalarial potency (Table 1). The high antimalarial activities of these C-10 carbon-substituted artemisinin analogs in Table I provide biological evidence that the trioxane O–O bond in these semi-synthetic

analogs is intact; artemisinin derivatives lacking this O–O linkage are not antimalarially active.[5] Several of the C-10 derivatives in Table 1 as well as other analogs available easily via this new synthetic methodology may have especially desirable solubility and pharmacological properties.

Table 1. *In Vitro* Antimalarial Activities[a]



C10-trioxane	R	IC_{50} (nM)
4	2'-thiazolyl	14
Benzo-4	2'-benzothiazolyl	7.8
5	CHO	37
7a	C(O)*n*-Bu	4.3
7b	C(O)Ph	4.6
8	$C(OH)Ph_2$	4.5
9a	$CH=CH_2$	28
***E*-9c**	*E*-CH=CHPh	16
***Z*-9c**	*Z*-CH=CHPh	8.1
***E*-9d**	*E*-$CH=CHPhNO_2$-*p*	11
***Z*-9d**	*Z*-$CH=CHPhNO_2$-*p*	10
Artemisinin		10.1 ± 1.3

[a]Antimalarial activity against *Plasmodium falciparum* was determined as reported previously.[32] The standard deviation for each set of quadruplicates was an average of 9.8% (≤32%) of the mean. R^2 values for the fitted curves were ≥0.990. Artemisinin is ± standard deviation of concurrent control (n = 11).

In summary, the peroxide bond in artemisinin itself and in artemisinin-like trioxane aldehyde **5** has been shown for the first time to withstand exposure to powerful organometallic nucleophiles like heteroaryllithium and aryllithium reagents, *n*-butyllithium, a phenyl Grignard reagent, and phosphonium ylides. Several of these nucleophiles added with high chemoselectivity to the lactone carbonyl group of artemisinin and to the aldehyde and ketone carbonyl groups of artemisinin-derived aldehyde **5** and ketone **7b**. In this way, a series of new, enantiomerically pure, C-10 carbon-substituted derivatives of natural artemisinin was prepared. Antimalarial testing *in vitro* of these semi-synthetic, C-10 non-acetal analogs of artemisinin showed them to have high antimalarial activities.

Experimental

General. Unless otherwise noted, reactions were run in oven-dried glassware under an atmosphere of argon. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. All other compounds were purchased from Aldrich Chemical Company 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 flash silica gel (partical size 400-230 mesh). Yields are not optimized. Purity of final 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 a Rainin Dynamax 10 mm x 250 mm (semi-preparative) column packed with 60 Å silica gel (8 μm pore size) as bare silica. Melting points were measured using a Mel-Temp metal-block apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained either on a Varian XL-400 spectrometer, operating at 400 MHz for ^1H 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 ioniztion (EI or CI) either (1) at Johns Hopkins University on a VG Instruments 70-S Spectrometer run at 70 eV for EI and run wtih ammonia (NH_3), butane (C_4H_{10}) or methane (CH_4) as carrier gas for CI or (2) at the University of Illinois at Champaign-Urbana on a Finnigan-MAT CH5, a Finnigan-MAT 731, or a VG Instruments 70-VSE spectrometer run at 70 eV for EI and run with methane (CH_4) for CI. Combustion analyses were conducted by Atlantic Microlab (Norcross, GA).

10-Acetyl-10-(2'-thiazolyl)artemisinin 3 - 2-Bromothiazole (90 μL, 1.0 mmol) in Et_2O (1 mL) at -78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.70 mL, 1.1 mmol). The reaction mixture was stirred for 30 min at -78 °C and then artemisinin (**1**, 0.20 g, 0.71 mmol, in 1 mL THF) was added via cannula. The reaction mixture was stirred for 30 min at -78 °C and then for 30 min at -65 °C. At -65 °C, acetic anhydride (0.67 mL, 7.1 mmol) was added, after being stirred for 10 min at -65 °C the reaction mixture became viscous. The reaction mixture was warmed to room temperature, diluted (CH_2Cl_2) then poured into pH 7 phosphate buffer (100 mL) and extracted (CH_2Cl_2). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 50% EtOAc/hexanes as eluent to give 0.28 g of the desired product **3** as a white solid (0.68 mmol, 95%); mp 128 °C (dec.); $[\alpha]_D^{23}$ +232 ° (*c* 0.55, EtOAc); ^1H NMR ($CDCl_3$) δ 0.94-1.08 (m, 1 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 1.3-1.7 (m, 4 H), 1.49 (s, 3 H), 1.7-1.8 (m, 2 H), 1.9-2.1 (m, 3 H), 2.10 (s, 3 H), 2.35-2.45 (m, 1 H), 2.60-2.68 (m, 1 H), 5.54 (s, 1 H), 7.3 (d, *J* = 3.2 Hz, 1 H), 7.7 (d, *J* = 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 20.0, 21.7, 23.4, 24.5, 25.6, 34.3, 35.91, 35.96, 37.3, 45.5, 51.7, 79.7, 89.1, 101.4, 104.4, 119.9, 141.5, 167.2, 170.2; HRMS calcd for $C_{20}H_{27}NO_6S$: 409.1559, found: 409.1554. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 25% EtOAc/hexanes at 3 mL/min, R_t 12 min); characteristic data were identical to those given above.

10-(2'-Thiazolyl)anhydroartemisinin 4 - Acetate **3** (0.11 g, 0.27 mmol) and powdered 4Å MS (185 mg) in CH_2Cl_2 (2.5 mL) at room temperature were treated with triethylsilane (0.43 mL, 2.7 mmol) followed by trimethylsilyl triflate (0.14 mL, 0.76 mmol). The reaction mixture was stirred at room temperature for 30 min then quenched with triethylamine (2 mL), filtered through celite and concentrated. The crude product was chromatographed on a flash silica gel column with 15% EtOAc/hexanes as eluent to give 82 mg of the desired product **4** as a white solid (0.23 mmol, 87%); mp 164-167 °C; $[\alpha]_D^{23}$ +42 ° (*c* 0.56, EtOAc); ^1H NMR ($CDCl_3$)

δ 1.0 (d, J = 5.6 Hz, 3 H), 1.1-1.2 (m, 1 H), 1.25-1.40 (m, 1 H), 1.40-1.64 (m, 3 H), 1.45 (s, 3 H), 1.65-1.75 (m, 1 H), 1.9-2.0 (m, 2 H), 2.00-2.15 (m, 2 H), 2.25 (s, 3 H), 2.38-2.43 (m, 1 H), 5.77 (s, 1 H), 7.3 (d, J = 3.2 Hz, 1 H), 7.7 (d, J = 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.1, 20.1, 24.4, 25.6, 29.0, 34.1, 36.0, 37.5, 47.9, 50.6, 78.3, 90.2, 104.5, 110.6, 118.3, 138.0, 142.7, 165.0; HRMS calcd for $C_{18}H_{23}NO_4S$: 349.1348, found: 349.1354. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 5% EtOAc/hexanes at 3 mL/min, R_t 13 min); characteristic data were identical to those given above.

10-Formylanhydroartemisinin 5 - Reaction was performed under an atmoshere of air. Thiazole **4** (128 mg, 0.37 mmol) and powdered 4Å MS (0.75 g) in acetonitrile (4 mL) at room temperature were treated with methyl triflate (80 μL, 0.71 mmol), the suspension was stirred for 15 min and then concentrated to dryness. The crude *N*-methylthiazolium salt was suspended in methanol (4 mL), cooled to 0 °C and then treated with sodium borohydride (60 mg, 1.6 mmol). The reaction mixture was warmed to room temperature and stirred for 15 min, then quenched at 0 °C with acetone (8 mL). The crude reaction mixture was filtered through celite and then concentrated. The reduced product was then dissolved in acetonitrile (4 mL) and treated with $HgCl_2$ (140 mg) followed by H_2O (0.4 mL), the mixture was stirred for 15 min at room temperature then filtered through celite and concentrated. The crude product was dissolved (THF, CH_2Cl_2, Et_2O) and washed with (20% aq. KI soln. (twice), H_2O, brine). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a Florisil (~200 mesh) column with 25% EtOAc/hexanes as eluent to give 90 mg of the desired aldehyde **5** as a white solid (0.31 mmol, 87%); mp 115-117 °C; $[\alpha]_D^{23}$ +102 ° (c 0.33, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.0 (d, J = 6.0 Hz, 3 H), 1.10-1.32 (m, 2 H), 1.38-1.64 (m, 3 H), 1.43 (s, 3 H), 1.7-1.8 (m, 1 H), 1.88-1.98 (m, 2 H), 2.0-2.1 (m, 2 H), 2.10 (s, 3 H), 2.34-2.44 (m, 1 H), 5.7 (s, 1 H), 9.8 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 20.0, 24.2, 25.6, 28.7, 34.0, 36.0, 37.4, 47.8, 50.5, 78.0, 90.0, 104.7, 126.7, 142.8, 184.2; HRMS calcd for $C_{16}H_{22}O_5$: 294.1467, found: 294.1474. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 30% EtOAc/hexanes at 3 mL/min, R_t 9 min); characteristic data were identical to those given above.

10-Acetyl-10-(2'-benzothiazolyl)artemisinin Benzo-3 - Benzothiazole (76 μL, 0.70 mmol) in THF (1 mL) at -78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.44 mL, 1.1 equiv.). The reaction mixture was stirred for 30 min at -78 °C, then artemisinin (**1**, 0.14 g, 0.50 mmol, in 1.5 mL THF) was added via canula. The reaction mixture was stirred for 30 min at -78 °C and then for 30 min at -65 °C. At -65 °C, acetic anhydride (0.50 mL, 10 equiv.) was added, after being stirred for 10 min at -65 °C the reaction mixture became viscous. The reaction mixture was warmed to room temperature, diluted (CH_2Cl_2) then poured into pH 7 phosphate buffer (100 mL) and extracted (CH_2Cl_2). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 20-40% EtOAc/hexanes as eluent to give 0.21 g of the desired product **Benzo-3** as a white solid (0.45 mmol, 91%); mp 129-131 °C; $[\alpha]_D^{23}$ +183 ° (c 0.46, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.94-1.08 (m, 1 H), 0.99 (d, J = 6.0 Hz, 3 H), 1.18 (d, J = 7.2 Hz, 3 H), 1.28-1.84 (m, 6 H), 1.55 (s, 3 H), 1.90-2.14 (m, 3 H), 2.15 (s, 3 H), 2.38-2.48 (m, 1 H), 2.70-2.80 (m, 1 H), 5.57 (s, 1 H), 7.35 (m, 1 H), 7.43 (m, 1 H), 7.88 (m, 1 H), 7.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.7, 20.1, 21.8, 23.6, 24.7, 25.8,

34.5, 35.3, 36.1, 37.5, 45.6, 51.8, 79.9, 89.3, 101.4, 104.7, 121.6, 123.3, 124.9, 125.5, 135.8, 152.7, 167.4, 171.0

10-(2'-Benzothiazolyl)anhydroartemisinin Benzo-4 - Acetate **Benzo-3** (0.10 g, 0.22 mmol) and powdered 4Å MS (160 mg) in CH_2Cl_2 (3 mL) at room temperature were treated with triethylsilyl triflate (0.14 mL, 0.62 mmol). The mixture was stirred at room temperature for 1 h then quenched with triethylamine (2 mL), filtered through celite and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/hexanes as eluent to give 65 mg of the desired product **Benzo-4** as a white solid (0.16 mmol, 74%); mp 155-158 °C; $[\alpha]_D^{23}$ +36 ° (*c* 0.46, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.0 Hz, 3 H), 1.1-1.2 (m, 1 H), 1.25-1.40 (m, 1 H), 1.40-1.64 (m, 3 H), 1.47 (s, 3 H), 1.68-1.75 (m, 1 H), 1.9-2.0 (m, 2 H), 2.00-2.14 (m, 2 H), 2.35 (s, 3 H), 2.36-2.46 (m, 1 H), 5.80 (s, 1 H), 7.34 (m, 1 H), 7.44 (m, 1 H), 7.88 (m, 1 H), 8.01 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.4, 20.1, 24.4, 25.6, 28.9, 34.1, 36.0, 37.5, 48.1, 50.5, 78.3, 90.4, 104.6, 113.7, 121.3, 123.0, 124.7, 125.6, 134.5, 138.1, 153.7, 165.0; HRMS calcd for $C_{22}H_{25}NO_4S$: 399.1504, found: 399.1501. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 10% EtOAc/hexanes at 3 mL/min, R_t 10 min); characteristic data were identical to those given above.

10-(1'-Pentanoyl)anhydroartemisinin 7a - Aldehyde **5** (80 mg, 0.27 mmol) in THF (2 mL) at -78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.20 mL, 1.2 equiv.). The reaction mixture was stirred for 2 h at -78 °C then warmed to room temperature, diluted (Et_2O), washed (aq. NH_4Cl, aq. $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/petroleum ether as eluent to give 73 mg of the desired products **6a** as an oil (0.21 mmol, 77%), a *ca.* 1:1.5 mixture of diastereomers (as determined by ^{1}H NMR). The mixture of alcohols (73 mg, 0.21 mmol), powdered 4Å MS (150 mg) and NMO (50 mg, 0.43 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was treated with TPAP (catalytic amount, *ca.* 5 mg). The reaction mixture was stirred for 2h, then filtered through celite and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/petroleum ether as eluent to give 56 mg of the desired product **7a** as an oil (0.16 mmol, 76%); $[\alpha]_D^{23}$ +149 ° (*c* 0.43, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.6 Hz, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H), 1.06- 1.28 (m, 3 H), 1.30-1.40 (m, 2 H), 1.43 (s, 3 H), 1.46-1.64 (m, 5 H), 1.82 (dd, *J* = 4.4, 12.4 Hz, 1 H), 1.90-2.10 (m, 3 H), 2.00 (s, 3 H), 2.36-2.45 (m, 1 H), 2.63 (dt, *J* = 7.6, 16.4 Hz, 1 H), 2.77 (dt, *J* = 7.6, 16.4 Hz, 1 H), 5.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.2, 20.1, 22.5, 24.4, 25.6, 25.8, 28.9, 34.1, 36.1, 37.6, 39.8, 48.4, 50.4, 78.0, 90.0, 104.5, 117.3, 142.5, 199.8; HRMS calcd for $C_{20}H_{30}O_5$: 350.2093, found: 350.2096. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 10% EtOAc/hexanes at 3 mL/min, R_t 9 min); characteristic data were identical to those given above.

10-Benzoylanhydroartemisinin 7b - Aldehyde **5** (68 mg, 0.23 mmol) in THF (2 mL) at -78 °C was treated with PhMgBr (1.0 M in THF, 0.30 mL, 1.3 equiv.). The reaction mixture was stirred for 2 h at -78 °C, warmed to room temperature, diluted (Et_2O), washed (aq. NH_4Cl, aq. $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/petroleum ether as eluent to give 75 mg of the desired products **6b** as an oil (0.20 mmol, 87%), a *ca.* 1:7.5 mixture of diastereomers. The mixture of alcohols (75 mg, 0.20 mmol), powdered 4Å MS (150 mg) and NMO (50 mg, 0.43

mmol) in CH_2Cl_2 (1.5 mL) at room temperature was treated with TPAP (catalytic amount, *ca.* 5 mg). The reaction mixture was stirred for 2h, then filtered through celite and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/petroleum ether as eluent to give 72 mg of the desired product **7b** as an white solid (0.19 mmol, 97%); mp ~155 °C (dec.); $[\alpha]_D^{23}$ +244 ° (*c* 0.42, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz, 3 H), 1.10-1.22 (m, 1 H), 1.24-1.38 (dq, *J* = 3.2, 12.8 Hz, 1 H), 1.38-1.64 (m, 3 H), 1.46 (s, 3 H), 1.68-1.78 (m, 1 H), 1.86 (s, 3 H), 1.88-2.00 (m, 2 H), 2.04-2.16 (m, 2 H), 2.40-2.50 (m, 1 H), 5.66 (s, 1 H), 7.38-7.44 (m, 2 H), 7.48-7.56 (m, 1 H), 8.16-8.22 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.5, 20.1, 24.3, 25.5, 29.3, 34.0, 36.1, 37.4, 47.3, 50.8, 78.3, 90.1, 104.6, 114.6, 127.8, 130.4, 132.8, 136.6, 142.5, 191.4; HRMS calcd for $C_{22}H_{26}O_5$: 370.1780, found: 370.1788. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 10% EtOAc/hexanes at 3 mL/min, R_t 11 min); characteristic data were identical to those given above.

10-(Benzhydryl)anhydroartemisinin 8 - Ketone **7b** (60 mg, 0.16 mmol) in THF (2 mL) at -78 °C was treated with PhLi (1.8 M in cyclohexane-ether, 70 to 30, 0.14 mL, 1.5 equiv.). The reaction mixture was stirred at -78 °C for 2 h, then slowly warmed to room temperature (1 h), diluted (Et_2O), washed (brine, aq. NH_4Cl, aq. $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/petroleum ether as eluent to give 63 mg of the desired product **8** as an oil (0.15 mmol, 91%); mp 152-155 °C (dec.); $[\alpha]_D^{23}$ +146 ° (*c* 0.51, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.97 (d, *J* = 6.0 Hz, 3 H), 1.03 (s, 3 H), 1.04-1.14 (m, 1 H), 1.22-1.56 (m, 4 H), 1.33 (s, 3 H), 1.64-1.72 (m, 2 H), 1.90-2.06 (m, 3 H), 2.34-2.44 (m, 1 H), 4.20 (br s, 1 H), 5.65 (s, 1 H), 7.20-7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 20.1, 24.4, 25.5, 28.4, 34.1, 36.1, 37.6, 48.0, 50.4, 78.4, 80.1, 90.3, 104.4, 106.6, 127.17, 127.25, 127.59, 127.81, 127.86, 128.5, 144.9, 145.1, 146.0; HRMS calcd for $C_{28}H_{32}O_5$: 448.2250, found: 448.2259. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 10% EtOAc/hexanes at 3 mL/min, R_t 13 min); characteristic data were identical to those given above.

10-Vinylanhydroartemisinin 9a - Methyltriphenylphosphonium bromide (0.71 g, 2.0 mmol) was dried under vacuum/low heat for 2 days. The Wittig salt was suspended in THF (4 mL) and at 0 °C treated with *n*-BuLi (1.6 M in hexanes, 1.4 mL, 2.4 mmol). The solution was stirred at room temperature for 1 h. Aldehyde **5** (0.15 g, 0.50 mmol) in THF (3 mL) at -78 °C was treated with a portion of the prepared ylide solution (*ca.* 0.33 M, 2 mL, *ca.* 0.70 mmol) transferred via syringe. The mixture was stirred at -78 °C for 1 h then warmed to room temperature and stirred for 15 min; a precipitate was observed. The reaction was quenched (H_2O), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 5-10% EtOAc/hexanes as eluent to give 112 mg of the desired product **9a** as an oil (0.38 mmol, 77%); $[\alpha]_D^{23}$ +81 ° (*c* 0.49, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.04-1.30 (m, 2 H), 1.42 (s, 3 H), 1.44-1.80 (m, 5 H), 1.76 (s, 3 H), 1.88-2.08 (m, 3 H), 2.34-2.44 (m, 1), 5.10 (dd, *J* = 2.0, 10.8 Hz, 1 H), 5.62 (dd, *J* = 2.0, 10.8 Hz, 1 H), 5.66 (s, 1 H), 6.50 (dd, *J* = 10.8, 16.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.7, 20.2, 24.5, 29.3, 34.2, 36.2, 37.6, 46.7, 51.0, 78.7, 90.0, 104.3, 107.5, 113.2, 127.7, 141.7; HRMS calcd for $C_{17}H_{24}O_4$: 292.1675, found: 292.1678. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 5% EtOAc/hexanes at 3 mL/min, R_t 9 min); characteristic data were identical to those given above.

10-(1-Propenyl)anhydroartemisinin 9b - Ethyltriphenylphosphonium bromide (0.74 g, 2.0 mmol) was dried under vacuum/low heat for 2 days. The Wittig salt was suspended in THF (4 mL) and at 0 °C treated with *n*-BuLi (1.6 M in hexanes, 1.4 mL, 2.4 mmol). The solution was stirred at room temperature for 2 h. Aldehyde **5** (0.20 g, 0.67 mmol) in THF (3 mL) at -78 °C was treated with a portion of the prepared ylide solution (*ca.* 0.33 M, 5 mL, *ca.* 1.7 mmol) transferred via syringe. The reaction mixture was stirred at -78 °C for 30 min then warmed to room temperature and stirred for 1 h; a precipitate was observed. The reaction was quenched (H_2O), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 5% EtOAc/hexanes as eluent to give 170 mg of the desired product ***Z*-9b** as an oil (0.55 mmol, 83%); $[\alpha]_D^{23}$ +52 ° (*c* 0.50, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.02-1.28 (m, 3 H), 1.42 (s, 3 H), 1.50-1.78 (m, 4 H), 1.73 (s, 3 H), 1.80 (d, *J* = 6.0 Hz, 3 H), 1.88-2.08 (m, 3 H), 2.34-2.44 (m, 1), 5.64 (s, 1 H), 6.07-6.22 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.6, 18.2, 20.2, 24.5, 25.8, 29.4, 34.2, 36.2, 37.6, 46.6, 51.0, 78.8, 89.9, 104.3, 104.7, 122.3, 125.3, 141.4; HRMS calcd for $C_{18}H_{26}O_4$: 306.1831, found: 306.1833. The product was further purified prior to antimalarial testing using HPLC (Silica semipreparative column, 2% EtOAc/hexanes at 3 mL/min, R_t 15 min); characteristic data were identical to those given above.

10-(Styryl)anhydroartemisinin *Z/E*-9c - Benzyltriphenylphosphonium bromide (0.43 g, 1.0 mmol) was dried under vacuum/low heat for 3 h. The Wittig salt was suspended in THF (4 mL) and at 0 °C treated with *n*-BuLi (1.6 M in hexanes, 0.75 mL, 1.2 mmol). The solution was stirred at room temperature for 1 h. Aldehyde **5** (21 mg, 71 μmol) in THF (1.5 mL) at -78 °C was treated with a portion of the prepared ylide solution (*ca.* 0.16 M, 0.6 mL, *ca.* 1.5 equiv.) transferred via syringe. The reaction mixture was stirred at -78 °C for 30 min then warmed to room temperature and stirred for 30 min. The reaction was quenched (H_2O), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 10% EtOAc/hexanes as eluent to give 20 mg of the desired products ***Z/E*-9c** as an oil (54 μmol, 76%), *Z:E* = 1.2:1 (as determined by ^{1}H NMR). The 2 isomers were separated by HPLC (Silica semipreparative column, 1% EtOAc/hexanes at 5 mL/min), ***Z*** R_t 20 min, ***E*** R_t 22 min. ***Z*-9c**: oil, $[\alpha]_D^{23}$ +42 ° (*c* 0.48, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.02-1.28 (m, 2 H), 1.416 (s, 3 H), 1.422 (s, 3 H), 1.40-1.74 (m, 5 H), 1.88-2.08 (m, 3 H), 2.36-2.46 (m, 1), 5.64 (s, 1 H), 6.03 (d, *J* = 12.0 Hz, 1 H), 6.50 (d, *J* = 12.0 Hz, 1 H), 7.15-7.22 (m, 1 H), 7.23-7.30 (m, 2 H), 7.53 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.4, 20.3, 24.5, 25.8, 29.3, 34.1, 36.4, 37.6, 45.9, 51.2, 78.8, 90.0, 104.4, 105.6, 122.5, 127.1, 127.8, 129.2, 132.3, 137.2, 141.4; HRMS calcd for $C_{23}H_{28}O_4$: 368.1988, found: 368.1986. ***E*-9c**: oil, $[\alpha]_D^{23}$ +150 ° (*c* 0.51, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.02-1.28 (m, 2 H), 1.45 (s, 3 H), 1.40-1.74 (m, 4 H), 1.86 (s, 3 H), 1.80-2.10 (m, 4 H), 2.36-2.46 (m, 1), 5.72 (s, 1 H), 6.87 (d, *J* = 16.0 Hz, 1 H), 6.99 (d, *J* = 16.0 Hz, 1 H), 7.17-7.24 (m, 1 H), 7.27-7.34 (m, 2 H), 7.43-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.1, 20.2, 24.5, 25.8, 29.4, 34.2, 36.2, 37.6, 47.0, 51.0, 78.7, 90.1, 104.4, 108.5, 119.6, 126.6, 127.2, 127.6, 128.4, 137.7, 142.0; HRMS calcd for $C_{23}H_{28}O_4$: 368.1988, found: 368.1983.

10-(*p*-Nitrostyryl)anhydroartemisinin *Z/E*-9d - (*p*-Nitrobenzyl)triphenylphosphonium bromide (0.96 g, 2.0 mmol) was dried under vacuum overnight. The Wittig salt was suspended in THF (4 mL) and at 0 °C

treated with (1.6 M BuLi in hexanes, 1.4 mL, 2.2 mmol). The solution was stirred at room temperature for 30 min. Aldehyde **5** (83 mg, 0.28 mmol) in THF (2 mL) at -78 °C was treated with a portion of the prepared ylide solution (*ca.* 0.33 M, 1.4 mL, *ca.* 1.5 equiv.) transferred via syringe. The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched (H_2O), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 5-15% EtOAc/hexanes as eluent to give 80 mg of the desired products ***Z/E*-9d** as a yellow oil (0.19 mmol, 69%), *Z:E* = 1:4 (as determined by ^1H NMR). The 2 isomers were separated by HPLC (Silica semipreparative column, 5% EtOAc/hexanes at 3 mL/min), ***Z*** R_t 18 min, ***E*** R_t 21 min. ***Z*-9d**: yellow oil, $[\alpha]_D^{23}$ +105 ° (*c* 0.40, EtOAc); ^1H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.06-1.32 (m, 2 H), 1.39 (s, 3 H), 1.40-1.76 (m, 4 H), 1.50 (s, 3 H), 1.84-2.10 (m, 4 H), 2.36-2.46 (m, 1), 5.61 (s, 1 H), 6.25 (d, *J* = 12.0 Hz, 1 H), 6.51 (d, *J* = 12.0 Hz, 1 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 8.13 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.4, 20.2, 24.4, 25.8, 29.4, 34.0, 36.3, 37.6, 46.0, 51.2, 78.8, 90.1, 104.5, 108.2, 123.0, 125.7, 129.3, 130.1, 141.0, 144.1; HRMS calcd for $C_{23}H_{27}NO_6$: 413.1838, found: 413.1841. ***E*-9d**: yellow oil, $[\alpha]_D^{23}$ +53 ° (*c* 0.51, EtOAc); ^1H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.06-1.32 (m, 2 H), 1.46 (s, 3 H), 1.40-1.74 (m, 4 H), 1.90 (s, 3 H), 1.84-2.10 (m, 4 H), 2.36-2.46 (m, 1), 5.73 (s, 1 H), 7.02 (s, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 8.17 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.2, 20.1, 24.4, 25.8, 29.2, 34.0, 36.1, 37.5, 47.0, 50.8, 78.6, 90.1, 104.5, 112.2, 123.7, 123.9, 125.3, 126.8, 141.7, 144.4, 146.4; HRMS calcd for $C_{23}H_{27}NO_6$: 413.1838, found: 413.1845.

10-(*p*-Chlorostyryl)anhydroartemisinin *Z/E*-9e - (*p*-Chlorobenzyl)triphenylphosphonium bromide (0.85 g, 2.0 mmol) was dried under vacuum overnight. The Wittig salt was suspended in THF (4 mL) and at 0 °C treated with *n*-BuLi (1.6 M in hexanes, 1.4 mL, 2.2 mmol). The solution was stirred at room temperature for 30 min. Aldehyde **5** (97 mg, 0.33 mmol) in THF (2 mL) at -78 °C was treated with a portion of the prepared ylide solution (*ca.* 0.33 M, 2.1 mL, *ca.* 0.69 mmol) transferred via syringe. The reaction mixture was stirred at -78 °C for 30 min, warmed to room temperature and stirred for 10 min. The reaction was quenched (H_2O), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 5% EtOAc/hexanes as eluent to give 78 mg of the desired products ***Z/E*-9e** as an oil (0.19 mmol, 58%), *Z:E* = 2.2:1 (as determined by ^1H NMR). Upon storage at -15 °C in *ca.* 0.2 M solution of EtOAc:hexanes, ~1:10, a 1:1 complex of ***Z:E*** crystallized out. The mother liquor was concentrated to give 30 mg of ***Z*-9e** as an oil; $[\alpha]_D^{23}$ +119 ° (*c* 0.52, EtOAc); ^1H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3 H), 1.02-1.28 (m, 2 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.40-1.74 (m, 5 H), 1.88-2.08 (m, 3 H), 2.36-2.46 (m, 1), 5.63 (s, 1 H), 6.04 (d, *J* = 12.0 Hz, 1 H), 6.43 (d, *J* = 12.0 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.3, 20.3, 24.4, 25.8, 29.4, 34.1, 36.3, 37.6, 45.9, 51.2, 78.8, 90.0, 104.4, 106.2, 123.0, 127.9, 130.6, 130.8, 132.7, 135.6, 141.1. The remaining mixture of ***E/Z*** (1:1) resisted attempts at chromatographic separation by HPLC.

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