Pergamon

Bioorganic & Medicinal Chemistry 8 (2000) 1111–1116

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Antimalarial Activities of Base-Catalyzed Adducts of 11-Azaartemisinin

Belew Mekonnen,[a] Everett Weiss,[c,†] Esther Katz,[c,‡] Jingyuan Ma,[b] Herman Ziffer[c,*] and Dennis E. Kyle[d]

[a]*NIMH, Laboratory of Neurotoxicology, Bethesda, MD 20892-5100, USA*
[b]*NIDDK Laboratory of Bioorganic Chemistry, Bethesda, MD 20892, USA*
[c]*NIDDK, Laboratory of Chemical Physics, Room B1-31, Building 5, Bethesda, MD 20892-0510, USA*
[d]*Walter Reed Army Institute of Research, Department of Parasitology, Washington, DC. 20307-5100, USA*

Received 17 September 1999; accepted 14 January 2000

Abstract—A series of *N*-substituted 11-azaartemisinins were prepared in high yield employing base-catalyzed additions to an amide nitrogen of olefins and terminal acetylenes conjugated with electron withdrawing groups (EWGs). When the terminal acetylene was conjugated with carbomethoxy, *N,N*-dimethyl amide or carbonyl groups, the E-adducts resulted. A mixture of E- and Z-adducts were obtained when the EWG was a nitrile. In vitro antimalarial activities of each compound were determined against two drug-resistant strains of *Plasmodium falciparum*. Many of the compounds prepared were several times more active than artemisinin.

Introduction

Malaria is one of the most formidable health problems of this century affecting 300–500 million people world wide, of whom approximately 90% occur in sub-Saharan Africa.[1] According to a World Health Organization (WHO) estimate, malaria is responsible for 2–3 million deaths each year, the majority of whom are children under the age of five.[2] Whereas it has been possible to control and treat malaria with chloroquine, (**1**), the appearance of drug-resistant strains of *Plasmodium falciparum* in many countries in Africa and Southeast Asia is expected to increase the number of cases and morbidity. New drugs are required to treat these resistant strains and one lead compound for developing such drugs is artemisinin (**2**).[2] Artemisinin has been employed in combination with mefloquined (**3**), in Africa and Southeast Asia, to effect rapid cures.[3] Furthermore, use of a combination of drugs avoids recrudescence, which occurs when artemisinin alone is employed. A host of compounds have been prepared in an effort to obtain more active and longer lasting artemisinin derivatives.[4]

Avery et al.[5] reported the synthesis and antimalarial activity of a series of *N*-substituted 1l-aza-9-desmethyl-artemisinins, (**5**) (Fig. 1). We recently described the preparation of several *N*-substituted 11-azaartemisinins (**4**), which exhibited in vitro and in vivo activities several times greater than artemisinin. The greater stability of lactams to acid such as present in the stomach, compared to lactones or acetals, suggested that they would possess greater bioavailability than the more labile artemisinin derivatives. We decided to continue working on enhancing the in vitro activity of *N*-substituted 11-azaartemisinins before studying their bioavailability and toxicity in vivo.

Most of the compounds we had prepared were *N*-alkyl or -aryl derivatives; the most active of these **4a** contained an aldehyde moiety.[4] This unexpected discovery led us to investigate whether other electronegative substituents at the γ-carbon of the substituent on the lactam nitrogen could further increase antimalarial activity. The most efficient approach in preparing such *N*-substituted 11-azaartemisinins appeared to involve the use of base-catalyzed additions to 11-azaartemisinins.[6] We describe here the syntheses of a number of adducts that contain polar groups and their antimalarial activity against two drug-resistant strains of *P. falciparum*.

*Corresponding author. Tel.: +1-301-4969003; fax: +1-301-496-0825; e-mail: ziffer@sunder.niddk.nih.gov
†Participant in the Colgate/NIH Study Group during the summer of 1998.
‡On Sabbatical from Israel Institute for Biological Research. Ness Ziona, Israel.

0968-0896/00/$ - see front matter
PII: S0968-0896(00)00049-3

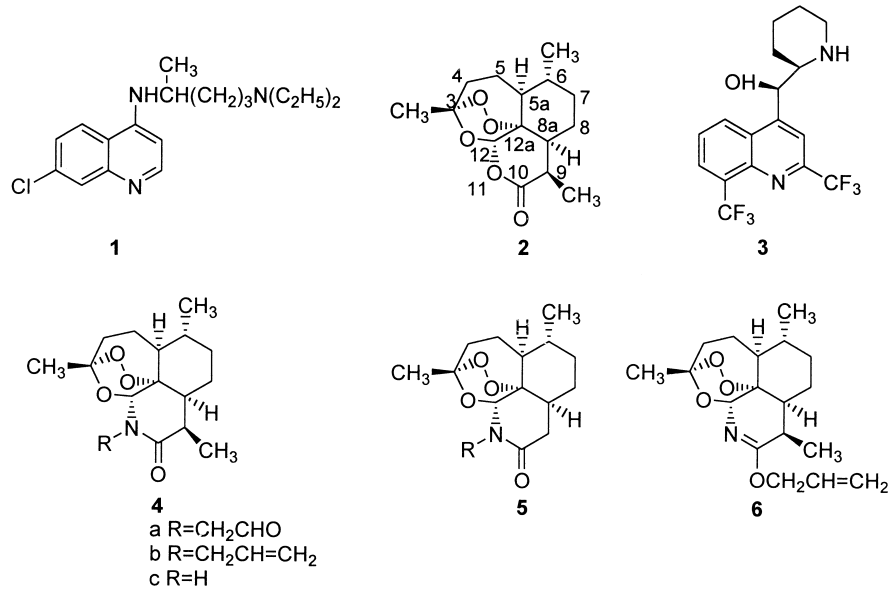


Figure 1.

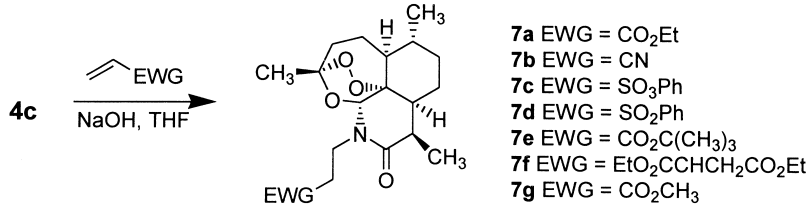
Results and Discussion

In an earlier study, we alkylated 11-azaartemisinin and isolated a single product, an *O*-allyl derivative (**6**), in low yield.[4] Danishefsky and co-workers[7] demonstrated that thioamides could be annulated by means of a Michael-type addition. Dijkink et al.[8] showed that amides reacted in a similar manner. In preliminary experiments with ethyl acrylate and **4c** we found that the reaction proceeded under mild conditions to yield **7a** in acceptable yields. Those observations enabled us to prepare a series of adducts (**7b**–**7g**) in 70–90% yields (Scheme 1).

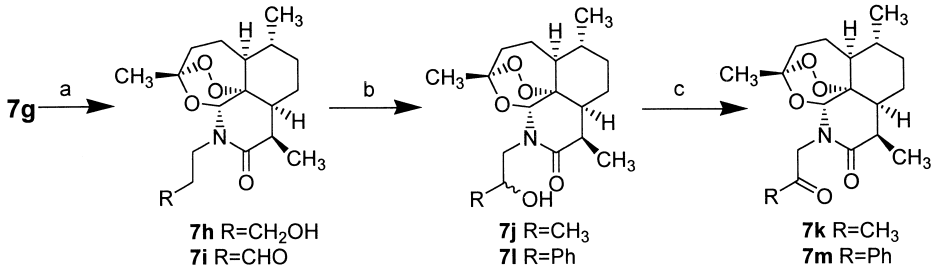
The structural assignments of the adducts are based on analyses of their ^{1}H and ^{13}C NMR spectra. Structural assignments for the ^{13}C NMR data are summarized in Table 2.

The preparation of some adducts from **4c** and a number of α,β-unsaturated aldehydes and ketones was only occasionally successful, therefore an alternate route to these compounds was required.[9] As one starting material in our synthesis we had employed the adduct of 11-azaartemisinin and methyl acrylate (**7g**), which had formed in high yield. The ester moiety was reduced with DIBAL to yield a mixture of the alcohol **7h**, and aldehyde, **7i** (Scheme 2). The aldehyde was separated and treated with methyl lithium at −78 °C to afford the methyl alcohol **7j**, which was oxidized with Jones reagent to the corresponding ketone **7k**. Under the same reaction conditions the phenyl alcohol **7l**, was prepared from **7i** and phenyl lithium and subsequently oxidized to the phenyl ketone **7m**. The antimalarial activities of **7h**, **7i**, **7k** and **7m** were determined.

In addition to the Michael-type additions described above we also wanted to determine the effect that a more rigid substituent on nitrogen would have on the compound's antimalarial activity. Faja et al.[10] described



Scheme 1.



Scheme 2. Reagents and conditions: (a) DIBAL, toluene, −78 °C; (b) lithium reagent, Et_2O, −78 to −40 °C; (c) Jones reagents, rt.

the reaction of methyl propynoate with the imide nitrogen of several uridines and thymidines in the presence of a base, e.g., DMAP. Although they had not examined additions to amides, we treated **4c** with methyl propynoate under Vilarrasa's conditions[10] and obtained **8a** in high yield (Scheme 3). The stereochemisty of the double bond was assigned as E based on the magnitude of the coupling constant ($J = 14$–16 Hz). The high yield and stereospecificity of the reaction prompted us to examine the reactivity of **4c** with a number of other terminal acetylenes conjugated with EWGs. The EWGs examined were: a carbonyl group (the ketone in 3-butyn-2-one yielding **8b**), a nitrile (part of cyanoacetylene yielding the adducts **8d** and **8e**) and an *N,N*-dimethylamide (which formed **8c**). Data on the ^{13}C NMR spectra of the above compounds is summarized in Tables 2 and 3. Their antimalarial activities were also determined.

When the EWG was an ester, a ketone or an *N,N*-dimethyl amide a single adduct **8a**–**c**, possessing the E-stereochemistry about the double bond was formed. However, when the EWG was a nitrile, two adducts **8d** and **8e** were obtained. The major product, **8e**, possessed a double bond Z-geometry and the minor adduct **8d**, was the E-isomer. The isomers were separated by flash chromatography on silica gel and the stereochemical assignments are based on the magnitude of the coupling constant for the olefinic protons. The coupling constant for the major isomer (Z) is 10.6 Hz, while it is 15 Hz for the minor (E) adduct.

We are unaware of any studies of the stereochemistry of the products formed from the addition of amides to terminal acetylenes conjugated with EWGs. Johnson et al. added 2-propynal, 1-butyn-3-one and cyanoacetylene to cytosine and indicated that the adducts had an E-stereochemistry.[11] However, their ^1H NMR data for the adducts indicates that the coupling constants for the olefinic protons in several cases were 10–11 Hz whereas in others it was 14–15 Hz. The two sets of values are similar to those we found for the major and minor adducts **8d** and **8e** respectively. The chemical shifts of the olefinic protons also differed in **8d** and **8e**. That information suggests that both geometries about the double bond may have also occurred in the formation of Johnson's adducts. Several of their adducts were prepared in acetonitrile, the same solvent we employed, and others in DMF. To determine whether the solvent influenced the stereochemical course of the reaction we examined the products formed from methyl propynoate and 11-azaartemisinin in DMF. The product **8a**, had the same E-stereochemistry as did the adduct formed in acetonitrile.

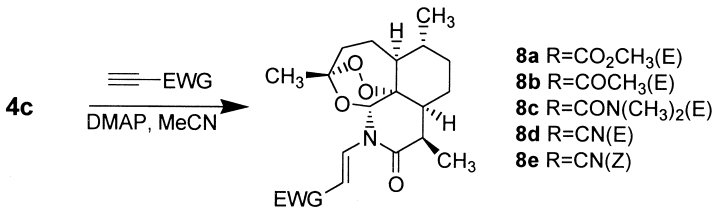
Antimalarial Activity

The in vitro antimalarial activities of the all the compounds described here were determined at the Walter Reed Army Institute of Research using two *P. falciparum* clones designated as Indochina (W-2) and Sierra Leone (D-6).[12] Since the activities of all the samples were not determined at the same time they have been reported relative to artemisinin (Table 1). The W-2 clone is chloroquine-resistant and mefloquine-sensitive, while the D-6 clone is chloroquine-sensitive and mefloquine-resistant. One of the purposes of this study was to examine the effect on antimalarial activity of a variety of substituents on the γ-carbon of the nitrogen substitutent. In our earlier study of *N*-substituted 11-azaartemisinins we found that the most active derivative, **4a**, contained an aldehyde moiety on the β-carbon of the nitrogen substituent. The synthetic route employed here generated a series of adducts containing electron-withdrawing groups (EWGs) as the γ-carbon of the nitrogen substituent. When the EWG was an aldehyde, the activity of the resulting compound **7i** was approximately half that of **7a**, **7b**, **7d**, **7g**, **7h** for the W-2 clone. Similar differences were noted for **7a**, **7b**, **7c**, **7d**, and the D-6 clone. The activity increased significantly on converting the aldehyde into the methyl **7k**, or phenyl **7m**, ketones. Introduction of an E-disubstituted double bond between the EWG and the nitrogen did not cause a dramatic change in the molecule's antimalarial activity.

Replacing the aldehyde group or corresponding carboxylate groups by SO_3Ph or SO_2Ph moieties, again,

Table 1. In vitro antimalarial activities of *N*-substituted 11-azaartemisinins relative to artemisinin with drug-resistant clones of *P. falciparum*

Compound	EWG	W-2 IC_{50} **2**/IC_{50} compound	D-6 IC_{50} **2**/IC_{50} compound
7a	CO_2Et	0.41	1.5
7b	CN	0.43	1.3
7c	SO_3Ph	0.96	1.7
7d	SO_2Ph	0.32	1.1
7e	$CO_2C(CH_3)_3$	0.0012	0.03
7f	$EtO_2CCH\text{-}CH_2CO_2Et$	0.066	0.24
7g	CO_2CH_3	1.0	1.77
7h	CH_2OH	0.64	1.02
7i	CHO	0.18	0.49
7k	$COCH_3$	3.0	3.2
7m	COPh	1.8	1.8
8a	CO_2CH_3	1.2	2.0
8b	$COCH_3$	1.25	2.54
8c	$CON(CH_3)_2$	0.35	0.39
8e (Z isomer)	CN	1.7	2.7



Scheme 3.

Table 2. Summary of ^{13}C assignments[a]

Carbon	**4c**	**7a**	**7b**	**7c**	**7d**	**7e**	**7g**	**7h**	**7i**	**7k**	**7m**
						δ ppm					
3	104.8	105.0	105.1	105.1	105.2	104.9	104.8	105.2	105.0	105.0	109.0
3methyl	25.1	25.1	24.8	24.8	25.1	25.1	24.9	25.1	25.1	25.1	25.1
4	36.5	36.7	36.4	36.4	36.7	36.7	36.5	36.7	36.7	36.8	36.8
5	25.5	25.5	25.3	25.3	25.6	25.4	25.3	25.4	25.5	25.6	25.7
5a	51	51.5	51.2	51.3	51.6	51.5	51.6	51.4	51.4	51.5	51.6
6	37.6	37.6	37.3	37.4	37.0	37.5	37.4	37.6	37.6	37.6	37.5
6methyl	19.0	19.8	19.6	19.6	19.9	19.8	18.6	19.8	19.8	19.9	19.9
7	33.8	33.8	33.5	33.5	33.8	33.8	33.6	33.6	33.7	33.8	33.8
8	23.0	22.7	22.6	22.5	22.7	22.6	22.5	23.0	22.8	22.8	22.8
8a	46.0	45.7	45.4	45.4	45.7	45.7	45.4	45.7	45.7	45.8	45.8
9	32.8	33.2	33.1	33.3	33.3	33.2	33.0	33.1	33.2	33.3	33.3
9methyl	12.1	12.9	12.5	12.6	12.8	12.9	12.6	12.9	12.8	12.9	12.9
10	173.0	172.0	172.3	172.5	172.5	172.1	172.9	173.8	172.3	172.2	172.3
12	75.6	79.0	79.2	79.4	79.3	78.7	78.8	79.6	79.1	79.1	79.5
12a	79.9	80.3	80.0	80.2	80.4	80.2	80.1	80.3	80.3	80.4	80.4
13		38.6	38.6	37.8	37.6	38.3	38.4	39.6	37.6	38.1	37.6
14		32.8	16.0	48.2	54.2	33.8	32.3	31.2	42.9	42.2	39.5
15		172.7	118.7	127.5	139.5	171.9	171.9	58.6	201.8	208.6	199.8
16		60.6		130.1	129.7	80.6	51.3			30.1	137.1
16a				130.1	129.7	28.1					
16b						28.1					
16c						28.1					
17				122.4	128.2						128.9
17a		14.2		122.4	128.2						128.9
18				115.4	134.2						128.5
18a											128.5
19											133.5

[a]See supplemental material for spectra.

did not significantly change their antimalarial activities compared to **7i**.

We had hoped that the presence of two carboxylate groups in **7f** would yield a compound that on hydrolysis would produce a water-soluble derivative suitable for use against cerebral malaria. Unfortunately, the activity of **7f** was a fraction of that of the methyl or ethyl ester of the mono carboxylates **7a** or **7g**. Whereas there were no changes in activity with different EWGs, it appears that the introduction of bulky substituents in the vicinity of the nitrogen can significantly decrease antimalarial activity. For example replacing the methyl or ethyl moieties of esters **7a or 7g** with a *t*-butyl group in the ester **7e** resulted in a large decrease in antimalarial activity.

Conclusion

Of the fifteen 11-azaartemisinin derivatives prepared in this study, ten were more active than artemisinin versus the D-6 clone and six were more active than artemisinin versus the W-2 clone. Two new synthetic routes were developed for the synthesis of these adducts. The first involved base-catalyzed additions to the lactam nitrogen of olefins conjugated with EWGs and the second employed DMAP-catalyzed additions to the lactam nitrogen of terminal acetylenes conjugated with EWGs. Various adducts have also been employed as intermediates in the preparation of additional artemisinin derivatives. Sufficient quantities of one or more of these compounds will be prepared for bioavailability, pharmacological and toxicological studies.

Table 3. Summary of ^{13}C assignment for compounds **8a**, **8b**, **8c** and **8e**[a]

Carbon	**2**	**4c**	**8a**	**8b**	**8c**	**8e**
			δ ppm			
3	105.3	104.8	105.4	105.6	105.3	105.6
3methyl	25.2	25.1	25.0	25.1	25.1	25.1
4	36.1	36.5	36.55	36.5	36.5	36.5
5	30.0	25.3	25.3	25.3	25.4	25.3
5a	50.3	51	51.5	51.6	51.5	51.6
6	37	37.6	37.5	37.5	37.6	37.5
6methyl	19.8	19.0	19.7	19.9	19.7	19.8
7	33.8	33.8	34.0	34.1	34.1	34.1
8	23.4	23.0	22.7	22.8	22.7	22.9
8a	45.1	46.0	45.4	45.1	45.4	45.1
9	33.0	32.8	33.6	33.7	33.7	33.7
9methyl	12.5	12.1	13.0	13.2	13.1	13.2
10	171.5	173.0	172.7	172.1	172.3	172.1
12	93.8	75.6	77.9	78.0	78.8	79.8
12a	79.6	79.9	79.9	79.9	80.1	81.1
13			139.8	139.8	137.9	139.8
14			114.3	102.9	104.2	117.2
15			199.3	168.5	168.2	139.8
16			26.4	51.5		
16a					35.9	
16b					29.8	

[a]See supplemental material for spectra.

Experimental

All NMR spectra were measured with a Varian Gemini-300 NMR spectrometer in $CDCl_3$. Chemical shifts are reported on the δ scale relative to $CDCl_3$ as an internal reference (7.27 ppm for ^1H and 77.23 ppm for ^{13}C). CI–

MS were determined on a Finnigan 4600 mass spectrometer. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254 TLC plates and Merck silica gel 60 (230–400 mesh) was used for flash chromatography. All compounds reported here were purified by chromatography on silica gel and were homogeneous by TLC in two or more solvent systems. Their ^{1}H and ^{13}C spectra did not contain any resonances that could be attributed to starting material or isomeric products. CI–MS of the products did not contain peaks that suggested the presence of impurities.

General procedure for base-catalyzed additions of olefins conjugated with EWGs to 11-azaartemisinin

To a solution of **4c** (27 mg, 0.1 mmol) in anhydrous THF (2 ml) were added at room temperature, 10–20 mg of 20–40 mesh beads of sodium hydroxide and the olefin (0.3 mmol). The mixture was stirred for 1 h and a second 10–20 mg portion of sodium hydroxide was added. The reaction was followed by TLC and stirring was continued for one or more hours as needed for the disappearance of **4c**. The reaction was quenched by addition of dilute aq Na_2SO_3 (5 mL). The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$, brine, water and dried over Na_2SO_4. Evaporation of the solvent gave an oily product which was purified by silica gel chromatography (ethyl acetate:hexane, 4:1). This procedure was employed for the preparation of compounds **7a**–**7g**. A summary of their ^{13}C NMR spectral data is given in Table 2.

11-*N*-(1-(2-Ethoxycarbonyl-ethyl))-azaartemisinin (7a). This was prepared in 86% yield. ^{1}H NMR δ 0.92–0.98 (2H, m), 0.99 (3H, d, $J=6.0$ Hz), 1.13 (3H, d, $J=7.2$ Hz), 1.25 (3H, t, $J=7.1$ Hz), 1.37 (3H, s), 1.26–1.43 (3H, m), 1.63–1.78 (3H, m), 2.01 (2H, m), 2.41 (1H, m), 2.50–2.61 (1H, m), 2.75–2.85 (1H, m), 3.27 (1H, m), 3.61–3.70 (1H, m), 3.79–3.88 (1H, m), 4.12 (2H, q, $J=7.1$ Hz), 5.33 (1H, s). CI–MS (NH_3) 499 $(M+NH_4)^+$.

11-*N*-(1-(2-Cyano-ethyl))-azaartemisinin (7b). This was prepared in 88% yield. ^{1}H NMR δ 0.90–0.97 (2H, m), 1.01 (3H, d, $J=6.0$ Hz), 1.15 (3H, d, $J=7.3$ Hz), 1.38 (3H, s), 1.27–1.51 (3H, m), 1.62–1.84 (3H, m), 1.99 (2H, m) 2.37–2.48 (1H, m), 2.50–2.57 (1H, m), 2.86–3.02 (1H, m), 3.29 (1H, m), 3.52–3.71 (1H, m), 3.85–4.98 (1H, m), 5.41 (1H, s). CI–MS (NH_3) 352 $(M+NH_4)^+$.

11-*N*-(1-(2-Phenoxysulfonyl-ethyl))-azaartemisinin (7c). This was produced in 80% yield. ^{1}H NMR 0.87–0.94 (2H, m), 0.99 (3H, d, $J=6.0$ Hz), 1.14 (3H, d, $J=7.5$ Hz), 1.26–1.42 (3H, m), 1.34 (3H, 5), 1.60–1.79 (3H, m), 2.02 (2H, m), 2.34–2.47 (1H, m), 3.29 (1H, m), 3.37–3.49 (1H, m), 3.69–3.91 (2H, m), 4.22–4.33 (1H, m), 7.29–7.46 (5H, m). CI–MS (NH_3) 483 $(M+NH_4)^+$.

11-*N*-(1-(2-Benzenesulfonyl-ethyl))-azaartemisinin (7d). This was produced in 90% yield. ^{1}H NMR δ 0.86–0.93 (2H, m), 0.98 (3H, d, $J=6.0$ Hz), 1.10 (3H, d, $J=7.8$ Hz), 2.01 (2H, m), 2.35–2.46 (1H, m), 3.19–3.35 (2H, m), 3.60–3.73 (2H, m), 3.91–4.01 (1H, m), 5.41 (1H, 5), 7.56–7.70 (3H, m), 7.93 (2H, m). CI–MS (NH_3) 467 $(M+NH_4)^+$.

11-*N*-(1-(2-*tert*-Butoxycarbonyl-ethyl))-azaartemisinin (7e). This was prepared in 80% yield. ^{1}H NMR δ 0.85–0.93 (2H, m), 0.92 (3H, d, $J=5.7$ Hz), 1.13 (3H, d, $J=7.8$ Hz), 1.24–1.4 (3H, m), 1.43 (12H, s), 1.57–1.82 (3H, m), 1.88–1.98 (2H, m), 2.52 (1H, dt, $J=17.5$, 6.6 Hz), 2.7 (1H, dt, $J=17.5$, 7.8 Hz), 3.01 (1H, m), 3.53–3.72 (2H, m), 5.25 (1H, s). CI–MS (NH_3) 411 $(M+H)^+$.

11-*N*-(1-(1,2-Bis-ethoxycarbonyl-ethyl))-azaartemisinin (7f). This was produced in 78% yield. ^{1}H NMR δ 0.90–1.02 (2H, m), 1.08 (3H, d, $J=6.9$ Hz), 1.16–1.36 (12H, m), 1.42 (3H, s), 1.62–2.01 (5H, m), 2.64–2.82 (1H, m), 3.39 (1H, m), 3.87 (2H, m), 4.09–4.28 (4H, m), 4.65 (1H, dd, $J=5.1$, 5.4 Hz), 5.33 (1H, s). CI–MS (NH_3) 471 $(M+NH_4)^+$.

11-*N*-(1-(2-Methoxycarbonyl-ethyl))-azaartemisinin (7g). This was synthesized in 85% yield. ^{1}H NMR δ 0.86–0.98 (2H, m), 0.99 (3H, d, $J=6.0$ Hz), 1.13 (3H, d, $J=7.2$ Hz), 1.25 (3H, t, $J=7.1$ Hz), 1.37 (3H, s), 1.26–1.43 (3H, m), 1.63–1.78 (3H, m), 1.96–2.01 (2H, m), 2.41 (1H, m), 2.59 (1H, m), 2.82 (1H, m), 3.27 (1H, m), 3.65 (1H, m), 3.67 (3H, s), 3.84 (1H, m), 5.33 (1H, s). CI–MS (NH_3) 385 $(M+NH_4)^+$.

11-*N*-(1-(3-Oxo-propyl))-azaartemisinin (7i). This was prepared from a solution of **7g** (260 mg, 0.7 mmol) in toluene to which was added dropwise DIBAL (1 mL, 1.5 mmol) at −78 °C under N_2. After stirring at −78 °C for 1.5 h, saturated aqueous ammonium chloride was added to quench the reaction, the aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. Chromatography on silica gel with 10% EtOAc/hexanes gave aldehyde **7i** (120 mg) in 50% yield and alcohol **7h** (70 mg) in 29% yield. **7i** ^{1}H NMR δ 0.8–1.1 (2H, m), 0.98 (3H, d, $J=5.7$ Hz), 1.09 (3H, d, $J=8.1$ Hz), 1.34 (3H, s), 1.2–1.6 (3H, m), 1.6–1.77 (3H, m), 1.93–2.05 (2H, m), 2.39 (1H, m), 2.66 (1H, m), 2.92 (1H, m), 3.25 (1H, m), 3.60 (1H, m), 3.88 (1H, m), 5.28 (1H, s), 9.78 (1H, s). CI–MS (NH_3) 338 $(M+H)^+$.

11-*N*-(1-(3-Hydroxy-propyl))-azaartemisinin (7h). ^{1}H NMR δ 0.8–1.1 (2H, m), 0.99 (3H, d, $J=5.7$ Hz), 1.12 (3H, d, $J=7.8$ Hz), 1.33 (3H, s), 1.2–1.6 (3H, m), 1.6–1.9 (3H, m), 1.94–2.05 (2H, m), 2.4 (1H, m), 2.66 (1H, m), 2.92 (1H, m), 3.36 (1H, ddd, $J=13.8$, 7.8, 4.8 Hz), 3.52 (1H, m), 3.9 (1H, ddd, $J=13.8$, 7.8, 5.1 Hz), 4.0 (1H, br), 5.21 (1H, s). CI–MS (NH_3), 340 $(M+H)^+$.

Procedure for the addition of a lithium reagent to 7i and the subsequent oxidation of the resulting alcohol to the ketone

To a solution of the aldehyde **7i** in Et_2O was added dropwise the lithium reagent (2 equiv) at −78 °C under N_2, the solution was allowed to stir at −40 °C for 2 h, then water was added, and the mixture was extracted with more Et_2O. The organic phase was dried over Na_2SO_4 and concentrated. Chromatography on silica

gel with 15% EtOAc/hexane yielded the alcohol. The alcohol was dissolved in 10 mL acetone and the solution was cooled to 0 °C, then the Jones reagent was added. After starting material had disappeared, *iso*-propanol was added to destroy excess reagent. The solution was evaporated and the residue was dissolved in EtOAc, washed with water and brine, dried and concentrated. Chromatography on silica gel with 10% EtOAc/hexanes yielded the desired ketone.

11-*N*-(1-(3-Oxo-butyl))-azaartemisinin (7k). This was obtained in 58% yield. ^{1}H NMR δ 0.8–1.0 (2H, m), 1.0 (3H, d, J = 6.3 Hz), 1.12 (3H, d, J = 7.5 Hz), 1.36 (3H, s), 1.2–1.6 (3H, m), 1.6–1.8 (3H, m), 1.9–2.1 (2H, m), 2.16 (3H, s), 2.41 (1H, m), 2.66 (1H, ddd, J = 17.1, 8.1, 5.4 Hz), 3.01 (1H, ddd, J = 17.1, 8.1, 6 Hz), 3.27 (1H, m), 3.59 (1H, ddd, J = 13.5, 8.7, 5.4 Hz), 3.79 (1H, ddd, J = 13.5, 8.1, 6.3 Hz), 5.34 (1H, s). CI–MS (NH_3) 352 $(M+H)^+$.

11-*N*-(1-(3-Oxo-3-phenyl-propyl))-azaartemisinin (7m). This was prepared in 80% yield. ^{1}H NMR δ 0.8–1.1 (2H, m), 1.0 (3H, d, J = 5.7 Hz), 1.14 (3H, d, J = 7.8 Hz), 1.2–1.6 (3H, m), 1.35 (3H, s), 1.6–1.8 (3H, m), 1.98–2.1 (2H, m), 2.41 (1H, m), 3.18 (1H, m), 3.3 (1H, m), 3.6–3.8 (2H, m), 4.01 (1H, m), 5.39 (1H, s), 7.6–7.4 (3H, m), 8.1–8.0 (2H, m). CI–MS (NH_3) 414$(M+H)^+$.

General procedure for 8a–e. Methyl propynoate (30 mg, 0.36 mmol) was added at room temperature to a solution of **4c** (27 mg, 0.1 mmol) and DMAP (20 mg) in anhydrous acetonitrile (2 mL). Color developed immediately (yellow to red). An examination of the reaction by TLC revealed that **4c** had completely disappeared and a less polar product had formed. The reaction mixture was concentrated on a rotovap and the residue purified by chromatography on silica gel with 20% EtOAc/ hexanes.

E-11-*N*-(1-(2-Methoxycarbonyl-vinyl))-azaartemisinin (8a). This was prepared in 56% yield. ^{1}H NMR δ 0.8–1.1 (2H, m), 1.01 (3H, d, J = 6 Hz), 1.19 (3H, d, J = 7 Hz), 1.2–1.6 (3H, m), 1.33 (3H, s), 1.6–1.8 (3H, m), 1.98–2.1 (2H, m), 2.41 (1H, m), 3.5 (1H, m), 3.74 (3H, s), 5.52 (1H, s), 5.78 (1H, d, J = 15.6 Hz), 8.47 (1H, d, J = 15.6 Hz). CI–MS (NH_3) 383 $(M+NH_4)^+$.

E-11-*N*-(1-(3-Oxo-but-1-enyl))-azaartemisinin (8b). This was prepared in 56% yield. ^{1}H NMR δ 0.8–1.1 (2H, m), 1.01 (3H, d, J = 6 Hz), 1.19 (3H, d, J = 6.6 Hz), 1.31 (3H, s), 1.2–1.6 (3H, m), 1.6–1.8 (3H, m), 1.98–2.1 (2H, m), 2.29 (3H, s), 2.41 (1H, m), 3.5 (1H, m), 5.54 (1H, s), 6.06 (1H, d, J = 15.6 Hz), 8.37 (1H, d, J = 15.6 Hz). CI–MS (NH_3), 350 $(M+H)^+$.

E-11-*N*-(1-(2-Dimethylcarbamoyl-vinyl))-azaartemisinin (8c). was obtained in 47% yield. ^{1}H NMR δ 0.8–1.1 (2H, m), 1.01 (3H, d, J = 5.7 Hz), 1.17 (3H, d, J = 7.8 Hz), 1.33 (3H, s), 1.2–1.6 (3H, m), 1.6–1.8 (3H, m), 1.9–2.2 (2H, m), 2.41 (1H, m), 3.04 (6H, s), 3.45 (1H, m), 5.52 (1H, s), 6.47 (1H, d, J = 13.8 Hz), 8.17 (1H, d, J = 13.8.6 Hz). CI–MS (NH_3) 379 $(M+H)^+$.

Z-11-*N*-(1-(2-Cyano-vinyl)-azaartemisinin (8e)This was prepared in 40% yield and E-11-*N*-(1-(2-cyano-vinyl)-azaartemisinin (8d). This in 4% yield. **8e** ^{1}H NMR δ 0.8–1.1 (2H, m), 1.01 (3H, d, J = 6 Hz), 1.19 (3H, d, J = 7.8 Hz), 1.37 (3H, s), 1.3–1.6 (3H, m), 1.6–1.8 (3H, m), 1.98–2.1 (2H, m), 2.41 (1H, m), 3.5 (1H, m), 4.83 (1H, d, J = 10.8 Hz), 6.24 (1H, s), 7.48 (1H, d, J = 10.8 Hz). EI–MS 332 $(M)^+$, 300. 8d ^{1}H NMR δ 0.8–1.1 (2H, m), 1.03 (3H, d, J = 6 Hz), 1.19 (3H, d, J = 7.8 Hz), 1.35 (3H, s), 1.2–1.6 (3H, m), 1.7–1.9 (3H, m), 1.98–2.2 (2H, m), 2.29 (3H, s), 2.43 (1H, m), 3.5 (1H, m), 5.33 (1H, d, J = 15.6 Hz), 5.51 (1H, s), 8.08 (1H, d, J = 15.6 Hz). CI–MS (NH_3) 350 $(M+NH_4)^+$.

References

1. Collaborative efforts under way to combat malaria. *The Scientist*, **1997**, 11, 1.
2. World Health Organization. *Tenth Programme Report of UNDPI World Bank*, WHO Special Programme for Research and Training in Tropical Diseases. Geneva, Switzerland, 1991, p 30.
3. (a) Luo, X.-D.; Shen, C. C. *Med. Res. Rev*. **1987**, *7*, 29. (b) Ziffer, H.; Highet, R. J.; Klayman, D. L. In *Progress in the Chemistry of Organic Natural Products*; Springer, New York; 1997; Vol. 72, pp 123–214.
4. Torok, D. S.; Ziffer, H.; Meshnick, S. R.; Pan, X.-Q.; Ager, A. *J. Med. Chem*. **1995**, *38*, 5045.
5. Avery, M. A.; Bonk, J. D.; Chong, W. K. M.; Mehrotra; Miller, R.; Mihous, W.; Coins, D. K.; Venkatesan, S.; Wyandt, C.; Khan, I.; Avery, B. A. *J. Med. Chem*. **1995**, *38*, 5038.
6. Mekonnen, B.; Ziffer, H. *Tetrahedron Lett*. **1997**, *38*, 731.
7. Fang, F. G.; Prato, M.; Kim, O.; Danishefsky, S. J. *Tetrahedron Lett*. **1989**, *30*, 3625.
8. Dijkink, J.; Eriksen, K.; Goubitz, K.; van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron Asymmetry* **1996**, *7*, 515.
9. Unpublished observations by Ma, Katz and Ziffer.
10. Faja, M.; Ariza, X.; Galvez, C.; Vilarrasa, S. *Tetrahedron Lett*. **1995**, *36*, 3261.
11. Giloni, L.; Takeshita, M.; Johnson, F.; Iden, C.; Grollman. A. P. *J. Biol. Chem*. **1981**, *56*, 8608. (b) Johnson, F.; Pillai, K. M. R.; Grollman, A. P.; Tseng, L.; Takeshita, M. *J. Med. Chem*. **1984**, *27*, 954.
12. Lin, A. J.; Zikri, A. B.; Kyle, D. E. *J. Med. Chem*. **1997**, *40*, 1396.