Syntheses and Antimalarial Activities of N-Substituted 11-Azaartemisinins

Daniel S. Torok and Herman Ziffer*

National Institutes of Health, Building 5, B1-31, Bethesda, Maryland 20892-0510

Steven R. Meshnick and Xing-Qing Pan

Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan 48109-2029

Arba Ager

University of Miami School of Medicine, Center for Tropical Parasitic Diseases, Department of Microbiology and Immunology, 12500 S. W. 152nd Street, Miami, Florida 33177

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A two-step reaction sequence between artemisinin and methanolic ammonia followed by treatment with Amberlyst 15 yielded 11-azaartemisinin in 65% yield. Substituting a variety of primary alkyl- and heteroaromatic amines for ammonia in the reaction sequence yields N-substituted 11-azaartemisinins in similar or greater yield. When Amberlyst 15 is replaced by a mixture of sulfuric acid/silica gel, both 11-azaartemisinin and the expected metabolite, 10-azadesoxyartemisinin, are formed in 45% and 15% yields, respectively. *In vitro* and *in vivo* test data for a number of novel N-substituted 11-azaartemisinins, against drug-resistant strains of *Plasmodium falciparum*, show they possess antimalarial activities equal to or greater than that of artemisinin. The most active derivative, *N*-(2′-acetaldehydo)-11-azaartemisinin, **17**, was 26 times more active *in vitro* and 4 times more active *in vivo* than artemisinin.

Introduction

Malaria continues to be the most prevalent and deadly parasitic disease in the world, infecting some 300 million people and causing *ca.* 3 million deaths each year.[1] Clinical studies in Thailand,[2a-c] China,[2d] Somalia,[2e] and Sudan[2f] of artemisinin derivatives in combination with older antimalarial drugs have demonstrated substantial improvements over conventional treatments including more rapidly decreasing parasitemia and fever, as well as fewer deaths. Patients infected with drug-resistant strains of *Plasmodium falciparum* recovered completely. Although several studies have shown that artemisinin derivatives can be administered by means of transdermal patches and suppositories, in the above studies they were administered orally despite their poor bioavailability. Apparently alternative modes of administration in Africa, India, and Southeast Asia posed problems that could not be circumvented.

The majority of artemisinin derivatives prepared to date have been either ester, ether, carbonate, or urethane derivatives of the hydroxyl group of dihydroartemisinin, **1a**.[3] The greater stability of lactams to acidic conditions, such as those present in the stomach, should reduce the destruction of the drug that occurs there and might, therefore, lead to an increase in the drug's bioavailability. Moreover, incorporating a lipophilic or hydrophilic substituent on the lactam nitrogen provides a means to control the drug's solubility properties. Furthermore, preliminary data by Avery *et al.*[4a] on a totally synthetic azaartemisinin analog, *N*-benzyl-11-aza-9-desmethylartemisinin, indicated that it was 50% more potent than artemisinin, **2**. We report here a short synthetic route for the conversion of **2** into a series of novel N-substituted 11-azaartemisinin derivatives as well as *in vitro* and *in vivo* test data for these compounds.

Results and Discussion

A complex mixture of products results from the reaction of a methanolic solution of ammonia with artemisinin as determined by TLC. A ^{1}H NMR spectrum of the mixture suggested the presence of a methyl ketone, but no signal characteristic of an aldehydic proton was observed. Apparently the amide nitrogen or hydroperoxide moieties form adducts with the aldehyde (*e.g.*, **3c**,**d**, respectively, in Scheme 1). Prolonged reaction of **2** and ammonia produces a more complex mixture containing polar products. Avery *et al.*[4] synthesized several artemisinin derivatives by treating crude mixtures of hydroperoxides with acid. They employed Amberlyst 15 in their early work[4b] but in later publications reported superior yields with a mixture of aqueous sulfuric acid/silica gel (H_2SO_4/SiO_2).[4c]

Treatment of the crude reaction mixture from **2** and ammonia with H_2SO_4/SiO_2, as described by Avery *et al.*,[4c] produced a mixture of two products separable by column chromatography.[5] The major product, 11-azaartemisinin (**4**), was obtained in 45% yield and a more polar product, 10-azadesoxyartemisinin (**5**), in 9% yield. The structural assignments of **4** and **5** were based on ^{1}H and ^{13}C NMR and mass spectrometric data. Additional data supporting the assigned structures were obtained employing $^{15}NH_3$ in the synthesis. The ^{13}C NMR spectra of both ^{15}N-containing products showed that in **4** the ^{15}N was attached to C-12 (^1J = 11.9 Hz) and C-10 (^1J = 10.3 Hz) and showed a long-range coupling with C-9 (^3J = 5.9 Hz). In **5** the ^{15}N was coupled to C-11 (10.4 Hz) and C-9 (11.7 Hz) and exhibited a long-range coupling to C-8 (5.9 Hz). When

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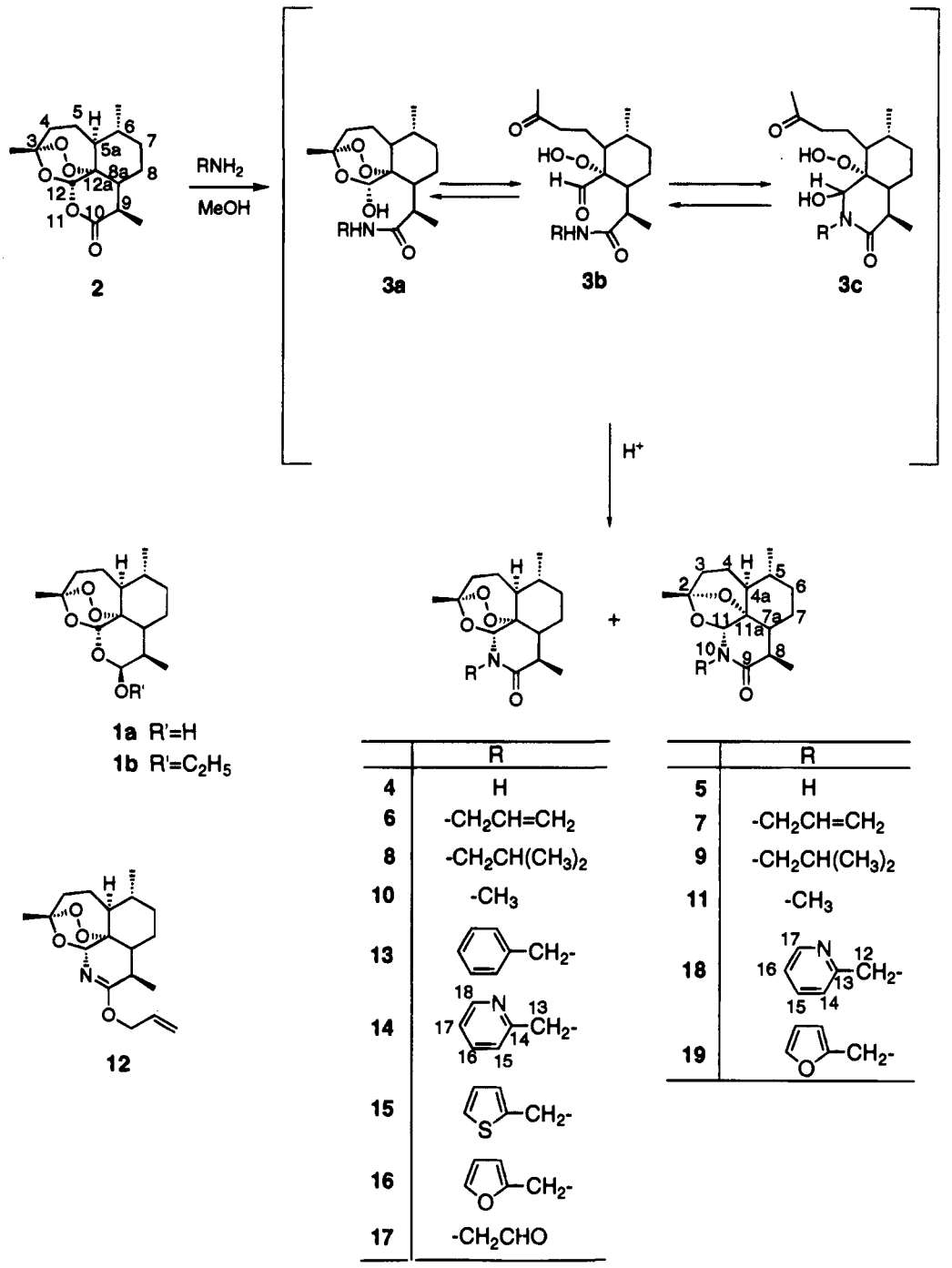
Scheme 1



	R
4	H
6	$-CH_2CH=CH_2$
8	$-CH_2CH(CH_3)_2$
10	$-CH_3$
13	$-CH_2-$
14	$-CH_2-$
15	$-CH_2-$
16	$-CH_2-$
17	$-CH_2CHO$

	R
5	H
7	$-CH_2CH=CH_2$
9	$-CH_2CH(CH_3)_2$
11	$-CH_3$
18	$-CH_2-$
19	$-CH_2-$

Amberlyst 15 was substituted for H_2SO_4/SiO_2, the yield of **4** increased to 65% and compound **5** was not observed.

The conversion of artemisinin into a lactam led us to attempt to prepare N-substituted 11-azaartemisinins using alkylamines instead of ammonia. The reaction of a methanolic solution of allylamine with **2** produced a mixture of products which on treatment with dilute H_2SO_4/SiO_2 yielded *N*-allyl-11-azaartemisinin, **6**, in 45% yield along with *N*-allyl-10-azadesoxyartemisinin, **7**, in 15% yield. Here again, use of Amberlyst 15 produced only **6** in high yield (84%). Since **7** is an expected metabolite of **6**,[3a] a sample of **7** will facilitate biological studies with **6** by facilitating identification of the expected metabolite. When isobutylamine was utilized in an analogous manner, *N*-isobutyl-11-azaartemisinin, **8**, and *N*-isobutyl-10-azadesoxyartemisinin, **9**, were obtained. Use of methylamine in methanol yielded *N*-methyl-11-azaartemisinin, **10**, and *N*-methyl-10-azadesoxyartemisinin, **11**. NMR data for these compounds are summarized in Tables 1 and 2.

Reaction of **2** with aromatic and heteroaromatic amines was also examined. In order to obtain N-substituted 11-azaartemisinins, it proved essential to remove any unreacted amine present in the reaction mixture prior to treatment with acid. Failure to do so resulted in formation of N-substituted 10-azadesoxyartemisinins. Volatile amines could be removed *in vacuo*, whereas the less volatile amines required extraction of a methylene chloride solution of the crude reaction mixture with an aqueous citrate buffer (pH 4.5). Freshly distilled benzylamine and **2** with the modified workup yielded **13**. Reaction of **2** with the heterocyclic

Table 1. Summary of ^{13}C NMR Data and Assignments for N-Substituted 11-Azaartemisinins

	δ (ppm)											
carbon	**2**	**4**	**4a**	**6**	**8**	**10**	**12**	**13**	**14**	**15**	**16**	**17**
3	105.2	104.8	104.7	104.7	104.6	104.6	104.6	104.7	104.7	104.8	104.8	105.0
4	35.8	36.5	36.6	36.7	36.6	36.5	36.8	36.6	36.6	36.6	36.6	36.5
5	24.8	25.5	25.6	25.3	25.2	25.3	26.0	25.0[a]	24.8[a]	25.2	25.3	25.3
5a	49.9	51.0	51.0	51.4	51.4	51.3	55.9	51.4	51.3	51.4	51.4	51.5
6	37.4	37.6	37.6	37.6	37.5	37.6	37.6	37.5	37.4	37.5	37.6	37.5
7	33.4	33.8	33.8	33.7	33.7	33.7	34.1	33.6	33.7	33.6	33.7	33.7
8	23.3	23.0	23.0	22.8	23.0	22.9	23.6	22.8	22.6	22.6	22.7	22.7
8a	44.8	46.0	46.0	45.8	45.3	45.5	45.7	45.6	45.7	45.7	45.7	45.7
9	32.8	32.8	32.8 (5.9)[b]	33.1	33.1	33.0	30.7	33.2	33.1	33.1	33.2	33.0
10	171.9	173.0	173.0 (11.9)	171.4	171.8	171.7	163.2	171.8	172.0	171.7	171.7	172.3
12	93.6	75.6	75.5 (10.3)	77.8	78.6	79.7	79.9	78.0	79.4	77.1	77.9	79.3
12a	79.4	79.9	79.8	80.2	80.1	80.2	81.8	80.2	80.3	80.1	80.2	80.2
3-Me	25.1	25.1	25.1	25.1	25.0	25.1	25.1	24.9[a]	24.9[a]	25.0	25.1	25.0
6-Me	19.7	19.7	19.7	19.8	19.7	19.8	20.1	19.7	19.7	19.7	19.8	19.7
9-Me	12.5	12.1	12.1	12.8	13.1	12.9	12.5	13.0	12.8	12.9	12.9	12.6
13				44.3	48.9	29.3	68.1	45.3	47.6	39.3	29.7	51.2
14				133.0	26.3		136.6	137.7	158.3	139.4	151.4	198.5
15				117.7	20.4		116.8	128.2[a]	121.6[b]	126.2	108.3	
16								128.1[a]	136.3	127.0	110.3	
17								127.9	122.1[b]	125.3	141.6	
18									148.6			

[a] Assignments may be interchanged. [b] The ^{15}N coupling constant in hertz is in parentheses.

Table 2. Summary of ^{13}C NMR Data and Assignments for N-Substituted 10- Azadesoxyartemisinins

	δ (ppm)							
carbon	**5**	**5a**	**7**	**9**	**10**	**18**	**19**	desoxyart
2	107.5	107.5	107.3	107.0	107.3	107.3	107.4	109.1
3	34.7	34.7	34.9	34.8	34.8	34.7	34.7	33.9
4	22.8	22.9	22.3	22.8	22.7	22.6	22.7	23.8
4a	45.6	45.7	46.4	45.9	45.8	45.9	45.8	44.6
5	35.2	35.3	35.5	35.4	35.2	35.1	35.3	35.2
6	33.6	33.6	33.7	33.6	33.6	33.7	33.6	33.4
7	23.0	23.0	24.4	23.0	23.2	24.2	24.3	23.4
7a	43.6	43.6	43.2	42.9	43.0	43.3	43.1	42.3
8	32.8	32.9 (5.9)[a]	33.2	33.3	33.3	33.2	33.2	32.6
9	173.8	173.4 (11.7)	171.2	171.9	171.7	171.9	171.4	171.6
11	81.5	81.5 (10.4)	84.7	86.0	86.1	86.4	84.7	99.5
11a	82.2	82.2	82.1	82.0	82.1	82.3	82.1	82.3
2-Me	22.2	22.2	22.3	20.6	20.7	22.1	22.2	21.9
5-Me	18.5	18.6	18.7	18.6	18.6	18.6	18.6	18.4
8-Me	11.9	11.9	12.7	12.8	12.8	12.5	12.6	12.5
12			34.9	51.4	29.8	49.0	39.5	
13			132.9	29.4		157.7	151.0	
14			117.8	26.7		122.0	108.4	
15				24.3		136.4	110.3	
16						122.5	141.9	
17						148.9		

[a] The ^{15}N coupling constant in hertz is in parentheses.

amines, 2-(aminomethyl)pyridine, 2-(aminomethyl)-thiophene, and 2-(aminomethyl)furan, followed by acid treatment yielded compounds **14**–**16**.

In exploring the use of 11-azaartemisinins as potential intermediates for the preparation of antimalarial drugs, several reactions of **4** and **6** were investigated. Reaction of compound **4** with allyl bromide in the presence of silver oxide yielded a compound isomeric with **6**. Its structure has been assigned as that of the *O*-allyl derivative **12** based on an analysis of its ^1H and ^{13}C NMR spectra, mass spectrometric data, and the known reactivity of amides with alkyl halides in the presence of base.[6] Ozonolysis of the double bond in **6** yielded aldehyde **17**.

The above N-substituted 11-azaartemisinins were screened against a chloroquine-resistant strain (FCR3) of *P. falciparum* using a previously published[8] modification of the method of Desjardins *et al.*[9] The *in vitro* test results are summarized in Table 3 and demonstrate that replacement of the lactone moiety of **2** by a lactam, as in **4**, yields an antimalarial drug with equivalent biological activity. The antimalarial activities of **8**, **14**, and **17** were 1 order of magnitude greater than that of artemisinin. These findings are consistent with those found by Avery *et al.*[4a] for their desmethylartemisinin derivatives, *i.e.*, the antimalarial activities of lactams were as great as or greater than that of artemisinin.

Table 3. *In Vitro* Antimalarial Activities of N-Substituted Azaartemisinins

compd	IC_{50}(**2**)/IC_{50}(compd)
4	1.0
5	0.01
6	0.8
8	9.0
9	0.001
10	2.6
14	22.0
15	1.1
16	1.
17	26.0
18	0.008

Table 4. *In Vivo* Study of *Plasmodium berghei* in Mice

compd	dose (mg/kg/day)	no. of dead mice/ day postinfection	no. of mice alive 60 days after infection
17	128		5/5
	32		5/5
	8	1/15, 1/16, 1/19, 1/20, 1/26	0/5
control	0	3/7, 8/10, 2/9	0/13
2	128	1/17	6/7
	32	1/12, 1/18, 1/19, 1/20, 1/27	2/7
	8	1/13, 2/14, 2/16	0/7
control	0	3/7, 2/8, 1/9, 1/10	0/7
1b	256		7/7
	64		7/7
	16	1/18	6/7
	4	1/8, 1/9, 1/11, 1/12, 1/16, 2/18	0/7

The presence of the endoperoxide for antimalarial activity was essential as with other artemisinin derivatives;[3a] the oxides possess no significant antimalarial activity. Although additional data are needed for a precise comparison of the relative *in vitro* activities of **17** and **2**, we proceeded to prepare sufficient quantities of **17** for *in vivo* testing. The *in vivo* test data are given in Table 4, which shows that **17** is at least 4 times more active than **2**; *i.e.*, it is approximately as active as β-arteether.

Neither recent clinical trials[2a,b,d,e] nor earlier clinical studies in China[2c] found artemisinin derivatives to be toxic. However, reports by Brewer *et al.*[7] indicate that repeated administration of β-arteether, **1b**, produces neurotoxic reactions in animals. In evaluating the potential of **17** as an antimalarial drug, data on its toxicity and bioavailability will be required. Additional azaartemisinin derivatives will be prepared as part of our planned structure–activity relationship (SAR) studies.

Conclusion

Conversion of the lactone moiety of artemisinin into a lactam does not reduce its biological activity. Two N-substituted 11-azaartemisinins were found to exhibit enhanced *in vitro* antimalarial activity compared to **2**. *In vivo* test data show that the lactam **17** is *ca.* 4 times more active than **2** and as potent as β-arteether. Replacement of the endoperoxide moiety in 11-azaartemisinins by an oxide results in loss of antimalarial activity. The *in vitro* and *in vivo* activities of N-substituted azaartemisinins indicate that additional derivatives should be prepared and studied.

Experimental Section

Melting points were determined on a Reichert melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Varian Gemini 300 spectrometer, using $CDCl_3$ as solvent. CIMS analysis were performed on a Finnigan 4600 mass spectrometer. IR spectra were obtained from neat films on a Perkin Elmer Model BIO-Rad FTS-45 spectrophotometer. Optical rotations were measured at 589 nm on a Perkin-Elmer 241 MC polarimeter. Thin layer chromatography was performed on EM silica gel 60 F_{254} plates. Radial dispersion chromatography (RDC) was performed on a chromatotron (Harrison Research, Palo Alto, CA) using 1 or 2 mm silica gel-coated plates. All reagents are commercially available and used as supplied with the exception of the amines which were distilled prior to use. Microanalysis were performed by Galbraith Laboratories (P.O. Box 51610, Knoxville, TN 37950-1610) and are within +0.4% of the theoretical values. The compounds with satisfactory microanalyses are indicated in Table 5 by the letter A and those by high-resolution mass spectrometry by the letter B. In those cases where the molecular ion was too weak for high-resolution mass spectrometry, the molecular ion by CI-MS (NH_3) was readily detected by low-resolution mass spectrometry and is indicated by the letter C. The identities and purities were established by mass spectroscopy and the absence of extraneous resonances in their ^1H and ^{13}C NMR spectra.

Table 5. Physical and Chemical Data of Compounds **4**–**17**[a]

compd	formula	anal.	MS high res	MS low res
4	$C_{15}H_{23}NO_4$	A	B	
6	$C_{16}H_{27}NO_4$	A		C
7	$C_{18}H_{23}NO_3$			C
8	$C_{19}H_{31}NO_4$	A		C
9	$C_{19}H_{31}NO_3$			C
10	$C_{16}H_{25}NO_3$			C
12	$C_{18}H_{27}NO_4$			C
13	$C_{22}H_{29}NO_4$	A	B	C
14	$C_{21}H_{28}N_2O_4$			C
15	$C_{20}H_{27}NO_4S$		B	C
16	$C_{20}H_{27}NO_5$			C
17	$C_{17}H_{25}NO_5$	A		C

[a] A. indicates that the microanalysis for C, H, and N was within 0.4% of the theoretical value. B Indicates that the high-resolution mass spectrometric analysis was satisfactory. C indicates that the low-resolution CIMS (NH_3) was correct.

Preparation of N-Substituted Derivatives from Volatile Amines with Sulfuric Acid/Silica Gel. 11-Azaartemisinin (4). To a saturated solution of methanolic ammonia (12 mL) at room temperature was added artemisinin (1.128 g, 4 mmol). The solution was stirred for 1.5 h and concentrated under reduced pressure to give a light yellow solid. The solid was dissolved in CH_2Cl_2 (180 mL), and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (80 mg, 0.36 mmol), 15% H_2SO_4 (0.8 mL), and silica gel (8.0 g) were added in succession. After stirring overnight at room temperature, the reaction mixture was filtered and the silica gel washed with CH_2Cl_2. The combined organic solution and washes were concentrated under reduced pressure. Column chromatography of the residue on silica gel with acetone:CH_2Cl_2 (8:92) gave crystalline solid **4** (510 mg, 45%): mp 143–145 °C; R_f = 0.40 (acetone:CH_2Cl_2, 15:85); $[\alpha]^{25}_D$ = −40.9° (*c* 0.127, CH_2Cl_2); IR 3313, 3223, 2928, 2873, 1668 cm^{-1}; CIMS (NH_3) 299 (M + NH_4^+, 76), 282 (M + 1, 100); ^1H NMR δ 0.93–1.01 (2H, m), 0.93 (3H, d, *J* = 5.5 Hz), 1.07 (3H, d, *J* = 7.2 Hz), 1.30 (3H, s), 1.25–1.42 (3H, m), 1.61–1.70 (2H, m), 1.71–1.77 (1H, m), 1.92 (2H, dm, *J* = 10.2 Hz), 2.34 (1H, m), 3.17 (1H, pent, *J* = 6.8 Hz), 5.33 (1H, s), 5.93 (1H, bs).

Further elution provided crystalline **5**, 10-azadesoxyartemisinin (120 mg, 9%): mp 169–171 °C; R_f = 0.41 (acetone:CH_2Cl_2, 15:85); $[\alpha]^{25}_D$ = −151.5° (*c* 0.033, CH_2Cl_2); IR 3250, 3325, 2936, 3050, 1681 cm^{-1}; CIMS (NH_3) 283 (M + NH_4^+, 50), 266 (M + 1, 100); ^1H NMR δ 0.88 (3H, d, *J* = 5.7 Hz), 0.95–1.08 (2H, m), 1.08 (3H, d, *J* = 7.5 Hz), 1.10–1.28 (2H, m), 1.43 (3H, s), 1.55–1.97 (7H, m), 2.92–3.01 (1H, m), 5.09 (1H, d, *J* = 2.7 Hz), 6.49 (1H, bs).

11-[^{15}N]Azaartemisinin (4a). Artemisinin (141 mg, 0.5 mmol) was reacted with gaseous $^{15}NH_3$ (100 mL) in MeOH (10 mL) as described for **4** and purified by RDC to yield **4a** (26 mg, 19%): mp 144–146 °C; R_f = 0.40 (acetone:CH_2Cl_2, 15:85); IR 3297, 2936, 2850, 1674 cm^{-1}; CIMS (NH_3) 300 (M + NH_4^+, 100), 283 (M + 1, 55); ^1H NMR δ 0.99–1.12 (2H, m), 0.99 (3H, d, *J* = 5.8 Hz), 1.14 (3H, d, *J* = 7.3 Hz), 1.36 (3H, s), 1.30–1.69 (3H, m), 1.70–1.79 (2H, m), 1.80–1.85 (1H, m), 2.00 (2H, dm, *J* = 9.2 Hz), 2.40 (1H, m), 3.23 (1H, pent, *J* = 6.2 Hz), 5.39 (1H, s), 6.00 (1H, d, *J* = 86.9 Hz).

10-[^{15}N]Azadesoxyartemisinin (5a). Further elution of the above reaction mixture from the silica gel plate yielded **5a** (5 mg, 3%): mp 170–172 °C; R_f = 0.38 (acetone:CH_2Cl_2, 15:85); IR 3297, 2936, 3050, 1674 cm^{-1}; CIMS (NH_3), 384 (M + NH_4^+, 28), 267 (M + 1, 100); ^1H NMR δ 0.93 (3H, d, *J* = 5.7

Hz), 0.95–1.37 (4H, m), 1.13 (3H, d, J = 7.2 Hz), 1.47 (3H, s), 1.62–1.90 (6H, m), 1.96–2.04 (1H, m), 3.05 (1H, m), 5.13 (1H, t, J = 2.5 Hz), 6.24 (1H, dd, J = 88.2, 2.7 Hz).

***N*-Allyl-10-azadesoxyartemisinin (7).** Artemisinin (282 mg, 1.0 mmol) was reacted with allylamine (1.5 mL, 20 mmol) as described for **4** to yield crystalline **7** (40 mg, 15%): mp 97–99 °C; R_f = 0.62 (EtOAc:hexane, 1:4); $[\alpha]^{25}_D$ = −105.7° (c 0.07, CH_2Cl_2); IR 2926, 2812, 1661 cm^{-1}; CIMS (NH_3) 306 (100); ^{1}H NMR δ 0.78–1.40 (5H, m), 0.92 (3H, d, J = 5.8 Hz), 1.15 (3H, d, J = 6.9 Hz), 1.45 (3H, s), 1.55–2.00 (6H, m), 3.04–3.10 (1H, m), 3.60 (1H, dd, J = 15.0, 8.1 Hz), 4.55 (1H, dm, J = 16.0 Hz), 5.04 (1H, s), 5.16–5.30 (2H, m), 5.73–5.81 (1H, m).

***N*-Allyl-11-azaartemisinin (6).** Further chromatography of the reaction mixture used to prepare **7** yielded the solid **6** (144 mg, 45%): mp 101–103 °C; R_f = 0.55 (EtOAc:hexane, 1:4); $[\alpha]^{25}_D$ = 14.0° (c 0.417, CH_2Cl_2); IR 2926, 2873, 1658 cm^{-1}; CIMS (NH_3) 339 (M + NH_4^+, 42), 322 (M + 1, 100); ^{1}H NMR δ 0.91 (1H, dd, J = 3.0, 2.8 Hz), 0.99 (3H, d, J = 5.8 Hz), 0.95–1.05 (1H, m), 1.03–1.52 (3H, m), 1.14 (3H, d, J = 7.5 Hz), 1.36 (3H, s), 1.63–1.82 (3H, m), 1.95–2.03 (2H, m), 2.36–2.47 (1H, m), 3.29–3.33 (1H, m), 3.97 (1H, dd, J = 14.9, 3.1 Hz), 4.29 (1H, dd, J = 14.8, 4.5 Hz), 5.14–5.25 (2H, m), 5.22 (1H, s), 5.80 (1H, m).

***N*-Isobutyl-10-azadesoxyartemisinin (9).** Artemisinin (282 mg, 1.0 mmol) was reacted with isobutylamine (2 mL, 20 mmol) as described for **4** to yield two products after RDC. **9** (0.015 g, 4%): mp 91–93 °C; R_f = 0.74 (EtOAc:hexane, 3:7); $[\alpha]^{25}_D$ = −5.9° (c 0.32, CH_2Cl_2); IR 2926, 2812, 1661 cm^{-1}; CIMS (NH_3) 322 (100); ^{1}H NMR δ 0.90–1.50 (4H, m), 0.90 (3H, d, J = 6.7 Hz), 0.98 (6H, d, J = 6.6 Hz), 1.17 (3H, d, J = 7.3 Hz), 1.45 (3H, s), 1.61–2.15 (8H, m), 3.02–3.10 (2H, m), 3.50–3.60 (1H, m), 5.09 (1H, s).

***N*-Isobutyl-11-azaartemisinin (8).** The second product obtained by continued elution of the reaction mixture that provided **9** yielded crystalline **8** (153 mg, 45%) as the major product: mp 100–101 °C; R_f = 0.72 (EtOAc:hexane, 3:7); $[\alpha]^{25}_D$ = 9.8° (c 0.275, CH_2Cl_2); IR 2926, 2873, 1658 cm^{-1}; CIMS (NH_3) 355 (M + NH_4^+, 24), 338 (M + 1, 100); ^{1}H NMR δ 0.87–1.12 (3H, m), 0.87 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 5.9 Hz), 1.14 (3H, d, J = 7.3 Hz), 1.36 (3H, s), 1.23–1.52 (2H, m), 1.53–1.88 (3H, m), 1.92–2.13 (3H, m), 2.37–2.46 (1H, m), 3.27–3.36 (2H, m), 3.42–3.49 (1H, m), 5.25 (1H, s).

***N*-Methyl-10-azadesoxyartemisinin (11).** Chromatography of the mixture from the reaction sequence with artemisinin (52 mg, 0.2 mmol) and methylamine (2 mL, 2.0 M MeOH, 4 mmol) as described for **4** yielded crystalline 11 (5 mg, 8%): R_f = 0.70 (EtOAc:hexane, 3:7); CIMS (NH_3) 297 (M + NH_4^+, 8), 280 (M + 1, 100); ^{1}H NMR δ 0.90–0.93 (1H, m), 0.93 (3H, d, J = 5.5 Hz), 1.14 (3H, d, J = 7.4 Hz), 1.44 (3H, s), 1.58–2.00 (10H, m), 2.95 (3H, s), 2.96–3.04 (1H, m), 4.97 (1H, s).

***N*-Methyl-11-azaartemisinin (10).** Continued elution of the reaction mixture from 11 yielded the major product **10** (10 mg, 17%): R_f = 0.67 (EtOAc:hexane, 3:7), as a solid; $[\alpha]^{25}_D$ = 15.9° (c 0.375, CH_2Cl_2); IR 2926, 2873, 1648 cm^{-1}; CIMS (NH_3) 313 (M + NH_4^+, 24), 296 (M + 1, 100); ^{1}H NMR δ 0.9–1.06 (2H, m), 0.96 (3H, d, J = 6.8 Hz), 1.14 (3H, d, J = 7.4 Hz), 1.36 (3H, s), 1.35–1.55 (2H, m), 1.63–1.81 (4H, m), 1.97–2.04 (2H, m), 2.42 (1H, m), 2.95 (3H, s), 3.27 (1H, pent, J = 5.6 Hz), 5.15 (1H, s).

***O*-Allyl-11-azaartemisinin (12).** To a solution of 11-azaartemisinin, **4** (38 mg, 0.13 mmol), in DMF (3 mL) were added allyl bromide (70 μL, 0.81 mmol) and silver oxide (126 mg, 054 mmol). The reaction mixture was stirred for 20 h at room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and washed with H_2O (10 mL). The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated, and the residue was purified by PTLC (1 mm silica gel, EtOAc:hexane, 1:4) to yield **12** (5 mg, 11%): R_f = 0.70 (EtOAc:hexane, 1:4); $[\alpha]^{25}_D$ = 50.9° (c 0.055, CH_2Cl_2); IR 2926, 2750, 1676 cm^{-1}; CIMS (NH_3) 322 (M + 1, 100); ^{1}H NMR δ 0.99 (3H, d, J = 6.2 Hz), 0.87–1.05 (2H, m), 1.11 (3H, d, J = 7.3 Hz), 1.16–1.74 (7H, m), 1.38 (3H, s), 1.92–2.03 (2H, m), 2.32–2.43 (1H, m), 3.14–3.18 (1H, m), 4.63 (1H, d, J = 6.5 Hz), 5.18 (1H, d, J = 10.6 Hz), 5.32 (1H, d, J = 16.7 Hz), 5.40 (1H, s), 5.95–6.06 (1H, m).

Preparation of an N-Substituted Azaartemisinin from a Nonvolatile Amine. *N*-Benzyl-11-azaartemisinin (13). To a solution of artemisinin (141 mg, 0.5 mmol) in methanol (1 mL) was added freshly distilled benzylamine (1.00 mL, 10 mmol). The reaction mixture was stirred for 1.5 h at room temperature, diluted with CH_2Cl_2 (50 mL), washed with pH 4.5 citrate buffer (6 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a light yellow solid. The solid was dissolved in CH_2Cl_2 (80 mL) containing BHT (80 mg, 0.36 mmol), and 15% H_2SO_4 (0.8 mL) and silica gel (8.0 g) were added in succession. After stirring overnight, the reaction mixture was filtered and the silica gel washed with CH_2Cl_2. The combined solution and washes were concentrated under reduced pressure to afford a crude product which was purified by RDC (2 mm silica gel plate) with an EtOAc/hexane gradient to give **13** (121 mg, 65%) as a crystalline solid: mp 113–115 °C; R_f = 0.42 (EtOAc:hexane, 1:4); $[\alpha]^{25}_D$ = 27.2° (c 0.58, CH_2Cl_2); IR 2928, 2873, 1653 cm^{-1}; CIMS (NH_3) 389 (M + NH_4^+, 65), 372 (M + 1, 100); ^{1}H NMR δ 0.70–0.87 (2H, m), 0.94 (3H, d, J = 6.1 Hz), 0.94–1.08 (1H, m), 1.15 (3H, s), 1.20 (3H, d, J = 7.3 Hz), 1.15–1.42 (3H, m), 1.62–1.81 (3H, m), 1.92–2.00 (2H, m), 2.36 (1H, m), 3.39 (1H, m), 4.62 (1H, d, J = 14.5 Hz), 4.95 (1H, d, J = 14.6 Hz), 7.22–7.32 (5H, m).

***N*-(2-Methylpyridyl)-10-azadesoxyartemisinin (18).** Artemisinin (282 mg, 1.0 mmol) was reacted with 2-(aminomethyl)pyridine (2 mL, 20 mmol) as described for **13**. RDC of the residue yielded two products. First, solid **18** (18 mg, 5%): R_f = 0.32 (EtOAc:hexane, 2:3), after RDC; ^{1}H NMR δ 0.89 (3H, d, J = 5.8 Hz), 1.14 (3H, d, J = 7.2 Hz), 1.44 (3H, s), 1.56–2.00 (11H, m), 3.11–3.15 (1H, m), 4.45 (1H, d, J = 15.6 Hz), 5.06 (1H, d, J = 15.6 Hz), 5.33 (1H, s), 7.15 (1H, t, J = 5.2 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.62 (1H, t, J = 7.7 Hz), 8.50 (1H, d, J = 4.5 Hz).

***N*-(2-Methylpyridyl)-11-azaartemisinin (14).** Further elution of the reaction mixture that produced **18** yielded a second product, **14** (144 mg, 39%): mp 111–113 °C; R_f = 0.19 (EtOAc:hexane, 2:3); $[\alpha]^{25}_D$ = 6.9° (c 0.117, CH_2Cl_2); IR 2932, 2873, 1654, 1591 cm^{-1}; CIMS (NH_3) 373 (M + H^+, 100); ^{1}H NMR δ 0.87–1.50 (4H, m), 0.99 (3H, d, J = 5.8 Hz), 1.05 (3H, s), 1.17 (3H, d, J = 7.1 Hz), 0.94–1.08 (1H, m), 1.68–1.81 (3H, m), 1.92–2.00 (2H, m), 2.35–2.41 (1H, m), 3.39 (1H, pent, J = 5.4 Hz), 4.68 (1H, d, J = 15.6 Hz), 4.98 (1H, d, J = 15.7 Hz), 5.52 (1H, s), 7.12 (1H, t, J = 6.1 Hz), 7.34 (1H, d, J = 7.5 Hz), 7.62 (1H, t, J = 7.3 Hz), 8.49 (1H, d, J = 4.7 Hz).

***N*-(2-Methylthiophene)-11-azaartemisinin (15).** The reaction of artemisinin (141 mg, 0.5 mmol) with 2-(aminomethyl)thiophene (1.0 mL, 10 mmol) as described for **13** yielded solid **15** (40 mg, 21%). Crystallization from hexane yielded a pure sample of **15**; mp 129–131 °C; R_f = 0.69 (EtOAc:hexane, 3:7); $[\alpha]^{25}_D$ = 12.3° (c 0.30, CH_2Cl_2); IR 2929, 2871, 1655 cm^{-1}; CIMS (NH_3) 395 (M + NH_4^+, 42), 378 (M + 1, 100); ^{1}H NMR δ 0.69–0.77 (1H, m), 0.94 (3H, d, J = 6.0 Hz), 1.17 (3H, d, J = 7.4 Hz), 1.32 (3H, s), 1.60–1.74 (6H, m), 1.94–2.04 (3H, m), 2.37–2.42 (1H, m), 3.33 (1H, m), 4.60 (1H, d, J = 14.8 Hz), 5.18 (1H, s), 5.25 (1H, d, J = 15.0 Hz), 6.93 (1H, t, J = 4.1 Hz), 7.01 (1H, m), 7.21 (1H, d, J = 5.0 Hz).

***N*-(2-Methylfurfuryl)-11-azaartemisinin (16).** The reaction of artemisinin (141 mg, 0.5 mmol) with 2-(aminomethyl)-furan (0.88 mL, 10 mmol) as described for **13** yielded **16** (51 mg, 28%), and crystallization from hexane afforded a pure sample: mp 148–151 °C; R_f = 0.47 (EtOAc:hexane, 1:4); $[\alpha]^{25}_D$ = 8.4° (c 0.25, CH_2Cl_2); IR 2944, 2921, 2881, 2851, 1654 cm^{-1}; CIMS (NH_3) 379 (M + NH_4^+, 30), 362 (M + 1, 100); ^{1}H NMR δ 0.73–1.00 (3H, m), 0.97 (3H, d, J = 5.7 Hz), 1.16 (3H, d, J = 7.4 Hz), 1.33 (3H, s), 1.53–1.76 (5H, m), 1.94–2.04 (2H, m), 2.36–2.41 (1H, m), 3.33 (1H, pent, J = 4.8 Hz), 4.45 (1H, d, J = 15.2 Hz), 5.05 (1H, d, J = 15.2 Hz), 5.20 (1H, s), 6.26 (1H, d, J = 3.1 Hz), 6.31 (1H, t, J = 2.2 Hz), 7.33 (1H, d, J = 4.7 Hz).

***N*-(2′-Acetaldehydo)-11-azaartemisinin (17).** A stream of ozone was bubbled into a cold (−78 °C) solution of **7** (25 mg, 0.78 mmol) in CH_2Cl_2 (30 mL) containing a trace of pyridine. Ozone bubbling was stopped when a persistant blue-colored solution was obtained. The solution was allowed to warm to room temperature and then concentrated and purified by RDC (2 mm silica gel) with a hexane:EtOAc gradient to

yield **17** as a white solid (150 mg, 60%): mp 80–81 °C; R_f = 0.34 (EtOAc:hexane, 3:7); $[\alpha]^{25}_D = -10.7°$ (*c* 0.566, CH_2Cl_2); IR 2935, 2875, 1735, 1660 cm^{-1}; CIMS (NH_3) 341 (M + NH_4^+, 11), 324 (100); ^1H NMR δ 0.94 (1H, d, J = 3.9 Hz), 1.01 (3H, d, J = 6.8 Hz), 1.17 (3H, d, J = 7.1 Hz), 1.34 (3H, s), 1.00–1.50 (3H, m), 1.70–1.86 (4H, m), 2.01 (2H, d, J = 13.6 Hz), 2.36–2.47 (1H, m), 3.36–3.40 (1H, m), 4.39 (2H, q, J = 18.0 Hz), 5.29 (1H, s), 9.58 (1H, s).

Preparation of N-Substituted Derivatives with Amberlyst 15. *N*-Allyl-11-azaartemsinin (6). Artemisinin (1.41 g, 5.0 mmol) was reacted with allylamine (7.5 mL, 100 mmol) as described for **4**. The crude mixture was dissolved in CH_2Cl_2 (100 mL), Amberlyst 15 (2.1 g) was added and the solution was stirred at room temperature for 15 h. Additional Amberlyst 15 (1 g) was added, and stirring continued for 6 h. The solution was filtered and concentrated to a pure sample of **6** (1.35 g, 84%).

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