New Products from the Reactions of Artemisinin with Ammonia and Amines

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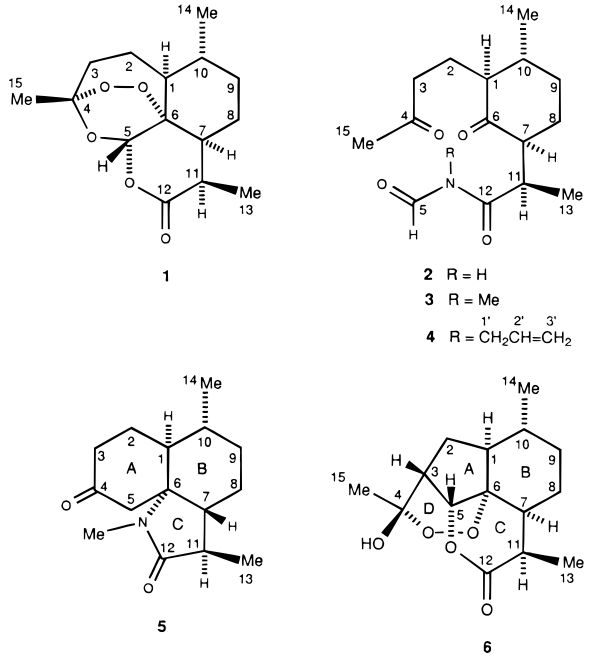
Reaction of artemisinin (**1**) with ammonia, methylamine, dimethylamine, and allylamine afforded five unexpected products **2**−**6**, in addition to the previously reported compounds **7**−**12**. The identities of the new compounds were established from their spectral data, by chemical derivatization and by comparison with published reports. The stereochemistries of compounds **5** and **6** were confirmed by single-crystal X-ray analysis.

In the course of preparing azaartemisinin derivatives[1] by treating artemisinin (**1**) with ammonia and the amines methylamine, dimethylamine, and allylamine, unexpected by-products were obtained, some of them in good yields. This paper describes the isolation and characterization of these new compounds, *viz*. formyl amides **2**−**4**, the lactam **5**, and the hemiketal peroxide **6**.



Results and Discussion

Artemisinin (**1**) was allowed to react with a methanolic solution of anhydrous ammonia following a literature procedure.[1] After workup, the mixture of crude products was chromatographed on Si gel, using $CH_3CN-CH_2Cl_2$ (1:9) as eluent, to yield **2**. Further elution with increasing concentrations of CH_3CN (up to 30%), produced the expected[1] products, azaartemisinin (**7**), followed by deoxyazaartemisinin (**8**). Compound **2**, $C_{15}H_{23}NO_4$, mp 166−167 °C, had a ^{13}C NMR spectrum (see Table 1) that was in agreement with the assigned structure. It exhibited four carbonyl groups at δ 213.8, 208.8, 174.8, and 162.2, due to C-6, C-4, C-12, and C-5, respectively. The ^1H NMR spectrum (see Experimental Section) corroborated the presence of the C-5 amide group by exhibiting the formyl proton signal at δ 9.08 as a doublet, J = 10.0 Hz, and a slow-to-exchange >NH broad doublet at δ 9.17. The ^1H NMR spectrum also showed the characteristic singlet at δ 2.12 due to H-15.

Table 1. ^{13}C-NMR Chemical Shift Assignments for Compounds **2**−**6**[a]

	compound				
carbon	**2**	**3**	**4**	**5**	**6**
1	54.5 (1)	54.8 (1)	57.3 (1)	50.0 (1)	42.8 (1)
2	20.0 (2)	20.1 (2)	20.5 (2)	23.1 (2)	31.6 (2)
3	41.0 (2)	41.2 (2)	41.5 (2)	36.0 (2)	42.1 (1)
4	208.8 (0)	208.8 (0)	209.2 (0)	209.7 (0)	103.0 (0)
5	162.2 (0)	162.4 (0)	162.5 (0)	46.9 (2)	75.9 (1)
6	213.8 (0)	212.1 (0)	212.4 (0)	66.8 (0)	81.5 (0)
7	56.3 (1)	56.6 (1)	55.2 (1)	46.0 (1)	39.4 (1)
8	34.2 (2)	34.4 (2)	34.0 (2)	22.6 (2)	23.8 (2)
9	28.9 (2)	30.9 (2)	31.5 (2)	29.8 (2)	32.8 (2)
10	40.2 (1)	40.6 (1)	41.0 (1)	30.4 (1)	40.9 (1)
11	38.3 (1)	37.1 (1)	37.7 (1)	36.6 (1)	34.6 (1)
12	174.8 (0)	177.9 (0)	178.0 (0)	176.6 (0)	173.3 (0)
13	14.8 (3)	16.7 (3)	17.4 (3)	13.6 (3)	12.8 (3)
14	20.4 (3)	20.4 (3)	20.0 (3)	19.3 (3)	20.1 (3)
15	29.3 (3)	29.4 (3)	30.2 (3)		23.6 (3)
N-Me		26.8 (3)		29.4 (3)	
1′			42.6 (2)		
2′			132.3 (1)		
3′			117.8 (2)		

[a] Numbers in parentheses designate the number of attached protons at the respective carbon.

The formation of **2** in yields as high as 25% could not be explained by a mechanism involving the degradation of azaartemisinin (**7**, Scheme 1a), as suggested[2] earlier for the conversion of **1** to an analogous diketone, for **7** was found to be remarkably stable under both acidic and basic conditions. A more plausible mechanism (Scheme 1b) depends on the formation of the intermediate **9**[1] from the reaction of **1** with ammonia followed by an internal Baeyer−Villiger oxidation to give the formate ester **10**. A similar pathway has been previously proposed[3] in the conversion of dihydroartemisinin to deoxyartemisinin, where the formyl group becomes attached to the nitrogen, with the ensuing formation of a ketone group to produce **2**.

By reacting artemisinin (**1**) with a number of organic amines, compounds analogous to **2**, **7**, and **8** were obtained.

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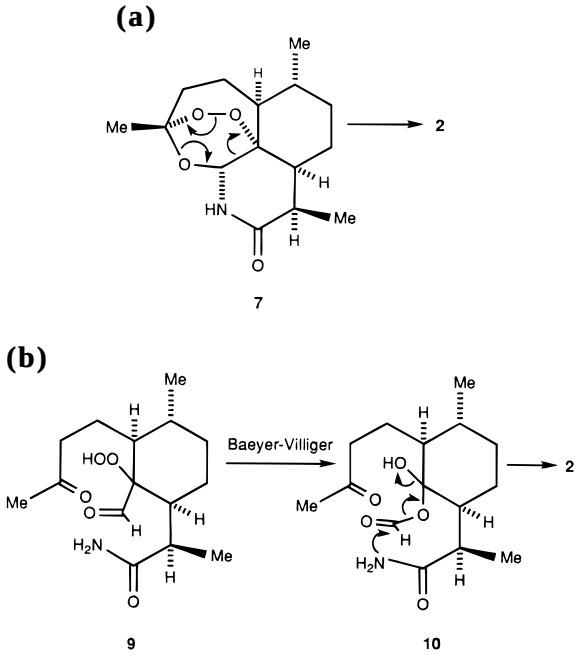
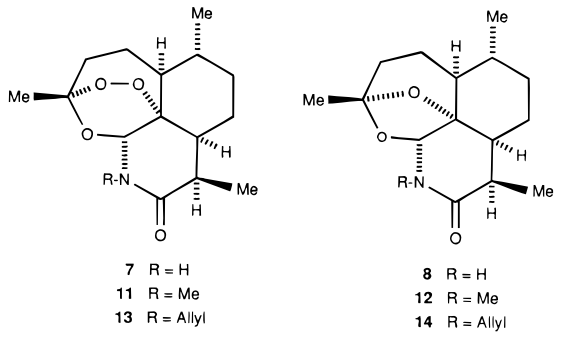
Scheme 1



Thus, methylamine yielded **3**, **11**, and **12**, while **4**, **13**, and **14** were obtained from allylamine. The structure of **3** was further confirmed by its formation from **2**, almost quantitatively, by methylation using methyl iodide in the presence of silver oxide.



The amination of **1** with methylamine produced the lactam **5** as the most polar product during column chromatography of the crude reaction mixture. The formation of an analogous product from the reaction with ammonia or other amines was not observed. The structure of **5** was unambiguously deduced from its spectral data, and its stereochemistry was established by single-crystal X-ray analysis. Nonhydrogen atom fractional coordinates are listed in Table 2. Bond lengths are in accord with expectations.[6] A view of the solid-state conformation is presented in Figure 1 [endocyclic torsion angles ω_{ij} (σ 0.3−0.5°) follow: $\omega_{1,2}$ 57.6, $\omega_{2,3}$ −53.5, $\omega_{3,4}$ 44.7, $\omega_{4,5}$ −40.6, $\omega_{5,6}$ 43.4, $\omega_{6,1}$ −51.2° in cyclohexanone ring A; $\omega_{1,6}$ −49.8, $\omega_{6,7}$ 44.6, $\omega_{7,8}$ −47.6, $\omega_{8,9}$ 55.7, $\omega_{9,10}$ −60.1, $\omega_{10,1}$ 57.2° in cyclohexane ring B; $\omega_{6,7}$ 33.9, $\omega_{7,11}$ −33.0, $\omega_{11,12}$ 18.8, $\omega_{12,15}$ 3.4, $\omega_{15,6}$ −23.8° in γ-lactam ring C]. Rings A and B have flattened chair conformations, while ring C has an envelope form with C-7 as the out-of-plane atom. The remarkable feature of the stereochemistry of **5** is the inversion of configuration at C-7 relative to that of **1**. The formation of **5** can be explained, as shown in Scheme 2, by an aldol-type condensation of intermediate **15** that can be produced by the

Table 2. Nonhydrogen Atom Fractional Coordinates and Equivalent Isotropic Thermal Parameters for Compound **5**, with Estimated Standard Deviations in Parentheses

atom	*x*	*y*	*z*	B_{eq} (Å^2)
C-1	0.4324 (4)	0.1308 (1)	0.2034 (3)	3.69 (5)
C-2	0.3499 (5)	0.1973 (2)	0.1846 (5)	5.18 (8)
C-3	0.3993 (6)	0.2454 (2)	0.3139 (6)	6.4 (1)
C-4	0.3787 (5)	0.2190 (2)	0.4829 (5)	5.97 (8)
C-5	0.4346 (4)	0.1503 (2)	0.5117 (4)	4.51 (7)
C-6	0.3984 (3)	0.1014 (1)	0.3741 (3)	3.35 (5)
C-7	0.4870 (4)	0.0374 (1)	0.4018 (3)	3.67 (5)
C-8	0.6601 (4)	0.0381 (2)	0.3480 (4)	4.47 (7)
C-9	0.6808 (4)	0.0665 (2)	0.1779 (4)	4.67 (7)
C-10	0.6106 (4)	0.1344 (2)	0.1650 (4)	4.44 (6)
C-11	0.3816 (4)	−0.0138 (1)	0.3214 (4)	3.87 (6)
C-12	0.2176 (4)	0.0133 (1)	0.3496 (4)	3.65 (5)
C-13	0.3997 (5)	−0.0830 (2)	0.3850 (5)	5.45 (8)
C-14	0.6401 (5)	0.1609 (2)	−0.0084 (6)	7.3 (1)
N-15	0.2320 (3)	0.0777 (1)	0.3843 (3)	3.61 (5)
C-16	0.0922 (4)	0.1164 (2)	0.4208 (5)	5.08 (7)
O-17	0.3214 (5)	0.2503 (1)	0.5947 (4)	8.97 (8)
O-18	0.0924 (3)	−0.0161 (1)	0.3443 (3)	5.26 (5)

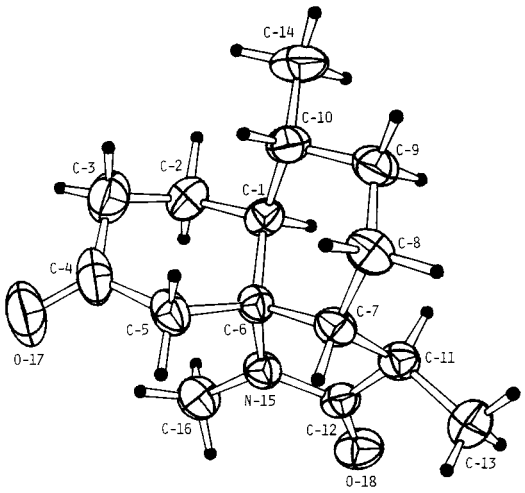


Figure 1. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom-numbering scheme and solid-state conformation of **5**; small filled circles represent hydrogen atoms.

hydrolysis of intermediate **16**. Compound **5** is produced by Michael addition of the amide group to the α,β-unsaturated ketone in intermediate **17**. The inversion of configuration at C-7 was made possible in **15** by the proximity of the ketone group and by the formation of the favored cis-lactam.

It then became of interest to explore the products arising from the reaction of artemisinin (**1**) with the secondary amine dimethylamine. The product **6** was found to be nitrogen free, $C_{15}H_{22}O_5$, mp 165−167 °C, and its spectral data (see Table 1 and Experimental Section) were closely related to those of **18**,[4] a compound previously reported as a product of treating artemisinin (**1**) with K_2CO_3 in MeOH. However, unlike **18**, the spectral data of **6** did not indicate the presence of a methoxy group. Instead, there was a lactone carbonyl group as suggested by the absorption band at ν_{max} 1770 cm^{-1} and the carbon signal at δ 173.3. Single-crystal X-ray analysis established the complete structure and stereochemistry of **6**. Nonhydrogen atom fractional coordinates are listed in Table 3. Although bond lengths, in general, lie close to expected values,[6] bond strain is reflected in the C-1−C-2 distance of 1.560 (3) Å, and the C-12−O-18 bond is also longer than normal (see below). A view of the solid-state conformation is illustrated in Figure 2 [endocyclic torsion angles ω_{ij} (σ 0.2−0.4°) follow: $\omega_{1,2}$

Scheme 2

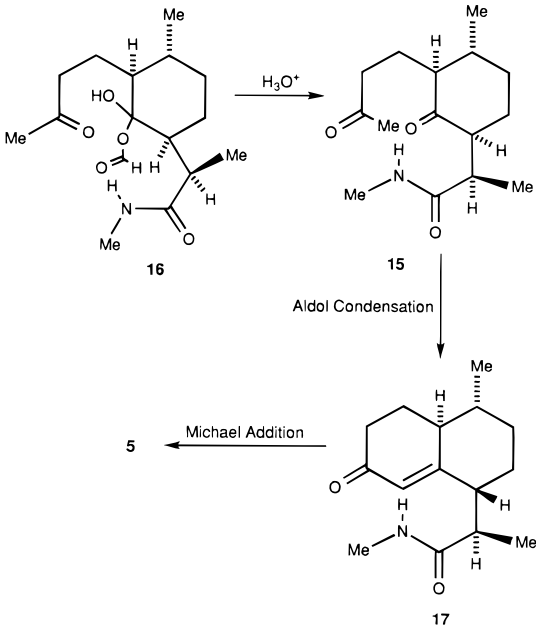


Table 3. Nonhydrogen Atom Fractional Coordinates and Equivalent Isotropic Thermal Parameters for Compound **6**, with Estimated Standard Deviations in Parentheses

atom	*x*	*y*	*z*	B_{eq} (Å^2)
C-1	0.41816 (8)	0.3746 (4)	0.1304 (3)	3.37 (4)
C-2	0.42592 (9)	0.4105 (5)	−0.0599 (3)	4.02 (5)
C-3	0.38427 (9)	0.3006 (5)	−0.1622 (3)	3.89 (5)
C-4	0.39666 (9)	0.0756 (5)	−0.1867 (4)	4.64 (6)
C-5	0.34623 (8)	0.3289 (4)	−0.0381 (3)	3.34 (4)
C-6	0.37231 (8)	0.2485 (4)	0.1234 (3)	3.06 (4)
C-7	0.34166 (8)	0.2488 (5)	0.2724 (3)	3.66 (5)
C-8	0.33841 (9)	0.4629 (5)	0.3463 (3)	4.15 (5)
C-9	0.38810 (10)	0.5502 (5)	0.3857 (3)	4.62 (6)
C-10	0.41396 (9)	0.5765 (4)	0.2262 (3)	3.81 (5)
C-11	0.29329 (9)	0.1468 (5)	0.2176 (3)	4.43 (5)
C-12	0.27134 (8)	0.2042 (5)	0.0432 (4)	4.24 (5)
C-13	0.25639 (11)	0.1700 (8)	0.3482 (4)	6.95 (9)
C-14	0.46300 (10)	0.6749 (6)	0.2626 (4)	5.40 (7)
C-15	0.43661 (11)	0.0386 (7)	−0.2988 (4)	6.19 (8)
O-16	0.41604 (7)	0.0000 (−)[a]	−0.0245 (3)	4.66 (4)
O-17	0.38104 (6)	0.0323 (3)	0.1003 (2)	4.11 (4)
O-18	0.30118 (6)	0.2303 (4)	−0.0838 (2)	4.27 (4)
O-19	0.22939 (6)	0.2039 (5)	0.0033 (3)	5.99 (5)
O-20	0.35797 (8)	−0.0429 (4)	−0.2517 (3)	6.50 (5)

[a] The *y*-coordinate of O-16 was held constant throughout the least-squares parameter refinement to define the space group origin in this direction.

−0.6, $\omega_{2,3}$ 31.7, $\omega_{3,5}$ −51.9, $\omega_{5,6}$ 52.9, $\omega_{6,1}$ −31.3° in cyclopentane ring A; $\omega_{1,6}$ −35.3, $\omega_{6,7}$ 40.7, $\omega_{7,8}$ −52.6, $\omega_{8,9}$ 63.6, $\omega_{9,10}$ −58.0, $\omega_{10,1}$ 41.9° in cyclohexane ring B; $\omega_{5,6}$ −52.8, $\omega_{6,7}$ 49.5, $\omega_{7,11}$ −41.9, $\omega_{11,12}$ 37.7, $\omega_{12,18}$ −38.8, $\omega_{18,5}$ 46.2° in δ-lactone ring C; $\omega_{3,4}$ −62.4, $\omega_{4,16}$ 57.0, $\omega_{16,17}$ −63.5, $\omega_{17,6}$ 68.6, $\omega_{6,5}$ −65.2, $\omega_{5,3}$ 64.1° in 1,2-dioxane ring D. Ring A has an envelope form with C-5 as the out-of-plane atom; rings B, C, and D all have chair-like conformations. The trigonal planar geometry at C-12 and the C−O−C−C torsion angle of −38.8(4)° in δ-lactone ring C indicate that the atoms of the C−O−C(=O)−C moiety are distinctly noncoplanar, thereby reducing the contribution from the C−O$^+$=C(O$^-$)−C resonance form. Accordingly, the C-12−O-18 bond at 1.374 (3) Å in **6** is longer than the corresponding lengths of 1.344 (5) Å and 1.350 (6) Å associated with the smaller endocyclic C−O−C−C torsion angles of −5.3(6)° and −15.5(5)° in the δ-lactone rings of desoxyartemisinin[7] and desethanoqinghaosu,[8] respectively.

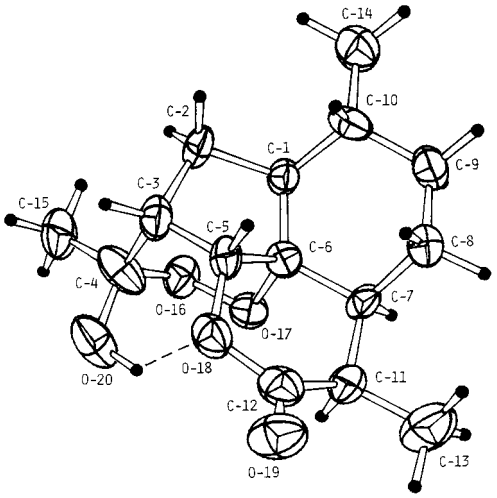
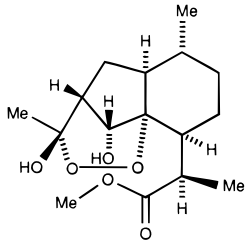


Figure 2. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom-numbering scheme and solid-state conformation of **6**; small filled circles represent hydrogen atoms. The broken line indicates an intramolecular O−H...O hydrogen bond (O...O = 2.809 (3) Å].



Experimental Section

General Experimental Procedures. Melting points were determined on an Electrothermal 9100 instrument. Optical rotations were recorded in CH_2Cl_2 at ambient temperature using a Perkin−Elmer 241 MC polarimeter. IR spectra were determined in KBr disks on a Perkin−Elmer 5808 spectrophotometer. NMR spectra were obtained in $CDCl_3$ on a Bruker Avance instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C), using TMS as internal standard. Spectral editing (APT and DEPT) and 2D NMR spectra (COSY and HETCOR) were obtained using standard Bruker software. MS were recorded on a Finnigan MAT 300 mass spectrometer, using methane as ionizing gas or a JEOL-JMS-D-300 spectrometer in the EI mode. TLC was performed on precoated Si gel G plates using EtOAc−*n*-hexane (2:3) or CH_3CN−CH_2Cl_2 (3:7) as solvent systems A or B, respectively. Visualization was accomplished by spraying with *p*-anisaldehyde spray reagent followed by heating using a hot-air gun. Artemisinin (**1**) was isolated from locally grown *Artemisia annua* L., using a literature procedure.[7]

Compounds 2, 7, and 8. To a saturated solution of methanolic ammonia (6 mL), at room temperature, artemisinin (**1**, 564 mg) was added as previously reported.[1] The crude reaction mixture was subjected to column chromatography on Si gel (40 g), using CH_2Cl_2−CH_3CN (9:1) as eluent to yield **2** (97 mg) as colorless crystals: mp 166−167 °C; R_f 0.41 (solvent system B); $[\alpha]^{22}_D$ −94.8° (*c* 0.112, CH_2Cl_2); IR (KBr) ν_{max} 3270 and 3220 (NH) and four carbonyl groups at 1735, 1710, 1700, 1675 cm^{-1}; ^{1}H NMR δ 1.08 (3H, d, *J* = 6.0 Hz, H-14), 1.17 (3H, d, *J* = 7.0 Hz, H-13), 1.34 (1H, dd, *J* = 12.8, 3.3 Hz, H-9a), 1.47−1.56 (2H, m, H-8a, H-10), 1.74−1.84 (2H, m, H-2a, H-8b), 1.90 (1H, dd, *J* = 12.3, 3.0 Hz, H-2b), 2.12 (3H, s, H-15), 2.09−2.17 (2H, m, H-7, H-9b), 2.39 (1H, m, H-3a), 2.49−2.56 (2H, m, H-1, H-3b), 3.00 (1H, dq, *J* = 7.0, H-11), 9.08 (1H, d, *J* = 10.0 Hz, H-5), 9.17 (1H, br d, exchangeable, NH); ^{13}C NMR, see Table 1; EIMS *m/z* 281 (2.2) with the base peak at 43. By

increasing the polarity to $CH_3CN-CH_2Cl_2$ (3:7), compounds **7**[1] and **8**[1] were eluted from the column. When **7** was subjected to treatment with NH_3 followed by further workup as described earlier, there was no formation of **2**.

Compounds 3, 11, and 12. Artemisinin (**1**, 520 mg) was stirred with a saturated solution of methanolic methylamine (20 mL) for 22 h. The mixture was further treated as above for **2** to yield a residue (590 mg) that was chromatographed on a Si gel (50 g) column using *n*-hexane−EtOAc (7:3) as eluent. Compounds **12**[1] then **11**[1] were eluted first followed by **3** (57 mg), which was obtained as colorless crystals: R_f 0.32 (solvent system A), mp 94.5−95.5 °C; $[\alpha]^{22}_D$ −67° (*c* 0.1, CH_2Cl_2); IR (KBr) ν_{max} no NH bands and two double intensity carbonyl bands at 1705 and 1655 cm^{-1}; ^1H NMR δ 1.06 (3H, d, J = 6 Hz, H-14), 1.20 (3H, d, J = 7.0 Hz, H-13), 1.45−1.61 (3H, m, H-2a, H-8a, H-10), 1.72−1.8 (3H, m, H-2b, H-8b, H-9a), 2.06 (2H, m, H-7, H-9b), 2.10 (3H, s, H-15), 2.27−2.38 (1H, m, H-3a), 2.46−2.56 (1H, m, H-3b), 2.63−2.71 (1H, m, H-1), 3.11 (3H, s, >NMe), 3.32 (1H, dq, J = 7.1 Hz, H-11), 9.34 (1H, s, H-5); ^{13}C NMR, see Table 1; EIMS *m*/*z* 295(12.2) with the base peak at 43.

Methylation of 2 to 3. Compound **2** (112 mg) was dissolved in Me_2CO (4 mL) following which MeI (1.5 mL) and anhydrous K_2CO_3 (67 mg) were added, and the mixture was stirred at room temperature for 26 h. The reaction mixture was filtered and the filtrate evaporated to yield 115 mg of crude product that was crystallized from ether−*n*-hexane to yield a compound identical in all aspects with **3**, obtained above (same mp, mixed mp, identical IR and NMR spectra).

Compounds 4, 13, and 14. Artemisinin (**1**, 710 mg) was treated with allylamine (2.9 mL), and the mixture was stirred at room temperature for 70 min. The reaction mixture was then evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (35 mL), following which Amberlyst 15 (1.0 g) was added and the suspension stirred for 6 h. More Amberlyst 15 (0.35 g) was added and stirring continued overnight. The mixture was filtered, and the filtrate was evaporated to yield 650 mg of a yellowish residue that was purified by column chromatography on Si gel using *n*-hexane−EtOAc (7:3) as eluent. Compounds **14**[1] and **13**[1] were eluted first, followed by **4** (217 mg), as colorless crystals: mp 119.5−121 °C; R_f 0.40 (solvent system A); $[\alpha]^{22}_D$ −53° (*c* 0.104, CH_2Cl_2); IR (KBr) ν_{max} four carbonyl bands at 1735, 1710, 1700, and 1690 cm^{-1}); ^1H NMR δ 1.06 (3H, d, J = 6.0 Hz, H-14), 1.20 (3H, d, J = 6.8 Hz, H-13), 1.50 (3H, m, H-8a, H-9a, H-10), 1.81 (3H, m, H-2a, H-2b, H-8b), 2.07 (2H, m, H-1, H-9b), 2.10 (3H, s, H-15), 2.35 (1H, m, H-3a), 2.53 (1H, m, H-3b), 2.68 (1H, m, H-7), 3.30 (1H, dq, J = 6.9 Hz, H-11), 4.31 (2H, m, H-1′), 5.12 (1H, br s, H-3′), 5.17 (1H, d, J = 5.0 Hz, H-3′), 5.75 (1H, m, H-2′), 9.37 (1H, s, H-5); ^{13}C NMR, see Table 1; EIMS *m*/*z* 321(2.4) with the base peak at 178.

Compound 5. The reaction was performed as for the preparation of **3**, but stirring was limited to 4 h only. Compound **12**[1] was eluted first, without the formation of either **3** or **11**.[1] Further elution yielded **5** (146 mg) as colorless crystals: mp 156.3−156.9 °C; R_f 0.15 (solvent system A); $[\alpha]^{22}_D$ −31° (*c* 0.12, CH_2Cl_2); IR (KBr) ν_{max} two carbonyl bands at 1715 and 1680 cm^{-1}; ^1H NMR δ 0.97 (3H, d, J = 6.2 Hz, H-14), 1.10 (3H, d, J = 6.8 Hz, H-13), 1.26 (1H, br dd, J = 12.0, 5.5 Hz, H-9a), 1.45−1.50 (2H, m, H-1, H-7), 1.63 (1H, m, H-9b), 1.69 (1H, m, H-10), 1.77 (2H, m, H-8), 1.90 (1H, m, H-2a), 2.15 (1H, m, H-2b), 2.23 (1H, d, J = 16.8 Hz, H-5a), 2.33 (2H, m, H-3), 2.45 (1H, m, H-11), 2.79 (1H, d, J = 16.8 Hz, H-5b), 2.84 (3H, s, >N-Me); ^{13}C NMR, see Table 1; EIMS *m*/*z* 249(73) with the base peak at 164.

Compound 6. Artemisinin (**1**, 500 mg) was dissolved in MeOH (25 mL) then dimethylamine (5 mL) was added, and the mixture was stirred for 6 h at room temperature. The reaction mixture was further treated as for **2** to give a residue that was chromatographed on a column of Si gel (47 g), eluted with 2% Me_2CO in CH_2Cl_2 to yield **6** (86 mg) as colorless needles: mp 165−167 °C; R_f 0.63 (*n*-hexane−EtOAc, 1:1); $[\alpha]^{22}_D$ −114° (*c* 0.1, CH_2Cl_2); IR (KBr) ν_{max} 3580 (OH) and 1770 (CO) cm^{-1}; ^1H NMR δ 0.95 (3H, d, J = 5.1 Hz, H-14), 1.03 (2H, m, H-9a, H-10), 1.06 (1H, br s, H-8a), 1.16 (3H, d, J = 7.3 Hz, H-13), 1.30 (3H, s, H-15), 1.32 (1H, dd, J = 5.1, 1.2 Hz, H-2a), 1.69 (1H, m, H-9b), 1.86-1.95 (2H, m, H-1, H-8b), 2.08 (1H, m, H-7), 2.19 (1H, dd, J = 9.0, 5.0 Hz, H-2b), 2.51 (1H, dd, J = 5.6, 5.6 Hz, H-3), 3.06 (1H, dq, J = 7.3 Hz, H-11), 4.53 (1H, d, J = 5.4 Hz, H-5), 5.00 (1H, s, OH); ^{13}C NMR, see Table 1; CIMS *m*/*z* 562 (24, $2M^+ + 1$) with the base peak at 265.

X-Ray Crystal Structure Analysis of Compounds 5 and 6.[9] Crystal data for **5**: $C_{15}H_{21}NO_2$; MW 247.34, orthorhombic, space group $P2_12_12_1(D_2^4)$−no.19 from the Laue symmetry and systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$; a = 8.436(1) Å, b = 20.552(3) Å, c = 8.176(1) Å, V = 1417.5(5) Å^3, Z = 4, D_c = 1.159 g cm^{-3}, μ (Cu Kα radiation, λ = 1.5418 Å) = 5.7 cm^{-1}; crystal dimensions: 0.16 × 0.20 × 0.20 mm.

Crystal data for 6: $C_{15}H_{22}O_5$; MW 282.34, monoclinic, space group $C2(C_2^3)$−no.5 from Laue symmetry and systematic absences: hkl when $h + k \neq 2n$ and the fact that **6** is chiral; a = 28.116(3) Å, b = 6.557(1) Å, c = 7.928(1) Å, β = 94.82(1)°, V = 1456.4(6) Å^3, Z = 4, D_c = 1.288 g cm^{-3}, μ(Cu Kα radiation) = 7.5 cm^{-1}; crystal dimensions: 0.10 × 0.12 × 0.60.

Oscillation and Weissenberg photographs yielded preliminary unit-cell parameters and space group information for each crystal. Intensity data (1703 $+h,+k,+l$ reflections for **5**, 1629 $\pm h,-k,+l$ nonequivalent reflections for **6**) were recorded at 25 °C on an Enraf−Nonius CAD-4 diffractometer [Cu Kα radiation, graphite monochromator; ω-2θ scans, θ_{max} = 75° (scan-widths: 0.80 + 0.14tanθ for **5**, 1.00 + 0.14tanθ for **6**]. The intensities of four reference reflections, monitored every 2 h during data collection, showed no significant variation (<1%) throughout. Refined unit-cell parameters were computed from the diffractometer setting angles for 25 reflections (36°<θ<40°). The usual Lorentz and polarization corrections were applied to the intensity data; 1074 and 1288 reflections with $I > 3.0\sigma(I)$ for **5** and **6**, respectively, were retained for the structure analysis and refinement.

Both crystal structures were solved by direct methods (MULTAN11/82). Initial coordinates for all nonhydrogen atoms were obtained from *E*-maps. The enantiomer in each case was chosen to yield the same stereochemistries at C-1 and C-10 as in **1**. Positional and thermal parameters of these atoms (first isotropic and then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations during which $\sum w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized. Hydrogen atoms were located in difference Fourier syntheses, and their positional and isotropic thermal parameters were also adjusted in the subsequent least-squares cycles. An extinction correction, g, was included as a variable during the later iterations. The parameter refinements converged (max shift: esd = 0.03) at $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.035$, $R_w = [\sum w(|F_o| - |F_c|)^2]^{1/2} = 0.049$, GOF = $[\sum w\Delta^2/(N_{observns} - N_{param})]^{1/2} = 1.29$, $g = 6.1(3) \times 10^{-6}$ for **5**, and $R = 0.036$, $R_w = 0.049$, GOF = 1.26, $g = 3.5\ (7) \times 10^{-6}$ for **6**. Final difference Fourier syntheses contained no unusual features [$\Delta\rho$ (e/Å^3) max:min = 0.12:−0.10 for **5**, 0.18:−0.13 for **6**].

Crystallographic calculations were performed by use of the Enraf−Nonius Structure Determination Package. For all structure−factor calculations, neutral atom scattering factors, and their anomalous dispersion corrections were taken from the literature.[10]

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