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J. Nat. Prod., **1993**, 56 (6), 857-863• DOI:
10.1021/np50096a008 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 6, pp. 857-863, June 1993

PREPARATION OF A CYCLOPROPANE-CONTAINING ANALOGUE OF ARTEMISININ

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ABSTRACT.—The structure of the 1,3-dipolar addition product of diazomethane with artemisinic acid [**2**], a biogenetic and synthetic precursor of artemisinin [**1**], was confirmed by X-ray crystallography as having the 11*S* configuration as predicted by molecular mechanics calculations. The cyclic diazo product **4** was photo- or thermolyzed to give 13-methylartemisinate [**8**] and a cyclopropane-containing analogue **7** of **2**. The analogue was utilized to prepare a cyclopropane-containing analogue **10** of **1**, opening a new route to a variety of artemisinin analogues.

Artemisia annua L. (Compositae), an oriental medicinal herb, yields a variety of sesquiterpenes of which artemisinin [**1**] is known for its antimalarial activity (1).

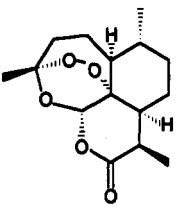
Artemisinic acid [**2**], sharing an analogous carbon skeleton with artemisinin, is a putative biogenetic precursor of **1** (2,3) and is a good starting compound in the semi-synthetic approach for **1** (4–6). Considering the complex structure of **1**, which possesses endoperoxide, lactone, and acetal functionalities, this approach utilizes a surprisingly simple one- or two-step peroxidation.We now report a facile way to prepare alkyl homologues of artemisinic acid, which in turn could serve as precursors for alkyl homologues of **1** via the aforementioned methods. Also reported is the stereochemistry of a 1,3-cycloaddition product of **2** which is an intermediate of the synthesis.

RESULTS AND DISCUSSION

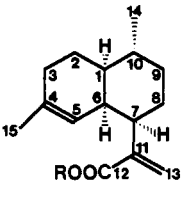
Artemisinic acid [**2**] was treated with excess CH_2N_2 to give adduct **4** in quantitative yield. The presence of the azo moiety in the adduct was deduced from elemental analysis, ms, and a typical λ max at 320–330 nm in the uv spectra. The 1-pyrazoline type ring was further confirmed by the absence of C=C, C=N, and N-N stretches and by the presence of an N=N stretch at 1560–1570 cm^{-1} in the ir spectra (7). Regiochemistry at the site of addition was established essentially by the nmr spectra. In compound **4**, ^{1}H-nmr signals at δ 4.49 and 4.65 ppm appeared as ddd pattern and thus excluded the structure of the regioisomer **6** with the symmetrical arrangement. This confirmed the expectation that nucleophilic carbon of diazoalkanes would be added to C-13, a sterically less hindered position, to give a more stable azo-product **4** (8).

The regiochemistry of the 1-pyrazoline ring created during the above reaction could be predicted by a molecular mechanics calculation (MMX force field). Calculations indicated that **4** is somewhat more stable than regioisomer **6** (Table 1).

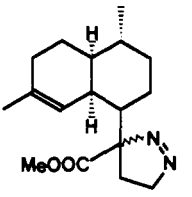
Stereochemistry at the newly created chiral center (C-11) of azo compound **4** was also predicted by molecular mechanics calculations. The *S* configuration **4** was favored over the *R* configuration **5** by an energy difference of about 6 kcal/mol, mostly due to the torsional term (Table 1). The absolute stereochemistry at C-11 was determined unambiguously by a single crystal X-ray analysis: the configuration was *S*. Results of the X-ray study, closely comparable with the molecular mechanics calculations, are presented in Figure 1 and Table 2. Of the six-membered rings, ring B had a normal chair conformation, while C-3, C-4, C-5, and C-6 in ring A were roughly on a plane, and the



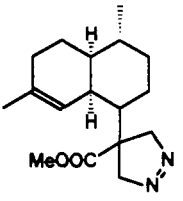
1



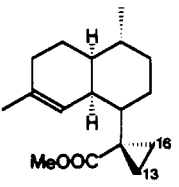
2 R=H
3 R=Me



4 11*S*
5 11*R*



6



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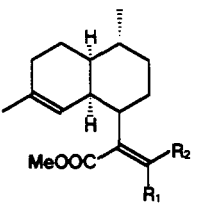
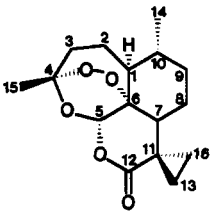


8 R_1=Me, R_2=H
9 R_1=H, R_2=Me



10

six-membered ring angles at C-4 and C-5 were 121.4 and 124.9 degrees, respectively. The five-membered ring C had a twisted conformation. All the ring bond lengths were in the normal ranges.

The thermal or photochemical denitrogenation of azo compounds constitutes an effective and convenient method for the preparation of unusual organic molecules, including highly strained rings and sterically crowded cyclopropane structures (9,10). Therefore, compound **4** was subjected to denitrogenation to introduce the cyclopropane ring into **2**. The reaction products obtained through photolysis and thermolysis of **4** were analyzed by gc-ms, and the major products were identified as a cyclopropane-containing analogue **7** of **3** and 13-methylartemisinates **8** and **9**.

TABLE 1. Comparison of MMX Energies and Heat of Formation of **4**, **5**, **6**, **8**, and **9** as Calculated (values in kcal/mol).

	4	**5**	**6**	**8**	**9**
MME[a]	24.6	30.6	34.6	21.4	26.1
Strain	1.7	1.8	2.1	1.3	1.5
Bond	9.8	9.4	9.1	4.1	5.6
Torsion	3.6	9.5	11.7	8.8	10.3
VDW[a]	8.5	8.9	9.1	8.4	10.4
HF[a]	−63.0	−57.8	−55.5	−117.6	−109.0

[a]MME=molecular mechanics minimum energy, VDW=van der Waals, HF=heat of formation.

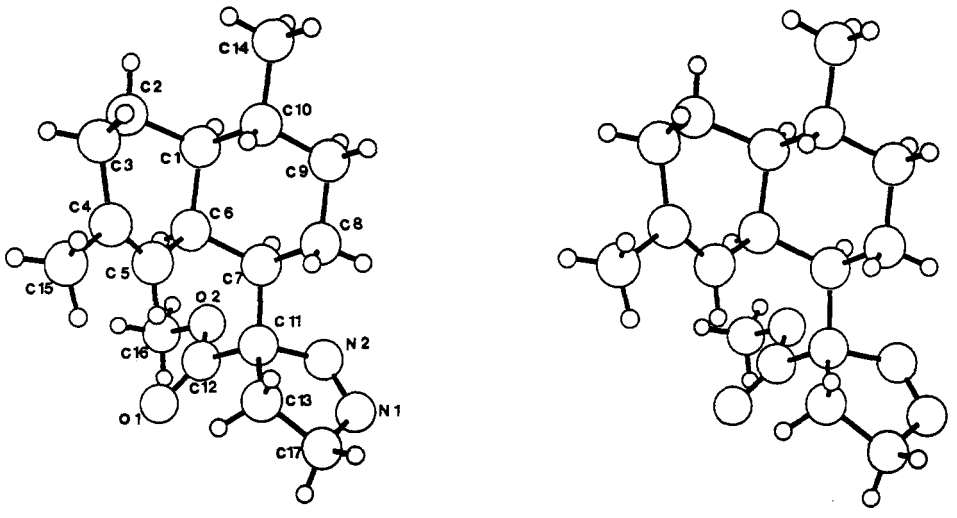


FIGURE 1. Atom numbering scheme and solid-state conformation of compound **4** obtained from X-ray analysis. Small circles represent hydrogen atoms.

In **4**, gc-ms analysis of the benzophenone-sensitized photolysis product gave four major gc peaks. The first peak was methyl artemisinate [**3**]. The peak following methyl artemisinate and the one that eluted last were virtually indistinguishable by ms and were assigned to methyl (*Z*)-13-methylartemisinate [**8**] and methyl (*E*)-13-methylartemisinate [**9**]. The major gc peak, which eluted between the *Z* and *E* compounds, was assigned to analogue **7**. This assignment was largely due to analysis of the ^{1}H-nmr spectra of the reaction mixture and **8** and **7** purified through preparative hplc. (*Z*)- and (*E*)-Methylartemisinate have additional methyl signals at δ 1.91 and 1.89 ppm, respectively. Presence of the olefinic hydrogen at C-13 was also apparent by a larger peak at δ 5.77 for methyl (*Z*)-13-methylartemisinate [**8**] and a smaller peak at δ 6.82 ppm for methyl (*E*)-13-methylartemisinate [**9**]. The ms of **7** showed the base peak at *m/z* 162 and a small peak at 121; the abundance of the fragments was vice versa in **8** and **9** as in the case of **2** and **3**. The peak at *m/z* 162 in **7** arose from cleavage of C-7–C-11 and loss of a hydrogen atom. The presence of a cyclopropane moiety in **7** was apparent from the upfield cyclopropyl proton signals at δ 0.71 and 0.82 ppm.

Subsequent experiments were performed without benzophenone in hopes of changing the composition of the photolysis products. Little change in product composition was observed except for formation of a small amount of the starting compound **3** generated from a retro-cycloaddition reaction of CH_2N_2 (11). However, thermal decomposition of **4** gave two major products, **8** and **7**, in 45:55 ratio.

On the basis of the above, it was concluded that thermal and photolytic decompositions of the azo compound **4** in solution proceed via a short-lived excited biradical which undergoes ring closure, faster than the relaxation to a delocalized configuration, to form a double bond as suggested by Mackenzie (11). Therefore, the product with a cyclopropane ring was the major one. Formation of the *Z* compound **8** over the *E* compound **9** was again predicted by a molecular mechanics calculation as shown in Table 1.

The next goal was the preparation of an artemisinin analogue using the resulting cyclopropane-containing analogue of artemisinic acid. Hplc-purified **7** was treated according to a known photochemical oxygenation procedure (6). The structure of the resulting product **10** was confirmed by a spectral analysis, and hreims of the purified

TABLE 2. Fractional Coordinates and Isotropic Equivalent Displacement Parameters for the Non-hydrogen Atoms of Compound **4** (ESDs in parentheses).

Atom	x	y	z	B (Å^2)
C-1	0.7832 (3)	0.8759 (3)	−0.0057 (2)	4.06 (6)
C-2	0.7897 (4)	0.9764 (3)	−0.0672 (2)	5.39 (8)
C-3	0.9382 (5)	1.0389 (3)	−0.0748 (2)	6.21 (9)
C-4	1.0033 (4)	1.0777 (3)	−0.0029 (2)	5.19 (7)
C-5	0.9473 (4)	1.0362 (3)	0.0589 (2)	4.62 (7)
C-6	0.8143 (3)	0.9501 (3)	0.0657 (1)	3.85 (6)
C-7	0.8113 (3)	0.8511 (3)	0.1303 (1)	3.66 (6)
C-8	0.9143 (3)	0.7344 (3)	0.1179 (2)	4.25 (6)
C-9	0.8768 (3)	0.6625 (3)	0.0476 (2)	4.37 (6)
C-10	0.8842 (3)	0.7551 (3)	−0.0172 (1)	3.94 (6)
C-11	0.8297 (3)	0.9135 (3)	0.2067 (1)	3.92 (6)
C-12	0.7270 (4)	1.0318 (3)	0.2178 (1)	4.77 (7)
C-13	0.9834 (4)	0.9449 (3)	0.2326 (2)	5.06 (7)
C-14	0.8508 (4)	0.6774 (4)	−0.0865 (2)	5.86 (8)
C-15	1.1335 (5)	1.1676 (4)	−0.0060 (2)	7.70 (1)
C-16	0.4827 (5)	1.1002 (4)	0.2181 (2)	8.20 (1)
C-17	0.9914 (4)	0.8747 (3)	0.3046 (2)	5.40 (8)
N-1	0.8632 (3)	0.7882 (3)	0.3100 (1)	5.01 (6)
N-2	0.7768 (3)	0.8062 (3)	0.2597 (1)	4.78 (6)
O-1	0.7642 (3)	1.1411 (2)	0.2359 (2)	7.86 (7)
O-2	0.5914 (3)	0.9963 (2)	0.2073 (1)	6.51 (6)

product indicated $[M+H]^+$ ion with *m/z* 295.1547. The mol wt of the compound clearly demonstrated the presence of one more carbon unit than artemisinin. In the ir spectrum, absorptions at 840, 881, and 1115 cm^{-1}, which had been assigned to the peroxy group of artemisinin, were also present (12). The ^{1}H-nmr spectrum of **10** revealed that the multiplet at δ 3.40, assigned to H-1.11 of **1**, was missing (13). The presence of a cyclopropane moiety was apparent from upfield proton signals at 0.82 ppm for the C-13 protons and 1.21 ppm for C-16 protons on a cyclopropane ring. The close relationship of **10** to **1** was most clearly demonstrated by comparison of the ^{13}C-nmr spectra of the two compounds. Being part of the newly formed cyclopropane ring, the C-11 of **10** was shifted upfield by 4.5 ppm as compared with that of **1**, and the other two cyclopropane carbons appeared at 21.0 and 12.3 ppm. Considering that the H-13α signal of the epi series is more deshielded than the H-13β signal of **1** and arteether by 7–8 ppm (14,15), we assigned the signals at 12.3 and 21.0 ppm to C-13 and C-16, respectively. The same reasoning was applied to assignment of hydrogens on C-13 and C-16 as above.

The above results demonstrated that the presence of the cyclopropane ring did not prevent **7** from photochemical peroxygenation and opened a way to prepare modified artemisinins via the cycloaddition product **4**. Manipulation of **4** could yield a variety of compounds, including amines, in addition to alkyl derivatives of **2** as demonstrated above. Additional compounds could be obtained using diazoalkanes other than CH_2N_2 (16).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points were determined on an Electrothermal® melting point apparatus and were uncorrected. Specific rotations were measured on Perkin-Elmer Polarimeter 243. Ir spectra were obtained on Perkin-Elmer 1710 FT-IR or Bruker IFS-80 instrument and are reported in cm^{-1}. Nmr spectra were determined on a Bruker AM 300 (300 MHz), AC 80 (80 MHz), or Varian VXR-200 (200 MHz) spectrometer, and chemical shift values are given in δ (ppm) with TMS as an internal standard. Eims was obtained on VG 70VS 2Q or HP 5988 GC/MS mass spectrometers using the

solid probe. Elemental analyses were performed using a Yanaco MT-2 CHN corder or a Carlo Erba 1108 system. Gc-ms was obtained on a Hewlett-Packard 5980 GC-5988 MS spectrometer operating in the ei mode at 70 eV. Gc analyses were performed using HP-1 or HP-FFAP columns (25 m×0.33 μm×0.2 mm), and a temperature program was used with He as the carrier gas (split ratio of 10:1). Uv spectra were recorded on a Cecil series 5000 double beam or an HP 8452A diode array spectrophotometer. Tlc was performed on pre-coated Si gel G UV254 plates (0.25 mm, Merck) using CH_2Cl_2-EtOAc (92.5:7.5) and cyclohexane-Et_2O (1:1) as solvents and visualized under short wavelength uv light, by I_2 vapor, or by spraying with anisaldehyde spray reagent (17). The adsorbent used for vlc was Merck Kieselgel 60 G (Art. 7731). X-ray crystal structure analysis was done on an Enraf-Nonius CAD4 diffractometer (Mo Kα radiation) and solved by direct methods (MULTAN 11/82). Photolysis products of the methyl-azo compound were separated with a Recycling Prep-HPLC (Model LC-908, JAI Co., Japan) using MeOH as an eluent on a JAIGEL 1H column (Φ 20×600 mm), equipped with a UV-Detector 3702 (JAI, Japan) at 220 nm. Artemisinic acid [**2**] used in this study was isolated from the leaves of *A. annua* using a literature procedure (18). The preparation possessed physical and spectral data consistent with those reported in the literature as follows: mp 123–126° [lit. (18) 123–126° and 131°], ^{1}H nmr ($CDCl_3$, 80 MHz) δ 6.45 (1H, br s, H-13), 5.55 (1H, br s, H-13), 4.98 (1H, br s, H-5), 1.59 (3H, s, Me-15), 0.91 (3H, d, J=6.0 Hz, Me-14). PCMODEL Molecular Modeling Software for the IBM computer (version 3), obtained from Serena Software, Bloomington, IN, was used for molecular mechanics calculations. To obtain the energy-minimized structure, the subroutines MMX, MLTOR, and RANDOMIZ were employed in series.

PLANT MATERIAL.—The leaves of *A. annua* used in this study were collected from the garden of the College of Agriculture and Life Sciences, Seoul National University in October 1990, and a voucher specimen of the plant is preserved at the herbarium of the Department of Forest Resources, Seoul National University.

CONVERSION OF **2** TO ADDUCT **4**.—Artemisinic acid [**2**] or methylartemisinate [**3**] was dissolved in 5 ml of MeOH. The ethereal solution of CH_2N_2 was added to the solution in portions under a blanket of dry N_2. After standing for 2 days at room temperature, excess CH_2N_2 was removed under reduced pressure. The crude products were purified by vlc (19), using mixtures of *n*-hexane/Me_2CO with an increasing step-wise Me_2CO gradient, to give >95% yield and crystallized from *n*- hexane/Me_2CO when possible.

Pyrazoline **4**.—Mp 90.0–91.5°; $[\alpha]^{25}D$ −116.4° (c=0.01, EtOH). Found $C_{17}H_{26}O_2N_2$, C 70.31, H 9.02, N 9.65 (calcd C 69.84, H 8.94, N 9.56); ms *m/z* (rel. int.) $[M]^+$ 290 (14.6), 231 (82.0), 162 (base peak, 100), 149 (26.9), 135 (10.9), 127 (27,4), 107 (50.1), 95 (75.0); ir (neat) cm^{-1} 2950 (s), 1740 (s, C=O, ester), 1560 (w, N=N), 1450 (s), 1260 (s, C-O), 1220 (s); uv (MeOH) nm λ max 321.7 (ε=140); ^{1}H nmr ($CDCl_3$, 300 MHz) δ 5.15 (1H, br s, H-5), 4.65 (1H, ddd, J=4.5, 9.9, 18 Hz, H-17), 4.49 (1H, ddd, J=7.4, 9.4, 18 Hz, H-17), 3.79 (3H, s, Me-16), 3.00 (1H, m), 2.46 (1H, br s), 2.33 (1H, ddd, J= 4.5, 9.4, 13 Hz), 1.16 (3H, s, Me-15), 0.88 (3H, d, J=6.0 Hz, Me-14), 0.85 (1H, m); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 170.5 (s, C-12), 136.1 (s, C-4), 120.0 (d, C-5), 103.9 (s, C-11), 79.3 (t, C-17), 52.8 (q, C-16), 45.8 (d), 41.9 (d), 38.6 (d), 34.9 (t, C-13), 27.8 (d, C-10), 26.0 (t), 25.5 (t), 24.0 (q, C-15), 22.6 (t), 21.5 (t), 19.6 (q, C-14).

PHOTOLYSIS OF **4**.—The adducts were dissolved in 5 ml of C_6H_6 and irradiated with a high pressure mercury lamp (300 W, Kwangjin Electric Co., Seoul) at room temperature. After 7 h, tlc showed the disappearance of the adduct and the presence of one spot with R_f 0.82 using CH_2Cl_2/EtOAc as solvent. The solution was evaporated in vacuo at 40°, purified by vlc, and further separated through preparative hplc when necessary.

Methyl artemisinate [**3**].—(Not isolated): Gc/eims *m/z* (rel. int.) 248 $[M]^+$ (17.5), $[M-MeO]^+$ 217 (6.4), $[M-MeOH]^+$ 216 (13.4), 189 (17.3), 188 (19.7), 163 (11.5), 162 (17.6), 136 (25.9), 121 (base peak, 100), 119 (72.9), 107 (29.2), 105 (36.1), 93 (59.9), 91 (50.4), 81 (34.8), 79 (50.9).

Compound **7**.—Mp 186–187°; $[\alpha]^{25}D$ −17.8° (c=0.01, EtOH); gc-eims *m/z* (rel. int.) $[M]^+$ 262 (16.9), 231 (30.7), 230 (27.0), 215 (9.3), 188 (9.1), 187 (11.0), 162 (base peak, 100), 160 (12.1), 147 (31.2), 145 (13.1), 129 (21.9), 121 (28.7), 119 (20.4), 107 (22.2), 105 (28.8), 93 (32.3), 91 (36.8), 81 (26.3), 79 (39.8), 77 (27.5); ^{1}H nmr ($CDCl_3$, 300 MHz) δ 5.41 (1H, br s, H-5), 3.64 (3H, s, OMe), 2.74 (1H, br s), 2.17 (1H, m), 1.61 (3H, s, Me-15), 0.87 (3H, d, J=6.2) Hz, Me-14), 0.82 (1H, m, H-13 or H-16), 0.71 (1H, m, H-16 or H-13); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 175.1 (s, C-12), 134.1 (s, C-4), 121.2 (d, C-5), 51.3 (q, OMe), 41.8 (d), 40.4 (d), 39.9 (d), 35.4 (t), 27.8 (d), 26.2 (t), 25.7 (s, C-11), 25.5 (t), 23.7 (q, C-15), 22.9 (t), 19.6 (q, C-14), 10.7 (t, C-13), 10.5 (t, C-16).

Methyl (Z)-13-methylartemisinate [**8**].—Mp 30.5–31°; $[\alpha]^{25}D$ +54.5° (c=0.01, EtOH); gc-eims *m/z* (rel. int.) $[M]^+$ 262 (15.1), 231 (14.0), 230 (53.0), 215 (7.1), 202 (17.5), 187 (9.6), 162 (53.1), 147 (18.3), 145 (13.1), 136 (21.7), 121 (base peak, 100), 119 (52.3), 107 (24.4), 105 (29.3), 93 (47.3), 91 (34.5), 79 (43.4); ^{1}H nmr ($CDCl_3$, 300 MHz) δ 5.73 (1H, dq, J=1.6, 7.0 Hz, H-13) 5.04 (1H, br s, H-5), 3.74 (3H,

s, OMe), 2.61 (1H, br s, J=13.4 Hz), 2.38 (1H, br s), 1.92 (3H, dd, J=1.6, 7.1 Hz, Me-16), 1.60 (3H, s, Me-15), 1.25 (1H, dq, J=3.1, 12.5 Hz), 1.04 (1H, br dq, J=3.1, 11.5 Hz), 0.88 (3H, d, J=5.9 Hz, Me-14); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 169.5 (s, C-12), 136.5 (s, C-11), 134.6 (s, C-4), 131.4 (d, C-13), 120.4 (d, C-5), 51.1 (q, OMe), 43.8 (d), 41.4 (d), 38.6 (d), 35.3 (t), 27.6 (d), 26.4 (t), 25.7 (t), 25.5 (t), 23.6 (q, C-16), 19.7 (q, C-15), 15.5 (q, C-14).

Methyl (E)-13-methylartemisinate [**9**].—(Not isolated): Gc-eims *m/z* (rel. int.) $[M]^+$ 262 (15.6), 231 (13.2), 230 (48.5), 215 (7.8), 202 (19.1), 187 (8.9), 162 (31.8), 147 (15.5), 145 (11.8), 136 (23.2), 121 (base peak, 100), 119 (45.1), 107 (25.3), 105 (29.2), 93 (52.5), 91 (32.7), 79 (45.7).

THERMOLYSIS OF **4**.—The adduct was dissolved in C_6H_6 (2 ml) and heated at 140° in an oil bath for 4 h. The solution was evaporated under reduced pressure. Separation of products by hplc yielded **7** and **8**.

PREPARATION OF **10**, A CYCLOPROPANE-CONTAINING ANALOGUE OF ARTEMISININ.—Rose bengal (10 μmol) was added to **7** (1 mmol) in MeCN at −30° and was irradiated with a 300 W mercury lamp for 3 h with O_2 passing through the solution. The rest of the procedure was as described by Haynes and Vonwiller (6). The reaction mixture was chromatographed directly on a preparative Si gel plate [cyclohexane-Et_2O (1:1)] to give **10**. It was further purified by crystallization in *n*-hexane/CH_2Cl_2.

Compound **10**.—Mp 186–187°; $[\alpha]^{25}D$ +41.9° (c=0.01, EtOH); ir cm^{-1} 1730 (s, C=O), 1115, 881, 840 (m, w, w, peroxide); hreims 295.1547 (calcd 295.1546 for $[M+H]^+$ of $C_{16}H_{22}O_5$); ^{1}H nmr ($CDCl_3$, 200 MHz) δ 6.00 (1H, s, H-5), 2.40 (1H, m), 2.00 (2H, m), 1.74 (2H, m), 1.49 (2H, dd, J=1.8, 5.0 Hz), 1.45 (3H, s, Me-15), 1.11 (2H, m, H-16), 0.97 (3H, d, J=5.9 Hz, Me-14), 0.82 (2H, m, H-13); ^{13}C nmr ($CDCl_3$, 67.5 MHz) δ 172.4 (C-12), 105.4 (C-4), 93.7 (C-5), 80.2 (C-6), 50.3 (C-1), 47.1 (C-7), 37.7 (C-10), 35.9 (C-3), 33.8 (C-9), 28.2 (C-11), 25.3, (C-15), 24.9 (C-2), 23.8 (C-8), 21.0 (C-16), 19.8 (C-14), 12.3 (C-13).

X-RAY CRYSTAL STRUCTURE ANALYSIS OF COMPOUND **4**.[1]— Crystal data: $C_{17}H_{26}O_2N_2$, F.W.=290.41, orthorhombic, space group $P2_12_12_1$, a=9.254 (2) Å, b=9.963 (1) Å, c=18.413 (2) Å, V=1697.48 (71) Å^3, Z=4, D_C=1.136 g·cm^{-3}. Crystal dimensions: 0.50×0.50×0.40 mm. Three-dimensional intensity data were measured on an Enraf-Nonius CAD-4 diffractometer using Mo-Kα radiation (λ=0.71073 Å, μ=0.7 cm^{-1}). From a total of 1735 measurements, those 1570 reflections with Fo>1.0 (Fo) were retained for the analysis, and the usual Lorentz and polarization corrections were applied.

The crystal structure was solved by direct methods. Hydrogen atoms were included as a fixed contribution to the structure factor. Least-squares refinement of atomic parameters converged to R=0.043 over 1570 reflections. Crystallographic calculations were performed on VAX computers by the use of the Enraf-Nonius Structure Determination Package. In the least-squares iterations, Σ W(|Fo|−|Fc|)^2 was minimized.

ACKNOWLEDGMENTS

Financial support from The Korea Science and Engineering Foundation through The Research Center for New Bio-Materials in Agriculture is greatly appreciated.

LITERATURE CITED

1. D.L. Klayman, *Science*, **228**, 1049 (1985).
2. F.S. El-Feraly, I.A. Al-Meshal, M.L. Al-Yahya, and M.S. Hifnawy, *Phytochemistry*, **25**, 2777 (1986).
3. J.J. Huang, Y. Wang, Z.Q. Xia, F.Y. Zhou, Y.L. Wu, and Z.Z. Wang, *Acta Chim. Sin.*, **4**, 386 (1988).
4. R.J. Roth and N. Acton, *J. Nat. Prod.*, **52**, 1183 (1989).
5. Y.L. Wu and B. Ye, *J. Chem. Soc., Chem. Commun.*, 726 (1990).
6. R.K. Haynes and S.C. Vonwiller, *J. Chem. Soc., Chem. Commun.*, 449 (1990).
7. R.S. Bly, F.B. Culp, and R.K. Bly, *J. Org. Chem.*, **35**, 2235 (1970).
8. F.M. Dean and P.G. Jones, *J. Chem. Soc.*, 5342 (1963).
9. K.P. Zeller and H. Meier, *Angew. Chem., Int. Ed. Engl.*, **16**, 835 (1977).
10. O.D. Lucchi and W. Adam, *Angew. Chem., Int. Ed. Engl.*, **19**, 762 (1980).
11. K. Mackenzie, in: "The Chemistry of the hydrazo, azo, and azoxy groups." Ed. by S. Patai, John Wiley & Sons, 1975, Vol. 1, p. 356.
12. N. Acton and D.L. Klayman, *Planta Med.*, **47**, 441 (1985).
13. G. Blasko, G.A. Cordell, and D.C. Lankin, *J. Nat. Prod.*, **51**, 1273 (1988).

[1]Atomic coordinates for this compound have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

14. N. Acton and D.L. Klayman, *Planta Med.*, 266 (1987).
15. F.S. El-Feraly, M.A. Al-Yahya, K.Y. Orabi, D.R. McPhail, and A.T. McPhail, *J. Nat. Prod.*, **55**, 878 (1992).
16. J.-H. Choi, Master's Thesis, "Synthesis of Artemisinin Analogue from Artemisinic Acid Derivative." Seoul National University, Seoul, Korea (1992).
17. F.S. El-Feraly and C.D. Hufford, *J. Org. Chem.*, **47**, 1527 (1982).
18. S.-U. Kim and H.-J. Lim, *J. Korean Agric. Chem. Soc.*, **32**, 178 (1989).
19. J.C. Coll and B.F. Bowden, *J. Nat. Prod.*, **49**, 934 (1986).

Received 12 October 1992