Semisynthesis of 3-β-Hydroxyartemisinin

Nancy Acton*

Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100

Received December 7, 1998

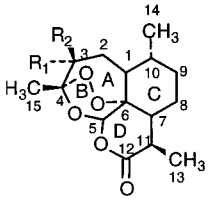
3-β-Hydroxyartemisinin (**5**) was synthesized from 3-β-hydroxydihydroartemisinic acid (**7c**) via singlet oxygen oxidation followed by air (triplet oxygen) oxidation. Compound **7c** was synthesized in two steps from dihydroartemisinic acid, **7a**.

Because of its efficacy in the treatment of strains of malaria which have developed resistance to drugs now in use, the sesquiterpene endoperoxide artemisinin (qinghaosu), **1**, isolated from *Artemisia annua*, has received considerable attention in the chemical and medical literature. Reduction of **1** affords dihydroartemisinin, **2a**, and this can be converted into arteether, **2b**, and artemether, **2c**. Artemether is in clinical use in many parts of the world, and arteether is undergoing extensive preclinical and clinical studies.[1−4] Artelinic acid, **2d**, is of particular interest to the U.S. Army because of its stability, good activity, and enhanced water solubility.[5]

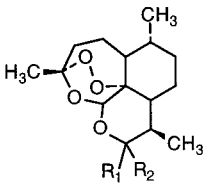
Drug development requires identifying the drug's metabolites. Since metabolites are frequently hydroxylated analogues of the drug, the Walter Reed Army Institute of Research has a continuing interest in obtaining authentic samples of hydroxylated artemisinin and of hydroxylated artemisinin derivatives. Microbial transformations are often found to mimic mammalian metabolism, and, indeed, the research groups of Hufford and of Ziffer have demonstrated that microbial oxidation of **1**, **2a**, **2b**, and **2c** can provide a rich source of relatively large amounts of potential drug metabolites. The compounds isolated from these fermentations include 1-,[6] 2-,[7] 9-,[7−9] and 14-hydroxylated[7−10] derivatives in which the core structure of the artemisinin is unchanged. Microbial metabolites in which the artemisinin core is altered include deoxy (**3a**),[11] 3-α-hydroxydeoxy (**3b**),[7,9,11] and rearranged acetate (**4**)[8,9,12] derivatives. Deoxy compound **3a** can be obtained by catalytic hydrogenation using palladium on calcium carbonate,[13] and **3b** and **4** are obtained by treatment with iron-containing compounds.[14] I report here a semisynthesis of a thus far unreported hydroxy artemisinin, the 3β-analogue, **5**, which starts from artemisinic acid, **6a**, a sesquiterpene constituent of *A. annua*.

Several years ago, Acton and Roth reported a simple conversion of **6a** into **1** which involves the known reduction of artemisinic acid to dihydroartemisinic acid, **7a**, followed by reaction with singlet oxygen to give the ene reaction hydroperoxide, **8a**, and then air oxidation of the hydroperoxide to afford artemisinin.[15] A similar conversion was reported shortly after by Haynes et al.[16] Since those reports, the method has been used to prepare artemisinin derivatives in which alterations have been made in the lactone (D) ring,[17] but no changes have been introduced in the rest of the molecule via this route.

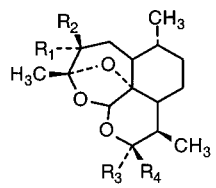
One can readily envisage synthesis of 3-hydroxyartemisinin by allylic oxidation of artemisinic or dihydroartemisinic acid followed by singlet, then triplet oxygen oxidation of the hydroxydihydroartemisinic acid as described above for the parent compound. Indeed, treatment



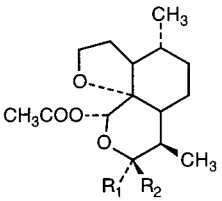
1: R_1=R_2=H
5: R_1=H, R_2=β-OH



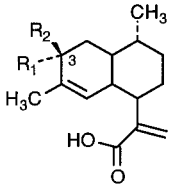
2a: R_1=H, R_2=OH
2b: R_1=H, R_2=β-OEt
2c: R_1=H, R_2=β-OMe
2d: R_1=H,
R_2=β-$OCH_2C_6H_4$-p-COOH



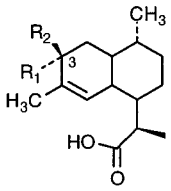
3a: R_1=R_2=H: R_3,R_4= =O;
R_3=H, R_4=OMe, OEt
3b: R_1=OH, R_2=H: R_3,R_4= =O;
R_3=H, R_4=OMe, OEt



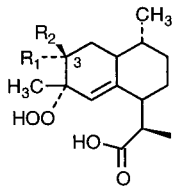
4: R_1,R_2= =O,
R_1=H, R_2=OMe, OEt



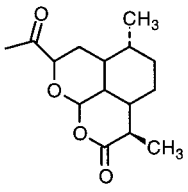
6a: R_1=R_2=H
6b: R_1=OH, R_2=H
6c: R_1=H, R_2=OH



7a: R_1=R_2=H
7b: R_1=OH, R_2=H
7c: R_1=H, R_2=OH
7d: R_1, R_2= =O



8a: R_1=R_2=H
8b: R_1=OH, R_2=H
8c: R_1=H, R_2=OH



9

* Tel.: (301) 295-7796. Fax: (301) 295-7755. E-mail: dr._nancy_roth@wrsmtp-ccmail.mil.army.

10.1021/np980555w
Published on Web 04/09/1999

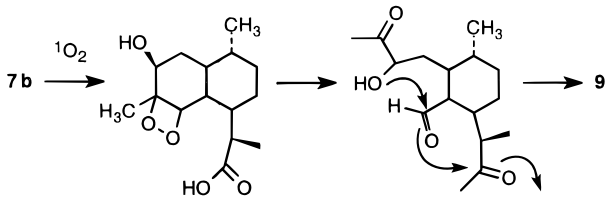
of **6a** with selenium dioxide in methylene chloride afforded a 36% yield of 3-α-hydroxyartemisinic acid, **6b**. This compound, as well as the β-isomer, **6c**, was previously obtained by Hufford et al., by microbial transformation.[18] Hydroxy derivative **6b** was converted into 3-α-hydroxydihydroartemisinic acid, **7b**, by reaction with sodium borohydride and nickel chloride in methanol according to literature procedures for the comparable reduction of **6a** to **7a**.[19] Photooxidation of **7b** in acetone-d_6 appeared to produce the expected hydroperoxide, **8b**, but attempted air oxidation of this hydroperoxide failed to produce material that could be identified as an artemisinin derivative.

The 3-β analogue, **7c**, was obtained as follows. Dihydroartemisinic acid, **7a**, was treated with *N*-bromosuccinimide and acetic acid in methylene chloride. The crude bromide so obtained (a ca. 2:1 epimer mixture according to the ^{13}C NMR spectrum) was treated with silver oxide in aqueous THF. After workup and silica gel chromatography, a 22% yield of **7c** was isolated.[20] To demonstrate that **7b** and **7c** differ only with respect to the stereochemistry at position 3, each was oxidized using 4-methylmorpholine *N*-oxide and tetrapropylammonium perruthenate. Ketone **7d** was obtained from each isomer.

When **7c** was photooxidized in a mixture of MeOH-d_4 and acetone-d_6 in NMR tubes, the expected hydroperoxide, **8c**, was identified by ^{1}H and ^{13}C NMR. Solvent was removed and replaced with hexane containing a trace of TFA. After several days at room temperature, liquid chromatography of the reaction mixture using reductive electrochemical detection[21] displayed a single peak indicating a peroxide-containing product. Silica gel chromatography afforded a product identified as **9**, in trace amounts, and 3-β-hydroxyartemisinin, **5**, an oil, in ca. 16% yield. The electrospray MS of **5** in the presence of ammonium acetate displayed a peak at *m*/*z* 316 (M + NH_4), confirming a molecular weight of 298 for the compound. HRMS (FAB with added CsI) showed a base MCs^+ peak with observed *m*/*z* of 431.0475 (calculated value 431.0471). NMR spectra of **5** are in accord with the artemisinin structure. The ^{1}H NMR spectrum of **5** is similar to that of **1**[22] except for the expected downfield shift of H-3α which appears as a doublet of doublets at 4.05 ppm with coupling constants of 5.2 and 1.4 Hz. The coupling constant of 5 Hz is smaller than one might expect for an axial−axial coupling, but it is the same as that observed for **7c** (5.2 Hz, see Experimental Section), essentially the same as that reported for **6c** (4.5 Hz),[18] and larger than that reported for **6b** (2.5 Hz).[18] The ^{13}C NMR of **5** displays a doublet at 78.8 ppm attributable via a HETCORR experiment to C-3. The chemical shifts of those carbons remote from the hydroxy group (i.e. carbons 8−14) are within 1 ppm of the comparable values for **1**. Carbon 2, adjacent to the electronegative OH-bearing carbon, shows a downfield shift of 5.8 ppm relative to the same position in **1**. Of the remaining carbons, two show a slight downfield shift relative to the resonances in **1** (1.6 ppm for carbon 5 and 3.7 ppm for carbon 6). Carbons 1, 4, 7, and 15 in **5** are shifted upfield by 6.3, 1.6, 6.8, and 4.6 ppm, respectively, relative to the same carbons in **1**. The infrared absorption at 1749 cm^{-1} is indicative of a lactone.

The small amount of **9** formed is assumed to arise from rearrangement of a dioxetane as depicted in Scheme 1. The reason for the failure of hydroperoxide **8b** to produce any trace of 3-α-hydroxyartemisinin is not obvious. Apparently competing reactions are more favorable. The reductive electrochemical LC trace of the complex mixture obtained from allowing **8b** in hexane and TFA to stand in air displayed no peaks, thus indicating that there was no peroxide product and no residual hydroperoxide starting material.

Scheme 1



This work demonstrates that the artemisinic acid to artemisinin conversion can be expanded to produce artemisinin derivatives with new functionality in the A ring of the molecule. The route described here is a reasonably simple pathway to 3-β-hydroxyartemisinin.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF 300 spectrometer at 300 and at 75 MHz, respectively, using $CDCl_3$ as solvent unless otherwise stated. The NMR assignments were determined from COSY, DEPT, and HETCORR experiments. EIMS were determined on a Hewlett-Packard GC interfaced with a model 5970 mass selective detector. Electrospray MS (ESMS) were recorded on a Finnegan LCQ instrument. HRMS of **5** was obtained using a JEOL SX102 mass spectrometer. IR spectra were recorded on a Nicolet 20 SXB spectrometer.

Chemical Material. Artemisinic acid used in this work was isolated from *A. annua* L. (Asteraceae).

3-α-Hydroxyartemisinic acid (6b): a mixture of **6a** (500 mg, 2.14 mmol) and selenium dioxide (250 mg, 2.25 mmol) in 10 mL of methylene chloride was stirred for 4 h at room temperature. The reaction mixture was filtered, and the filtrate washed with water (1×) and with brine (1×). After drying (Na_2SO_4) and removal of solvent, the crude product was flash chromatographed on silica gel eluting with 5% methanol in CH_2Cl_2 to afford a 36% yield of **6b** as a foam. It was identified by comparison of its NMR spectra with those in the literature.[18]

3-α-Hydroxydihydroartemisinic acid (7b): nickel(II) chloride hexahydrate (175 mg, 0.73 mmol) was added to a solution of **6b** (300 mg, 1.20 mmol) in 5 mL of methanol. $NaBH_4$ (175 mg, 4.6 mmol) was then added in small portions. After 25 min at ambient temperature, the reaction was worked up by pouring into 10% aqueous HCl and extracting with CH_2Cl_2. The extract was washed with water (1×), brine (1×), and dried (Na_2SO_4). The ^{1}H NMR of this crude material indicated that it contained some starting material and product. It was redissolved in MeOH and treated again with the same amounts of $NiCl_2 \cdot 6H_2O$ and $NaBH_4$. After workup as above, the crude material was flash chromatographed on silica gel eluting with 1:1 hexane/ethyl acetate to yield 127 mg (42%) of product as a gum. The ^{13}C NMR of this material showed that it contained ca. 5% impurity. IR (KBr) ν_{max} 3450, 2921, 1709, 1457, 1031 cm^{-1}; ^{1}H NMR δ 0.92 (4H, d superimposed on m, J = 5.9 Hz), 1.05 (1H, m), 1.18 (3H, d, J = 6.9 Hz), 1.3−1.7 (6H, m's), 1.76 (3H, s), 2.45 (2H, m's), 2.59 (1H, br s), 4.11 (1H, m), 5.26 (1H, s); ^{13}C NMR δ 15.02 (q), 19.57 (2× q), 27.41 (t), 28.75 (d), 35.11 (t), 36.54 (t), 36.80 (d), 42.28 (d), 43.35 (d), 44.35 (d), 68.56 (d), 123.1 (d), 137.5 (s), 182.8 (s); ESMS (negative ion) *m*/*z* 252 (M).

3-β-Hydroxydihydroartemisinic acid (7c): NBS (151 mg, 0.85 mmol) was added to 2.5 mL of CH_2Cl_2. After cooling to −78 °C, 600 μL of acetic acid was added, followed by dropwise addition of 200 mg (0.85 mmol) of dihydroartemisinic acid in 1.5 mL of CH_2Cl_2. After an additional 20 min at −78 °C, the dry ice bath was removed, and the mixture was stirred at ambient temperature for 1 h. It was again cooled to −78 °C,

and a solution of 590 mg of diethylphenylamine in 1 mL of CH_2Cl_2 was added. The cooling bath was removed, and the mixture stirred for 1 h at ambient temperature. It was then poured into 5% aqueous H_2SO_4. The organic layer was washed with water (2×) and dried (Na_2SO_4), and solvent was removed, leaving 280 mg of residue. The ^{13}C NMR of this presumed allylic bromide indicated that it was a ca. 2:1 mixture of epimers. Bromide: IR (neat) ν_{max} 2922, 1706 cm^{-1}; major ^1H NMR peaks δ 0.91 (d, J = 5.4 Hz), 1.20 (d, J = 7.1 Hz), 1.86 (br s) 4.7 (br m), 5.4 (s); major ^{13}C NMR peaks δ 15.0, 19.5, 23.0, 27.5, 27.9, 34.8, 36.6, 39.4, 42.1, 43.0, 45.2, 53.1, 125.8, 135.3, 183.5. The crude bromide was dissolved in 4 mL of THF, diluted with 1 mL of water, and AgO (200 mg) was added. After stirring at room temperature for 2 h, the mixture was filtered through Celite and the solvent removed. The residue was taken up in CH_2Cl_2 and the solution dried over Na_2SO_4. After removal of solvent, the ^1H NMR of the residue (230 mg) indicated that it was largely 3-β-hydroxydihydroartemisinic acid. It was flash chromatographed on 20 mL of silica gel eluting with 1:1 hexane/ethyl acetate to afford 48 mg of product. 3-β-Hydroxydihydroartemisinic acid (**7c**) was obtained as colorless crystals (acetonitrile): mp (uncorr) 199−201 °C; IR (KBr) ν_{max} 3400, 2919, 1709, 1442, 1256, 1010 cm^{-1}; ^1H NMR (MeOH-d_4) δ 0.90 (1H, m, H-9), 0.93 (3H, d, J = 6.3 Hz, 14-CH_3), 1.12 (4H, d, J = 6.9 Hz, superimposed on m, 13-CH_3, H-8), 1.23 (1H, m, H-8), 1.40 (1H, m, H-8), 1.51−1.80 (3H, m, H-2, H-7, H-9), 1.80 (3H, br s, 15-CH_3), 1.90 (1H, m, H-10), 2.25 (1H, dd, J = 14, 2.2 Hz, H-2), 2.46 (2H, m, H-6, H-11), 3.95 (1H, d, J = 5.2 Hz, H-3a), 5.34 (1H, s, H-5); ^{13}C NMR (MeOH-d_4) δ 15.6 (q, C-14), 20.6 (q, C-13), 21.2 (q, C-15), 28.9 (t, C-8), 30.0 (d, C-10), 35.9 (t, C-2), 37.1 (t, C-9), 38.4 (d, C-6), 42.6 (d, C-1), 43.5 (d, C-11), 45.1 (d, C-7), 68.3 (d, C-3), 124.1 (d, C-5), 137.9 (s, C-4), 181.2 (s, C-12); ESMS (NH_4OAc, negative ion): m/z 311 (M + acetate); *anal.* C 71.15%, H 9.51%, calcd for $C_{15}H_{24}O_3$, C 71.39%, H 9.59%. A considerable amount of product is lost on silica gel chromatography.

3-Ketodihydroartemisinic acid (7d): 3-α-hydroxydihydroartemisinic acid (**7b**) (90 mg, 0.36 mmol) and 4-methylmorpholine *N*-oxide (NMO, 99 mg, 0.85 mmol) were dissolved in 10 mL of CH_2Cl_2. After stirring for 15 min, ca. 10 mg of tetrapropylammonium perruthenate (TPAP) was added, and the mixture stirred at room temperature for 1 h. The reaction mixture was washed with 1N aqueous HCl, then with water (2×). After drying (Na_2SO_4), removal of solvent afforded 60 mg (66%) of product. ^1H NMR showed it to be a single material. Color was removed by flash chromatography on silica gel (1:1 hexane/ethyl acetate) to give 30 mg of product as an oil. IR (neat) ν_{max} 2925, 1708, 1674, 1456 cm^{-1}; ^1H NMR δ 0.87 (3H, d, J = 6.4 Hz, H-14), 0.9−1.2 (2H, m's, H-8,9), 1.25 (3H, d, J = 6.9 Hz, H-13), 1.3−1.7 (3H, m's, H-8, 9, 10), 1.79 (5H, s superimposed on m's, H-1, 2, 15), 2.45−2.65 (2H, m's, H-2, 11), 2.80 (1H, dd, J = 16.5, 2.3 Hz, H-2), 2.95 (1H, br s, H-6), 6.44 (1H, s, H-5); ^{13}C NMR δ 15.2 (q, C-13), 16.0 (q, C-15), 19.4 (q, C-14), 27.8 (t, C-8), 28.6 (d, C-10), 34.9 (t, C-9), 38.1 (d, C-6), 42.3 (d, C-11), 42.8 (t, C-2), 43.2 (d, C-7), 45.7 (d, C-1), 137.2 (s, C-4), 142.7 (d, C-5), 182.1 (s, C-12), 199.7 (s, C-3); EIMS m/z 250 [M^+] (6), 177 [$M^+ - C_3H_5O_2$] (100).

In a similar manner, **7c** (12 mg), NMO (14 mg), and TPAP (1−2 mg) afforded a ca. quantitative yield of **7d** with NMR spectra identical with those obtained from the α isomer, above.

3-β-Hydroxyartemisinin (5): 3-β-hydroxydihydroartemisinic acid (**7c**) (28 mg, 0.11 mmol) was dissolved in 1 mL of MeOH-d_4 and 2 mL of acetone-d_6. The solution was divided between two NMR tubes, and a trace of methylene blue was added to each. The tubes were cooled in ice and purged with O_2 while irradiating with a Westinghouse street lamp. After 30 min, the ^1H NMR spectrum showed formation of the hydroperoxide "ene" product (**8b**). **8b**: ^1H NMR (MeOH-d_4 + acetone-d_6) δ 0.91 (3H, d, J = 5.8 Hz), 1.08 (10H, s and 1.20 d, J = 6.6 Hz superimposed on m's), 1.75 (3H, m), 1.90 (1H, m), 2.10 (1H, m), 2.67 (1H, m), 4.05 (1H, m), 5.36 (1H, s); ^{13}C NMR (MeOH-d_4 + acetone-d_6) δ 16.8, 18.1, 20.0, 31.7, 34.5, 36.1, 42.0, 42.4, 45.9, 47.3, 68.9, 85.3, 124.2, 142.0, 178.4.

The contents of the two NMR tubes were combined, and the solvent removed. The residue was taken up in ether and filtered to remove most of the methylene blue. Solvent was again removed, and the residue was mixed with 25 mL of hexane containing 1−2 drops of trifluoroacetic acid. After standing for a day at room temperature, liquid chromatography (lc) using an electrochemical detector (reduction) displayed a single peak with retention time of 11.5 min (15 cm C18 column, eluting with 30% acetonitrile in water containing 1 N NH_4OAc as electrolyte, 1 mL/min[20]). After 4 days, the lc profile was unchanged. The mixture was concentrated. TLC (silica gel, 2:1 hexane/ethyl acetate) showed two major constituents with R_f 0.4 and 0.6. Flash chromatography on silica gel using the same solvent system afforded 1−2 mg of **9** followed by 5−6 mg (ca 16% from **7c**) of **5** as an oil. **9**: IR (smear) ν_{max} 2925, 2875, 1742, 1722, 1131, 1076 cm^{-1}; ^1H NMR δ 1.00 (3H, d, J = 6.15 Hz), 1.26 (3H, d, J = 7.02 Hz), 0.9−1.9 (9H, m's), 2.00 (1H, br d, J = 14.0 Hz), 2.29 (3H, s), 2.80 (1H, m), 4.16 (1H, dd, J = 12.6, 2.7 Hz), 5.50 (1H, d, J = 9.5 Hz). ^{13}C NMR δ 13.2 (q), 20.1 (q), 23.2 (t). 25.9 (q), 28.6 (d), 29.2 (t), 34.6 (t), 28.1 (d), 40.2 (d), 40.7 (d), 41.5 (d), 78.0 (d), 97.9 (d), 171.9 (s), 207.8 (s); ESMS (NH_4OAc) m/z 283 [M^++NH_3]. **5**: IR (3M polyethylene and poly(tetrafluoroethylene) substrate cards): ν_{max} 3524, 2912, 2855, 1749, 1078 cm^{-1};^1H NMR δ 0.93 (1H, m, H-8), 1.06 (3H, d, J = 6.3 Hz, H-14), 1.12 (1H, m, H-9), 1.19 (3H, d, J = 7.3 Hz, H-13), 1.30 (1H, m, H-10), 1.35 (3H, s, H-15), 1.8−1.95 (3H, m's, H-2, H-8, H-9), 2.09 (2H, m, H-1, H-7), 2.35 (1H, ddd, J = 14.8, 9.5, 1.3 Hz, H-2), 3.10 (1H, apparent pent, J = 7.2 Hz, H-11), 4.05 (1H, dd, J = 5.2, 1.4 Hz, H-3), 4.85 (1H, s, OH), 5.56 (1H, s, H-5); ^{13}C NMR δ 12.6 (q, C-13), 20.0 (q, C-14), 20.6 (q, C-15), 24.5 (t, C-8), 30.7 (t, C-2), 32.8 (t, C-9), 34.0 (d, C-11), 38.3 (d, C-7), 38.5 (d, C-10), 44.0 (d, C-1), 78.8 (d, C-3), 83.3 (s, C-6), 95.4 (d, C-5), 103.7 (s, C-4), 171.2 (s, C-12); ESMS (NH_4OAc): m/z 316 [M^+ + 18]; HRMS (FAB with CsI): m/z 431.0475 [MCs^+], calcd for $C_{15}H_{22}O_6$, 431.0471.

Acknowledgment. I am grateful to Dr. David Skanchy (WRAIR) for acquiring electrospray mass spectral data, to Dr. Lewis Pannell (NIDDK, NIH) for the HRMS of **5**, and to Dr. John P. Scovill (WRAIR) for helpful suggestions.

References and Notes

(1) Jefford, C. *Adv. Drug Res.* **1997**, *29*, 271−325.
(2) Ziffer, H.; Highet, R. J.; Klayman, D. L. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: Vienna, New York, 1997; Vol. 72, pp 121−213.
(3) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*(2), 73−79.
(4) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microb. Rev.* **1996**, *60*, 301−315.
(5) Lin, A. J.; Klayman, D. L.; Milhous, W. K. *J. Med. Chem.* **1987**, *30*, 2147−2150.
(6) Hufford, C. D.; Khalifa, S. I.; Orabi, K. Y.; Wiggers, F. T.; Kumar, R.; Rogers, R. D.; Campana, C. F. *J. Nat. Prod.* **1995**, *58*, 751−755.
(7) Hufford, C. D.; Lee, I.-S.; ElSohly, H. N.; Chi, H. T. Baker, J. K. *Pharm. Res.* **1990**, *7*, 923−927.
(8) Hu, Y.; Ziffer, H.; Li, G.; Yeh, H. J. C. *Bioorganic Chem.* **1992**, *20*, 148−154.
(9) Abourashed, E. A.; Hufford, C. D. *J. Nat. Prod.* **1996**, *59*, 251−253.
(10) Hu, Y.; Highet, R. J.; Marion, D.; Ziffer, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1176−1177.
(11) Lee, I.-K.; ElSohly, H. N.; Croom, E. M.; Hufford, C. D. *J. Nat. Prod.* **1989**, *52*, 337−340.
(12) Lee, I. K.; ElSohly, H. N.; Hufford, C. D. *Pharm. Res.* **1990**, *7*, 199−203.
(13) Luo, X.-D.; Shen, C. C. *Med. Res. Rev.* **1987**, *7*, 29−52.
(14) (a). Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 5885−5886. (b) Wu, W.-M.; Wu, Y.; Yao, Z. J.; Zhou, C.-M.; Li, Y.; Shan, F. *J. Am. Chem. Soc.* **1998**, *120*, 3316−3325. (c) Haynes, R. K.; Vonwiller, S. C. *Tetrahedron Lett.* **1996**, *37*, 253−256.
(15) (a) Roth, R. J.; Acton, N. *J. Nat. Prod.* **1989**, *53*, 1183−1185. (b) Roth, R. J.; Acton, N. *J. Chem. Ed.* **1991**, *68*, 612−613. (c) Acton, N.; Roth, R. J. *J. Org. Chem.* **1992**, *57*, 3610−3614.
(16) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 451−453.
(17) (a) Jung, M.; Lee, S. *Heterocycles* **1997**, *45*, 1055−1058. (b) Vroman, J. A.; Khan, I. A.; Avery, M. A. *Tetrahedron Lett.* **1997**, *38*, 6173−6176. (c) Haynes, R. K.; Vonwiller, S. C.; Wang, H.-J. *Tetrahedron Lett.* **1995**, *36*, 4641−4642, and Corrigenda, *Tetrahedron Lett.* **1997**, *38*, 2587. (d) Bustos, D. A.; Jung, M.; ElSohly, H. N.; McChesney, J. D. *Heterocycles* **1989**, *29*, 2273−2277. (e) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Tetrahedron Lett.* **1989**, *44*,

5973−5976. (f) Jung, M.; Freitas, A. C. C.; McChesney, J. D.; ElSohly, H. N. *Heterocycles* **1994**, *39*, 23−29. (g) Jung, M.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Synlett*. **1990**, 743−744. (h) Jung, M., ElSohly, H. N.; McChesney, J. D. *Synth. Lett*. **1993**, 43−44.
(18) Elmarakby, S. A.; El-Feraly, F. S.; ElSohly, H. N.; Croom, E. M.; Hufford, C. D. *Phytochemistry* **1988**, *27*, 3089−3091.
(19) Xu, X.-X.; Ahu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819−828.
(20) Acton, N.; Brandt, B. Unpublished results.
(21) Acton, N.; Klayman, D. L.; Rollman, I. J. *Planta Medica* **1985**, 445−446.
(22) Zhongshan, W.; Nakashima, T. T.; Kopecky, K. R.; Molina, J. *Can. J. Chem*. **1985**, *63*, 3070−3074.

NP980555W