Journal of Natural Products
Vol. 51, No. 1, pp. 145-149, Jan-Feb 1988

STEREOSTRUCTURE OF SALVIANOLIC ACID B AND ISOLATION OF SALVIANOLIC ACID C FROM *SALVIA MILTIORRHIZA*

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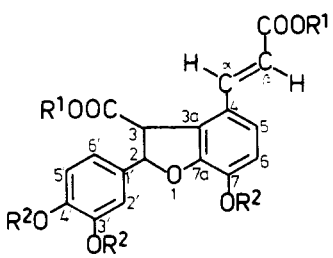
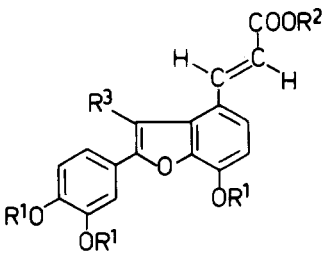
The roots of *Salvia miltiorrhiza* Bunge (Labiatae) are a traditional Chinese medicine, widely used for the treatment of coronary diseases (1). In our previous paper (2), we reported the isolation of a new depside, salvianolic acid A, from the roots of *S. miltiorrhiza*. Subsequent investigation on the chemical constituents of the aqueous extract has led to the isolation of three more depsides, salvianolic acid B [**1a**], salvianolic acid C [**2a**], and rosmarinic acid, among which **2a** has hitherto not been reported. Salvianolic acid B was also isolated from the same source by Chen *et al.* (3) and the plane structure assigned; based on chemical degradation and spectral analysis, we established a 2*R*, 3*R* configuration and 2β-pseudoequatorial aryl, 3α-pseudoaxial carboxyl conformation.

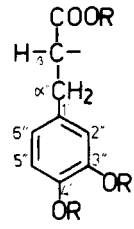
Salvianolic acid B [**1a**], an amorphous, yellowish compound showed $[\alpha]_D$ +92. Its fdms displayed $M^+ = 718$. Methylation of **1a** yielded compound **1b** with a molecular ion of *m/z* 844. The loss of two *m/z* 222 units in the mass fragmentation of **1b** revealed the presence of two β-(3,4-dimethoxyphenyl)-lactic ester moieties (4). A 2,3-disubstituted dihydrobenzofuranoid skeleton in the chemical structure of **1b** was deduced from the fact that the ^{1}H-nmr spectrum displayed a pair of doublets at δ 4.43 (1H, d, J=5.4, C-3H) and δ 6.05 (1H, d, J=5.4, C-2H) (5), while the ^{13}C nmr showed a signal at δ 87.3 (C-2). Hydrolysis of **1b** with 10% KOH/MeOH yielded *R*-(+)-methyl-β-(3,4-dimethoxyphenyl)-lactate (6) and two olefinic compounds **3a** and **3b**, instead of the expected dihydrobenzofuranoid. Treatment of **1b** with sodium methoxide under mild condition gave (*R,S*)-methyl-β-(3,4-dimethoxyphenyl)-lactate, caused by base-induced racemization (7), and the 2-aryl dihydrobenzofuranoid compound **1c**, which was readily assigned according to its ms, ^{1}H-nmr, and ^{13}C-nmr spectra. Catalytic hydrogenation of **1c** yielded compound **4**. A positive Cotton effect at 299 nm in the ord and a peak at 288 nm in the cd spectra of **4** revealed a 2β-aryl configuration (8). The lack of strong shielding (δ 3.03 in *cis* and δ 3.73 in *trans* configuration) (9) of the methoxycarbonyl signals in the ^{1}H-nmr spectra of **4** as well as that of **1c** indicated that the C-3 carboxyl group should be *trans* to the C-2 aryl group; thus, a 2*R*, 3*R* configuration was assigned for **1a**. A Dreiding model examination shows two possible conformations for



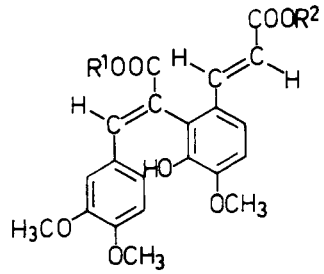
1a R^1=**X**, R^2=H
1b R^1=**Y**, R^2=Me
1c R^1=R^2=Me



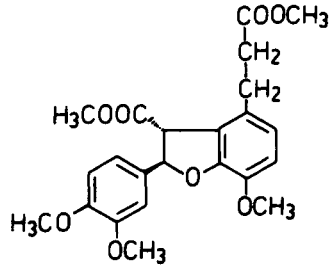
2a R^1=R^3=H, R^2=**X**
2b R^1=Me, R^2=**Y**, R^3=H
2c R^1=Me, R^2=R^3=H
2d R^1=R^2=Me, R^3=COOMe



X R=H
Y R=Me



3a $R^1=R^2=H$
3b R^1(or R^2)=H, R^2(or R^1)=Me



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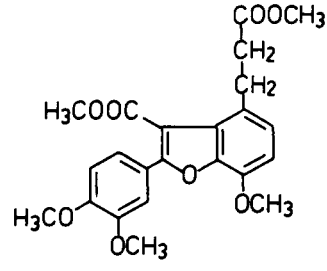

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the dihydrobenzofuran ring; however, a pseudoaxial aryl and pseudoaxial carboxyl conformation in which the dihedral angle between C-2H and C-3H is 90° (J=0) is excluded by the coupling constant ($J_{2,3}$=5.4) of **1a**. So **1a** should have a pseudoequatorial aryl and a pseudoaxial carboxyl conformation with

TABLE 1. ^{13}C-Nmr Chemical Shifts ($CDCl_3$, ppm) of **1b** and **1c**.

Carbon	Compound		Carbon	Compound
	1b	**1c**		**1b**
2	87.3	87.5	1″	128.0
3	55.8	55.9		128.5
3a	132.5	132.5	2″	111.4
4	128.0	125.1		111.4
5	116.4	117.4	3″	148.1
6	111.4	111.4		148.3
7	149.5	149.5	4″	148.7
7a	148.7	148.6		149.5
3-C	170.2	171.8	5″	112.7
β-C	165.8	167.3		112.7
α	142.0	141.1	6″	121.0
β	121.0	120.5		121.6
1′	124.7	124.7	α″	36.6
2′	108.9	109.0		37.0
3′	149.5	149.5	β″	73.1
4′	146.2	146.2		74.1
5′	113.2	113.4	β″-C	169.3
6′	117.9	118.0		170.2
$COOCH_3$		51.5	$COOCH_3$	52.2
		52.7		52.2
OCH_3		55.9(×3)	OCH_3	55.8(×4)
				56.1(×2)
				56.4

a dihedral angle of 135° between C-2H and C-3H. Dehydrogenation of **1c** with sulfur yielded compound **2d**. Attempts to obtain a 2,3-*cis* addition by high pressure catalytic hydrogenation of **2d** were unsuccessful.

Salvianolic acid C [**2a**], an amorphous yellow compound, showed $[\alpha]_D$ +70. Its fdms displayed $M^+ = 492$. Uv maxima at 202, 215, 288, 312, and 340 nm (log ε 4.79, 4.52, 4.40, 4.32, and 4.31) revealed the presence of a highly conjugated system. The hrms of the methylated compound **2b** showed $M^+ = 576.1989$ (calcd for $C_{32}H_{32}O_{10}$, 576.1995) and diagnostic fragments of a β-(3,4-dimethoxyphenyl)-lactic ester (*m/z* 222, 191, 151) (4). Hydrolysis of **2b** with 10% KOH/MeOH yielded *R*-(+)-β-(3,4-dimethoxyphenyl)-lactic acid (2) and a yellow crystalline compound **2c** with a molecular ion of *m/z* 354.1109 (calcd for $C_{20}H_{18}O_6$, 354.1103). The ^{1}H-nmr spectrum of **2c** showed signals for three methoxyl groups (δ 3.97, 4.04, 4.12), a *trans* disubstituted double bond (δ 6.32, 7.96, each with $J = 16$), five aromatic protons, and a vinylic proton of a trisubstituted double bond (δ 7.40). Based on the above chemical and spectral analysis, structure **2a** was assigned for salvianolic acid C. The fact that salvianolic acid A was converted into **2a** on a tlc plate impregnated with 2% HCOOH suggested the latter to be a cyclization product of the former. Therefore, the natural occurrence of **2a** in *S. miltiorrhiza* is not assured.

EXPERIMENTAL

GENERAL.—^{1}H-nmr and ^{13}C-nmr spectra were recorded on a JEOL FX-90Q spectrometer. Uv spectra were obtained on a Shimadzu UV-300 spectrometer, and optical rotations were measured on a Perkin-Elmer 241 polarimeter. Cd were recorded on a Jobin CD-5 polarimeter, and ord was obtained on a Perkin-Elmer 241 MC polarimeter. Mass spectra were obtained from a ZAB-2F mass spectrometer. Melting points were measured on a Kofler melting point apparatus and are uncorrected. SiO_2, 140–160 mesh (Qingdao Marine Chemical Factory, Qingdao, China), was used for cc and SiO_2-GF_{254} for tlc. Plant material was purchased from Sing-lung Pharmaceutical Company, Hebei Province, China, and a voucher specimen is deposited at the Herbarium of our Institute under the number 133, 57-5-29.

EXTRACTION AND ISOLATION.—Slices of the dried roots of *S. miltiorrhiza* (32 kg) were extracted with 95% EtOH under reflux. After evaporation of the solvent, the residue was thoroughly extracted with hot H_2O. The aqueous extract was filtered and concentrated under reduced pressure. The concentrated aqueous extract was mixed with 3000 g of SiO_2 and successively extracted with $CHCl_3$, EtOAc, and EtOH in a modified Soxhlet apparatus. The EtOH extract was concentrated in vacuo to give a brown powder (1170 g) of which 500 g was dissolved in H_2O and extracted with EtOAc. The organic extract was concentrated under reduced pressure to yield an amorphous powder (104 g), 90 g of which was divided into two portions. Each portion was developed on SiO_2 (2300 g) dry column chromatography with $CHCl_3$-MeOH-HCOOH (85:15:1) as solvent. The column was cut into 16 equal sections that were individually eluted with warm EtOH and numbered from the bottom to the top. Sections 13–14 showed a blue fluorescent spot on tlc; purification on Sephadex LH-20 (100 g) using MeOH as solvent yielded 2.06 g of salvianolic acid B [**1a**]. Preparative tlc of sections 10–12 using $CHCl_3$-MeOH-HCOOH (85:15:1) as solvent yielded 0.7 g of salvianolic acid A and 0.4 g of salvianolic acid C [**2a**]. Rosmarinic acid (4.8 g) was obtained from sections 7–9 after purification on Sephadex LH-20.

SALVIANOLIC ACID B [**1a**].—Amorphous yellowish powder, $[\alpha]^{18}_D$ +92 (*c* = 0.07, EtOH); fdms *m/z* 719 $[M+1]^+$, 741 $[M+Na]^+$; uv λ max (EtOH) nm (log ε) 203 (4.93), 253 (4.13), 288 (4.16), 308 (4.09), 330 (4.05); ^{1}H nmr (Me_2CO-d_6) δ 4.47 (1H, d, $J = 5.2$, C-3H), 5.90 (1H, d, $J = 5.2$, C-2H), 7.66 (1H, d, $J = 16$, C-αH), 6.30 (1H, d, $J = 16$, C-βH), 3.58 (4H, m, C-α″H), 5.23 (2H, dd, $J = 5/8$, C-β″H), 6.48–7.00 (11H, Ar-H).

SALVIANOLIC ACID C [**2a**].—Amorphous yellow compound, $[\alpha]^{14}_D$ +70 (*c* = 0.102, EtOH); fdms *m/z* 493 $[M]^+ + 1$; uv λ max (EtOH) nm (log ε) 202 (4.79), 215 (sh, 4.52), 288 (4.40), 312 (4.32), 340 (4.31); ^{1}H nmr (Me_2CO-d_6) δ 6.55 (1H, d, $J = 16$, C-βH), 7.97 (1H, d, $J = 16$, C-αH), 5.18 (1H, dd, $J = 4/7$, C-β″H), 6.7–7.6 (9H, Ar-H).

METHYLATION OF **1a**.—Anhydrous K_2CO_3 (2.0 g) was suspended in a solution of **1a** (2.0 g) in anhydrous Me_2CO (25 ml) under an atmosphere of N_2. Portions of 1.3 ml of Me_2SO_4 were added dropwise every 6 h and the mixture continually stirred for 48 h at room temperature. The mixture was filtered and concentrated under re-

duced pressure. The residue was mixed with SiO_2 (20 g), applied on a SiO_2 (20 g) column, and consecutively eluted with petroleum ether, petroleum ether/CH_2Cl_2, CH_2Cl_2, CH_2Cl_2/MeOH, and MeOH. Fractions of CH_2Cl_2-MeOH (9:1–7:3) showed a blue fluorescent spot on tlc. After removal of the solvent, the residue was purified by preparative tlc with $CHCl_3$-MeOH-HCOOH (100:0.5:0.5) as solvent, yielding 1.3 g of dimethyl heptamethylsalvianolate B [**1b**].

COMPOUND **1b**.—Yellowish gum, $[\alpha]^{18}D$ +40 (c=0.049, EtOH); ms m/z (%) 844 $[M]^+$ (3), 622 (9), 400 (19), 382 (16), 377 (31), 309 (12), 222 (97), 191 (30), 181 (45), 163 (21), 151 (100); ^1H nmr ($CDCl_3$) δ 4.43 (1H, d, J=5.4, C-3H), 6.05 (1H, d, J=5.4, C-2H), 6.21 (1H, d, J=16, C-βH), 7.59 (1H, d, J=16, C-αH), 3.10 (4H, m, C-α″H), 5.28 (2H, m, C-β″H), 3.70 (9H, s, 3×OCH_3), 3.85 (12H, s, 4×OCH_3), 3.87, 3.96 (each 3H, s, 2×OCH_3), 6.5–7.3 (11H, Ar-H); ^{13}C nmr see Table 1.

HYDROLYSIS OF **1b**.—*Method A*.—Compound **1b** (45 mg) was refluxed with 4 ml of 10% KOH/MeOH for 1 h. After acidification and work-up with EtOAc and H_2O, the organic layer was concentrated and the residue applied on preparative tlc using C_6H_6-EtOAc-HCOOH (80:20:1) as solvent. Elution of the individual bands with Me_2CO yielded 10 mg of **3a**, 10 mg of **3b**, and 8 mg of *R*-(+)-methyl-β-(3,4-dimethoxyphenyl)-lactate.

Method B.—To a cool solution of **1b** (1 g) in $CHCl_3$ (50 ml), 5 ml of 0.6 N MeONa was added dropwise, and the mixture was stirred at 0° for 1 h. After acidification and work-up with EtOAc and H_2O, the organic layer was concentrated. Preparative tlc of the residue as described in method A yielded 335 mg of **1c** and 250 mg of (*R,S*)-methyl-β-(3,4-dimethoxyphenyl)-lactate.

COMPOUND **3a**.—Amorphous powder, showed a positive test with ferric ferricyanide, ms m/z (%) 400.1155 $[M]^+$ (33, calcd for $C_{21}H_{20}O_8$, 400.1158), 382 (94), 337 (100), 165 (33), 151 (77), 138 (71); ^1H nmr (Me_2CO-d_6) δ 3.40, 3.78, 3.98 (each 3H, s, 3×OCH_3), 6.32 (1H, d, J=16, C-βH), 7.65 (1H, d, J=16, C-αH), 7.12 (1H, d, J=8, C-6H), 7.47 (1H, d, J=8, C-5H), 8.00 (1H, s, C-2H), 6.64–6.89 (3H, Ar-H).

COMPOUND **3b**.—Amorphous powder, showed a positive test with ferric ferricyanide, ms m/z (%) 414 (100), 396 (13), 382 (39), 337 (96), 165 (14), 151 (68), 138 (31); ^1H nmr ($CDCl_3$) δ 3.44, 3.80, 3.82, 3.97 (each 3H, s, 4×OCH_3), 6.24 (1H, d, J=16, C-βH), 7.64 (1H, d, J=16, C-αH), 6.96 (1H, d, J=8, C-6H), 7.37 (1H, d, J=8, C-5H), 8.04 (1H, s, C-2H), 6.52 (1H, d, J=2, C-2′H), 6.80 (1H, dd, J=2/8, C-6′H), 6.80 (1H, d, J=8, C-5′H).

COMPOUND **1c**.—Yellowish crystals, mp 46–48° (MeOH), $[\alpha]^{18}D$ +41 (c=0.092, EtOH); ms m/z (%) 428.1464 $[M]^+$ (54, calcd for $C_{23}H_{24}O_8$, 428.1470), 397 (15), 368 (36), 337 (100), 309 (27), 181 (29), 151 (53); uv λ max (EtOH) nm (log ε) 205 (4.60), 240 (3.99), 288 (3.87), 302 (3.91), 330 (3.83); ^1H nmr ($CDCl_3$) δ 4.51 (1H, d, J=5.4, C-3H), 6.07 (1H, d, J=5.4, C-2H), 6.31 (1H, d, J=16, C-βH), 7.79 (1H, d, J=16, C-αH), 7.27 (1H, d, J=8, C-5H), 6.93 (1H, d, J=8, C-6H), 6.92 (1H, d, J=2, C-2′H), 6.84 (1H, dd, J=2/8, C-6′H), 6.90 (1H, d, J=8, C-5′H), 3.88 (6H, s, 2×OCH_3), 3.80, 3.82, 3.96 (each 3H, s, 3×OCH_3); ^{13}C nmr see Table 1; cd (c=0.066, $CHCl_3$) [θ] (nm) +1040 (370), +2880 (350), +6240 (330), +5280 (310), +6720 (294), +960 (281), +43200 (256), 0 (240).

(*R,S*)-METHYL-β-(3,4-DIMETHOXYPHENYL)-LACTATE.—White crystalline needles mp 56–57° ($CHCl_3$); $[\alpha]^{18}D$ =0; ms m/z (%) 240 $[M]^+$ (16), 222 (1), 181 (3), 151 (100); ^1H nmr ($CDCl_3$) 2.96 (1H, d, J=7, C-αH), 2.99 (1H, d, J=4, C-αH), 4.41 (1H, dd, J=4/7, C-βH), 3.74 (3H, s, OCH_3), 3.82 (6H, s, 2×OCH_3), 6.77 (3H, J=2, Ar-H).

R-(+)-METHYL-β-(3,4-DIMETHOXYPHENYL)-LACTATE.—Yellowish crystals mp 64–65°, ($CHCl_3$); $[\alpha]^{12}D$ +15 (c=0.103, EtOH); ms m/z (%) 240 $[M]^+$ (16), 222 (1), 181 (3), 151 (100); ^1H nmr (Me_2CO-d_6) δ 2.90 (1H, d, J=7, C-αH), 2.98 (1H, d, J=4, C-αH), 4.37 (1H, dd, J=4/7, C-βH), 3.70, 3.80, 3.81 (each 3H, s, 3×OCH_3), 6.87 (1H, d, J=2, C-2H), 6.89 (1H, dd, J=2/8, C-6H), 6.90 (1H, d, J=8, C-5H).

HYDROGENATION OF **1c**.—Compound **1c** (20 mg) was hydrogenated in 10 ml of EtOAc with 20 mg of PtO_2 as catalyst. The catalyst was filtered and the filtrate concentrated to dryness yielding 17 mg of the hydrogenated product **4**.

COMPOUND **4**.—Yellow gum, $[\alpha]^{18}D$ +29 (c=0.124, EtOH); uv λ max (EtOH) nm (log ε) 207 (4.77), 255 (sh, 4.29), 282 (3.95); ms m/z (%) 430 $[M]^+$ (75), 398 (100), 371 (9), 325 (45), 297 (55); ^1H nmr ($CDCl_3$) δ 4.42 (1H, d, J=5.4, C-3H), 6.02 (1H, d, J=5.4, C-2H), 2.88 (2H, t, J=8, C-αH), 2.59 (2H, t, J=8, C-βH), 6.92 (1H, d, J=8, C-6H), 6.97 (1H, d, J=8, C-5H), 3.68, 3.85, 3.92, 3.93, 3.94 (each 3H, s, 5×OCH_3), 7.02 (1H, dd, J=2/8, C-6′H), 6.96 (1H, d, J=2, C-2′H), 6.88 (1H, d, J=8, C-5′H); ord (c=0.013, EtOH) [Φ] (nm) +330 (420), +10000 (299), 0 (288), −4290 (270), −1320 (255); cd (c=0.100, EtOH) [θ] (nm) +284 (360), +2554 (328), +2270 (303), +9646 (288), +3122 (274), +22704 (252), 0 (240).

DEHYDROGENATION OF **1c**.—Compound **1c** (170 mg) was refluxed in diphenyl ether (3 ml) with 60 mg of sulfur for 3 h. The mixture was purified by preparative tlc with C_6H_6-EtOAc-HCOOH (90:10:1) as solvent, yielding 40 mg of the dehydrogenated product **2d**.

COMPOUND **2d**.—Yellowish needles, mp 138–140° (CH_2Cl_2); uv λ max (EtOH) nm (log ε) 206 (4.17), 235 (3.37), 335 (3.71); ms *m/z* (%) 426 $[M]^+$ (100); ^1H nmr ($CDCl_3$) δ 4.02 (6H, s, 2×OCH_3), 3.86, 3.99, 4.10 (each 3H, s, 3×OCH_3), 6.36 (1H, d, *J*=16, C-βH), 8.23 (1H, d, *J*=16, C-αH), 7.02 (1H, d, *J*=8, C-5H), 6.92 (1H, d, *J*=8, C-6H), 7.52 (1H, d, *J*=2, C-2′H), 7.60 (1H, d, *J*=8, C-5′H), 7.61 (1H, dd, *J*=2/8, C-6′H).

HYDROGENATION OF **2d**.—A solution of **2d** (15 mg) in 3 ml of EtOAc and 17 ml of EtOH was hydrogenated over 5% Rh/C (15 mg) at 80 kg/cm^2 H_2 for 10 h at 35°. After filtration and removal of the solvent, the residue was purified by tlc yielding 10 mg of the hydrogenated product **5**.

COMPOUND **5**.—White needles, mp 76–78° (EtOH); uv λ max (EtOH) nm (log ε) 214 (4.53), 235 (sh, 4.28), 312 (4.38); ms *m/z* (%) 428 $[M]^+$ (30), 368 (25), 337 (83), 181 (25), 151 (100); ^1H nmr ($CDCl_3$) δ 2.64 (2H, t, *J*=8, C-βH), 3.20 (2H, t, *J*=8, C-αH), 3.98 (6H, s, 2×OCH_3), 3.72, 3.94, 4.04 (each 3H, s, 3×OCH_3), 6.83 (1H, d, *J*=8, C-6H), 7.09 (1H, d, *J*=8, C-5H), 6.96 (1H, d, *J*=2, C-2′H), 7.48 (1H, d, *J*=8, C-5′H), 7.48 (1H, dd, *J*=2/8, C-6′H).

METHYLATION OF **2a**.—200 mg of **2a** was methylated as described for the methylation of **1a**. Purification on preparative tlc yielded 110 mg of methyl pentamethylsalvianolate C [**2b**].

COMPOUND **2b**.—Yellow gum, ms *m/z* (%) 576.1989 $[M]^+$ (13, calcd for $C_{32}H_{32}O_{10}$, 576.1995), 354 (100), 222 (42), 191 (10), 151 (42); ^1H nmr ($CDCl_3$) δ 3.80, 3.89, 3.90, 3.98, 4.05, 4.12 (each 3H, s, 6×OCH_3), 6.52 (1H, d, *J*=16, C-βH), 8.00 (1H, d, *J*=16, C-αH), 3.22 (2H, d, *J*=6, C-α″H), 5.43 (1H, t, *J*=6, C-β″H), 6.70–7.70 (9H, Ar-H).

HYDROLYSIS OF **2b**.—Compound **2b** (85 mg) was refluxed with 10% KOH/MeOH (5 ml) for 1 h. After acidification and work-up with EtOAc and H_2O, the organic layer was concentrated, giving 30 mg of yellow crystals [**2c**]; the mother liquor was applied on tlc using C_6H_6-EtOAc-HCOOH (90:10:1) as solvent, yielding 10 mg of **2c** and 8 mg of *R*-(+)-β-(3,4-dimethoxyphenyl)-lactic acid.

COMPOUND **2c**.—Yellow crystals, mp 221–223° (EtOAc); ms *m/z* (%) 354.1109 $[M]^+$ (100, calcd for $C_{20}H_{18}O_6$, 354.1103); ^1H nmr ($CDCl_3$) δ 3.97, 4.04, 4.12 (each 3H, s, 3×OCH_3), 6.32 (1H, d, *J*=16, C-βH), 7.96 (1H, d, *J*=16, C-αH), 6.84 (1H, d, *J*=8, C-6H), 7.00 (1H, d, *J*=8, C-5H), 7.40 (1H, s, C-3H), 7.42 (1H, d, *J*=8, C-5′H), 7.44 (1H, d, *J*=2, C-2′H), 7.56 (1H, dd, *J*=2/8, C-6′H).

CYCLIZATION OF SALVIANOLIC ACID A.—A 20×20 cm^2 tlc plate was impregnated with $CHCl_3$-MeOH-HCOOH (85:15:2). After evaporation of the solvent, 50 mg of salvianolic acid A was applied and the plate left for 48 h at room temperature. Multiple development (×3) with $CHCl_3$-MeOH-HCOOH (85:15:1) yielded a dark yellow fluorescent band and a bright green fluorescent band. Elution of the individual bands with Me_2CO yielded 10 mg of salvianolic acid A and 20 mg of **2a**.

ACKNOWLEDGMENTS

We thank Ge Da-lun and Kung Man for the ^{13}C nmr and ^1H nmr, Xiao Yuxia for the uv and cd, Hu Zhao-hong for the ms and Xue Hong for the optical rotation measurements.

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Received 10 February 1987