A SYNTHESIS OF THE DERIVATIVES OF 1,2,3,5,10,10a-HEXAHYDROBENZ[*f*]INDOLIZINE-6,9-DIONE HAVING ANTIFUNGAL ACTIVITY AS A SIMPLE MODEL OF SAFRAMYCIN A[1]

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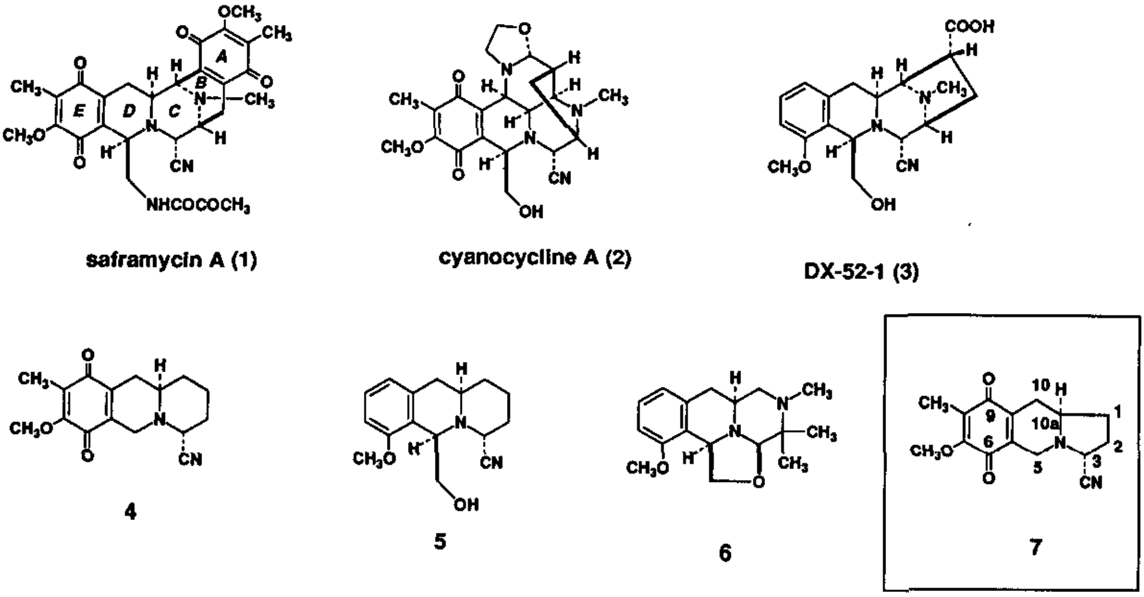
Abstract —— A simple and efficient synthesis of 1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-6,9-dione (**7**) and its analogs (**28-30**) is described starting from the corresponding lactam (**15b**).

This paper is dedicated to the memory of Dr. Yoshio Ban, Professor Emeritus, Hokkaido University.

Saframycin A (**1**) is a novel antibiotic discovered in the culture broths of *Streptomyces lavendulae* along with saframycins B-H, R, and S. It has been shown to possess the highest biological activity and to be a potent antitumor agent against various experimental tumors.[2] The α-amino nitrile functionality could produce an iminium ion that would be highly reactive toward nucleophiles on DNA, which has been proposed for cyanocycline A (**2**) and DX-52-1 (**3**).[3] The mode of action and computer simulation of the binding of these isoquinoline derivatives have been extensively studied.[4] Furthermore, in order to elucidate a rule for a latent iminium ion functionality, simple structures (**5** and **6**) that might mimic the biological action of natural products have been synthesized.[5] In our previous studies on the left half of saframycin A, we synthesized a simple model compound (4).[1] Unfortunately, against L 1210 murine leukemia *in vitro*, **4** (ED_{50} = 3.0 μg/kg) was shown to possess low cytotoxic potency relative to **1** (ED_{50} = 0.003 μg/kg). However, we observed characteristic activity of **4** against dermatophytes such as *Trichophyton mentagrophytes* (MIC = 6.25 μg/ml).[1] In order to increase its antifungal activity, we report here the synthesis of 1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-6,9-dione (7).

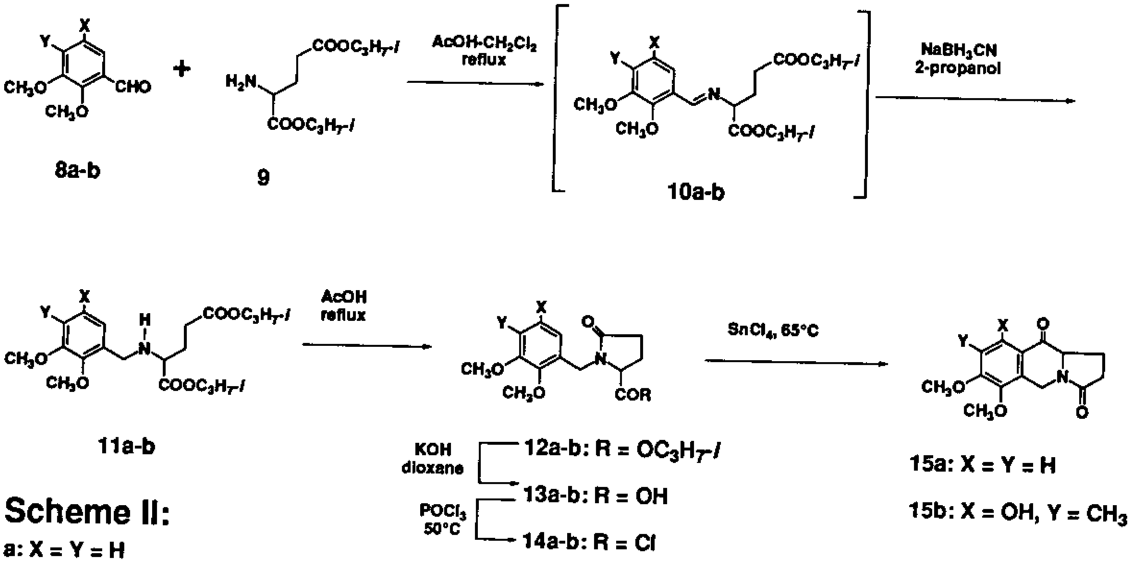


saframycin A (1) **cyanocycline A (2)** **DX-52-1 (3)**

4 **5** **6** **7**

Scheme I

The preparation of the basic skeleton (**15**) is detailed in Scheme II and made by a modification of the known procedure.[6] 2,3-Dimethoxybenzaldehyde (**8a**) was condensed with (±)-diisopropyl glutamate (**9**) to give a Schiff base (**10a**), which upon treatment with sodium cyanoborohydride afforded the diester (**11a**). Cyclization of **11a** with acetic acid afforded the ester (**12a**) in 56.6 % overall yield. The compound (**12a**) was hydrolyzed to give the acid (**13a**) in 85.8 % yield. Because the direct cyclization of **13a** with 85% H_3PO_4 and P_2O_5 at 110°C for 1 h gave **15a** in low yield (21.3 %), we used the procedure of Rigo and Kolocouris.[7] The reaction of **13a** with phosphorous oxychloride gave the acid chloride (**14a**), which was subsequently treated with tin tetrachloride to provide **15a** in 35.8 % overall yield. By employing 4-methyl-2,3,5-trimethoxybenzaldehyde (**8b**)[8] instead of **8a**, the compound (**13b**) was obtained in the same manner in high yield. After treating **13b** with 85% H_3PO_4 and P_2O_5, no cyclized compound could be isolated. Accordingly, the sequence of reactions as previously described was studied. The reaction of **13b** with phosphorous oxychloride gave the acid chloride (**14a**), which was subsequently treated with tin tetrachloride to provide **15b** with partial cleavage of the aromatic ether in 57.1 % overall yield. The structure of **15b** was supported by the ^{1}H nmr spectrum, which showed a peak at δ 12.17 assignable to a hydroxyl peak due to the hydrogen bonding of the hydroxyl group bearing an oxygen functional group at the 10 position.



Scheme II:
a: X = Y = H
b: X = OCH$_3$, Y = CH$_3$

Next, we turned our attention to the conversion of **15b** to compound (**18**) (Scheme III). Numerous efforts for the direct reduction of **15b** were totally unsuccessful because of the instability of compound (**15b**). This problem was solved by using the hydride reduction and reductive removal of hydroxyl group sequence. The reduction of **15b** with sodium borohydride afforded the alcohol (**16**) in 73 % yield along with its epimer (**17**) in 0.7 % yield. The stereochemistry of the C-10 position in **16** is supported by the ^{1}H nmr spectrum, which displays H-10 as a doublet at δ 4.68 (J = 9 Hz), whereas the ^{1}H nmr spectrum of **17** shows the H-10 as a doublet at δ 4.71 (J = 2.7 Hz). The reductive removal of the benzylic hydroxyl group of **16** with triethylsilane in trifluoroacetic acid[9] gave the amide (**18**) in 92 % yield.[10]

The introduction of a cyano group into the C-3 position of the amide was achieved by partial reduction followed by sodium cyanide treatment. The reduction of **19**, which was prepared from **18** in the usual manner with lithium aluminum hydride in tetrahydrofuran (THF) at -18°C, afforded the unstable αhydroxylamine, which was treated with sodium cyanide to give the amino nitriles (**20**) and (**21**) in 40.2 % and 20.5 % yields, respectively, along with the amine (**22**) in 17 % yield. The stereochemical assignments of **20** and **21** are based on ^{1}H nmr and ^{13}C nmr spectral analyses. A strongly deshielding γ-steric effect was observed at the C-10a carbon in **20** (δ 56.6), but not at C-10a in **21** (δ 60.0) and **22** (δ 59.8). On the other hand, reduction of the phenol (**18**) with lithium aluminum hydride in THF at -18°C followed by treatment of sodium cyanide gave an inseparable mixture of amino nitriles (**23**) and (**24**) in 56.1 % yield along with the amine (**25**) in 19 % yield (11 % of the starting material recovered). Finally, treatment of a mixture of phenols (**23** and **24**) with 10N HNO_3 gave the quinones (**7**) and (**26**) in 25.9 % and 14.5 % yields, respectively. A strongly deshielding γ-steric effect was also observed at the C-10a carbon in **7** (δ 55.7), but not at C-10a in **26** (δ 58.7). This was confirmed by observation of an NOE between H-3 and H-10a in **26**. Thus, the reaction of cyanide ion on the iminium ion mainly gave an axial orientation to the cyano group. The stereochemical course of the reaction could be rationalized by invoking a stereoelectronically controlled antiperiplanar addition of cyanide ion.[11]

Other quinone derivatives (**28-30**) were also synthesized from the corresponding benzene derivatives (**18**, **16**, and **27**) using oxidative demethylation with 10N HNO_3.[12]

With various tricyclic quinones (**7**, **26**, **28-30**) in hand, the cytotoxicity of these compounds *in vitro* against L 1210 murine leukemia was studied. Neither compound showed any significant cytotoxic activity (**7**: ED_{50} = 3.0 μg/kg, **26**: ED_{50} = 3.0 μg/kg, **28**: ED_{50} = 2.0 μg/kg, **29**: ED_{50} = 3.5 μg/kg, **30**: ED_{50} = 3.0 μg/kg). However, we observed that the amino nitriles (**7**) and (**26**) were active against fungi with relatively low MIC values against *Trichophyton mentagrophytes*.[13] Interestingly, the α-cyano compound (**7**: MIC = 6.25 μg/ml) has a 4 times higher antifungal activity against dermatophytes than that of the β-cyano compound (**26**: MIC = 25 μg/ml). Further studies on the preparation of new derivatives of **7** having even more antifungal activity are now in progress.

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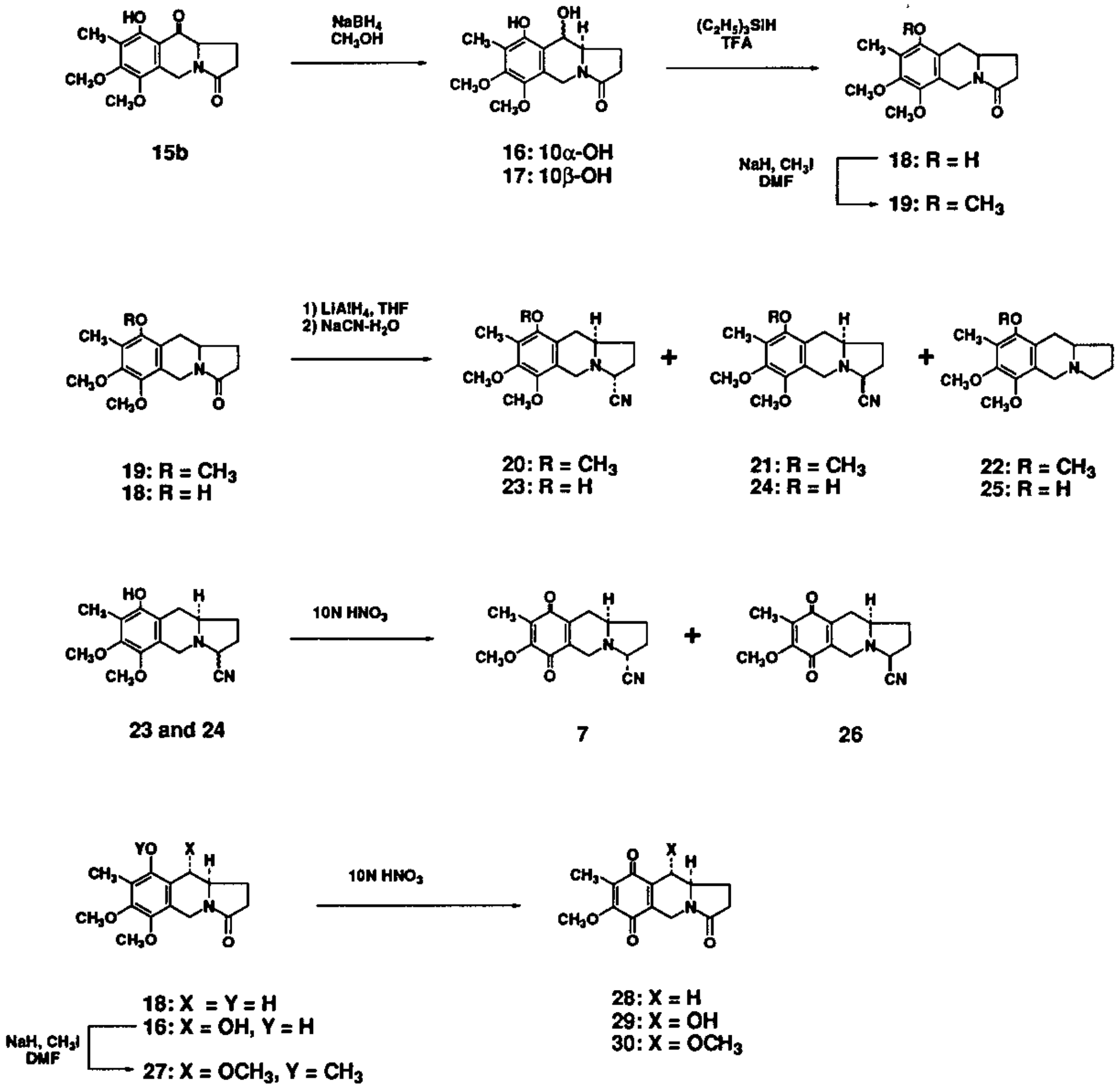

Scheme III

EXPERIMENTAL SECTION

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Uv spectra were determined in methanol with a Hitachi 200-20 spectrophotometer. Ir spectra were obtained with a Hitachi 260-10 spectrophotometer and ^{1}H nmr spectra and ^{13}C nmr spectra were measured on a

JEOL JNM-EX 270 (operating at 270 MHz and 67.5 MHz, respectively). Nmr spectra were taken in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to internal tetramethylsilane standard. Ms spectra were recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were obtained by a Perkin-Elmer Model 240B elemental analyzer. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts; removal of the solvent was done with a rotary evaporator and finally, under high vacuum. Column chromatography was performed with E. Merck silica gel 60 (230-400 mesh).

N-[(2,3-Dimethoxyphenyl)methyl]-5-carboxy-2-pyrrolidone (**13a**)

2,3-Dimethoxybenzaldehyde (**8a**) (1.66 g, 10 mmol) was added to a stirred solution of diisopropyl (±)-glutamate (**9**) (2.31g, 10 mmol) in dichloromethane (100 ml) and 10 drops of acetic acid. After the mixture was heated at reflux for 2 h under a Dean-Stark separator, an additional 100 mol % of glutamate was added in two portions, every 30 min, together with 10 more drops of acetic acid. Refluxing was continued for an additional 8 h and then the solution was evaporated in vacuo to give the Schiff base (**10a**) which was used in the following reaction without further purification. The crude Schiff base (**10a**) was dissolved in 2-propanol (100 ml) and sodium cyanoborohydride (1.26 g, 20 mmol) was added in one portion with stirring at 0°C. The reaction mixture was stirred for 12 h, and the solvent was removed in vacuo. The residue was diluted with water (100 ml) and then extracted with dichloromethane (100 ml x 3). The combined extracts were washed with 5% $NaHCO_3$ (100 ml), dried, and concentrated in vacuo to give the residue (**11a**) which was used for the next step without further purification. A solution of the ester (**11a**) (5.43 g) in acetic acid (25 ml) was heated under reflux for 7 h. The reaction mixture was diluted with water (100 ml), made alkaline with powdered Na_2CO_3, and then extracted with dichloromethane (50 ml x 3). The combined extracts were washed with water (100 ml), dried, and concentrated in vacuo. The residue (5.11 g) was subjected to chromatography (silica gel, 130 g; elution with 1:1 = hexane-ethyl acetate) to give **12a** (1.82 g, 56.6 %) as colorless syrup; ν_{max} (neat) 1740, 1690 cm^{-1}; δ_H 1.31 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.56-2.63 (4H, m), 3.73, 3.78 (each 3H, s, OCH_3), 4.02 (1H, d, J = 14 Hz, ArCH), 4.33 (1H, m, CHN), 4.87 (1H, d, J = 14 Hz, ArCH), 4.92 (1H, sept, J = 6 Hz, OCH), 6.54-7.00 (3H, m, ArH). A solution of the ester (**12a**) (1.55 g, 4.8 mmol) in dioxane (20 ml) was cooled at 0°C, and a methanol (15 ml) solution of 2N KOH (10 ml) was added and stirring was continued at room temperature for 3 h. The solution was evaporated, and the residue was diluted with water (100 ml) and then washed with ether (100 ml). The aqueous phase was then adjusted pH 3. The resulting precipitate was recrystallized from ethanol to give

13a (1.15 g, 85.8 %) as colorless needles, mp 157-160°C; ν_{max} (KBr) 3300-2200, 1720, 1630 cm^{-1}; λ_{max} nm (log ε) 227 (3.80), 276sh (3.25), 284 (3.20); δ_H 1.70-2.80 (4H, m), 3.76, 3.79 (each 3H, s, OCH_3), 3.89-4.00 (1H, m, CHN), 4.08, 4.97 (each 1H, d, *J* = 15 Hz, ArCH), 6.56-7.00 (3H, m, ArH), 7.00 (1H, br s, D_2O exchangeable); *m/z* (%) 279 (M^+, 42), 234 (14), 223 (23), 206 (38), 151 (100), 136 (69), 91 (40). Anal. Calcd for $C_{14}H_{17}NO_5$-1/5H_2O: C, 59.44; H, 6.06; N, 4.95. Found: C, 59.37; H, 6.13; N, 5.07.

6,7-Dimethoxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (**15a**) (a) Direct Method: A solution of **13a** (76.6 mg, 0.27 mmol) in 85% H_3PO_4 (0.64 ml, 11 mmol) was cooled at 0°C, and phousphorus pentoxide (1.0 g, 16.2 mmol) was added and then this mixture was heated at 110°C for 1 h. The reaction mixture was diluted with water (20 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml x 3). The combined extracts were washed with water, dried, and concentrated in vacuo. The residue (26.8 mg) was subjected to chromatography (silica gel, 5 g; elution with 3:1 = hexane-ethyl acetate) to give **15a** (15.0 mg, 21.3 %) as a pale yellow oil. (b) 2 Steps Procedure: A solution of **13a** (34.6 mg, 0.12 mmol) in phosphorous oxychloride (1 ml, 10.7 mmol) was heated at 50°C for 30 min. The solution was cooled at room temperature, and then $SnCl_4$ (0.5 ml, 4.28 mmol) was added in one portion with stirring. The mixture was heated at 65°C for 45 min, then poured into water (10 ml). The resulting solution was made alkaline with powdered Na_2CO_3, and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue (24.4 mg) was subjected to chromatography (silica gel, 5 g; elution with 3:1 hexane-ethyl acetate) to give **15a** (11.2 mg, 35.8 %) as a pale yellow oil; ν_{max} (neat) 1675 cm^{-1}; λ_{max} nm (log ε) 228 (3.90), 276sh (3.20), 284 (3.22), 344 (3.50); δ_H 2.10-2.50 (4H, m), 3.83, 3.87 (each 3H, s, OCH_3), 4.10 (1H, d, *J* = 18 Hz, 5-H), 4.29-4.33 (1H, m, 10a-H), 5.31 (1H, d, *J* = 18 Hz, 5-H), 6.79, 7.69 (each 1H, d, *J* = 8 Hz, ArH); *m/z* (%) 261 (M^+, 100), 233 (37), 219 (30), 178 (29), 163 (21), 150 (42), 92 (16). High resolution-ms Calcd for $C_{14}H_{15}NO_4$: 261.1001. Found: 261.1020.

Diisopropyl *N*-[(2,3,5-trimethoxy-4-methylphenyl)methyl]glutamate (**11b**) 2,3,5-Trimethoxy-4-methylbenzaldehyde (**8b**) (8.4 g, 40 mmol) was added to a stirred solution of diisopropyl (±)-glutamate (**9**) (9.24 g, 40 mmol) in dichloromethane (400 ml) and 10 drops of acetic acid. After the mixture was heated at reflux for 3 h under a Dean-Stark separator, an additional 100 mol % of glutamate was added in two portions, every 30 min, together with 10 more drops of acetic acid. Refluxing was continued for an additional 8 h and then the solution was evaporated in vacuo to give the Schiff base (**10b**) which was used in the following reaction without further purification. The crude Schiff base (**10b**) was dissolved in 2-propanol (100 ml) and sodium cyanoborohydride (4.69 g, 80 mmol) was added in one portion with stirring at 0°C. The reaction mixture was stirred for 5 h, and the solvent was removed in vacuo. The residue was diluted with water (100 ml) and then extracted with dichloromethane (100 ml x 3). The combined extracts were washed with 5% $NaHCO_3$ (100 ml), dried, and concentrated in vacuo. The residue (21.7 g) was subjected to chromatography (silica gel, 210 g; elution with 5:1 = hexane-ethyl acetate) to give **11b** (15.08 g, 88.7 %) as a pale yellow oil; ν_{max} (neat) 1730 cm^{-1}; λ_{max} nm (log ε) 211 (4.26), 225sh (3.94), 275sh (3.30), 284 (3.37); δ_H 1.20, 1.26 (each 6H, d, *J* = 6 Hz, $CH(CH_3)_2$), 1.81-2.05 (3H, m), 2.11 (3H, s, $ArCH_3$), 2.38-2.44 (2H, m), 3.24 (1H, dd, *J* = 8, 2 Hz, CH), 3.65, 3.78 (each 1H, d, *J* = 13 Hz, ArCH), 3.79, 3.81, 3.81 (each 3H, s, OCH_3), 4.98, 5.06 (each 1H, sept, *J* = 6 Hz, OCH), 6.61 (1H, s, ArH); δ_C 8.8 (q, $ArCH_3$), 21.7, (q, $CH(CH_3)_2$), 21.7 (q, $CH(CH_3)_2$), 21.8 (q, $CH(CH_3)_2$), 21.9 (q, $CH(CH_3)_2$), 28.4 (t, CH_2), 31.1 (t, CH_2), 46.7 (t, NCH_2Ar), 55.8 (q, OCH_3), 60.2 (d, NCH), 60.2 (q, OCH_3), 60.9 (q, OCH_3), 67.6 (d, OCH), 68.3 (d, OCH), 106.3 (d), 119.6 (s), 130.2 (s), 145.3 (s), 151.8 (s), 154.0 (s), 172.7 (s, CO), 174.4 (s, CO); *m/z* (%) 425 (M^+, 6), 339 (12), 338 (60), 230 (19), 210 (20), 196 (15), 195 (100), 180 (39). High-resolution ms Calcd for $C_{22}H_{35}NO_7$: 425.2413. Found: 425.2417.

N-[(2,3,5-Trimethoxy-4-methylphenyl)methyl]-5-isopropyloxycarbonyl-2-pyrrolidone (**12b**)

A solution of the ester (**11b**) (14.88 g, 35 mmol) in acetic acid (100 ml) was heated under reflux for 7 h. The reaction mixture was diluted with water (100 ml), made alkaline with powdered Na_2CO_3, and then extracted with dichloromethane (50 ml x 3). The combined extracts were washed with water (100 ml), dried, and concentrated in vacuo. The residue (12.76 g) was subjected to chromatography (silica gel, 130 g; elution with 1:1 = hexane-ethyl acetate) to give **12b** (11.06 g, 86.6 %) as colorless syrup; ν_{max} (neat) 1738, 1702 cm^{-1}; λ_{max} nm (log ε) 217 (4.03), 226sh (3.96), 274sh (3.07), 285 (3.39); δ_H 1.26 (6H, d, *J* = 6 Hz, $CH(CH_3)_2$), 1.95-2.05 (1H, m), 2.11 (3H, s, $ArCH_3$), 2.16-2.60 (3H, m), 3.75, 3.76, 3.81 (each 3H, s, OCH_3), 4.00 (1H, dd, *J* = 9, 3 Hz, CHN), 4.12, 4.91 (each 1H, d, *J* = 14 Hz, ArCH), 5.07 (1H, sept, *J* = 6 Hz, OCH), 6.49 (1H, s, ArH); δ_C 8.8 (q, $ArCH_3$), 21.6, (q, $CH(CH_3)_2$), 21.7 (q, $CH(CH_3)_2$), 22.8 (t, CH_2), 29.5 (t, CH_2), 40.1 (t, NCH_2Ar), 55.7 (q, OCH_3), 58.9 (d, NCH), 60.1 (q, OCH_3), 60.7 (q, OCH_3), 68.8 (d, OCH), 106.8 (d), 120.8 (s), 126.1 (s), 145.5 (s), 151.6 (s), 154.1 (s), 171.4 (s, CO), 175.0 (s, CO); *m/z* (%) 365 (M^+, 74), 334 (36), 292 (13), 278 (15), 250 (20), 196 (13), 195 (100), 180 (34), 132 (12). High-resolution ms Calcd for $C_{19}H_{27}NO_6$: 365.1838. Found: 365.1841.

N-[(2,3,5-Trimethoxy-4-methylphenyl)methyl]-5-carboxy-2-pyrrolidone (13b) A solution of the ester (**12b**) (10.95 g, 30 mmol) in dioxane (50 ml) was cooled at 0°C, and a methanol (30 ml) solution of 2N KOH (22.5 ml) was added and stirring was continued at room temperature for 3 h. The solution was evaporated, and the residue was diluted with water (100 ml) and then washed with ether (100 ml). The aqueous phase was then adjusted pH 3. The resulting precipitate (**13b**) (10.9 g) was recrystallized from ethanol to give **13b** (8.31 g, 85.9 %) as colorless needles, mp 132-133°C; ν_{max} (KBr) 3000-2500, 1724, 1640 cm^{-1}; λ_{max} nm (log ε) 227 (3.77), 226sh (3.96), 276sh (3.33), 284 (3.40); δ_H 2.11 (3H, s, $ArCH_3$), 2.13-2.67 (4H, m), 3.77, 3.77, 3.80 (each 3H, s, OCH_3), 4.11 (1H, dd, *J* = 9, 3 Hz, CHN), 4.17, 4.94 (each 1H, d, *J* = 15 Hz, ArCH), 6.51 (1H, s, ArH), 8.64 (1H, br s, D_2O exchangeable); δ_C 8.9 (q, $ArCH_3$), 23.0 (t, CH_2), 29.5 (t, CH_2), 40.6 (t, NCH_2Ar), 55.8 (q, OCH_3), 58.8 (d, NCH), 60.2 (q, OCH_3), 60.7 (q, OCH_3), 107.0 (d), 121.1 (s), 125.7 (s), 145.5 (s), 151.7 (s), 154.2 (s), 175.3 (s, CO), 176.0 (s, CO); *m/z* (%) 323 (M^+, 100), 308 (13), 292 (49), 195 (33), 180 (24). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.40; H, 6.56; N, 4.29.

9-Hydroxy-6,7-dimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (15b)

A solution of **13b** (1.62 g, 5 mmol) in phosphorous oxychloride (5 ml, 53.6 mmol) was heated at 50°C for 30 min. The solution was cooled at room temperature, and then $SnCl_4$ (2.5 ml, 21.4 mmol) was added in one portion with stirring. The mixture was heated at 65°C for 30 min, then poured into water (50 ml). The resulting solution was made alkaline with powdered Na_2CO_3, and extracted with ethyl acetate (50 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue (1.35 g) was subjected to chromatography (silica gel, 100 g; elution with 3:1 hexane-acetone) to give **15b** (832 mg, 57.1 %) as a pale yellow oil; ν_{max} (nujol) 3472, 1688, 1642 cm^{-1}; λ_{max} nm (log ε) 206 (4.32), 220sh (4.26), 280 (4.05), 350 (3.62); δ_H 2.13 (3H, s, $ArCH_3$), 2.33-2.59 (4H, m), 3.81, 3.93 (each 3H, s, OCH_3), 4.09 (1H, d, *J* = 18 Hz, 5-H), 4.29-4.35 (1H, m, 10a-H), 5.40 (1H, d, *J* = 18 Hz, 5-H), 12.17 (1H, br s, D_2O exchangeable); δ_C 8.1 (q, $ArCH_3$), 20.7 (t, CH_2), 29.9 (t, CH_2), 37.2 (t, 5-C), 60.4 (q, OCH_3), 60.5 (q, OCH_3), 60.6 (d, 10a-C), 110.2 (s), 119.1 (s), 129.9 (s), 141.2 (s), 159.3 (s), 159.3 (s), 173.6 (s, CO), 199.2 (s, CO); *m/z* (%) 291 (M^+, 100), 277 (13), 276 (37), 248 (15), 222 (11), 193 (16), 180 (15). High-resolution-ms Calcd for $C_{15}H_{17}NO_5$: 291.1107. Found: 291.1117.

Reduction of the Ketoamide (15b) A solution of the ketoamide (**15b**) (694 mg, 2.38 mmol) in methanol (10 ml) was cooled at 0°C, and sodium borohydride (108 mg, 2.85 mmol) was added and stirring was continued at room temperature for 1 h. The mixture was diluted with water (10 ml) and then it was acidified with 3% HCl, and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo to give the residue (689 mg). This material was subjected to chromatography (silica gel, 70 g; elution with ethyl acetate) to give **16** (511 mg, 73 %) as colorless solid, recrystallization of which from ethyl acetate gave an analytical sample as colorless prisms. Further elution with ethyl acetate-methanol (20:1) as the eluent gave **17** (5 mg, 0.7 %) as colorless solid, recrystallization of which from ethyl acetate gave an analytical sample as colorless prisms. **16**: mp 180-181°C; ν_{max} (KBr) 3308, 3204, 1668, 1620, 1584 cm^{-1}; λ_{max} nm (log ε) 210 (4.53), 225sh (4.03), 276sh (3.38), 286 (3.49); δ_H 2.12 (3H, s, $ArCH_3$), 2.06-2.21 (1H, m), 2.40-2.48 (3H, m), 3.61-3.67 (1H, m), 3.79, 3.80 (each 3H, s, OCH_3), 4.04 (1H, d, *J* = 18 Hz, 5-H), 4.60 (1H, br s, OH, D_2O exchangeable), 4.68 (1H, d, *J* = 9 Hz, 10-H), 4.89 (1H, d, *J* = 18 Hz, 5-H), 8.49 (1H, br s, D_2O exchangeable); δ_C 8.6 (q, $ArCH_3$), 22.2 (t, CH_2), 29.6 (t, CH_2), 38.6 (t, 5-C), 59.3 (d, 10-C), 60.2 (q, OCH_3), 60.2 (q, OCH_3), 71.6 (d, 10a-C), 116.0 (s), 118.3 (s), 123.4 (s), 142.2 (s), 151.1 (s), 151.4 (s), 174.4 (s, CO); *m/z* (%) 293 (M^+, 38), 276 (17), 275 (100), 274 (29), 261 (16), 260 (93), 245 (22), 210 (16), 195 (41). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.42; H, 6.53; N, 4.63. **17**: mp 178-180°C; ν_{max} (KBr) 3328, 3204, 1664, 1606, 1586 cm^{-1}; λ_{max} nm (log ε) 225 (3.89), 276sh (3.38), 284 (3.46); δ_H 2.06-2.48 (5H, m), 2.17 (3H, s, $ArCH_3$), 3.73-3.87 (2H, m), 3.80, 3.81 (each 3H, s, OCH_3), 4.03 (1H, d, *J* = 18 Hz, 5-H), 4.71 (1H, d, *J* = 2.7 Hz, 10-H), 4.99 (1H, d, *J* = 18 Hz, 5-H); δ_C 9.0 (q, $ArCH_3$), 19.2 (t, CH_2), 30.7 (t, CH_2), 38.5 (t, 5-C), 58.9 (d, 10-C), 60.2 (q, OCH_3), 60.3 (q, OCH_3), 63.6 (d, 10a-C), 118.7 (s), 119.0 (s), 123.6 (s), 143.0 (s), 149.6 (s), 151.5 (s), 176.0 (s, CO); *m/z* (%) 293 (M^+, 9), 276 (19), 275 (100), 274 (27), 261 (14), 260 (93), 245 (28), 195 (13). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.26; H, 6.50; N, 4.69.

9-Hydroxy-6,7-dimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-one (**18**)

Triethylsilane (0.956 ml, 1.6 mmol) was added to a stirred solution of **16** (439.5 mg, 1.5 mmol) in trifluoroacetic acid (2 ml) at 0°C, and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with water (10 ml), made alkaline with powdered Na_2CO_3, and then extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (530 mg) was subjected to chromatography (silica gel, 60 g; elution with 20:3 = chloroform-acetone) to give **18** (381 mg, 92 %) as a solid, recrystallization of which from ethyl acetate gave colorless prisms, mp 209-211°C; ν_{max} (KBr) 3296, 1666, 1586 cm^{-1}; λ_{max} nm (log ε) 219 (4.04), 274sh (3.28), 283 (3.36); δ_H 1.77-1.89 (1H, m), 2.17 (3H, s, $ArCH_3$), 2.27-2.52 (4H, m), 3.14 (1H, dd, J = 16, 4 Hz, 10-H), 3.65-3.76 (1H, m), 3.80, 3.80 (each 3H, s, OCH$_3$), 3.80 (1H, m), 4.16 (1H, d, J = 18 Hz, 5-H), 4.99 (1H, d, J = 18 Hz, 5-H); δ_C 8.9 (q, ArCH$_3$), 25.1 (t, CH$_2$), 30.1 (t, CH$_2$), 30.4 (t, CH$_2$, 10-C), 38.8 (t, 5-C), 53.6 (d, 10a-C), 60.2 (q, OCH$_3$), 60.4 (q, OCH$_3$), 116.0 (s), 116.0 (s), 123.7 (s), 143.4 (s), 147.7 (s), 149.6 (s), 174.4 (s, CO); m/z (%) 278 (M$^+$, 18), 277 (100), 262 (31), 246 (11), 194 (63), 179 (78), 164 (12), 151 (19). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.75; H, 6.89; N, 4.98.

6,7,9-Trimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-one (19) Sodium hydride (60 %, oil dispersion, washed with dry hexane three times, 28.8 mg, 1.2 mmol) was added to a stirred solution of **18** (277 mg, 1 mmol) in dry DMF (12 ml) under ice-cooling, and stirring was continued for 1.5 h at room temperature. Methyl iodide (284 mg, 2 mmol) in dry DMF (1 ml) was added for 5 min at 0°C. The reaction mixture was stirred for 17 h at room temperature, poured into water (100 ml), and extracted with dichloromethane (50 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue (330 mg) was subjected to chromatography (silica gel, 30 g; elution with 4:1 = chloroform-acetone) to give **19** (287 mg, 98.5 %) as pale yellow oil; ν_{max} (neat) 1666, 1604, 1584 cm^{-1}; λ_{max} nm (log ε) 224 (3.96), 274sh (3.06), 284 (3.36); δ_H 1.78-1.90 (1H, m), 2.19 (3H, s, ArCH$_3$), 2.33-2.54 (3H, m), 3.20 (1H, dd, J = 16, 4 Hz, 10-H), 3.65-3.72 (2H, m), 3.67, 3.81, 3.84 (each 3H, s, OCH$_3$), 4.18 (1H, d, J = 18 Hz, 5-H), 4.88 (1H, d, J = 18 Hz, 5-H); δ_C 9.3 (q, ArCH$_3$), 25.2 (t, CH$_2$), 30.2 (t, CH$_2$), 30.6 (t, CH$_2$, 10-C), 38.8 (t, 5-C), 53.6 (d, 10a-C), 60.0 (q, OCH$_3$), 60.1 (q, OCH$_3$), 60.1 (q, OCH$_3$), 122.5 (s), 123.6 (s), 123.9 (s), 146.1 (s), 150.0 (s), 152.1 (s), 174.3 (s, CO); m/z (%) 291 (M$^+$, 100), 276 (20), 260 (11), 208 (53), 193 (51). High-resolution ms Calcd for $C_{16}H_{21}NO_4$: 291.1470. Found: 291.1469.

Formation of 3-Cyano-6,7,9-Trimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-ones (20 and 21) Lithium aluminum hydride (33 mg, 0.87 mmol) was added to a stirred solution of **19** (125 mg, 0.43 mmol) in dry THF (10 ml) at -18°C. After being kept at the same temperature for 10 min and then 0°C for 1 h, the solution was treated sequentially with NaCN (84 mg, 1.7 mmol) in water (0.2 ml) and allowed to stir for 3 h. The mixture was filtered and the filter cake was carefully washed with dichloromethane (100 ml). The combined filtrates were concentrated in vacuo. The residue (119 mg) was subjected to chromatography (silica gel, 15 g; elution with 10:1 = benzene-ethyl acetate) to give **20** (52.3 mg, 40.2 %) and **21** (26.7 mg, 20.5 %). Further elution with ethyl acetate-methanol (20:1) gave **22** (20.3 mg, 17 %). **20**: colorless oil; ν_{max} (neat) 2940, 2838, 1462, 1412, 1378, 1342, 1308, 1288, 1260, 1212, 1192, 1170, 1146, 1116, 1076, 992, 964, 896 cm^{-1}; λ_{max} nm (log ε) 222 (3.88), 275 (2.93); δ_H 1.61-1.83 (1H, m), 2.14-2.39 (3H, m), 2.19 (3H, s, $ArCH_3$), 2.45 (1H, dd, *J* = 16, 5 Hz, 10-H), 2.68-2.80 (1H, m), 3.17 (1H, dd, *J* = 16, 3 Hz, 10-H), 3.67 (3H, s, OCH_3), 3.70 (1H, d, *J* = 15 Hz, 5-H), 3.80, 3.83 (each 3H, s, OCH_3), 4.16 (1H, d, *J* = 15 Hz, 5-H), 4.19 (1H, d, *J* = 7 Hz, 3-H); δ_C 9.3 (q, $ArCH_3$), 28.0 (t, CH_2), 29.2 (t, CH_2), 30.8 (t, CH_2, 10-C), 47.0 (t, 5-C), 54.5 (d), 56.6 (d), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 117.5 (s, CN), 123.1 (s), 123.3 (s), 125.8 (s), 146.0 (s), 149.8 (s), 152.3 (s); *m/z* (%) 302 (M^+, 25), 275 (26), 208 (100), 193 (68). High-resolution ms Calcd for $C_{17}H_{22}N_2O_3$: 302.1630. Found: 302.1635. **21**: colorless prisms from dichloromethane-hexane, mp 105-106°C; ν_{max} (KBr) 2996, 2944, 2900, 2836, 2800, 1464, 1412, 1384, 1342, 1310, 1260, 1200, 1114, 1078, 1058, 996 cm^{-1}; λ_{max} nm (log ε) 224 (3.92), 278 (2.94); δ_H 1.72-1.83 (1H, m), 2.13-2.33 (3H, m), 2.18 (3H, s, $ArCH_3$), 2.35-2.55 (2H, m), 3.12 (1H, d, *J* = 15 Hz, 10-H), 3.27 (1H, d, *J* = 15 Hz, 5-H), 3.30 (1H, t, *J* = 8 Hz), 3.67, 3.80, 3.84 (each 3H, s, OCH_3), 4.47 (1H, d, *J* = 15 Hz, 5-H); δ_C 9.2 (q, $ArCH_3$), 27.9 (t, CH_2), 30.0 (t, CH_2), 30.4 (t, CH_2, 10-C), 49.9 (t, 5-C), 54.3 (d), 59.8 (q, OCH_3), 60.0 (d, 10a-C), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 119.8 (s, CN), 123.2 (s), 123.4 (s), 125.6 (s), 145.8 (s), 149.7 (s), 152.2 (s); *m/z* (%) 302 (M^+, 35), 208 (100), 193 (49). Anal. Calcd for $C_{17}H_{22}N_2O_3$-1/20H_2O: C, 67.33; H, 7.34; N, 9.24. Found: C, 67.14; H, 7.28; N, 9.24. **22**: colorless oil; ν_{max} (neat) 2944, 2832, 2788, 2464, 1410,1380, 1338, 1318, 1304, 1256, 1114, 1066, 998, 966 cm^{-1}; λ_{max} nm (log ε) 224 (3.83), 273 (2.92); δ_H 1.51-1.65 (1H, m), 1.78-2.02 (2H, m), 2.05-2.33 (3H, m), 2.18 (3H, s, $ArCH_3$), 2.46 (1H, dd, *J* = 16, 5 Hz, 10-H), 3.11 (1H, dd, *J* = 16, 4 Hz, 10-H), 3.19 (1H, d, *J* = 16 Hz, 5-H), 3.31 (1H, dt, *J* = 8, 2 Hz), 3.67, 3.80, 3.81 (each 3H, s, OCH_3), 4.27 (1H, d, *J* = 15 Hz, 5-H); δ_C 9.2 (q, $ArCH_3$), 21.5 (t, CH_2), 30.4 (t, CH_2), 30.7 (t, CH_2,), 51.1 (t, CH_2), 54.9 (t, CH_2), 59.8 (q, OCH_3),, 60.1 (d, 10a-C), 60.1 (q, OCH_3), 60.1 (q, OCH_3), 122.7 (s), 124.2 (s), 127.2 (s), 145.8 (s), 149.5 (s), 152.4 (s); *m/z* (%) 277 (M^+, 54), 276 (28), 209 (15), 208 (100), 193 (57). High-resolution ms Calcd for $C_{16}H_{23}NO_3$: 277.1686. Found: 277.1682.

Formation of 3-Cyano-9-hydroxy-6,7-dimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizin-3-ones (23 and 24) Lithium aluminum hydride (38 mg, 1 mmol) was added to a stirred solution of **18** (139 mg, 0.5 mmol) in dry THF (20 ml) at -18°C. After being kept at the same temperature for 30 min and then 0°C for 1 h, the solution was treated sequentially with NaCN (98 mg, 2 mmol) in water (0.3 ml) and allowed to stir for 3 h. The mixture was filtered and the filter cake was carefully washed with dichloromethane (100 ml). The combined filtrates were concentrated in vacuo. The residue (128 mg) was subjected to chromatography (silica gel, 15 g; elution with 20:1 = chloroform-acetone) to give **23** and **24** (81.1 mg, 56.1 %) as a ca 3:1 mixture of isomers. Further elution with ethyl acetate-methanol (4:1) gave the starting material (**18**) (14.6 mg, 11 % recovery) and **25** (25.2 mg, 19 %). For the mixture; ν_{max} (neat) 3700-3100, 2240 cm^{-1}; δ_H (major isomer: **23**) 1.61-1.72 (1H, m), 2.15 (3H, s, ArCH$_3$), 2.17-2.19 (1H, m), 2.17-2.35 (2H, m), 2.39 (1H, dd, *J* = 16, 11 Hz, 10-H), 2.73-2.78 (1H, m, 10a-H), 3.03 (1H, dd, *J* = 16, 4 Hz, 10-H), 3.69 (1H, d, *J* = 15 Hz, 5-H), 3.80, 3.81 (each 3H, s, OCH$_3$), 4.16 (1H, d, *J* = 15 Hz, 5-H), 4.19 (1H, d, *J* = 8 Hz, 3-H), 4.56 (1H, br, OH); δ_H (minor isomer **24**) 1.71-1.81 (1H, m), 2.08-2.23 (1H, m), 2.15 (3H, s, ArCH$_3$), 2.25-2.33 (2H, m), 2.40-2.47 (2H, m), 2.97 (1H, dd, *J* = 21, 9 Hz, 10-H), 3.27 (1H, d, *J* = 15 Hz, 5-H), 3.28 (1H, t, *J* = 8 Hz, 3-H), 3.80, 3.81 (each 3H, s, OCH$_3$), 4.47 (1H, d, *J* = 15 Hz, 5-H), 4.52 (1H, br, OH); δ_C (major isomer: **23**) 8.7 (q, ArCH$_3$), 28.0 (t, CH$_2$), 29.3 (t, CH$_2$), 30.5 (t, CH$_2$), 46.9 (t, CH$_2$), 54.5 (d, 3-C), 56.6 (d, 10a-C), 60.3 (q, OCH$_3$), 60.4 (q, OCH$_3$), 115.3 (s), 116.0 (s), 117.4 (s, CN), 125.8 (s), 143.3 (s), 147.6 (s), 149.4 (s); δ_C (minor isomer **24**) 8.7 (q, ArCH$_3$), 27.9 (t, CH$_2$), 30.1 (t, CH$_2$), 30.1 (t, CH$_2$), 49.8 (t, CH$_2$), 54.3 (d, 3-C), 60.0 (d, 10a-C), 60.3 (q, OCH$_3$), 60.4 (q, OCH$_3$), 115.5 (s), 116.2 (s), 119.8 (s, CN), 125.6 (s), 143.2 (s), 147.6 (s), 149.4 (s); *m/z* (%) 288 (M$^+$, 24), 277 (18), 261 (19), 219 (12), 194 (100), 179 (60), 151 (20), 83 (12). **25**: colorless prisms from dichloromethane-hexane, mp 123-124°C; ν_{max} (KBr) 2940, 2884, 2832, 1462, 1416, 1380, 1354, 1310, 1264, 1120, 1066, 1004, 980 cm^{-1}; λ_{max} nm (log ε) 221 (3.86), 284 (3.32); δ_H 1.51-1.61 (1H, m), 1.77-1.86 (1H, m), 1.88-1.98 (1H, m), 2.06-2.13 (1H, m), 2.12 (3H, s, ArCH$_3$), 2.26-2.30 (2H, m), 2.37 (1H, dd, *J* = 15, 11 Hz, 10-H), 2.90 (1H, dd, *J* = 15, 3 Hz, 10-H), 3.19 (1H, d, *J* = 15 Hz, 5-H), 3.32 (1H, t like), 3.69 (1H, s, D$_2$O exchangeable, OH), 3.77, 3.79 (each 3H, s, OCH$_3$), 4.26 (1H, d, *J* = 15 Hz, 5-H); δ_C 8.8 (q, ArCH$_3$), 21.4 (t, CH$_2$), 30.1 (t, CH$_2$), 30.9 (t, CH$_2$), 51.0 (t, CH$_2$), 54.8 (t, CH$_2$), 60.3 (q, OCH$_3$), 60.3 (q, OCH$_3$), 116.0 (s), 117.5 (s), 126.6 (s), 143.1 (s), 147.9 (s), 149.3 (s); *m/z* (%) 263 (M$^+$, 65), 262 (29), 195 (13), 194 (100), 193 (11), 179 (66), 131 (11), 70 (28). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.16; H, 7.97; N, 5.23.

Oxidative Demethylation of the phenols (**23**) and (**24**) with 10N HNO$_3$; (3*RS*, 10a*RS*)-3-Cyano-7-methoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-6,9-dione (**7**) and (3*RS*, 10a*SR*)-3-Cyano-7-methoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-6,9-dione (**26**) A solution of the mixture (**23**) and (**24**) (*ca* 3:1 mixture; 77.6 mg, 0.27 mmol) in 10N HNO$_3$ (1 ml) was stirred for 15 min at 0°C. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (10 ml x

3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (67.4 mg) was subjected to preparative layer chromatography on silica gel (Merck 5715, solvent 5:1 = benzene-ethyl acetate) to afford **7** (19.0 mg, 25.9 %) and **26** (10.6 mg, 14.5 %). **7**: pale yellow prisms from ether-hexane, mp 106-107°C; ν_{max} (KBr) 1685, 1636, 1610 cm^{-1}; λ_{max} nm (log ε) 270 (4.06), 362 (2.70); δ_H 1.60-1.68 (1H, m), 1.96 (3H, s, quinone CH$_3$), 2.12-2.19 (2H, m), 2.20-2.32 (2H, m), 2.62-2.69 (1H, m, 10a-H), 2.95 (1H, dt, *J* = 19, 3 Hz, 10-H), 3.46 (1H, ddd, *J* = 18, 4, 3 Hz, 5-H), 3.92 (1H, dd, *J* = 18, 3 Hz, 5-H), 4.00 (3H, s, OCH$_3$), 4.16 (1H, d, *J* = 8 Hz, 3-H); δ_C 8.7 (q, quinone CH$_3$), 27.8 (t, CH$_2$), 28.7 (t, CH$_2$), 29.8 (t, CH$_2$), 45.4 (t, CH$_2$), 53.7 (d, 3-C), 55.7 (d, 10a-C), 60.9 (q, OCH$_3$), 117.1 (s, CN), 128.8 (s), 137.6 (s), 139.8 (s), 155.5 (s), 181.8 (s), 187.2 (s); *m/z* (%) 272 (M$^+$, 79), 271 (35), 257 (39), 256 (11), 247 (11), 246 (12), 245 (58), 244 (100), 243 (12), 242 (14), 241 (50), 232 (16), 231 (10), 230 (62), 229 (52), 226 (20), 212 (10), 202 (13), 198 (13), 180 (15), 178 (42), 150 (14), 148 (10), 91 (11), 83 (16), 68 (10), 67 (13). Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.11; H, 5.94; N, 10.18. **26**: pale yellow prisms from ether-hexane, mp 110-111°C (dec.); ν_{max} (KBr) 1668, 1658, 1638, 1612 cm^{-1}; λ_{max} nm (log ε) 268 (4.11), 367 (2.27); δ_H 1.65-1.80 (1H, m), 1.96 (3H, s, quinone CH$_3$), 2.10-2.30 (4H, m), 2.32-2.44 (1H, m, 10a-H), 2.62-2.69 (1H, m), 2.89 (1H, dt, *J* = 19, 3 Hz, 10-H), 3.06 (1H, ddd, *J* = 18, 4, 3 Hz, 5-H), 3.33 (1H, t, *J* = 8 Hz, 3-H), 4.00 (3H, s, OCH$_3$), 4.23 (1H, dd, *J* = 18, 3 Hz, 5-H); δ_C 8.7 (q, quinone CH$_3$), 27.9 (t, CH$_2$), 29.6 (t, CH$_2$), 29.7 (t, CH$_2$), 47.8 (t, CH$_2$), 53.4 (d, 3-C), 58.7 (d, 10a-C), 61.0 (q, OCH$_3$), 119.4 (s, CN), 128.8 (s), 137.4 (s), 140.1 (s), 155.5 (s), 181.9 (s), 187.2 (s); *m/z* (%) 272 (M$^+$, 67), 271 (28), 257 (33), 246 (15), 245 (73), 244 (100), 243 (16), 242 (25), 241 (92), 232 (14), 231 (14), 230 (85), 229 (59), 228 (11), 227 (12), 226 (34), 213 (10), 212 (15), 211 (11), 202 (18), 198 (24), 184 (15), 183 (13), 180 (11), 178 (37), 154 (13), 150 (14), 144 (11), 142 (10), 118 (11), 115 (10), 91 (14), 83 (20), 77 (14), 68 (12), 67 (17). Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.37; H, 5.97; N, 10.20.

6,7,9,10-Tetramethoxy-9-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3-one (27) Sodium hydride (60 %, oil dispersion, washed with dry hexane three times, 26.4 mg, 1.1 mmol) was added to a stirred solution of **16** (147 mg, 0.5 mmol) in dry DMF (10 ml) under ice-cooling, and stirring was continued for 1 h at room temperature. Methyl iodide (156 mg, 1.1 mmol) in dry DMF (1 ml) was added for 5 min at 0°C. The reaction mixture was stirred for 3 h at room temperature, poured into water (100 ml), and extracted with ethyl acetate (50 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue (167 mg) was subjected to chromatography (silica gel, 30 g; elution with 10:1 = chloroform-acetone) to give **27** (139 mg, 87 %) as pale yellow oil; ν_{max} (neat) 1776, 1686 cm^{-1}; λ_{max} nm (log ε) 223 (3.98), 274sh (3.06), 284 (3.07); δ_H 1.68-1.81 (1H, m), 2.20 (3H, s, $ArCH_3$), 2.23-2.39 (1H, m), 2.41-2.57 (2H, m), 3.36, 3.72 (each 3H, s, OCH_3), 3.78 (1H, d, *J* = 16 Hz, 5-H), 3.84, 3.84 (each 3H, s, OCH_3), 4.05-4.12 (1H, m), 4.49 (1H, d, *J* = 3 Hz, 10-H), 5.16 (1H, d, *J* = 16 Hz, 5-H),; δ_C 9.6 (q, $ArCH_3$), 26.2 (t, CH_2), 31.0 (t, CH_2), 36.1 (t, CH_2), 56.6 (q, OCH_3), 60.2 (q, OCH_3), 60.3 (d, 10a-C), 60.8 (q, OCH_3), 61.5 (q, OCH_3), 76.1 (d, 10-C), 122.2 (s), 124.1 (s), 128.6 (s), 145.5 (s), 151.8 (s), 154.7 (s), 173.8 (s, CO); *m/z* (%) 321 (M$^+$, 90), 289 (11). 239 (16), 238 (100), 224 (14), 223 (93). High-resolution ms Calcd for $C_{17}H_{23}NO_5$: 321.1576. Found: 321.1580.

7-Methoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,6,9-trione (28) A solution of **18** (138.5 mg, 0.5 mmol) in 10N HNO_3 (2 ml) was stirred for 1 h at 0°C. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (135.4 mg) was subjected to chromatography (silica gel, 15 g; elution with 10:1 = chloroform-acetone) to give **28** (129 mg, 99 %) as a solid, recrystallization of which from ether-dichloromethane gave yellow prisms, mp 104-105°C; ν_{max} (KBr) 1688, 1656, 1640 cm^{-1}; λ_{max} nm (log ε) 267 (4.12), 376 (2.72); δ_H 1.78-1.88 (1H, m), 1.96 (3H, s, quinone CH_3), 2.04-2.17 (1H, m), 2.39-2.51 (3H, m), 3.03 (1H, d, *J* = 18 Hz, 10-H), 3.56-3.66 (1H, m, 10a-H), 3.85 (1H, dd, *J* = 21, 4 Hz, 5-H), 4.02 (3H, s, OCH_3), 4.75 (1H, dd, *J* = 21, 3 Hz, 5-H); δ_C 8.8 (q, quinone CH_3), 24.9 (t, CH_2), 29.4 (t, CH_2), 29.7 (t, CH_2), 37.8 (t, CH_2), 52.3 (d, 10-C), 61.0 (q, OCH_3), 128.7 (s), 136.2 (s), 139.0 (s), 155.5 (s), 174.2 (s), 181.5 (s), 186.6 (s); *m/z* (%) 261 (M$^+$, 100), 260 (56), 246 (32), 245 (12), 218 (17), 206 (11), 191 (13), 178 (12). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.44; H, 5.80; N, 5.31.

10-Hydroxy-7-methoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,6,9-trione (29)

A solution of **16** (147 mg, 0.5 mmol) in 10N HNO_3 (2 ml) was stirred for 1 h at 0°C. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (138 mg) was subjected to chromatography (silica gel, 15 g; elution with 10:1 = chloroform-acetone) to give **29** (127 mg, 92 %) as a solid, recrystallization of which from ether-dichloromethane gave yellow prisms, mp 151-152°C (decomp.); ν_{max} (KBr) 3368, 1680, 1654, 1638, 1614 cm^{-1}; λ_{max} nm (log ε) 265 (4.06), 384 (2.78); δ_H 1.95 (3H, s, quinone CH_3), 2.05-2.22 (1H, m), 2.42-2.52 (3H, m), 3.52-3.59 (1H, m, 10a-H), 3.81 (1H, dd, *J* =

21, 3 Hz, 5-H), 4.05 (3H, s, OCH_3), 4.32 (1H, br s, D_2O exchangeable, OH), 4.66 (1H, dt, J = 8, 3 Hz, 10-H), 4.79 (1H, dd, J = 21, 2 Hz, 5-H); δ_C 8.5 (q, quinone CH_3), 22.5 (t, CH_2), 29.3 (t, CH_2), 37.9 (t, CH_2), 57.4 (d, 10a-C), 61.1 (q, OCH_3), 68.6 (d, 10-C), 128.8 (s), 137.2 (s), 139.0 (s), 155.7 (s), 174.3 (s), 181.5 (s), 189.3 (s); *m/z* (%) 277 (M^+, 100), 261 (33), 260 (36), 259 (63), 258 (40), 248 (14), 246 (35), 244 (32), 241 (12), 230 (20), 216 (27), 205 (13), 204 (36), 195 (10), 194 (68), 188 (17), 165 (58), 84 (74), 83 (14), 77 (11), 67 (10). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.54; N, 5.05. Found: C, 60.66; H, 5.48; N, 4.98.

7,10-Dimethoxy-8-methyl-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,6,9-trione (**30**)

A solution of **27** (100 mg, 0.31 mmol) in 10N HNO_3 (1 ml) was stirred for 1 h at 0°C. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (67.3 mg) was subjected to chromatography (silica gel, 15 g; elution with 10:1 = chloroform-acetone) to give **30** (56.6 mg, 62 %) as a solid, recrystallization of which from ether-dichloromethane gave yellow prisms, mp 91-92°C; ν_{max} (KBr) 1692, 1642, 1608 cm^{-1}; λ_{max} nm (log ε) 266 (4.06), 367 (2.96); δ_H 1.97 (3H, s, quinone CH_3), 2.01-2.11 (1H, m), 2.44-2.65 (3H, m), 3.60-3.65 (1H, m), 3.68 (3H, s, OCH_3), 3.69 (1H, dd, J = 20, 2 Hz, 5-H), 3.99 (3H, s, OCH_3), 4.10 (1H, dt, J = 8, 2 Hz, 10-H), 4.80 (1H, dd, J = 20, 2 Hz, 5-H); δ_C 8.9 (q, quinone CH_3), 24.4 (t, CH_2), 29.6 (t, CH_2), 37.2 (t, CH_2), 58.3 (d, 10a-C), 60.9 (q, OCH_3), 61.0 (q, OCH_3), 77.1 (d, 10-C), 130.1 (s), 137.9 (s), 140.6 (s), 155.0 (s), 173.7 (s), 181.5 (s), 186.4 (s); *m/z* (%) 291 (M^+, 100), 208 (63), 193 (74), 180 (18), 179 (61), 165 (16). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.90; N, 4.79.

REFERENCES AND NOTES

1. A. Kubo, T. Nakai, Y. Koizumi, N. Saito, Y. Mikami, K. Yazawa, and J. Uno, Heterocycles, 1992, **34**, 1201.
2. A. Kubo and N. Saito, 'Studies in Natural Products Chemistry', ed. by Atta-Ur-Rahman, Elsevier, Inc., Amsterdam, 1992, Vol. 10, pp. 77-145.
3. Cyanocycline A *see*: T. Hayashi, T. Noto, Y. Nawata, H. Okazaki, M. Sawada, and K. Ando, J. Antibiot., 1982, **35**, 771; T. Hayashi and Y. Nawata, J. Chem. Soc., Perkin Trans. 2, 1983, 335: DX-52-1 *see*: H. Saito and T. Hirata, Tetrahedron Lett., 1987, **28**, 4065; H. Saito, S. Kobayashi, Y. Uosaki, A. Sato, K. Fujimoto, K. Miyoshi, T. Ashizawa, M. Morimoto, and T. Hirata, Chem. Pharm. Bull., 1990, **38**, 1278.

4. Saframycin A *see*: K. Ishiguro, K. Takahashi, K. Yazawa, S. Sakiyama, and T. Arai, J. Biol. Chem., 1981, **256**, 2162; J. W. Lown, A. V. Joshua, and J. S. Lee, Biochemistry, 1982, **21**, 419; G. C. Hill and W. A. Remers, J. Med. Chem., 1991, **34**, 1990: Cyanocycline A *see*: M. B. Cox, P. Arjunan, and S. K. Arora, J. Antibiot., 1991, **44**, 885: DX-52-1 *see*: K. Fujimoto, T. Oka, and M. Morimoto, Cancer Res., 1987, **47**, 1516; S. Inaba and M. Shimoyama, ibid., 1988, **48**, 6029; G. C. Hill, T. R. Wunz, and W. A. Remers, J. Comput. -Aided Mol. Des., 1988, **2**, 91; R. M. Williams, T. Glinka, M. E. Flanagan, R. Gallegos, H. Coffman, and D. Pei, J. Am. Chem. Soc., 1992, **114**, 733.
5. *Compound (5): S. Saito*, K. Tanaka, K. Nakatani, F. Matsuda, T. Katoh, S. Terashima, Tetrahedron, 1994, **50**, 6209; T. Katoh, M. Kirihara, T. Yoshino, O. Tamura, F. Ikeuchi, K. Nakatani, F. Matsuda, K. Yamada, K. Gomi, T. Ashizawa, and S. Terashima, ibid., 1994, **50**, 6259; T. Katoh and S. Terashima, J. Synth. Org. Chem. Jpn., 1994, **52**, 556: Compound **6**: R. M. Williams, T. Glinka, R. Gallegos, P. P. Ehrlich, M. E. Flanagan, H. Coffman, and G. Park, Tetrahedron, 1991, **47**, 2629.
6. T. F. Buckley III and H. Rapoport, J. Org. Chem., 1983, **48**, 4222.
7. B. Rigo and N. Kolocouris, J. Heterocycl. Chem., 1983, **20**, 893; L. L. Martin, S. J. Scott, M. N. Agnew, and L. L. Setescak, J. Org. Chem., 1986, **51**, 3697; and *see*: B. Rigo, P. Gautret, A. Legrand, S. E. Ghammarti, and D. Couturier, Synth. Commun., 1994, **24**, 2609.
8. K. Matsuo, M. Okumura, and K. Tanaka, Chem. Pharm. Bull., 1982, **30**, 4170; Y. Kitahara, S. Nakahara, R. Numata, and A. Kubo, ibid., 1985, **33**, 2122.
9. C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, J. Org. Chem., 1973, **38**, 2675; D. N. Kursanov, Z. N. Parnes, and N. M. Loim, Synthesis, 1974, 633.
10. Hydrogenolysis of **16** using usual catalyst (absence or presence of acid) and reductive removal of a hydroxyl group with sodium borohydride in acetic acid were totally failed, only starting material was recovered. The replacement of a hydroxyl group of **16** to the corresponding halide and treatment of **16** with mesyl chloride or tosyl chloride in pyridine caused decomposition of the starting material.
11. P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Pregamon Press, New York, 1983, Vol. 1, pp. 211-221.
12. As preliminary experiment , the oxidative demethylation of **16** employing cerium(IV) ammonium nitrate gave the quinone (**29**) in 52 % yield, and using argentic oxide in 39% yield (Y. Kitahara, S. Nakahara, Y. Koizumi, H. Muranishi, and A. Kubo, Chem. Pharm. Bull., 1988, **36**, 3623).
13. MIC was determined by the agar (Difco) for fungi. *In vitro* activity of compounds (**7** and **26**) was determined from the size of inhibition zone using paper disk and *T. mentagrophytes* as test organism.

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