A SYNTHESIS OF 4-CYANO-HEXAHYDRO-2*H*-BENZO[*b*]QUINOLIZINE-7,10-DIONE AS A SIMPLE MODEL COMPOUND OF SAFRAMYCIN A

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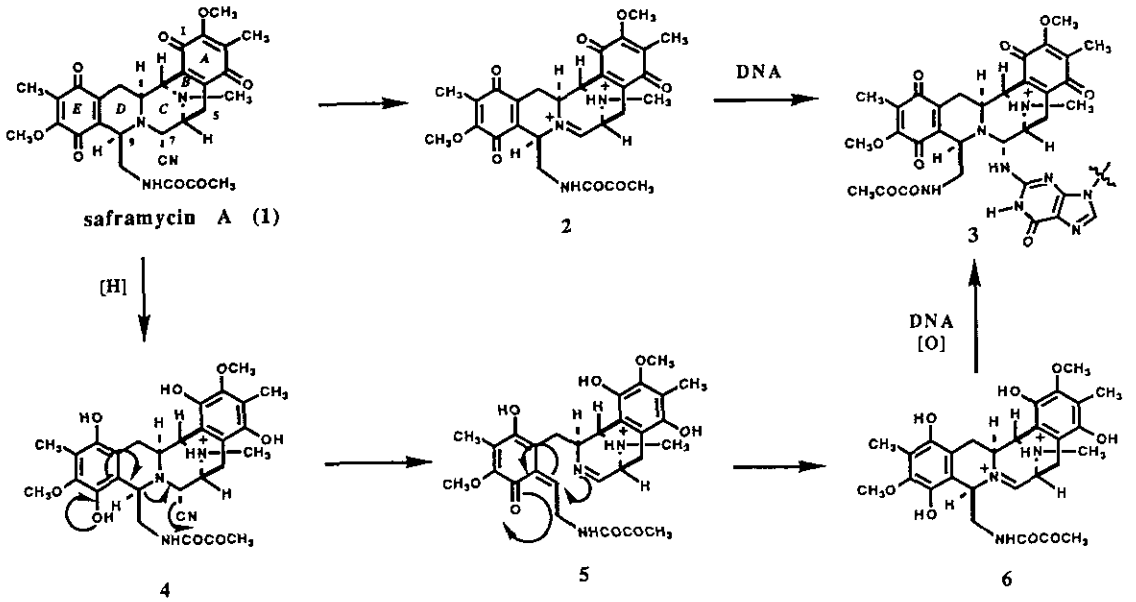
Abstract ——— A simple and efficient synthesis of 4-cyano-8-methoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine-7,10-dione (**20a**) as a simple model compound of saframycin A (**1**) is described starting from the corresponding lactam (**16**). Reduction of the lactam (**16**) with lithium aluminum hydride followed by sodium cyanide treatment afforded the α-amino nitrile (**19**) as an inseparable mixture in an excellent yield. Oxidative demethylation of compound (**19**) with 10N HNO_3 gave the title compound (**20a**) and its C-4 epimer (**20b**). The structure of **20a** was confirmed by ^1H nmr and ^{13}C nmr spectroscopic analysis.

Several naturally occurring isoquinolinequinones have been isolated from *Actinomycetes and marine sponges.*[1] *In* view of these novel structures and their chemical fragility, a great deal of research has gone into determining the mode *of antitumor action of these compounds.*[2] Saframycin A (**1**) is converted into a reactive intermediate such as an iminium ion before it binds covalently with DNA. If the quinone is reduced to a hydroquinone, the 7-cyano group can leave with formation of an iminium ion in a process involving participation by both the 10-hydroxy group and N-8 (Scheme I). An elegant total synthesis of racemic saframycin A (**1**) has been reported by Fukuyama and his co-workers.[3] As a part of our continuing program aimed at the total synthesis of

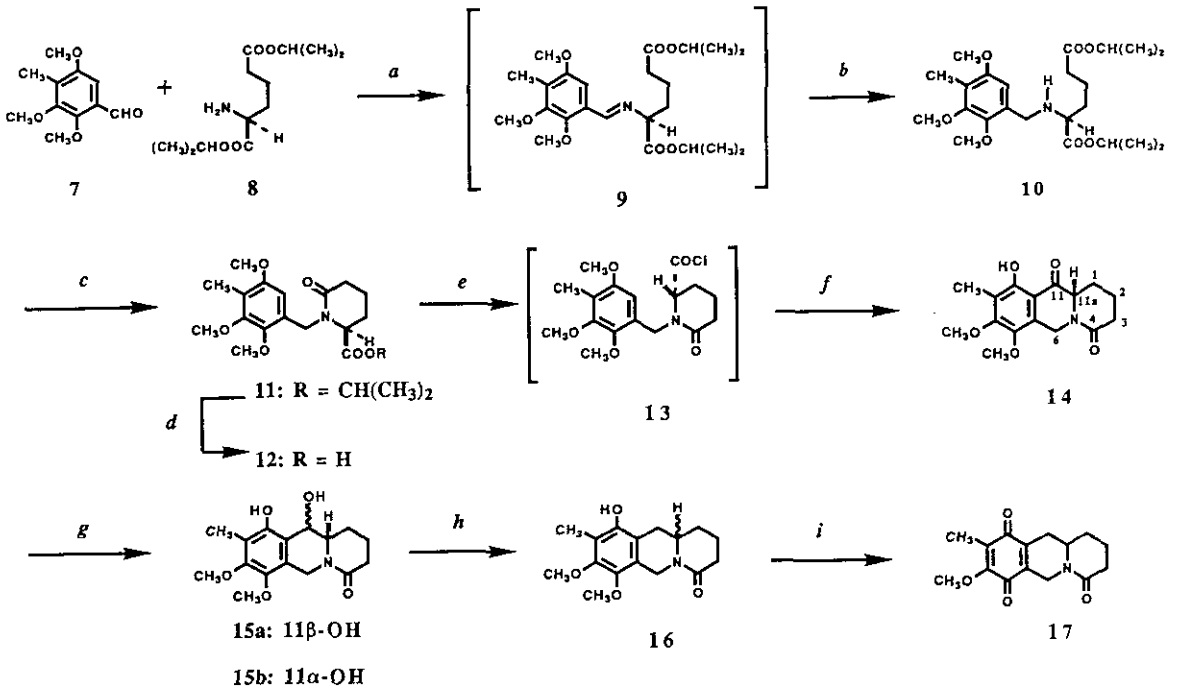
isoquinolinequinone antibiotics,[4] we have also engaged in the evaluation of simple structures that might mimic the biological action of natural products. Two syntheses of the right half of saframycin A have been reported by Kurihara and Mishima[5a] and us,[5b] but synthesis of the left half of saframycin A has not yet been accomplished. In this paper, we report the synthesis of a model compound as **20a**, which contains the quinone moiety.[6]



Scheme I

The synthesis of the tricyclic amide (**16**) from the readily available aldehyde (**7**) is outlined in Scheme II. 2,3,5-Trimethoxy-4-methylbenzaldehyde (**7**)[7] was condensed with optically pure diisopropyl α-aminoadipate (**8**)[8] and gave a Schiff base (**9**), which on treatment with sodium cyanoborohydride afforded the alkylated diester (**10**) in 53% yield. Cyclization of **10** with acetic acid afforded the ester (**11**) in 94.4% yield which in turn was hydrolyzed to the amido acid (**12**) in 93.4% yield. Friedel-Crafts intramolecular cyclization of **12** was carried out using an acid chloride intermediate according to the procedure of Rigo and Kolocouris.[9] The reaction of **12** with phosphorous oxychloride at 50°C for 30 min gave the acid chloride (**13**), which was subsequently treated with tin tetrachloride at 65°C for 30 min to provide the amido ketone (**14**) with partial cleavage of the aromatic ether in 54.6% overall yield. The structure of **14** was supported by the ^{1}H nmr spectrum, which showed a peak at δ 11.93 assignable to the hydroxy peak.[10] Reduction of **14** with sodium borohydride afforded the 11β alcohol

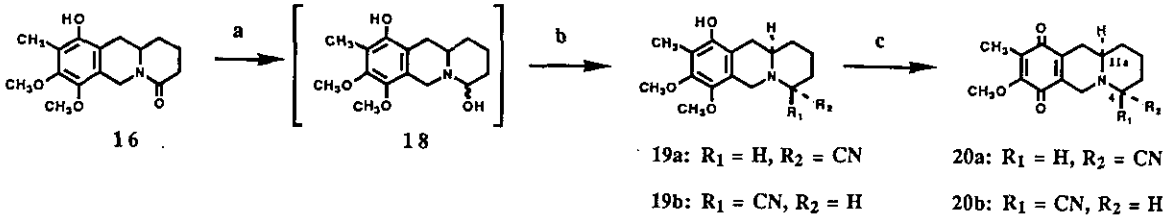
(**15a**) in 70.3% yield along with the 11α alcohol (**15b**) in 2.5% yield. The stereochemistry of the C-11 position in **15a** is supported by the ^{1}H nmr spectrum, which displays H-11 as a doublet at δ 4.77 (J ≈ 10 Hz), whereas the ^{1}H nmr spectrum of **15b** shows the H-11 as a doublet at δ 4.53 (J = 2.6 Hz). Reductive removal of the benzylic hydroxyl group of **15a** with triethylsilane in trifluoroacetic acid[11] gave the amide (**16**) as racemate in 96.9% yield. Oxidative demethylation of **16** with 10N HNO_3 at 25°C for 1 h afforded the *p*-quinone (**17**) in 90.9% yield.



Scheme II: *a*) AcOH-CH_2Cl_2, reflux, 17 h; *b*) $NaBH_3CN$, 2-propanol, 22 h, 53.0% overall yield; *c*) AcOH, reflux, 5 h, 94.4%; *d*) 2N KOH, MeOH-dioxane, room temperature, 4 h, 93.4%; *e*) $POCl_3$, 50°C, 30 min; *f*) $SnCl_4$, 65°C, 30 min, 54.6% overall yield; *g*) $NaBH_4$, MeOH, rt 1 h, 15a (70.3%) and 15b (2.5%); *h*) $(C_2H_5)_3SiH$, TFA, room temperature, 1 h, 96.9%; i) 10N HNO_3, room temperature, 1 h, 90.9%.

Introduction of a cyano group into the C-4 position of the amide (**16**) was achieved by partial reduction followed by sodium cyanide treatment (Scheme III).[12] Reduction of **16** with lithium aluminum hydride in THF at -17°C afforded the unstable α-hydroxy amine (**18**), which was treated with sodium cyanide to give an inseparable mixture of the 4α cyano derivative (**19a**) and the 4β cyano derivative (**19b**) in 69.9% overall yield (15.6% of **16** was recovered).[13] Finally, treatment of a diastereomeric mixture of phenols (**19a** and **19b**) with 10N HNO_3 at

25°C for 1 h afforded the *p*-quinones (**20a**) and (**20b**) in 66.9% and 10.9% yields, respectively. The stereochemical assignments of **20a** and **20b** are based on ^{1}H nmr and ^{13}C nmr spectral analysis. A strongly deshielding γ-steric effect was observed at C-11a carbon in **20a** (δ 51.3), but not at C-11a in **20b** (δ 55.9). This was confirmed by observation of an NOE between H-4 and H-11a in **20b**.[14]



Scheme III: *a*) **$LiAlH_4$, THF, 10 min, - 17°C;** *b*) **NaCN, THF-H_2O, room temperature, 2 h, 69.9% overall yield;** *c*) **10N HNO_3, 25°C, 1 h, 20a (66.9%) and 20b (10.9%).**

With **20a** and **20b** in hand, cytotoxicity of these compounds *in vitro* against L 1210 murine leukemia was studied. However, neither compound showed any significant cytotoxic activity (**20a**: ED_{50} = 3.0 μg/kg, **20b**: ED_{50} = 4.0 μg/kg). Interestingly, compound (**20a**) exhibits antimicrobial activity against *Bacillus subtilis* (MIC = 16.0 μg/ml). Further studies toward the synthesis of the left half of saframycin A are in progress in our laboratories.

ACKNOWLEDGMENTS

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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 were recorded at 270 MHz with a JEOL EX 270 spectrometer. ^{13}C Nmr spectra were recorded at 67.5 MHz (multiplicity determined from off-resonance decoupled or DEPT spectra). Nmr spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to internal tetramethylsilane standard. Ms was recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were obtained by a Perkin-Elmer Model 240B elemental analyzer. Measurement of optical

rotations were performed on a JASCO DIP-4 polarimeter in a 10 cm cell. 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).

Diisopropyl(*S*)-(-)-*N*-[(2,3,5-trimethoxy-4-methylphenyl)methyl]-α-aminoadipate (**10**) 2,3,5-Trimethoxy-4-methylbenzaldehyde (**7**) (10.5 g, 5 mmol) was added to a stirred solution of diisopropyl(*S*)-α-aminoadipate (**8**) (32.0 g, 13 mmol) in dichloromethane (200 ml) and acetic acid (1 ml). The mixture was heated at reflux for 17 h under a Dean-Stark separator. The organic layer was dried and the solvent was removed in vacuo to give the Schiff base (**9**) which was used in the following reaction without further purification. The crude Schiff base (**9**) was dissolved in 2-propanol (500 ml) and sodium cyanoborohydride (6.28 g, 100 mmol) was added in one portion with stirring. The mixture was stirred for 22 h, and the solvent was removed in vacuo. The residue was diluted with water (200 ml) and extracted with dichloromethane (200 ml x 3). The combined extracts were washed with 5% $NaHCO_3$ (200 ml), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 500 g; elution with 1:1 = hexane-ethyl acetate) to give **10** (11.63 g, 53.0 %) as a pale yellow oil; ν_{max} (neat) 1730 cm^{-1}; λ_{max} nm (log ε) 214 (4.03), 276sh (3.30), 282 (3.36); δ_H 1.21 (6H, d, *J* = 6 Hz, $CH(CH_3)_2$), 1.26 (3H, d, *J* = 6 Hz, $CH(CH_3)_2$), 1.59-1.79 (3H, m), 2.04-2.06 (1H, m), 2.11 (3H, s, $ArCH_3$), 2.25-2.30 (2H, m), 3.20-3.25 (1H, m), 3.64 (1H, d, *J* = 13 Hz, ArCH), 3.79 (1H, d, *J* = 13 Hz, ArCH), 3.80, 3.80, 3.81 (each 3H, s, OCH_3), 4.99 (1H, sept, *J* = 6 Hz, CH), 5.07 (1H, sept, *J* = 6 Hz, CH), 6.61 (1H, s, ArH); δ_C 8.8 (q, $ArCH_3$), 21.5 (t), 21.8 (q, $CH(CH_3)_2$), 21.9 (q, $CH(CH_3)_2$), 32.8 (t), 34.3 (t), 46.9 (t, NCH_2), 55.8 (q, OCH_3), 60.2 (d, CHNH), 60.7 (q, OCH_3), 60.9 (q, OCH_3), 67.5 (d, OCH), 68.1 (d, OCH), 106.3 (d), 119.6 (s), 130.2 (s), 145.8 (s), 151.7 (s), 154.0 (s), 172.7 (s, CO), 174.7 (s, CO); *m/z* (%) 439 (M^+, 4), 352 (78), 244 (19), 210 (16), 195 (100), 180 (25). Anal. Calcd for $C_{23}H_{37}NO_7$: C, 62.85; H, 8.48; N, 3.19. Found: C, 62.67; H, 8.40; N, 3.08. $[\alpha]_D^{25}$ - 8.6° (*c* = 1, MeOH).

(*S*)-(+)-*N*-[(2,3,5-Trimethoxy-4-methylphenyl)methyl]-6-isopropyloxycarbonyl-2-piperidone (**11**) A solution of the ester (**10**) (8.55 g, 19.5 mmol) in acetic acid (50 ml) was heated under reflux for 5 h. The mixture was diluted with water (100 ml) made alkaline with powdered Na_2CO_3, and then extracted with dichloromethane (100 ml x 3). The combined extracts were washed with water (100 ml), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 800 g; elution with 1:1 = hexane-ethyl acetate) to give **11** (6.97 g, 94.4%) as a solid, which was recrystallized from hexane-ethyl acetate to give colorless needles, mp 69-70°C; ν_{max} (KBr) 1736, 1648 cm^{-1}; λ_{max} nm (log ε) 219 (4.01), 276sh (3.31), 284 (3.39); δ_H 1.24 (3H, d, *J* = 6 Hz, $CHCH_3$), 1.27 (3H, s, *J* = 6 Hz, $CHCH_3$), 1.70-1.81 (2H, m), 1.83-1.95 (1H, m), 2.08-2.11 (1H,

m), 2.11 (3H, s, $ArCH_3$), 2.37-2.60 (2H, m), 3.20-3.30 (1H, m), 3.75, 3.76, 3.80 (each 3H, s, OCH_3), 3.94 (1H, d, J = 15 Hz, ArCH), 4.07 (1H, m, HCN), 5.08 (1H, sept, J = 6Hz, CH), 5.30 (1H, d, J = 15 Hz, ArCH), 6.53 (1H, s, ArH); δ_C 8.8 (q, $ArCH_3$), 18.2 (t), 21.7 (q, $CH(CH_3)_2$), 21.8 (q, $CH(CH_3)_2$), 26.6 (t), 31.7 (t), 43.5 (t, $ArCH_2N$), 55.8 (q, OCH_3), 58.4 (d, NCH), 60.2 (q, OCH_3), 60.8 (q, OCH_3), 69.0 (d, OCH), 106.7 (d), 120.5 (s), 127.0 (s), 145.8 (s), 151.6 (s), 154.2 (s), 170.1 (s, CO), 171.3 (s, CO); *m/z* (%) 379 (M^+, 61), 348 (15), 292 (20), 264 (17), 195 (100), 180 (37). Anal. Calcd for $C_{20}H_{29}NO_6$-1/5H_2O: C, 62.71; H, 7.63; N, 3.66. Found: C, 62.94; H, 7.88; N, 3.65. $[\alpha]_D^{25}$ + 9.0° (c = 1, MeOH).

(*S*)-(+)-*N*-[(2,3,5-Trimethoxy-4-methylphenyl)methyl]-6-carboxyl-2-piperidone (**12**) A solution of **11** (2.653 g, 7.0 mmol) in dioxane (10 ml) was cooled at 0°C, and a methanol (5 ml) solution of 2N KOH (5 ml) was added and stirring was continued at room temperature for 4 h. The solution was evaporated, and the residue was diluted with water (100 ml) and washed with ether (50 ml x 3). The aqueous phase was then adjusted to pH 7 with H_3PO_4, heated to boiling for 45 min, cooled to room temperature, and adjusted to pH 3 (H_3PO_4). The resulting precipate of the amido acid **12** (2.204 g, 93.4%) was obtained as colorless needles, mp 146-147°C; ν_{max} (KBr) 1722, 1598 cm^{-1}; λ_{max} nm (log ε) 218 (3.99), 276sh (3.31), 284 (3.37); δ_H 1.81-1.96 (4H, m), 2.11 (3H, s, $ArCH_3$), 2.20-2.66 (2H, m), 3.76, 3.77, 3.80 (each 3H, s, OCH_3), 4.00 (1H, d, J = 15 Hz, ArCH), 4.20 (1H, m, HCN), 5.32 (1H, d, J = 15 Hz, ArCH), 6.54 (1H, s, ArH), 7.74 (1H, br s, COOH); δ_C 8.9 (q, $ArCH_3$), 18.1 (t), 26.4 (t), 31.4 (t), 44.2 (t, $ArCH_2N$), 55.8 (q, OCH_3), 58.2 (d, NCH), 60.2 (q, OCH_3), 60.9 (q, OCH_3), 106.8 (d), 120.8 (s), 126.5 (s), 145.7 (s), 151.7 (s), 154.3 (s), 171.4 (s, CO), 174.9 (s, CO); *m/z* (%) 337 (M^+, 100), 305 (47), 264 (12), 195 (54), 180 (36). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.45; H, 7.03; N, 4.11. $[\alpha]_D^{25}$ + 19.3° (*c* = 1, MeOH).

(*S*)-(-)-10-Hydroxy-7,8-dimethoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine-4,11-dione (**14**) A solution of **12** (2.20g, 6.52 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 $SnCl_4$ (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 dichloromethane (50 ml x 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 150 g; elution with 1:2 = hexane-ethyl acetate) to give **14** (1.087 g, 54.6%) as a pale yellow oil; ν_{max} ($CHCl_3$) 1642 cm^{-1}; λ_{max} nm (log ε) 216 (4.28), 280 (4.07), 349 (3.65); δ_H 1.68-1.79 (2H, m), 2.06 (3H, s, $ArCH_3$), 2.08-2.19 (1H, m), 2.27-2.44 (3H, m), 3.74 (1H, d, J = 17 Hz, 6-H), 3.74, 3.86 (each 3H, s, OCH_3), 4.12 (1H, t, J = 6 Hz, 11a-H), 6.01 (1H, d, J = 17 Hz, 6-H), 11.93 (1H, s, OH); δ_C 8.1 (q, $ArCH_3$), 19.0 (t), 22.9 (t), 32.4 (t), 39.1 (t, 6-C), 60.5 (q, OCH_3), 60.8 (q, OCH_3), 62.1 (d, 11a-C), 110.2 (s), 118.8 (s), 130.7 (s), 141.0 (s), 158.9 (s), 159.1 (s), 169.2 (s, 4-CO), 197.9 (s, 11-CO); *m/z* (%) 305

(M^+, 100), 290 (54), 249 (24), 193 (14), 180 (14). High-resolution ms Calcd for $C_{16}H_{19}NO_5$: 305.1258. Found: 305.1253. $[\alpha]_D^{25}$ - 3.9° (*c* = 1, MeOH).

Reduction of the Ketoamide (**14**): (11*S*, 11a*S*)-(-)-10,11-Dihydroxy-7,8-dimethoxy-9-methyl-1,3,4,6,11,11a-hexahydro-*2H*-benzo[*b*]quinolizin-4-one (**15a**) and (11*R*, 11a*S*)-(-)-10,11-Dihydroxy-7,8-dimethoxy-9-methyl-1,3,4,6,11,11a-hexahydro-*2H*-benzo[*b*]quinolizin-4-one (**15b**) *A solution of the keto amide* (**14**) *(525 mg,* 1.7 mmol) in methanol (10 ml) was cooled at 0°C, and sodium borohydride (78 mg, 2.06 mmol) was added and stirring was continued at room temperature for 1 h. The mixture was diluted with water (15 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. Chromatography on a silica gel (50 g) with chloroform-acetone (4:1) as the eluent gave **15a** (371 mg, 70.3 %) as a colorless solid, recrystallization of which from ethanol gave an analytical sample as colorless prisms. Further elution with chloroform-acetone (3:1) as the eluent gave **15b** (13.0 mg, 2.5 %) as a colorless solid, recrystallization of which from ethanol gave an analytical sample as colorless prisms. ***15a:*** mp *192-193*°C; ν_{max} (KBr) *3168, 1618, 1582* cm^{-1}; λ_{max} *nm* (log ε) 214 (3.94), 276sh (3.08), 286 (3.14); δ_H 1.75-1.87 (1H, m), 1.98-2.23 (4H, m), 2.11 (3H, s, $ArCH_3$), 2.30-2.34 (2H, m), 3.46-3.51 (1H, m, 11a-H), 3.78 (1H, d, *J* = 17 Hz, 6-H), 3.78, 3.79 (each 3H, s, OCH_3), 4.77 (1H, d, *J* = 10 Hz, 11-H), 5.52 (1H, d, *J* = 17 Hz, 6-H), 8.14 (1H, br s, OH); δ_C 8.6 (q, $ArCH_3$), 17.2 (t), 23.5 (t), 32.0 (t), 40.6 (t, 6-C), 58.3 (d, 11a-C), 60.3 (q, OCH_3), 60.3 (q, OCH_3), 68.9 (d, 11-C), 116.7 (s), 118.0 (s), 124.3 (s), 142.0 (s), 150.2 (s), 151.3 (s), 169.5 (s, CO); *m/z* (%) 307 (M^+, 9), 289 (100), 274 (74), 259 (15). Anal. Clacd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.47; H, 6.86; N, 4.50. $[\alpha]_D^{25}$ - 2.1 ° (c = 1, MeOH). **15b**: mp 189-190°C; ν_{max} (KBr) 3416, 1614 cm^{-1}; λ_{max} nm (log ε) 222 (3.96), 275sh (3.37), 284 (3.44); δ_H *1.55-2.33 (6H, m), 2.09 (3H, s, $ArCH_3$), 3.48-3.55 (1H, m, 11a-H),* 3.74 *(6H, s, OCH_3),* 3.76 (1H, d, *J* = 18 Hz, 6-H), 4.53 (1H, d, *J* = 2.6 Hz, 11-H), 5.47 (1H, d, *J* = 18 Hz, 6-H), 8.22 (1H, br s, OH); δ_C (DMSO-d_6) 9.3 (q, $ArCH_3$), 18.9 (t), 25.0 (t), 32.5 (t), 39.5 (t, 6-C), 56.7 (d, 11a-C), 59.6 (q, OCH_3), 59.7 (q, OCH_3), 63.2 (d, 11-C), 116.8 (s), 120.5 (s), 124.1 (s), 141.7 (s), 148.8 (s), 150.4 (s), 169.5 (s, CO); *m/z* (%) 307 (M^+, 27), 289 (100), 274 (82), 259 (13), 210 (15), 195 (33). Anal. Clacd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.52; H, 6.83; N, 4.58. $[\alpha]_D^{25}$ - 3.2 ° (*c* = 0.13, MeOH).

(*S*)-(±)-10-Hydroxy-7,8-dimethoxy-9-methyl-1,3,4,6,11,11a-hexahydro-*2H*-benzo[*b*]quinolizine-4-one (**16**) Triethylsilane (0.32 ml, 2 mmol) was added to a stirred solution of **15a** (154 mg, 0.5 mmol) in trifluoroacetic acid (1 ml), and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 ml), made alkaline with powdered Na_2CO_3, and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water, dried, and concentrated in vacuo. The residue was subjected to

chromatography (silica gel, 15 g; elution with 100:3 = chloroform-methanol) to give **16** (141 mg, 96.9 %) as a solid, recrystallization of which from ethyl acetate gave colorless prisms, mp 206-207.5°C; ν_{max} (KBr) 3180, 1622 cm^{-1}; λ_{max} nm (log ε) 222 (3.97), 274sh (3.26), 283 (3.32); δ_H 1.75-1.96 (3H, m), 2.02-2.22 (1H, m), 2.16 (3H, s, $ArCH_3$), 2.45 (2H, t, J = 6 Hz, 3-H_2), 2.59 (1H, dd, J = 16.2, 11.6 Hz, 11-H), 2.85 (1H, dd, J = 16.2, 3.6 Hz, 11-H), 3.59 (1H, m, 11a-H), 3.79, 3.80 (each 3H, s, OCH_3), 4.04 (1H, d, J = 18 Hz, 6-H), 5.44 (1H, d, J = 18 Hz, 6-H), δ_C 8.8 (q, $ArCH_3$), 18.2 (t, 2-C), 28.8 (t, 1-C), 30.6 (t, 11-C), 32.7 (t, 3-C), 40.9 (6-C), 52.7 (d, 11a-C), 60.3 (q, OCH_3), 60.4 (q, OCH_3), 115.5 (s), 116.2 (s), 124.6 (s), 143.2 (s), 147.3 (s), 149.5 (s), 169.8 (s, CO); *m/z* (%) 291 (M^+, 100), 276 (25), 194 (64), 179 (44). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.91; H, 7.23; N, 4.81.

(±)-8-Methoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine-4,7,10-trione (**17**) A solution of **16** (58.2 mg, 0.2 mmol) in 10N HNO_3 (2 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (10 ml x 3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 20 g; elution with 1:2 = hexane-ethyl acetate) to give **17** (50.0 mg, 90.9 %) as a yellow solid, recrystallization of which from ether gave pale yellow prisms; mp 116-117°C; ν_{max} (KBr) 1658, 1636 cm^{-1}; λ_{max} nm (log ε) 205 (4.21), 268 (4.11); δ_H 1.73-1.94 (3H, m), 1.95 (3H, s, 9-CH_3), 2.10-2.20 (1H, m), 2.30-2.41 (1H, m), 2.43-2.47 (2H, m), 2.75 (1H, d, J = 18 Hz, 11-H), 3.45-3.55 (1H, m, 11a-H), 3.72 (1H, ddd, J = 21, 3, 3 Hz, 6-H), 4.01 (3H, s, OCH_3), 5.30 (1H, dd, J = 21, 2 Hz, 6-H); δ_C 8.7 (q, 9-CH_3), 18.1 (t), 28.5 (t), 30.0 (t, 11-C), 32.8 (t), 39.8 (t, 6-C), 51.9 (d, 11a-C), 60.9 (q, OCH_3), 128.5 (s), 136.6 (s), 138.9 (s), 155.5 (s), 169.7 (s, 4-CO), 181.5 (s, CO), 186.7 (s, CO); *m/z* (%) 275 (M^+, 100), 260 (30), 232 (18), 205 (44), 191 (11). Anal. Calcd for $C_{15}H_{17}NO_4$-1/10H_2O: C, 65.02; H, 6.26; N, 5.05. Found: C, 65.09; H, 6.20; N, 5.04.

Formation of (±)-4-Cyano-10-hydroxy-7,8-dimethoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]-quinolizine (**19a** and **19b**) as a 6:1 ratio of isomers Lithium aluminum hydride (38.0 mg, 1 mmol) was added to a stirred solution of **16** (145.5 mg, 0.5 mmol) in dry THF (10 ml) at - 17°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 (30 mg, 0.16 mmol) in water (0.3 ml) and allowed to stir for 2 h. The mixture was filtered and the filter cake was carefully washed with dichloromethane (30 ml). The combined filtrates were concentrated in vacuo. The residue (163.9 mg) was subjected to chromatography (silica gel, 20 g; 1:1 = hexane-ethyl acetate) to give **19a** and **19b** (105.0 mg, 69.9%) as a *ca.* 6:1 mixture of isomers. Further elution with ethyl acetate gave the starting material (**16**) (22.7 mg, 15.6 %) as a solid. For the mixture; ν_{max} (KBr) 3470, 2220w cm^{-1}; δ_H (major isomer: **19a**) 1.34 (1H, m), 1.77-1.86 (2H, m), 1.95-2.03 (3H, m), 2.14 (3H, s, $ArCH_3$), 2.38 (1H, dd, J = 16, 10 Hz, 11-Hβ), 2.67 (1H, m, 11a-H), 2.85 (1H, dd, J = 16, 4 Hz, 11-Hα), 3.66 (1H, d, J = 15 Hz, 6-Hα), 3.79, 3.79 (each

3H, s, OCH_3), 3.95 (1H, d, J = 15 Hz, 6-Hβ), 4.09 (1H, t, J = 3 Hz, 4-H), 4.49 (1H, s, OH); (minor isomer: **19b**) 1.38-1.48 (1H, m), 1.86-2.07 (3H, m), 2.13 (3H, s, $ArCH_3$), 2.17-2.33 (1H, m), 2.15-2.32 (1H, m, 11a-H), 2.48 (1H, dd, J = 16, 11 Hz, 11-Hβ), 2.76 (1H, dd, J = 16, 4 Hz, 11-Hα), 3.15 (1H, dd, J = 11, 3 Hz, 4-H), 3.20 (1H, d, J = 15 Hz, 6-Hα), 3.80, 3.80 (each 3H, s, OCH_3), 4.51 (1H, s, OH), 4.58 (1H, d, J = 15 Hz, 6-Hβ); δ_C (major isomer: **19a**) 8.6 (q, $ArCH_3$), 20.2 (t), 28.8 (t), 31.1 (t, 11-C), 33.2 (t), 50.4 (t, 6-C), 52.3 (d, 11a-C), 54.8 (d, 4-C), 60.4 (q, OCH_3), 60.4 (q, OCH_3), 115.0 (s), 115.2 (s), 116.8 (s), 124.8 (s), 142.6 (s), 147.0 (s), 149.2 (s); (minor isomer: **19b**) 8.6 (q), 22.8 (t), 30.7 (t), 31.3 (t, 11-C), 32.5 (t), 52.1 (t, 6-C), 55.7 (d, 4-C), 57.3 (d, 11a-C), 60.4 (q, OCH_3), 60.4 (q, OCH_3), 115.4 (s), 115.4 (s), 119.3 (s), 124.7 (s), 142.8 (s), 147.0 (s), 149.3 (s); *m/z* (%) 302 (M^+, 32), 275 (44), 194 (100), 179 (48).

Oxidative Demethylation of the Phenols **19a** and **19b** with 10N HNO_3: (4*RS*, 11a*RS*)-(±)-4-Cyano-8-methoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine-7,10-dione (**20a**) and (4*RS*, 11a*SR*)-(±)-4-Cyano-8-methoxy-9-methyl-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine-7,10-dione (**20b**) A solution of **20** (epimeric mixture: 117 mg, 0.38 mmol) in 10N HNO_3 (2 ml) was stirred at 25°C for 1 h. 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 (105 mg) was subjected to preparative layer chromatography on silica gel (Merck 5715, solvent 5:1 = hexane-ethyl acetate) to afford **20a** (73.6 mg, 66.9 %) and **20b** (12.0 mg, 10.9 %). Compound **20a**: pale yellow prisms from ether-hexane, mp 110-111°C; ν_{max} (KBr) 1668, 1634, 1612 cm^{-1}; λ_{max} nm (log ε) 204 (3.98), 269 (4.13); δ_H 1.24-1.34 (1H, m), 1.63-2.07 (5H, m), 1.95 (3H, s, 9-CH_3), 2.16 (1H, dddd, J = 19.5, 9.6, 4.3, 2.3 Hz, 11-Hβ), 2.54 (1H, m, 11a-H), 2.74 (1H, ddd, J = 19.5, 3.0, 3.0 Hz, 11-Hα), 3.39 (1H, ddd, J = 18.5, 4.3, 3.0 Hz, 6-Hα), 3.72 (1H, dd, J = 18.5, 2.3 Hz, 6-Hβ), 3.99 (3H, s, OCH_3), 4.03 (1H, dd, J = 3.0, 3.0 Hz, 4-H); δ_C 8.7 (q, 9-CH_3), 20.1 (t), 28.6 (t), 30.6 (t, 11-C), 32.6 (t), 48.5 (t, 6-C), 51.3 (d, 11a-C), 54.3 (d, 4-C), 60.9 (q, OCH_3), 116.5 (s, CN), 128.8 (s), 136.1 (s), 138.5 (s), 155.4 (s), 181.5 (s, CO), 186.9 (s, CO); *m/z* (%) 286 (M^+, 100), 271 (29), 259 (43), 244 (40), 232 (96), 217 (20), 205 (12), 190 (17), 178 (20). Anal. Calcd for $C_{16}H_{18}N_2O_3$-1/10 H_2O: C, 66.69; H, 6.30; N, 9.72. Found: C, 66.53; H, 6.30; N, 9.69. Compound **20b** (not crystallizable): ν_{max} ($CHCl_3$) 1660, 1644, 1620 cm^{-1}; λ_{max} nm (log ε) 203 (4.03), 270 (4.10); δ_H 1.35-1.42 (2H, m), 1.84-1.98 (3H, m), 1.94 (3H, s, 9-CH_3), 2.09-2.11 (1H, m), 2.19 (1H, m, 11a-H), 2.25 (1H, dddd, J = 14.2, 9.9, 4.3, 2.3 Hz, 11-Hβ), 2.67 (1H, ddd, J = 14.2, 3.0, 1.0 Hz, 11-Hα), 2.98 (1H, ddd, J = 18.1, 3.0, 3.0 Hz, 6-Hα), 3.16 (1H, dd, J = 11.6, 3.3 Hz, 4-H), 4.00 (3H, s, OCH_3), 4.31 (1H, dd, J = 18.1, 2.0 Hz, 6-H), δ_C 8.6 (q, 9-CH_3), 22.5 (t), 30.5 (t), 30.5 (t, 11-C), 31.8 (t), 50.1 (t, 6-C), 55.0 (d, 4-C), 55.9 (d, 11a-C), 60.9 (q, OCH_3), 118.9 (s, CN), 128.5 (s), 135.9 (s), 138.9 (s), 155.4 (s), 181.5 (s, CO), 187.0 (s, CO), *m/z* (%) 286

(M^+, 100), 271 (25), 259 (19), 244 (16), 232 (77), 217 (11), 190 (13), 180 (21), 178 (24), 109 (22). High-resolution ms Calcd for $C_{16}H_{18}NO_3$: 286.1313. Found: 286.1309.

REFERENCES AND NOTES

1 T. Arai and A. Kubo, ' The Alkaloids', ed. by A. Brossi, Academic Press, New York, 1983, Vol. 21, 1983, pp. 55-100; R. H. Thomson, ' Naturally Occurring Quinones III', Chapman and Hall, New York, 1987, pp. 633-666.

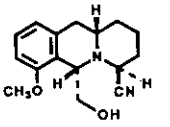
2 Saframycins *see*: K. Ishiguro, K. Takahashi, K. Yazawa, S. Sakiyama, and T. Arai, J. Biol. Chem., 1981, **256**, 2162; J. W. Lown, A. V. Joshua, and J. S. Lee, Biochemistry, 1982, **21**, 419; G. C. Hill and W. A. Remers, J. Med. Chem., 1991, **34**, 1990: Quinocarcins *see*: H. Saito, T. Hirata, M. Kasai, K. Fujimoto, T. Ashizawa, K. Morimoto, and A. Sato, J. Med. Chem., 1991, **34**, 1959; R. M. Williams, T. Glinka, M. E. Flanagan, R. Gallegos, H. Coffman, and D. Pei, J. Am. Chem. Soc., 1992, **114**, 733.

3 T. Fukuyama, L. Yang, K. L. Ajeck, and R. A. Sachleben, J. Am. Chem. Soc., 1990, **112**, 3712.

4 A. Kubo and N. Saito, Yuki Gosei Kagaku Kyoukai Shi, 1988, **46**, 121; A. Kubo and N. Saito, ' Studies in Natural Products Chemistry', ed. by Atta-Ur-Rahman, Elsevier, Inc., Amsterdam, 1991, in press.

5 a) H. Kurihara, H. Mishima, and M. Arai, Heterocycles, 1986, **24**, 1549; b) A. Kubo, N. Saito, H. Yamato, R. Yamauchi, K. Hiruma, and S. Inoue, Chem. Pharm. Bull., 1988, **36**, 3891.

6 The chiral synthesis of **25** has been reported by Terashima and his co-workers: S. Saito, K. Tanaka, K. Nakatani, F. Matsuda, and S. Terashima, Tetrahedron Lett., 1989, **30**, 7423; Another synthetic studies: N. Saito, N. Kawakami, E. Yamada, and A. Kubo, Chem. Pharm. Bull., 1989, **37**, 1493; C. W. Ong and H. C. Lee, Aust. J. Chem., 1990, **43**, 772.



25

7 K. Matsuo, M. Okumura, and K. Tanaka, Chem. Pharm. Bull., 1982, **30**, 4170; Y. Kitahara, S. Nakahara, R. Numata, and A. Kubo, Chem Pharm. Bull., 1985, **33**, 2122.

8 T. F. Buckley III and H. Rapoport, J. Am. Chem. Soc., 1982, **104**, 4446; T. F. Buckley III and H. Rapoport, J. Org. Chem., 1983, **48**, 4222.

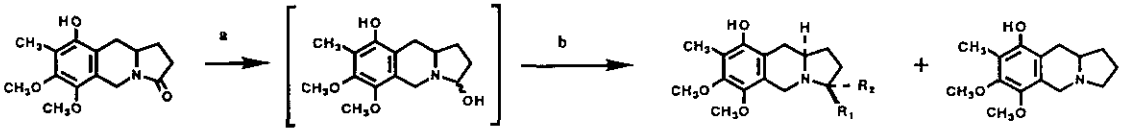
9 B. Rigo and N. Kolocouris, J. Heterocycl. Chem., 1983, **20**, 893; L. L. Martin, S. J. Scott, M. N. Agnew, and L. L. Setescak, J. Org. Chem., 1986, **51**, 3697.

10 C. E. Coburn, D. K. Anderson, and J. S. Swenton, J. Org. Chem., 1983, **48**, 1455.

11 C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, J. Org. Chem., 1973, **38**, 2675.

12 H. Saito and T. Hirata, Tetrahedron Lett., 1987, **28**, 4065; see: D. A. Evans, C. R. Illig, and J. C. Saddler, J. Am. Chem. Soc., 1986, **108**, 2479.

13 In contrast, reduction of **21** with litium aluminum hydride in THF followed by sodium cyanide treatment afforded the α-amino nitrile (**23**) as an inseparable mixture in 20% yield. However, the major product was amine (**24**) in 38% yield (19% yield of **21** was recovered) (Scheme IV): A. Kubo, Y. Koizumi, T. Nakai, Y. Kitahara, and N. Saito, unpublished results.



Scheme IV: *a*) $LiAlH_4$, THF, - 17°C; b) NaCN, THF-H_2O, 23a:23b = 3:2 (20%), 24 (38%), and 21 (19%).

14 E. Dominguez, E. M. de Marigorta, L. Carrillo, and R. Fananas, Tetrahedron, 1991, **47**, 9253.

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