[Chem. Pharm. Bull. 36(7)2607—2614(1988)]

Synthesis of Saframycins. II. Preparations and Reactions of *N*-Methyl-2,5-piperazinediones

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(Received January 22, 1988)

An efficient synthesis of 4-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione **5** and 1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione **10** from (*Z*)-1-acetyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione **2** is described.

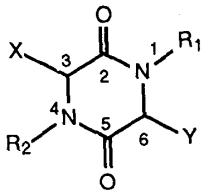
The 1-methyl-2,5-piperazinedione **10** is shown to be a useful intermediate for preparation of the 1,5-imino-3-benzazocine derivative **16**, which is the skeleton of the "right half" of saframycins.

Keywords——*N*-methyl-2,5-piperazinedione; preparation; 1,5-imino-3-benzazocine; saframycin; protective group

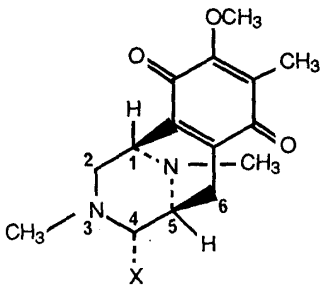
In recent years several isoquinolinequinones[1] have been isolated from *Actinomycetes* and marine sponge. Saframycins[1,2] are antitumor antibiotics produced by *Streptomyces lavendulae*. They constitute a class of the dimeric isoquinolinequinone antibiotic group, which includes safracins[3] and renieramycins.[4] In this group, saframycin A (**20**) has been shown to possess the highest antitumor activity. Two total syntheses of saframycin B (**19**) have been reported by Fukuyama and Sachleben,[5a] and by us,[5b] but a total synthesis of **20** has not been accomplished. Arai *et al.*[6] suggested that the dimeric quinone skeletons which are common to all saframycins may be formed by cyclization of two molecules of tyrosine to form a 2,5-piperazinedione biosynthetic precursor. 2,5-Piperazinediones are among the most ubiquitous peptides found in nature.[7] For the synthesis of 2,5-piperazinediones containing an alkyl substituent on the amide nitrogen, direct introduction of the substituent as the desired position (at N-1 or N-4 in **1**) should be one of the most important steps, but in general, alkylation of the 2,5-piperazinediones by lower alkyl halides gives a mixture from which mono-*N*-alkyl derivatives can not be readily separated.[8] We report herein the regioselective syntheses of 3-arylmethyl-4-methyl-2,5-piperazinedione (**5**) and 3-arylmethyl-1-methyl-2,5-piperazinedione (**10**) from (*Z*)-1-acetyl-3-arylidene-2,5-piperazinedione (**2**)[9] using an acetyl group and a 4-methoxybenzyl group for the protection of the amide nitrogen, and the synthesis of the hexahydro-1,5-imino-3-benzazocine derivative (**16**)[10] from the 2,5-piperazinedione (**10**), to provide a basis for approaching the synthesis of saframycin A (**20**).

As shown in Chart 1, the 4-methyl-2,5-piperazinedione (**5**) can be readily prepared from **2** in three steps. Namely, the *Z* isomer **2** was alkylated with methyl iodide in the presence of sodium hydride[11] in dimethylformamide (DMF) at 25 °C to afford **3** in 84.4% yield. Treatment of **3** with hydrazine hydrate afforded the 4-methyl derivative (**4**) in 74.2% yield. Catalytic reduction of **4** in ethanol in the presence of 20% palladium on carbon gave **5** in 62.1% yield.

Next, we planned to synthesize the 1-methyl-2,5-piperazinedione (**10**) from **2**, utilizing a protecting group for an amide nitrogen (Chart 2). The protection of the N–H group of amides is important in synthetic amide chemistry, and several methods for the protection of amide nitrogen have been developed.[12] The benzyl group is the most stable protecting group, and it

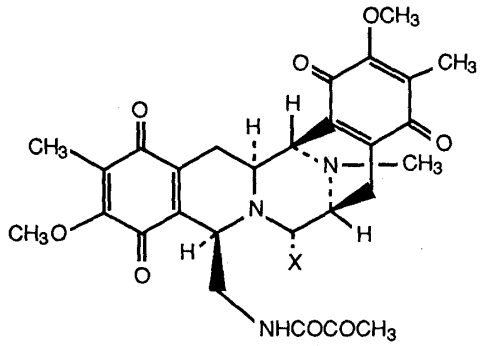


1



18 : X=CN

Fig. 1



19 : X=H
20 : X=CN

Fig. 2

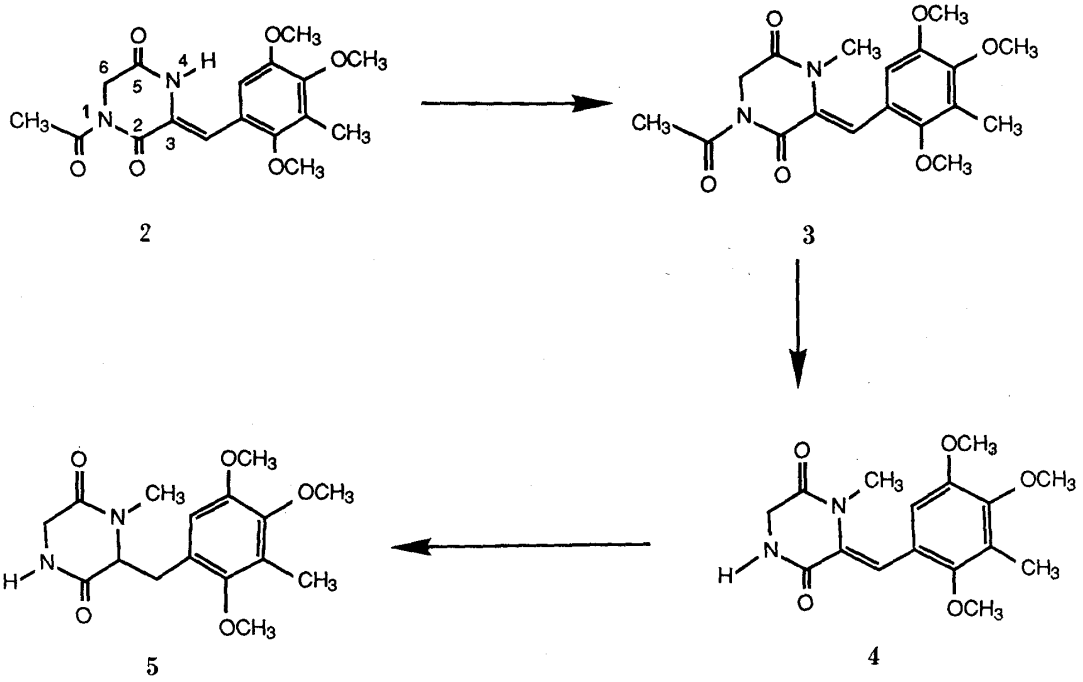


Chart 1

can be removed under reductive conditions.[13] Benzylation of **2** with benzyl bromide in the presence of sodium hydride in DMF at 25 °C furnished **6a** in 84% yield, and successive treatment with hydrazine hydrate afforded **7a** in 80.7% yield. Methylation of **7a** with methyl iodide in the presence of sodium hydride in DMF at 25 °C furnished **8a** in70% yield. Catalytic hydrogenation of **8a** led to **11** in 72% yield. Deprotection of **11** was not possible according to the procedure of Nakatsuka *et al.*[14] On the other hand, it is well known that the 4-methoxybenzyl group is a better protecting group than the benzyl group in terms of ease of removal.[15] Thus, 4-methoxybenzylation of **2** with 4-methoxybenzyl chloride in the presence of sodium hydride in DMF at 25 °C furnished **6b** in quantitative yield, and successive treatment with hydrazine hydrate afforded **7b** in 50.2% yield. Methylation of **7b** with methyl iodide in the presence of sodium hydride in DMF at 25 °C furnished **8b** in 75.1% yield. The oxidative removal of the 4-methoxybenzyl group can not be used in this case, because **8b** is susceptible to oxidative demethylation. Thus, facile deprotection of the 4-methoxybenzyl group of **8b** occurred on treatment with concentrated H_2SO_4 and trifluoroacetic acid at 25 °C,

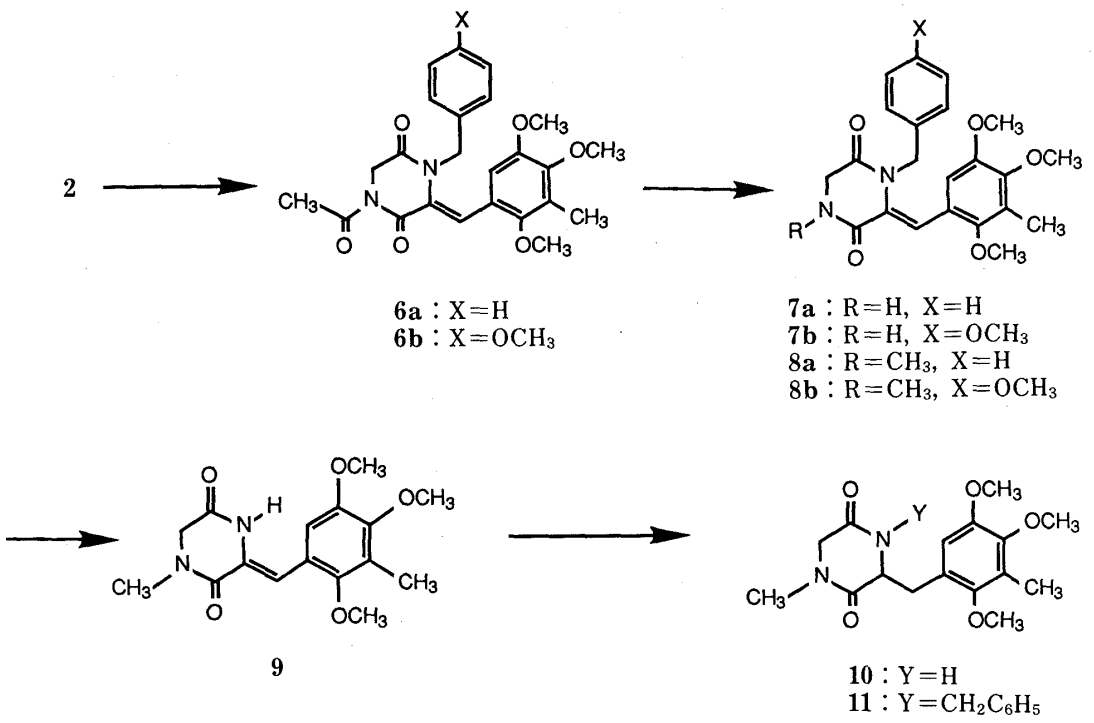


Chart 2

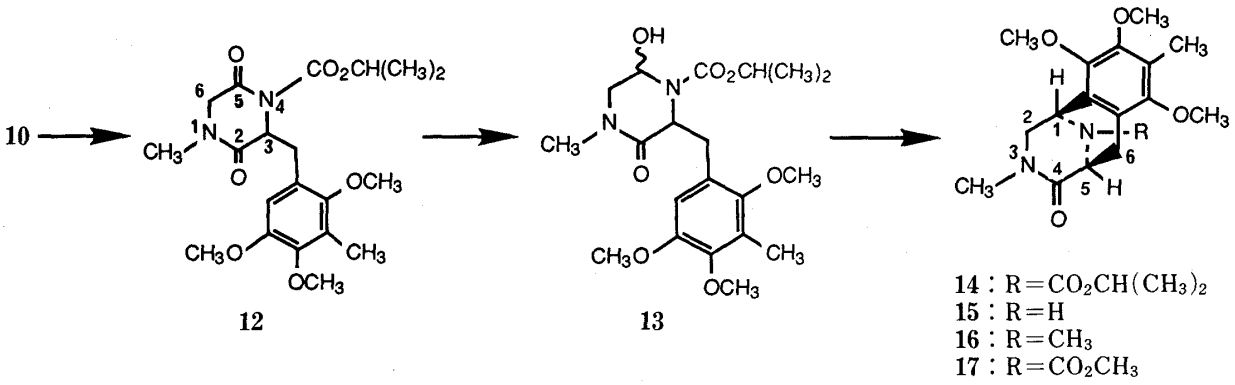


Chart 3

to give **9** in 69% yield. Catalytic hydrogenation of **9** furnished the 1-methyl-2,5-piperazinedione (**10**) in 68.3% yield.

The structures of the 4-methyl derivative (**5**) and 1-methyl derivative (**10**) were determined on the basis of elemental analyses and spectral data. In particular, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5**, irradiation of the doublet absorption at δ 6.565 (N–H) led to the collapse of the signal at δ 3.579 (6-H) from a doublet of doublets to a doublet. The same simplification was obtained by D_2O exchange. In the ^{1}H-NMR spectrum of **10**, irradiation of the broad absorption at δ 6.757 (N–H) led to the collapse of the signal at δ 4.261 (3-H) from a multiplet to a doublet of doublets. The same simplification was obtained by D_2O exchange.

Thus, we succeeded in a simple and efficient synthesis of the 4-methyl-2,5-piperazinedione (**5**) and the 1-methyl-2,5-piperazinedione (**10**). Next, we turned our attention to the construction of the 1,5-imino-3-benzazocine derivative (**16**) from **10** (Chart 3).

The 1-methyl derivative (**10**) was converted into the imide (**12**) in 81.4% yield according to our procedure.[16] The chemoselective reduction of **12** at the C-5 position to the corresponding alcohol (**13**), a crucial step for the synthesis of the "right half" of saframycins,

was achieved as follows. Compound **12** was reduced with an excess of lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran (THF) to afford a diastereomeric mixture of the alcohol (**13**), which, on treatment with formic acid at 60 °C, afforded the desired 1,5-imino-3-benzazocine derivatives (**14**) in 84.3% yield. The structure of the cyclization product (**14**) was fully supported by the molecular weight determined by mass spectrometry and the spectral data.[17]

Hydrolysis and decarboxylation of **14** with concentrated H_2SO_4 and trifluoroacetic acid gave rise to the secondary amine (**15**) in 89.9% yield; in its ^{1}H-NMR spectrum, a high-field shift of signals assignable to two methine protons (at C-1 and C-5) was observed. Finally, methylation of **15** with formalin and formic acid gave a 99.0% yield of **16**, which was identical with an authentic sample on comparison of spectroscopic (^{1}H-NMR, ^{13}C-NMR, infrared (IR), ultraviolet (UV), mass spectrum (MS)), and thin layer chromatography (TLC) data. Transformation of **16** to the *p*-quinone **18**, the "right half" of saframycin A (**20**), has been reported by Kurihara and co-workers.[18]

Thus, we succeeded in a simple and efficient synthesis of the 4-methyl-2,5-piperazinedione (**5**) and the 1-methyl-2,5-piperazinedione (**10**). Compound **10** was shown to be a useful intermediate for preparation of the 1,5-imino-3-benzazocine derivative **16**. We are presently exploring further versatile synthetic approaches to this class of compounds.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra (electron impact) were obtained on a JEOL JMS-D 300 spectrometer. IR spectra were recorded on Hitachi 260-10 and 270-30 spectrophotometers. UV spectra were determined in methanol with a Hitachi 340 spectrometer. ^{1}H-NMR were obtained at 400 MHz with a JEOL GX 400. ^{13}C-NMR were measured at 100 MHz with a JEOL GX 400. NMR spectra were taken in $CDCl_3$ and chemical shifts are reported in δ values in parts per million relative to tetramethylsilane as an internal standard. Column chromatography was performed with E. Merck silica gel 60 (70—230 mesh). Elemental analyses were obtained by using a Perkin-Elmer model 240B elemental analyzer, and were performed by Miss A. Koike of the Instrument Center of this college.

(*Z*)-1-Acetyl-4-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (3)——Sodium hydride (60% oil dispersion, washed with dry hexane three times, 259.2 mg, 10.8 mmol) was added to a stirred solution of **2** (3.078 g, 9 mmol) in dry DMF (15 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (0.68 ml, 10.9 mmol) in dry DMF (5 ml) was added. The reaction mixture was stirred for 12 h at 25 °C, poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give **3** (2.43 g, 84.4%), which was used without further purification. Recrystallization from benzene gave an analytical sample as pale yellow prisms, mp 164—165 °C. *Anal.* Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.48; H, 6.12; N, 7.69. MS *m/z* (%): 362 (M^+, 41), 331 (18), 290 (18), 289 (100), 274 (7), 220 (9), 43 (9). IR (KBr): 1705, 1680, 1625 cm^{-1}. UV λ_{max} nm (log ε): 242 (4.11), 324 (4.11). ^{1}H-NMR δ: 2.217 (3H, s, $ArCH_3$), 2.641 (3H, s, $COCH_3$), 2.925 (3H, s, NCH_3), 3.670 (3H, s, OCH_3), 3.813 (3H, s, OCH_3), 3.850 (3H, s, OCH_3), 4.530 (2H, s, 6-H_2), 6.592 (1H, s, ArH), 7.400 (1H, s, C=CH).

(*Z*)-4-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (4)——Hydrazine hydrate (0.5 ml) was added to a stirred solution of **3** (2.43 g, 6.71 mmol) in DMF (20 ml), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was poured into water and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a solid, recrystallization of which from AcOEt gave **4** (1.592 g, 74.2%) as pale yellow prisms, mp 171—172 °C. *Anal.* Calcd for $C_{16}H_{20}N_2O_5 \cdot 1/5H_2O$: C, 59.32; H, 6.37; N, 8.65. Found: C, 59.52; H, 6.36; N, 8.70. MS *m/z* (%): 320 (M^+, 23), 290 (18), 289 (200). IR (KBr): 3180, 1690, 1675, 1630 cm^{-1}. UV λ_{max} nm (log ε): 222 (4.23), 246 sh (4.17), 298 (4.18), 314 sh (4.15). ^{1}H-NMR δ: 2.212 (3H, s, $ArCH_3$), 2.917 (3H, s, NCH_3), 3.653 (3H, s, OCH_3), 3.813 (3H, s, OCH_3), 3.837 (3H, s, OCH_3), 4.149 (2H, d, J=2.2 Hz, 6-H_2), 6.587 (1H, s, ArH), 7.235 (1H, s, C=CH), 7.444 (1H, br s, NH).

4-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (5)——The arylidene derivative **4** (1.27 g, 3.97 mmol) was dissolved in ethanol (40 ml) and hydrogenated over 20% palladium on carbon (635 mg) at 1 atm for 4 h. After removal of the catalyst by filtration, the filtrate was partitioned between $CHCl_3$ and water. The organic phase was dried over Na_2SO_4, and evaporated to give a residue, recrystallization of which from acetone gave **5** (793.4 mg, 62.1%) as colorless needles, mp 160—161 °C. *Anal.* Calcd for $C_{16}H_{22}N_2O_5 \cdot 1/5H_2O$: C, 58.96; H, 6.93; N, 8.59. Found: C, 59.02; H, 6.99; N, 8.48. MS *m/z* (%): 322 (M^+, 9), 196 (13), 195 (100), 165 (15), 150 (7). IR (KBr): 3640, 3470, 1650 cm^{-1}. UV λ_{max} nm (log ε): 278 sh (3.52), 284 (3.56). ^{1}H-NMR δ: 2.185 (3H, s, $ArCH_3$), 2.885 (1H, d,

J=17.1 Hz, 6-H), 2.954 (3H, s, NCH_3), 3.121 (1H, dd, J=13.9, 4.6 Hz, ArCH), 3.217 (1H, dd, J=13.9, 4.8 Hz, ArCH), 3.579 (1H, dd, J=17.1, 3.9 Hz, 6-H), 3.654 (3H, s, OCH_3), 3.781 (6H, s, 2×OCH_3), 4.128 (1H, dd, J=4.8, 4.6 Hz, 3-H), 6.525 (1H, s, ArH), 6.565 (1H, d, J=3.9 Hz, NH).

(*Z*)-1-Acetyl-4-benzyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (6a)——Sodium hydride (60% oil dispersion, washed with dry hexane three times, 264 mg, 11 mmol) was added to a stirred solution of **2** (3.2 g, 9.2 mmol) in dry DMF (40 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Benzyl bromide (1.28 ml, 10.8 mmol) in dry DMF (20 ml) was added. The reaction mixture was stirred for 1 h at 25 °C, poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give **6a** (3.358 g, 84%), which was used without further purification. Recrystallization from benzene gave an analytical sample as pale yellow prisms, mp 154.5—156 °C. *Anal.* Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.98; H, 5.96; N, 6.27. MS *m/z* (%): 438 (M^+, 83), 408 (16), 407 (52), 392 (18), 366 (24), 365 (100), 332 (14), 306 (11), 305 (26), 91 (46). IR (KBr): 1720, 1700 cm^{-1}. UV λ_{max} nm (log ε): 242 sh (4.07), 340 (4.08). ^{1}H-NMR δ: 2.233 (3H, s, $ArCH_3$), 2.596 (3H, s, $COCH_3$), 3.538 (3H, s, OCH_3), 3.837 (3H, s, OCH_3), 3.882 (3H, s, OCH_3), 4.553 (2H, s, 6-H_2), 4.730 (2H, s, NCH_2), 6.695 (1H, s, ArH), 6.886—6.901 (2H, m, 2×ArH), 7.187—7.203 (4H, m, 3×ArH and C=CH).

(*Z*)-4-Benzyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (7a)——Hydrazine hydrate (0.8 ml) was added to a stirred solution of **6a** (3.358 g, 7.73 mmol) in DMF (60 ml), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was poured into water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a solid, recrystallization of which from acetone–ether gave **7a** (2.469 g, 80.7%) as pale yellow prisms, mp 161—161.5 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.93; H, 6.24; N, 6.68. MS *m/z* (%): 396 (M^+, 36), 366 (24), 365 (100), 290 (15), 274 (19), 91 (29). IR (KBr): 3170, 1680, 1620 cm^{-1}. UV λ_{max} nm (log ε): 240 sh (4.09), 300 (4.08), 330 sh (4.40). ^{1}H-NMR δ: 2.224 (3H, s, $ArCH_3$), 3.504 (3H, s, OCH_3), 3.809 (3H, s, OCH_3), 3.861 (3H, s, OCH_3), 4.139 (2H, d, J=2.4 Hz, 6-H_2), 4.739 (2H, s, NCH_2), 6.616 (1H, s, ArH), 6.900—6.923 (2H, m, 2×ArH), 7.155—7.209 (4H, m, 3×ArH and NH), 7.216 (1H, s, C=CH).

(*Z*)-4-Benzyl-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (8a)——Sodium hydride (60% oil dispersion, washed with dry hexane three times, 144 mg, 6 mmol) was added to a stirred solution of **7a** (1.584 g, 4 mmol) in dry DMF (16 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (0.37 ml, 6 mmol) in dry DMF (8 ml) was added. The reaction mixture was stirred for 1 h at 25 °C, poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give the residue. Chromatography on a silica gel (60 g) column with hexane–AcOEt (1 : 1) as the eluent gave **8a** (1.15 g, 70%) as a pale yellow amorphous powder. MS *m/z* (%): 410 (M^+, 8), 380 (25), 379 (100), 288 (12), 91 (37). High-resolution MS Calcd for $C_{23}H_{26}N_2O_5$: 410.1841. Found: 410.1839. IR ($CHCl_3$): 1680, 1625 cm^{-1}. UV λ_{max} nm (log ε): 242 sh (4.09), 296 (4.09), 325 (4.03). ^{1}H-NMR δ: 2.216 (3H, s, $ArCH_3$), 3.078 (3H, s, NCH_3), 3.499 (3H, s, OCH_3), 3.802 (3H, s, OCH_3), 3.852 (3H, s, OCH_3), 4.114 (2H, s, 6-H_2), 4.714 (2H, s, NCH_2), 6.590 (1H, s, ArH), 6.885—6.909 (2H, m, 2×ArH), 7.155—7.261 (4H, m, 3×ArH and C=CH).

4-Benzyl-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (11)——The arylidene derivative **8a** (1.89 g, 4.61 mmol) was dissolved in ethanol (15 ml) and hydrogenated over 10% palladium on carbon (0.4 g) at 1 atm for 72 h. After removal of the catalyst by filtration, the filtrate was evaporated to give the residue, recrystallization of which from AcOEt gave **11** (1.36 g, 72%) as colorless prisms, mp 135—136.5 °C. *Anal.* Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.82; H, 6.99; N, 6.68. MS *m/z* (%): 412 (M^+, 7), 196 (13), 195 (100), 91 (16). IR (KBr): 1655 cm^{-1}. UV λ_{max} nm (log ε): 284 (3.60). ^{1}H-NMR δ: 2.212 (3H, s, $ArCH_3$), 2.706 (1H, d, J=17.1 Hz, 6-H), 2.782 (3H, s, NCH_3), 3.055 (1H, dd, J=13.7, 4.2 Hz, ArCH), 3.252 (1H, dd, J=13.7, 4.6 Hz, ArCH), 3.476 (1H, d, J=17.1 Hz, 6-H), 3.676 (3H, s, OCH_3), 3.780 (3H, s, OCH_3), 3.794 (1H, d, J=15.1 Hz, NCH), 3.801 (3H, s, OCH_3), 4.133 (1H, dd, J=4.6, 4.2 Hz, 3-H), 5.478 (1H, d, J=15.1 Hz, NCH), 6.441 (1H, s, ArH), 7.220—7.346 (5H, m, 5×ArH).

Debenzylation of **11** with 20% palladium on carbon in ethanol at 80 °C (3 atm H_2) for 24 h failed, and only the starting material was recovered.

(*Z*)-1-Acetyl-4-(4-methoxyphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (6b)——Sodium hydride (60% oil dispersion, washed with dry hexane three times, 0.3 g, 12.5 mmol) was added to a stirred solution of **2** (3.48 g, 10 mmol) in dry DMF (80 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. 4-Methoxybenzyl chloride (1.956 g, 12.5 ml) in dry DMF (20 ml) was added. The reaction mixture was stirred for 12 h at 25 °C, poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give **6b** (4.68 g, 100%), which was used without further purification. Recrystallization from AcOEt–ether gave an analytical sample as pale yellow prisms, mp 130.5—131 °C. *Anal.* Calcd for $C_{25}H_{28}N_2O_7$: C, 64.09; H, 6.02; N, 5.91. Found: C, 64.03; H, 6.01; N, 5.91. MS *m/z* (%): 468 (M^+, 10), 122 (9), 121 (100). IR (KBr): 1725, 1705 cm^{-1}. UV λ_{max} nm (log ε): 222 (4.42), 276 (3.86), 284 (3.89), 342 (4.09). ^{1}H-NMR δ: 2.238 (3H, s, $ArCH_3$), 2.560 (3H, s, $COCH_3$), 3.549 (3H, s, OCH_3), 3.739 (3H, s, OCH_3), 3.839 (3H, s, OCH_3), 3.880 (3H, s, OCH_3), 4.528 (2H, s, 6-H_2), 4.655 (2H, s, NCH_2), 6.716 (1H, s, ArH), 6.720 (2H, d, J=8.4 Hz, 2×ArH), 6.852 (2H, d, J=8.4 Hz, 2×ArH), 7.375 (1H, s, C=CH).

(*Z*)-4-(4-Methoxyphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (7b)——Hydrazine hydrate (1.0 ml) was added to a stirred solution of **6b** (4.68 g, 10 mmol) in DMF (100 ml), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was poured into water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a solid, recrystallization of which from AcOEt-ether gave **7b** (2.140 g, 50.2%) as pale yellow prisms, mp 153—155 °C. *Anal.* Calcd for $C_{23}H_{26}N_2O_6$: C, 64.77; H, 6.15; N, 6.57. Found: C, 64.80; H, 6.24; N, 6.45. MS *m/z* (%): 426 (M^+, 13), 395 (13), 274 (9), 122 (9), 121 (100). IR (KBr): 3250, 1710, 1640 cm^{-1}. UV λ_{max} nm (log ε): 223 (4.48), 276 (4.07), 284 (4.14), 301 (4.11), 324 sh (4.14). ^{1}H-NMR δ: 2.229 (3H, s, $ArCH_3$), 3.553 (3H, s, OCH_3), 3.720 (3H, s, OCH_3), 3.819 (3H, s, OCH_3), 3.862 (3H, s, OCH_3), 4.106 (2H, d, J=2.0 Hz, 6-H_2), 4.668 (2H, s, NCH_2), 6.653 (1H, s, ArH), 6.711 (2H, d, J=9.0 Hz, 2 × ArH), 6.859 (2H, d, J=9.0 Hz, 2 × ArH), 7.202 (1H, s, C=CH), 7.827 (1H, br s, NH).

(*Z*)-4-(4-Methoxyphenylmethyl)-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (8b)——Sodium hydride (60% oil dispersion, washed with dry hexane three times, 108 mg, 4.5 mmol) was added to a stirred solution of **7b** (1.278 g, 3.0 mmol) in dry DMF (12 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (0.28 ml, 4.5 mmol) in dry DMF (6 ml) was added. The reaction mixture was stirred for 1 h at 25 °C, poured into ice-water, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give the residue. Chromatography on a silica gel (50 g) column with hexane–AcOEt (1 : 2) as the eluent gave **8b** (991.4 mg, 75.1%) as a pale yellow amorphous powder. MS *m/z* (%): 440 (M^+, 16), 423 (18), 409 (38), 304 (11), 288 (12), 121 (100). High-resolution MS Calcd for $C_{24}H_{28}N_2O_6$: 440.1947. Found. 440.1935. IR ($CHCl_3$): 1680, 1625 cm^{-1}. UV λ_{max} nm (log ε): 224 (4.48), 276 (4.12), 284 (4.17), 300 (4.18), 322 sh (4.14). ^{1}H-NMR δ: 2.221 (3H, s, $ArCH_3$), 3.056 (3H, s, NCH_3), 3.549 (3H, s, OCH_3), 3.728 (3H, s, OCH_3), 3.813 (3H, s, OCH_3), 3.852 (3H, s, OCH_3), 4.086 (2H, s, 6-H_2), 4.634 (2H, s, NCH_2), 6.625 (1H, s, ArH), 6.706 (2H, d, J=8.8 Hz, 2 × ArH), 6.856 (2H, d, J=8.8 Hz, 2 × ArH), 7.241 (1H, s, C=CH).

(*Z*)-1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (9)——Concentrated H_2SO_4 (2.0 ml) was added to a stirred solution of **8b** (1.134 g, 2.58 mmol) in trifluoroacetic acid (30 ml), and stirring was continued for 12 h at 25 °C. The reaction mixture was poured into water (200 ml) and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a solid. Recrystallization from AcOEt gave **9** (569 mg, 69%) as pale yellow prisms, mp 158—159.5 °C. *Anal.* Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 59.84; H, 6.36; N, 8.61. MS *m/z* (%): 320 (M^+, 31), 290 (18), 289 (100), 273 (6), 220 (10), 131 (13). IR (KBr): 3330, 1705, 1645 cm^{-1}. UV λ_{max} nm (log ε): 225 (4.23), 240 sh (4.15), 302 (4.27), 322 sh (4.17). ^{1}H-NMR δ: 2.233 (3H, s, $ArCH_3$), 3.104 (3H, s, NCH_3), 3.622 (3H, s, OCH_3), 3.827 (6H, s, 2 × OCH_3), 4.149 (2H, s, 6-H_2), 6.640 (1H, s, ArH), 6.914 (1H, s, C=CH), 9.349 (1H, s, NH).

1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (10)——The arylidene derivative **9** (498.1 mg, 1.57 mmol) was dissolved in ethanol (16 ml) and hydrogenated over 20% palladium on carbon (250 mg) at 1 atm for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried over Na_2SO_4, and evaporated to give the residue, recrystallization of which from AcOEt–ether gave **10** (342.1 mg, 68.3%) as colorless prisms, mp 164—165 °C. *Anal.* Calcd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.49; H, 6.97; N, 8.55. MS *m/z* (%): 322 (M^+, 10), 196 (13), 195 (100), 165 (17), 150 (10). IR (KBr): 3300, 1695, 1655 cm^{-1}: UV λ_{max} nm (log ε): 228 (3.91), 276 sh (3.35), 284 (3.42). ^{1}H-NMR δ: 2.195 (3H, s, $ArCH_3$), 2.933 (3H, s, NCH_3), 2.993 (1H, dd, J=13.7, 7.1 Hz, ArCH), 3.288 (1H, dd, J=13.7, 4.2 Hz, ArCH), 3.424 (1H, d, J=17.6 Hz, 6-H), 3.667 (3H, s, OCH_3), 3.779 (1H, d, J=17.6 Hz, 6-H), 3.784 (3H, s, OCH_3), 3.793 (3H, s, OCH_3), 4.261 (1H, m, 3-H), 6.557 (1H, s, ArH), 6.757 (1H, br s, NH).

1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-4-isopropyloxycarbonyl-2,5-piperazinedione (12)——A solution of **10** (1.61 g, 5 mmol), triethylamine (2.09 ml, 15 mmol), and 4-dimethylaminopyridine (1.83 g, 15 mmol) in dry methylene chloride (100 ml) was cooled with ice-water, and isopropyl chloroformate (3.41 ml, 30 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at 25 °C. The organic layer was washed with 1 N HCl, dried over Na_2SO_4, and concentrated *in vacuo* to give the residue, recrystallization of which from ether gave **12** (1.66 g, 81.4%) as colorless prisms, mp 67.5—68.5 °C. *Anal.* Calcd for $C_{20}H_{28}N_2O_7$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.75; H, 7.01; N, 6.78. MS *m/z* (%): 408 (M^+, 11), 322 (4), 196 (13), 195 (100), 165 (12). IR (KBr): 1740, 1730, 1680 cm^{-1}. UV λ_{max} nm (log ε): 212 (4.41), 234 sh (3.84), 278 (3.72), 284 (3.74). ^{1}H-NMR δ: 1.340 (3H, d, J=6.1 Hz, $CHCH_3$), 1.361 (3H, d, J=6.1 Hz, $CHCH_3$), 2.165 (3H, s, $ArCH_3$), 2.647 (1H, d, J=17.8 Hz, 6-H), 2.800 (3H, s, NCH_3), 3.115 (1H, dd, J=13.8, 3.9 Hz, ArCH), 3.434 (1H, dd, J=13.8, 5.1 Hz, ArCH), 3.485 (1H, d, J=17.8 Hz, 6-H), 3.611 (3H, s, OCH_3), 3.769 (3H, s, OCH_3), 3.782 (3H, s, OCH_3), 5.007 (1H, dd, J=5.1, 3.9 Hz, 3-H), 5.100 (1H, sept, OCH), 6.430 (1H, s, ArH).

. 7,9,10-Trimethoxy-3,8-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Isopropyl Ester (14)——A stirred solution of **12** (300 mg, 0.735 mmol) in dry THF (20 ml) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminohydride (750 mg, 2.95 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was filtered through a celite pad, which was then washed with $CHCl_3$ (200 ml), and the combined filtrate was concentrated *in vacuo*. The crude diastereomeric mixture of the alcohols **13** obtained was used for the next step without isolation. A solution of **13** in formic acid (10 ml) was heated at 60 °C for 1 h. The reaction mixture was diluted with water (50 ml) and extracted with $CHCl_3$ (50 ml × 3). The combined organic

extracts were washed with 10% NH_4OH (50 ml), and then with water (50 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give the residue (340 mg). Chromatography on a silica gel (15 g) column with hexane–AcOEt (2 : 1) as the eluent gave **14** (243 mg, 84.3%) as a colorless amorphous powder. MS *m/z* (%): 392 (M^+, 100), 320 (35), 306 (38), 278 (68), 234 (79), 204 (22). High-resolution MS Calcd for $C_{20}H_{28}N_2O_6$: 392.1947. Found: 392.1946. IR ($CHCl_3$): 1705, 1690, 1655, 1645 cm^{-1}. UV λ_{max} nm (log ε): 206 (4.63), 224 sh (4.05), 272 sh (3.24), 278 (3.26). ^{1}H-NMR (at 50 °C) δ: 1.254 (6H, d, J=6.3 Hz, $CH(CH_3)_2$), 2.173 (3H, s, $ArCH_3$), 2.846 (3H, s, NCH_3), 2.969 (1H, m, 6-Hα), 3.139 (1H, dd, J=17.1, 1.2 Hz, 6-Hβ), 3.195 (1H, d, J=11.7 Hz, 2-Hβ), 3.661 (3H, s, OCH_3), 3.798 (3H, s, OCH_3), 3.869 (1H, dd, J=11.7, 4.4 Hz, 2-Hα), 3.908 (3H, s, OCH_3), 4.944 (2H, m, 5-H and OCH), 5.540 (1H, m, 1-H). ^{13}C-NMR (at 50 °C) δ: 9.4 (q), 22.2 (q), 22.2 (q), 27.2 (t), 34.3 (t), 44.8 (q), 52.7 (d), 55.3 (d), 59.9 (q), 60.1 (q), 60.4 (q), 69.5 (d), 122.5 (s), 125.2 (s), 125.8 (s), 126.2 (s), 145.6 (s), 150.2 (s), 153.6 (s), 168.3 (s).

7,9,10-Trimethoxy-3,8-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (15)——Concentrated H_2SO_4 (0.2 ml) was added to a stirred solution of **14** (84.8 mg, 0.216 mmol) in trifluoroacetic acid (4 ml), and the resulting solution was stirred for 12 h at 25 °C. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to give a solid, recrystallization of which from AcOEt–ether gave **15** (59.5 mg, 89.9%) as colorless prisms, mp 153.5—155.5 °C. *Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.81; H, 7.35; N, 9.10. MS *m/z* (%): 306 (M^+, 26), 235 (20), 234 (100), 204 (14). IR (KBr): 3390, 1655 cm^{-1}. UV λ_{max} nm (log ε): 207 (4.23), 225 sh (3.98), 272 (2.85), 278 (2.90). ^{1}H-NMR δ: 2.183 (3H, s, $ArCH_3$), 2.291 (1H, s, NH), 2.856 (3H, s, NCH_3), 2.908 (1H, dd, J=17.6, 6.6 Hz, 6-Hα), 2.081 (1H, dd, J=17.6, 1.2 Hz, 6-Hβ), 3.213 (1H, d, J=11.7 Hz, 2-Hβ), 3.671 (3H, s, OCH_3), 3.795 (3H, s, OCH_3), 3.839 (1H, dd, J=11.7, 4.7 Hz, 2-Hα), 3.883 (3H, s, OCH_3), 3.967 (1H, d, J=6.4 Hz, 5-H), 4.458 (1H, d, J=4.7 Hz, 1-H).

7,9,10-Trimethoxy-3,8,11-trimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (16)——Formaldehyde (37% solution water, 0.96 ml) was added to a stirred solution of **15** (45.9 mg, 0.15 mmol) in formic acid (2.16 ml) at 50 °C. The mixture was stirred for 1 h at 70 °C, then removal of the solvent *in vacuo* afforded the residue, which was partitioned between $CHCl_3$ and 5% $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to obtain a colorless gum. Purification by chromatography on a silica gel (5 g) column with AcOEt–methanol (8 : 1) as the eluent give a solid (45.5 mg, 99%). Recrystallization from AcOEt–ether gave **16** as colorless prisms, mp 117—118 °C (lit.,[18] mp 115—116 °C). *Anal.* Calcd for $C_{18}H_{24}N_2O_6$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.49; H, 7.68; N, 8.66. MS *m/z* (%): 320 (M^+, 19), 249 (20), 248 (100), 218 (18), IR (KBr): 1655 cm^{-1}. UV λ_{max} nm (log ε): 208 (4.43), 224 sh (4.03), 272 (3.02), 278 (3.04). ^{1}H-NMR δ: 2.187 (3H, s, $ArCH_3$), 2.494 (3H, s, NCH_3), 2.856 (3H, s, NCH_3), 2.920 (1H, dd, J=17.6, 1.2 Hz, 6-Hβ), 3.037 (1H, dd, J=17.6, 6.6 Hz, 6-Hα), 3.091 (1H, dd, J=11.7, 0.7 Hz, 2-Hβ), 3.641 (1H, ddd, J=6.6, 1.2, 0.5 Hz, 5-H), 3.678 (3H, s, OCH_3), 3.801 (3H, s, OCH_3), 3.878 (3H, s, OCH_3), 3.942 (1H, dd, J=11.7, 4.9 Hz, 2-Hα), 4.112 (1H, ddd, J=4.9, 0.7, 0.5 Hz, 1-H). ^{13}C-NMR δ: 9.3 (q, $ArCH_3$), 23.7 (t, 6-CH_2), 33.9 (q, NCH_3), 40.1 (q, NCH_3), 51.1 (d, 5-CH), 53.3 (t, 2-CH_2), 58.8 (d, 1-CH), 59.8 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 122.1 (s), 124.5 (s), 126.3 (s), 146.1 (s), 149.8 (s), 152.3 (s), 170.1 (s, CO).

Acknowledgment We are grateful to Dr. Hideshi Kurihara, Central Research Laboratories, Sankyo Co., Ltd., for providing the IR and ^{1}H-NMR spectra of the lactam (**16**).

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17) The signals in the ^{1}H-NMR spectrum of **14** at 20 °C were not split, which indicated that it was a mixture of two rotational isomers. Treatment of **14** with $NaOCH_3$ in methanol gave **17**, and its ^{1}H-NMR signals at 20 °C were also not split. The data were identical with those reported for an authentic sample.[10a] ^{1}H-NMR (at 50 °C) δ: 2.171 (3H, s, $ArCH_3$), 2.842 (3H, s, NCH_3), 2.981 (1H, m, 6-Hα), 3.156 (1H, d, J=17.3 Hz, 6-Hβ), 3.192 (1H, d, J=11.5 Hz, 2-Hβ), 3.658 (3H, s, OCH_3), 3.739 (3H, s, OCH_3), 3.792 (3H, s, OCH_3), 3.870 (1H, m, 2-Hα), 3.913 (3H, s, OCH_3), 4.909 (1H, br m, 5-H), 5.540 (1H, br m, 1-H).
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