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Synthesis of Novel Octahydro-1,5-imino-3-benzazocin-4,7,10-trione Derivatives Having a Methyl Group at the C-2 Position as ABC Ring Models of Saframycins

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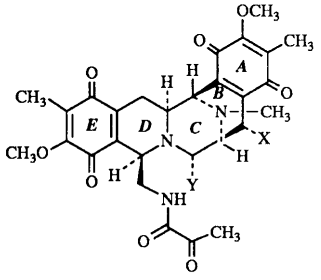
(*Z*)-3-(2,4,5-Trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (7a) was prepared by a simple regioselective *C*-monomethylation of (*Z*)-4-(4-methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1-methylpiperazine-2,5-dione (3) followed by deprotection. Compound 7a was also prepared from (*S*)-1,4-diacetyl-3-methylpiperazine-2,5-dione (8) and the benzaldehyde derivative (9) in five steps as an optically active form. It was shown to be a useful intermediate for the preparation of novel octahydro-1,5-imino-3-benzazocin-4,7,10-trione derivatives having a methyl group at the C-2 position, as ABC ring models of saframycins.

Key words piperazine-2,5-dione; preparation; alkylation; saframycin; 1,5-imino-3-benzazocine

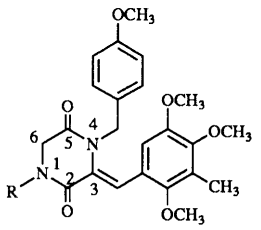
For some time, we have been interested in synthesis of the antitumor isoquinolinequinone antibiotics, saframycins A—C (**1a**—**c**). Although total syntheses of racemic **1a**—**c** have been reported,[1,2] recent efforts have focused on enantiospecific approaches to these DNA-reactive molecules.[3] To design anticancer compounds for practical use and to simplify their synthesis, it was decided to eliminate the left-hand half portion from the saframycin core. In a previous paper, a practical synthesis of ABC ring models of saframycins (**4a**—**c**) from the piperazine-2,5-dione derivative (**3**) was described,[4,5] and the cytotoxicity of these compounds *in vitro* against L 1210 murine leukemia was studied. Although **4a** and **4b** showed low cytotoxic potency (**4a**: $ID_{50}=0.22\,\mu g/ml$; **4b**: $ID_{50}=8.8\,\mu g/ml$) relative to **1a** ($ID_{50}=0.0012\,\mu g/ml$), we observed that introduction of a methoxy group at the C-6 position was effective (**4c**: $ID_{50}=0.158\,\mu g/ml$).[6] To extend the scope of the synthetic route to the ABC ring models, we utilized **3** for the preparation of the octahydro-1,5-imino-3-benzazocin-4,7,10-trione derivatives having a methyl group at the C-2 position as new ABC ring models of saframycins.

We reported previously that reaction of **2** with sodium hydride (1.5 eq) and methyl iodide (1.5 eq) in dimethylformamide (DMF) at 25 °C for 1 h gave **3** in 75.1% yield.[7] We recently developed an efficient, large-scale preparation, and obtained an additional minor product **5a** in 2.0% yield. The structure of **5a** was supported by the proton nuclear magnetic resonance (^{1}H-NMR) spectrum; irradiation of the doublet absorption at δ 1.55 (6-CH_3) led to the collapse of the signal at δ 4.03 (H-6) from a quartet to a singlet. We became interested in compound **5a**, which was a plausible intermediate with which to prepare new ABC ring models of saframycins having a methyl group at the C-2 position. After numerous experiments under a variety of conditions, we found that the following procedure was the best in terms of product yield and reproducibility of the reaction; methylation of **3** with methyl iodide (1 eq) in the presence of sodium hydride (1 eq) in tetrahydrofuran (THF) under reflux for 3 h afforded **5a** in 68.6% yield along with **6** (8.2%). Furthermore, methylation of **2** with methyl iodide (10 eq) in the presence of sodium hydride (2.1 eq) in THF under reflux for 3 h gave **5a** in 68.8% yield.[8] Benzylation of **3** with benzyl bromide and sodium hydride gave **5b** in 47.7% yield. Facile deprotection of the 4-methoxybenzyl group of **5a** and **5b** with concentrated H_2SO_4 and trifluoroacetic acid (TFA) at 25 °C for 24 h gave **7a** and **7b** in 79.6% and 83.4% yields, respectively.

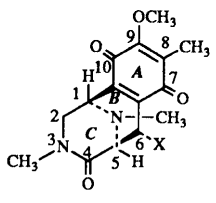
We then investigated asymmetric synthesis of **7a** from (+)-**8**[9,10] and benzaldehyde **9** (Chart 2). Chai *et al.* reported that radical bromination of 1,4-diacetyl-3-methylpiperazine-2,5-dione (**8**) gave the 6-bromide regioselectively.[11] A mixture of (+)-**8** and **9** was treated



saframycins:
A (1a): X = H, Y = CN
B (1b): X = Y = H
C (1c): X = OCH_3, Y = H



2: R = H
3: R = CH_3



4a: X = H
4b: X = OH
4c: X = OCH_3

Fig. 1

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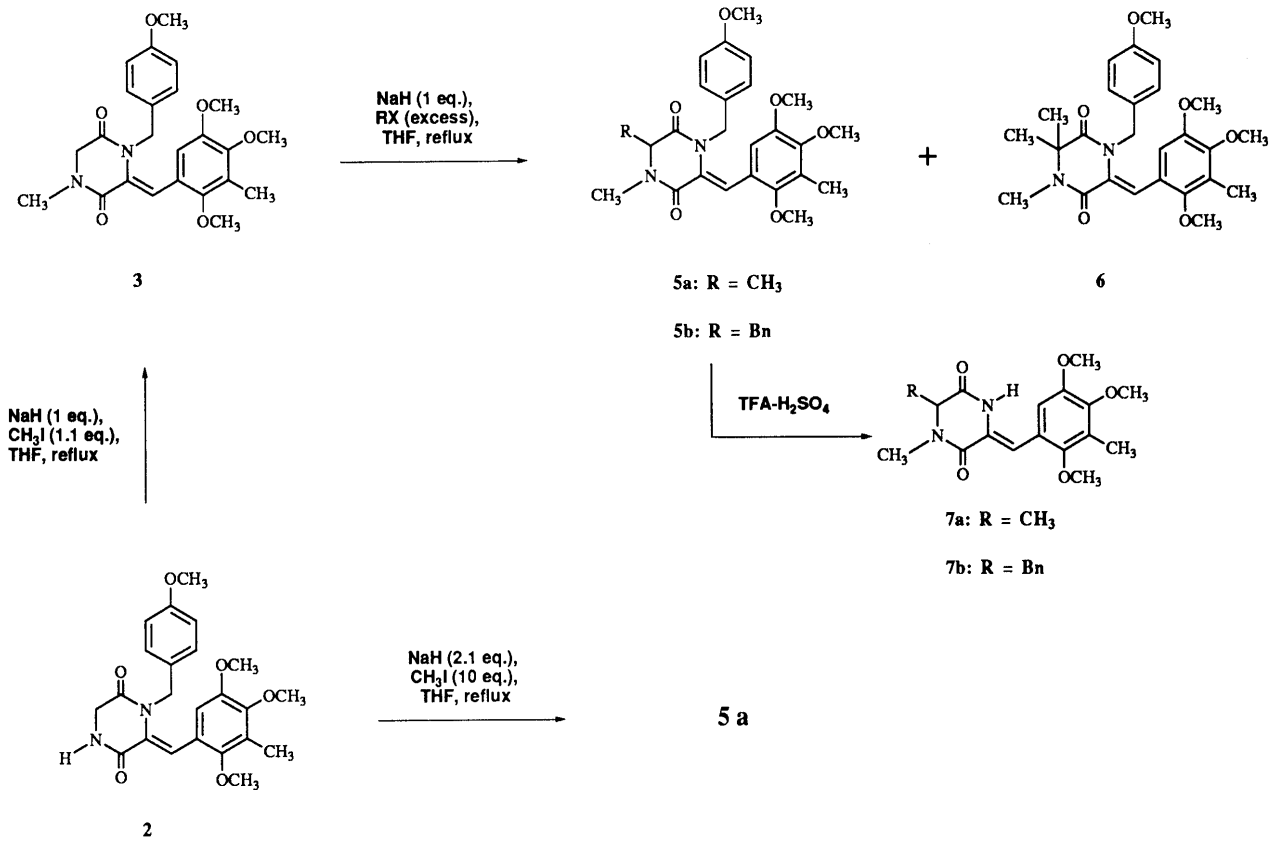

Chart 1

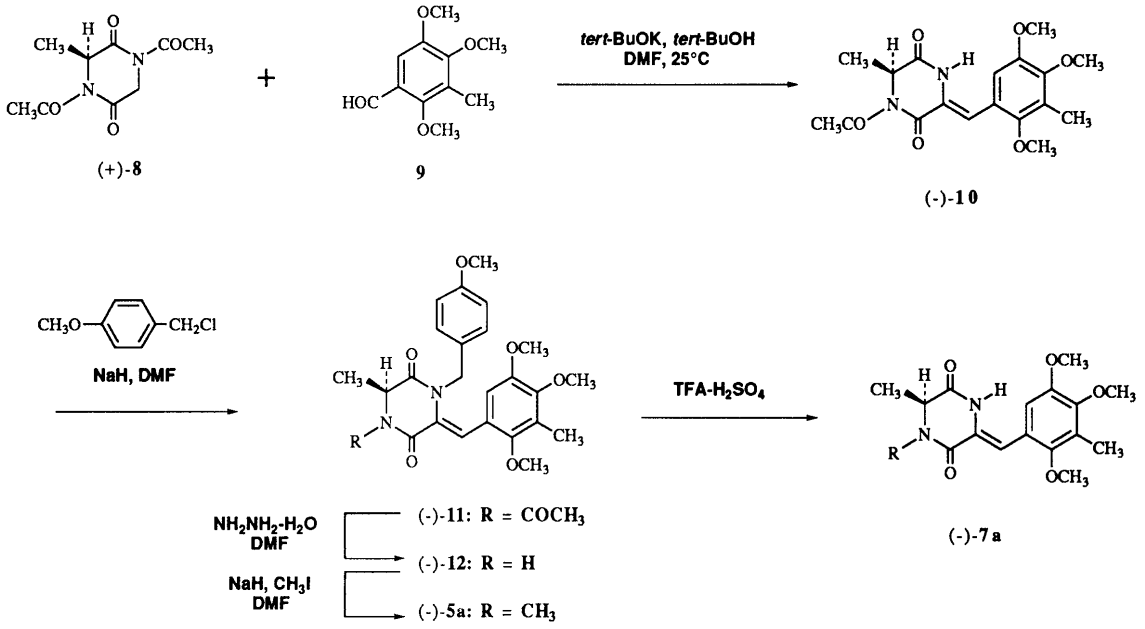

Chart 2

with potassium *tert*-butoxide in DMF to afford (−)-**10** in 64.7% yield as a sole product.[12] Protection of (−)-**10** with a 4-methoxybenzyl group furnished (−)-**11** in 82.9% yield, and successive treatment with hydrazine hydrate afforded (−)-**12** in 94.3% yield. Methylation of (−)-**12** with methyl iodide gave (−)-**5a** in 70.7% yield; this product was identical with a racemic sample on comparison of the spectroscopic data. Finally, deprotection of (−)-**5a** gave (−)-**7a** in 85.0% yield. Thus, we succeeded in developing a simple and efficient synthesis of (±)-**7a** and (−)-**7a**.

We turned our attention to the construction of the ABC ring model (**20**) having a methyl group at the C-2 position from **7a** using the methods described in connection with our previous synthesis of ABC ring models (**4a**—**c**) (Chart 3).

Catalytic hydrogenation of **7a** with hydrogen over 20% palladium on carbon at 25 °C gave **13** in 68.3% yield. The

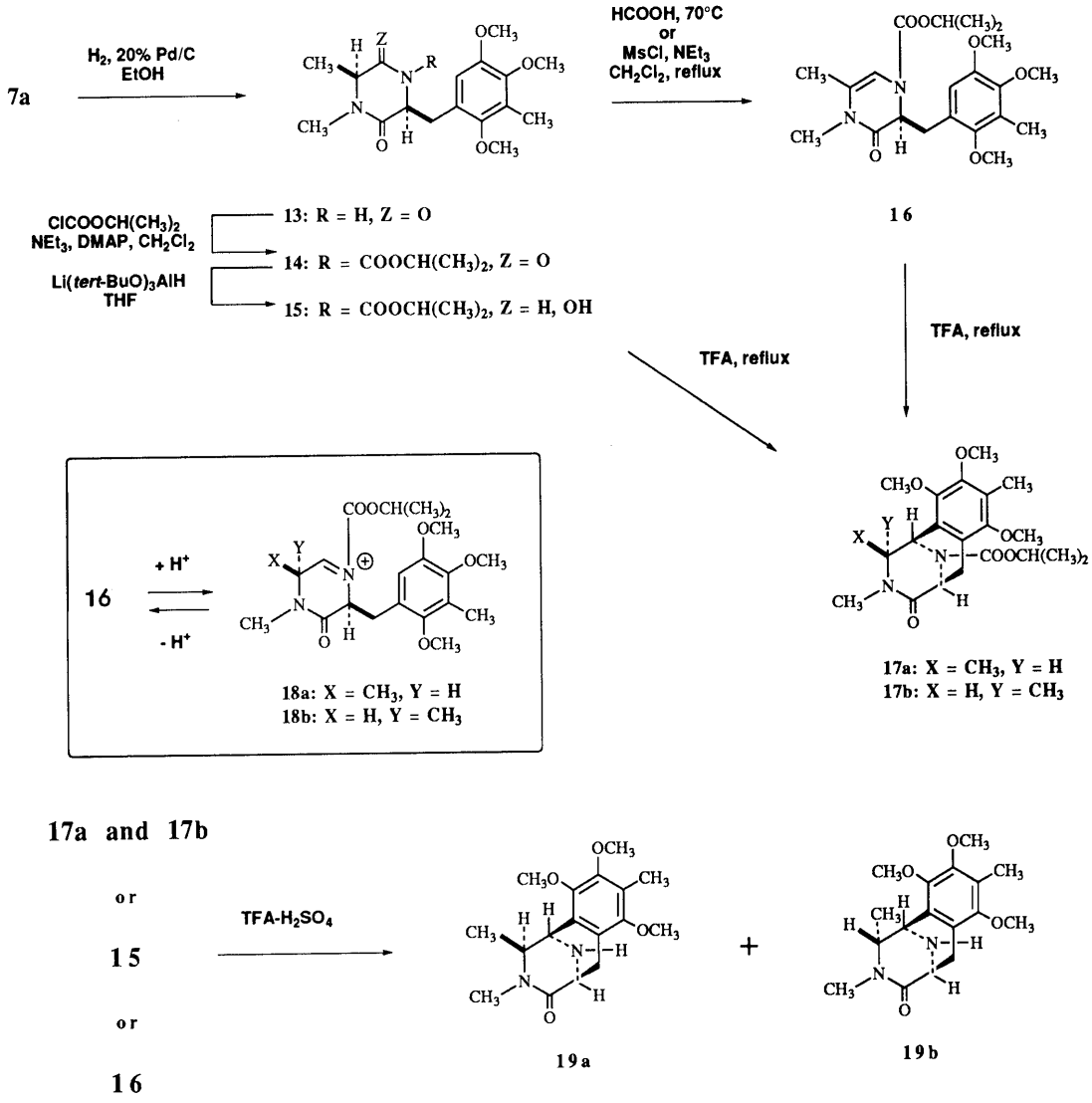

Chart 3

piperazine ring of **13** was activated by introduction of an isopropylcarbonyl group to give the imide **14** in 79.7% yield. Chemoselective reduction of **14** with lithium tri-*tert*-butoxyaluminum hydride in THF afforded a diastereomeric mixture of the alcohol **15**, which, when exposed to formic acid at 70 °C for 30 min, was converted into an enamine **16**[13] in 79.2% yield. Furthermore, treatment of **15** with methanesulfonyl chloride and triethylamine in dichloromethane, a mild and efficient nonacidic reaction,[14] gave **16** in 97.5% yield. Cyclization of **16** occurred smoothly using TFA under reflux for 24 h to give **17a** and **17b** as an inseparable diastereomeric mixture in 98.0% yield. The structure of the cyclization products was fully supported by the molecular weight determined by mass spectrometry and by the spectral data. However, at this stage, it was difficult to determine the ratio of the two diastereomers because each of them has rotational isomers. Treatment of **15** under similar conditions directly afforded **17a** and **17b** in 50.7% yield. Deprotection of a mixture of the cyclized products **17a** and **17b** gave the secondary amines, which were separated by chromatography on a silica gel column to give **19a** and **19b** in 42.4% and 38.4% yields, respectively. The ^{1}H-NMR

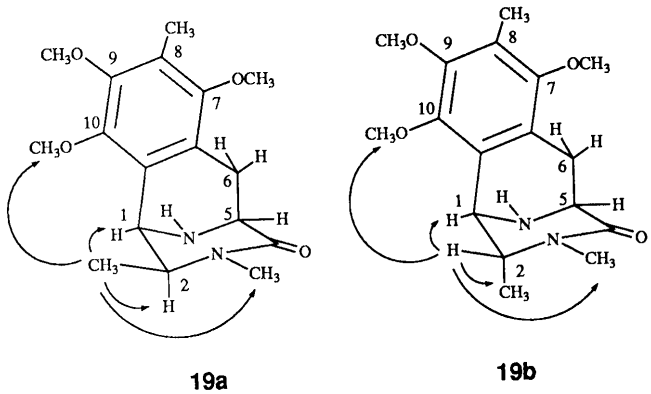

Fig. 2

spectrum of **19a** displayed a 5.2 Hz coupling between H-1 (δ 4.46) and H-2 (δ 3.92), whereas the ^{1}H-NMR spectrum of **19b** showed an H-1 (δ 4.07) and H-2 (δ 3.36) coupling of 1.0 Hz.[15] The relative stereochemical assignments for **19a** and **19b** are based upon extensive nuclear Overhauser effect (NOE) correlations, as shown in Fig. 2. When **15** was treated with TFA and H_2SO_4, it gave **19a** and **19b** in 50.5% and 41.7% yields, respectively, and treatment of

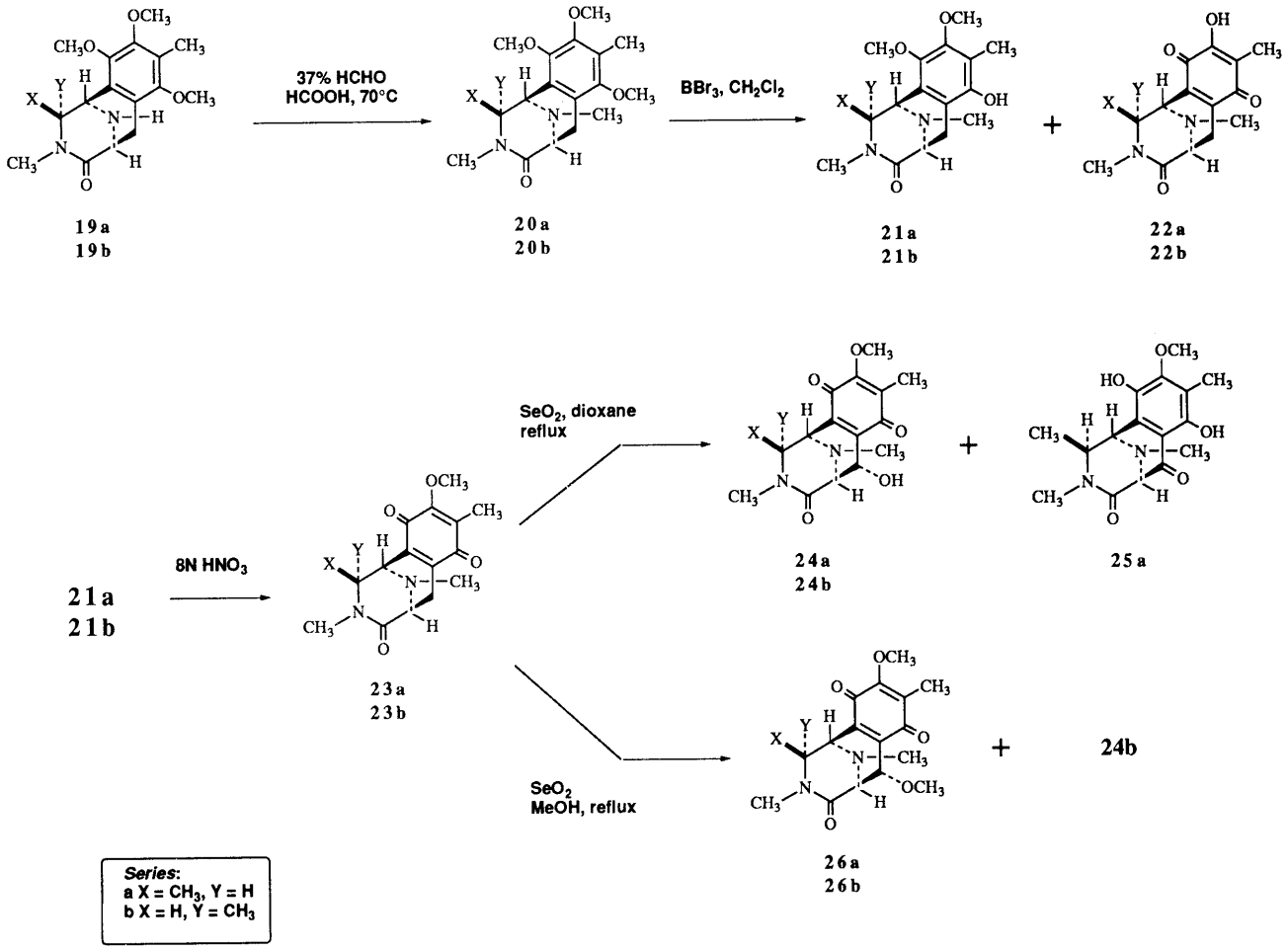

Chart 4

16 under similar conditions afforded **19a** and **19b** in 48.8% and 44.0% yields. The ratio of **19a** and **19b** was about the same in each case. These results indicated that the dehydrogenation of **15** generated **16**, which was converted to inimium salts **18a** and **18b**, followed by cyclization to afford **17a** and **17b**. Finally, **17a** and **17b** were transformed into **19a** and **19b**.

We then studied the conversion of **19a** to the quinone **23a** (Chart 4). Methylation of **19a** with formaldehyde and formic acid at 70 °C for 1 h gave **20a** in 93.7% yield. The partial demethylation of **20a** with 1.8 eq of boron tribromide in dichloromethane gave the phenol **21a** in 86.1% yield along with the *p*-quinone **22a** in 5.3% yield. The hydroxy group of **21a** was assigned to C-7 based upon the observation of an NOE enhancement of the hydroxy proton when 8-CH_3 was irradiated. Treatment of **21a** with 8 N HNO_3 at 0 °C for 1 h gave the quinone **23a** in 81.0% yield. Similarly, **19b** was converted to the *epi*-isomer **23b** in the same three-step sequence.

Finally, we turned our attention to the introduction of an oxygen functionality into the C-6 position of **23**. Treatment of **23a** with selenium oxide in dioxane under reflux for 5 h afforded the alcohols **24a** and **25a**[16] in 65.0% and 10.9% yields, respectively.[17] Furthermore, treatment of **23a** with selenium oxide in methanol afforded **26a** in 76.6% yield. The C-6 stereochemistry of **24a** and **26a** was assigned on the basis of a 1.0 Hz coupling between H-5 and H-6.[18] Oxidation of **23b** with selenium oxide in dioxane in contrast, was especially slow and, after refluxing for 24 h, afforded **24b** in 66.0% yield. Treatment of **23b** with selenium oxide in methanol gave **26b** and **24b** in 60.8% and 17.9% yields, respectively.

In summary, we have developed in a simple and efficient synthesis of (*Z*)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (**7a**) in both racemic and optically active forms. Compound **7a** was shown to be a useful intermediate for effective synthesis of ABC ring derivatives of saframycins having a methyl group at the C-2 position. Efforts are now being made to apply this transformation to the synthesis of versatile ABC ring models in optically active form.

Experimental

All melting points were determined with a Yanagimoto micromelting points apparatus and are uncorrected. Optical rotation $[\alpha]_D$ measurements were made on a Horiba-SEPA-200 automatic digital polarimeter. IR spectra were obtained with a Hitachi 260-10 IR Fourier-transform spectrometer. ^{1}H-NMR spectra were recorded at 270 MHz with a JEOL JNM-EX 270 spectrometer. Peak multiplicities are denoted by s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) or by a combination of these, *e.g.* dd (double doublet), with coupling constants (*J*) given in Hz. ^{13}C-NMR spectra were recorded at 67.5 MHz (multiplicity determined from off-resonance decoupled or distortionless enhancement by polarization transfer (DEPT) spectra). NMR spectra were measured in $CDCl_3$ and chemical shifts were recorded in δ_H values relative to internal $(CH_3)_4Si$ as a standard. Mass spectra were recorded on a JMS-DX 302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained on 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 (70—230 mesh).

(*Z*)-4-(4-Methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1-methylpiperazine-2,5-dione (3) Sodium hydride (60% oil dispersion) (washed with dry hexane three times, 13.2 mg, 0.55 mmol) was added to a stirred solution of **3** (220.0 mg, 0.5 mmol) in dry THF (5 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (34.2 μl, 0.55 mmol) was added at once, and the reaction mixture was stirred for 2 h at 25 °C, then concentrated *in vacuo*. The residue was diluted with water (10 ml), and extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a residue (240.1 mg). Chromatography of this on a silica gel (13 g) column with hexane–ethyl acetate (2 : 1) gave **3** (204.6 mg, 93.0%) as a colorless amorphous powder, whose spectra were identical with those of an authentic sample described earlier.[4a]

Methylation of Compound 3 (General Procedure). Method A (in DMF) Sodium hydride (60% oil dispersion) (washed with dry hexane three times, 12.0 mg, 0.5 mmol) was added to a stirred solution of **3** (220.0 mg, 0.5 mmol) in dry DMF (5 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (93.4 μl, 1.5 mmol) was added at once, and the reaction mixture was heated under reflux for 3 h, then concentrated *in vacuo*. The residue was diluted with water (10 ml), and extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a residue (236.9 mg). Chromatography of this on a silica gel (13 g) column with hexane–ethyl acetate (2 : 1) gave **6** (6.5 mg, 2.9%) as a colorless amorphous powder and further elution with hexane–ethyl acetate (1 : 1) gave **5a** (88.4 mg, 39.9%) as a colorless amorphous powder followed by **3** (49.1 mg, 21.9% recovery).

Method B (in THF) The same procedure as described above, but with heating under reflux in dry THF (5 ml), gave a residue (290.7 mg). Chromatography of this on a silica gel (13 g) column with hexane–ethyl acetate (2 : 1) gave **6** (19.1 mg, 8.2%) as a colorless amorphous powder and further elution with hexane–ethyl acetate (1 : 1) as an eluent gave **5a** (155.8 mg, 68.6%) as a colorless amorphous powder, followed by **3** (14.1 mg, 6.4% recovery).

(*Z*)-4-(4-Methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (**5a**): IR ($CHCl_3$): 1675, 1620 cm^{-1}. ^{1}H-NMR δ: 1.55 (3H, d, J=6.9 Hz, 6-CH_3), 2.22 (3H, s, $ArCH_3$), 3.04 (3H, s, NCH_3), 3.55, 3.73, 3.80, 3.85 (each 3H, s, OCH_3), 4.03 (1H, q, J=6.9 Hz, 6-H), 4.06 (1H, d, J=14.8 Hz, NCH), 5.14 (1H, d, J=14.8 Hz, NCH), 6.58 (1H, s, ArH), 6.70 (2H, d, J=8.6 Hz, 2 × ArH), 6.82 (2H, d, J=8.6 Hz, 2 × ArH), 7.19 (1H, s, C=CH). ^{13}C-NMR δ: 9.5 (q, $ArCH_3$), 17.3 (q, 6-CH_3), 32.2 (q, NCH_3), 46.3 (t, NCH_2), 55.1 (q, OCH_3), 56.0 (q, OCH_3), 59.2 (d, C-6), 60.3 (q, OCH_3), 61.1 (q, OCH_3), 110.2 (d), 113.6 (d × 2), 117.7 (d), 122.2 (s), 125.9 (s), 128.5 (s), 128.8 (d × 2), 129.3 (s), 148.9 (s), 148.9 (s), 151.7 (s), 158.8 (s), 162.8 (s, CO), 167.9 (s, CO). MS m/z (%): 454 (M^+, 31), 424 (29), 423 (100), 318 (18), 302 (12), 121 (47). High-resolution MS Calcd for $C_{25}H_{30}N_2O_6$: 454.2106. Found: 454.2104.

(*Z*)-4-(4-Methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1,6,6-trimethylpiperazine-2,5-dione (**6**): IR ($CHCl_3$): 1685, 1630 cm^{-1}. ^{1}H-NMR δ: 1.58 (6H, s, $C(CH_3)_2$), 2.23 (3H, s, $ArCH_3$), 3.04 (3H, s, NCH_3), 3.55, 3.72, 3.80, 3.85 (each 3H, s, OCH_3), 4.64 (2H, s, NCH_2), 6.60 (1H, s, ArH), 6.70 (2H, d, J=8.6 Hz, 2 × ArH), 6.83 (2H, d, J=8.6 Hz, 2 × ArH), 7.21 (1H, s, C=CH). ^{13}C-NMR δ: 9.5 (q, $ArCH_3$), 24.1 (q, 6-CH_3), 27.8 (q, NCH_3), 47.0 (t, NCH_2), 55.2 (q, OCH_3), 56.0 (q, OCH_3), 60.3 (s, C-6), 60.4 (q, OCH_3), 61.3 (q, OCH_3), 110.1 (d), 113.7 (d × 2), 117.0 (d), 122.4 (s), 126.0 (s), 128.7 (d × 2), 128.8 (s), 129.9 (s), 148.9 (s), 149.0 (s), 151.8 (s), 158.8 (s), 164.2 (s, CO), 169.9 (s, CO). MS m/z (%): 468 (M^+, 21), 438 (29), 437 (100), 332 (10), 121 (37). High-resolution MS Calcd for $C_{26}H_{32}N_2O_6$: 468.2265. Found: 468.2260.

Methylation of the Compound 2 Methylation of **2** (213.0 mg, 0.5 mmol) using Method A gave a residue (226.7 mg). Chromatography of this on a silica gel (13 g) column with hexane–ethyl acetate (2 : 1) gave **6** (2.5 mg, 1.0%) as a colorless amorphous powder and further elution with hexane–ethyl acetate (1 : 1) gave **5a** (80.2 mg, 35.3%) as a colorless amorphous powder. Further elution with hexane–ethyl acetate (1 : 2) gave **3** (53.1 mg, 24.1%).

Methylation of **2** (213.0 mg, 0.5 mmol) using method B gave a residue (261.0 mg). Chromatography of this on a silica gel (13 g) column with hexane–ethyl acetate (1 : 1) gave **5a** (156.2 mg, 68.8%) as a colorless amorphous powder. Further elution with hexane–ethyl acetate (1 : 2) gave **3** (19.0 mg, 8.9%).

(*Z*)-6-Benzyl-4-(4-methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1-methylpiperazine-2,5-dione (5b) This compound was prepared by method B, but using benzyl bromide (178.4 μl, 1.5 mmol). Chromatography of the residue (337.3 mg) on a silica gel (13 g) column with hexane–ethyl acetate (2 : 1) gave a solid, recrystallization of which from methanol gave **5b** (126.6 mg, 47.7%) as colorless needles, mp 167.5—170 °C. Further elution with the same solvent gave **3** (65.2 mg, 29.6% recovery).

Compound **5b**: IR (KBr): 1695, 1670, 1630 cm^{-1}. ^{1}H-NMR δ: 2.21 (3H, s, $ArCH_3$), 2.79 (3H, s, NCH_3), 3.13 (1H, dd, J=13.5, 7.6 Hz, 6-CH), 3.28 (1H, dd, J=13.5, 5.3 Hz, 6-CH), 3.54, 3.71, 3.85, 3.86 (each 3H, s, OCH_3), 4.09 (1H, d, J=14.9 Hz, NCH), 4.21 (1H, dd, J=7.6, 5.3 Hz, 6-H), 5.13 (1H, d, J=14.9 Hz, NCH), 6.46 (1H, s, ArH), 6.68 (2H, d, J=8.6 Hz, 2 × ArH), 6.82 (2H, d, J=8.6 Hz, 2 × ArH), 7.15—7.31 (6H, m, C=CH, 5 × ArH). ^{13}C-NMR δ: 9.5 (q, $ArCH_3$), 33.9 (q, NCH_3), 38.7 (t, 6-CH_2), 46.9 (t, NCH_2), 55.1 (q, OCH_3), 56.2 (q, OCH_3), 60.3 (q, OCH_3), 61.4 (q, OCH_3), 65.5 (d, C-6), 110.5 (d), 113.8 (d × 2), 117.5 (d), 121.9 (s), 125.8 (s), 127.5 (d), 128.5 (s), 128.9 (d × 2), 128.9 (d × 2), 129.2 (s), 129.3 (d × 2), 135.3 (s), 148.8 (s), 149.0 (s), 152.0 (s), 158.9 (s), 162.2 (s, CO), 169.9 (s, CO). MS m/z (%): 530 (M^+, 25), 500 (35), 499 (100), 121 (40), 44 (14). *Anal.* Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.45; N, 5.27. Found: C, 69.96; H, 6.42; N, 5.21.

(*Z*)-3-(2,4,5-Trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (7a) Concentrated H_2SO_4 (2.1 ml) was added to a stirred solution of **5a** (1.34 g, 2.94 mmol) in TFA (36 ml), and the resulting solution was stirred for 24 h at room temperature. The reaction mixture was poured into water (250 ml), made alkaline with concentrated NH_4OH, and extracted with dichloromethane (200 ml × 3). The combined extracts were washed with water (200 ml), dried, and concentrated *in vacuo* to give a solid (1.05 g), recrystallization of which from methanol gave **7a** (786.8 mg, 79.6%) as colorless prisms, mp 157—157.5 °C. IR (KBr): 3250, 1685, 1630 cm^{-1}. ^{1}H-NMR δ: 1.54 (3H, d, J=6.9 Hz, 6-CH_3), 2.23 (3H, s, $ArCH_3$), 3.09 (3H, s, NCH_3), 3.62, 3.83, 3.83 (each 3H, s, OCH_3), 4.05 (1H, q, J=6.9 Hz, 6-H), 6.64 (1H, s, ArH), 6.89 (1H, s, C=CH), 9.26 (1H, br s, NH). MS m/z (%): 334 (M^+, 32), 304 (19), 303 (100). *Anal.* Calcd for $C_{17}H_{22}N_2O_5$: 61.06; H, 6.63; N, 8.38. Found: C, 61.03; H, 6.78; N, 8.14.

(*Z*)-6-Benzyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1-methylpiperazine-2,5-dione (7b) This compound was prepared as described above, but using **5b** (106 mg, 0.2 mmol), to give a solid, recrystallization of which from methanol gave **7b** (68.4 mg, 83.4%) as colorless needles, mp 176—177.5 °C. IR (KBr): 3310, 1700, 1680, 1645 cm^{-1}. ^{1}H-NMR δ: 2.19 (3H, s, $ArCH_3$), 3.12 (3H, s, NCH_3), 3.22 (2H, d, J=4.3 Hz, 6-CH_2), 3.41, 3.82, 3.82 (each 3H, s, OCH_3), 4.33 (1H, t, J=4.3 Hz, 6-H), 6.38 (1H, s, ArH), 6.48 (1H, s, C=CH), 7.02—7.14 (2H, m, 2 × ArH), 7.15—7.18 (3H, m, 3 × ArH). ^{13}C-NMR δ: 9.4 (q, $ArCH_3$), 33.7 (q, NCH_3), 37.8 (t, 6-CH_2), 55.9 (q, OCH_3), 60.3 (q, OCH_3), 60.8 (q, OCH_3), 64.2 (d, C-6), 111.8 (d), 113.1 (d), 121.5 (s), 124.9 (s), 126.2 (s), 127.3 (d), 128.6 (d × 2), 129.9 (d × 2), 134.2 (s), 148.4 (s), 148.9 (s), 149.3 (s), 159.6 (s, CO), 164.9 (s, CO). MS m/z (%): 410 (M^+, 71), 380 (27), 379 (100), 320 (16), 319 (77), 288 (12), 220 (30). *Anal.* Calcd for $C_{23}H_{26}N_2O_5 \cdot 1/10\ H_2O$: C, 67.00; H, 6.41; N, 6.80. Found: C, 66.81; H, 6.36; N, 6.77.

(−)-6*S*-(*Z*)-1-Acetyl-3-(2,4,5-trimethoxy-3-methylbenzylidene)-6-methylpiperazine-2,5-dione (10) A solution of potassium *tert*-butoxide (258 mg, 2.30 mmol) in *tert*-butyl alcohol (4.6 ml) was added to a stirred solution of (+)-**8** (486 mg, 2.29 mmol) and **9** (481.5 mg, 2.29 mmol) in dry DMF (4.6 ml) at 0 °C over 10 min. After having been stirred for 2 h at room temperature, the reaction mixture was poured into water (20 ml), and extracted with ethyl acetate (30 ml × 3). The combined extracts were washed with saturated aqueous sodium chloride (30 ml), dried, and concentrated *in vacuo* to give a solid (875 mg), recrystallization of which from ether gave **10** (537.3 mg, 64.7%) as colorless needles, mp 135.5—137 °C. $[\alpha]_D^{20}$ −166.7° (c=1.0, methanol). IR (KBr) 3260, 1705, 1690, 1630, 1595 cm^{-1}. ^{1}H-NMR δ: 1.40 (3H, d, J=7.3 Hz, 6-CH_3), 2.17 (3H, s, $ArCH_3$), 2.55 (3H, s, $COCH_3$), 3.57, 3.77, 3.78 (each 3H, s, OCH_3), 5.03 (1H, q, J=7.3 Hz, 6-H), 6.60 (1H, s, ArH), 6.97 (1H, s, C=CH), 9.17 (1H, br s, NH). MS m/z (%): 362 (M^+, 84), 331 (17), 290 (18), 289 (100). *Anal.* Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.64; H, 6.17; N, 7.63.

(−)-6*S*-(*Z*)-1-Acetyl-4-(4-methoxybenzyl)-3-(2,4,5-trimethoxy-3-meth-

ylbenzylidene)-6-methylpiperazine-2,5-dione (11) Sodium hydride (60% oil dispersion) (washed with dry hexane three times, 8.6 mg, 0.36 mmol) was added to a stirred solution of **10** (118.7 mg, 0.328 mmol) in dry DMF (2.0 ml) under ice-cooling, and stirring was continued for 30 min. 4-Methoxybenzyl chloride (56.4 mg, 0.36 mmol) in dry DMF (1.3 ml) was added during 10 min, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water (10 ml) and extracted with ethyl acetate (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a solid (195.3 mg), recrystallization of which from ethyl acetate–ether gave **11** (131.1 mg, 82.9%) as colorless prisms, mp 130.5—132 °C. $[\alpha]_D^{20}$ −22.9° (c=1.0, methanol). IR (KBr) 1705, 1695, 1625 cm^{-1}. ^{1}H-NMR δ: 1.55 (3H, d, J=6.9 Hz, 6-CH_3), 2.25 (3H, s, ArCH_3), 2.56 (3H, s, COCH_3), 3.60, 3.79, 3.83, 3.88 (each 3H, s, OCH_3), 4.04 (1H, d, J=14.8 Hz, NCH), 5.26 (1H, d, J=14.8 Hz, NCH), 5.27 (1H, q, J=6.9 Hz, 6-H), 6.66 (1H, s, ArH), 6.72 (2H, d, J=8.6 Hz, 2 × ArH), 6.84 (2H, d, J=8.6 Hz, 2 × ArH), 7.34 (1H, s, C=CH). MS m/z (%): 482 (M^+, 38), 121 (100). *Anal.* Calcd for $C_{26}H_{30}N_2O_7$: C, 64.71; H, 6.27; N, 5.81. Found: C, 64.51; H, 6.34; N, 5.79.

(−)-6*S*-(*Z*)-4-(4-Methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-6-methylpiperazine-2,5-dione (12) Hydrazine monohydrate (53.4 μl, 1.10 mmol) was added to a stirred solution of **11** (106.1 mg, 0.220 mmol) in dry DMF (2 ml), and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was poured into water (10 ml), and extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a residue (100.4 mg). Chromatography of this on a silica gel (12 g) column with dichloromethane–methanol (100 : 1) gave **12** (91.6 mg, 94.3%) as a colorless amorphous powder. $[\alpha]_D^{20}$ −21.3° (c=1.0, methanol). IR ($CHCl_3$): 3430, 1695, 1640 cm^{-1}. ^{1}H-NMR δ: 1.56 (3H, d, J=6.9 Hz, 6-CH_3), 2.23 (3H, s, ArCH_3), 3.56, 3.72, 3.81, 3.86 (each 3H, s, OCH_3), 4.20 (1H, dq, J=6.9, 2.0 Hz, 6-H), 4.65 (2H, s, NCH_2), 6.63 (1H, s, ArH), 6.70 (2H, d, J=8.6 Hz, 2 × ArH), 6.84 (2H, d, J=8.6 Hz, 2 × ArH), 7.19 (1H, s, C=CH), 7.19 (1H, s, NH). MS m/z (%): 440 (M^+, 45), 410 (17), 409 (63), 319 (10), 304 (20), 288 (15), 121 (100). High-resolution MS Calcd for $C_{24}H_{28}N_2O_6$: 440.1952. Found: 440.1947.

(−)-6*S*-(*Z*)-4-(4-Methoxybenzyl)-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (5a) This compound was prepared by method A, but using **12** (97.7 mg, 0.222 mmol), sodium hydride (6.4 mg, 0.267 mmol), and methyl iodide (16.6 μl, 0.267 mmol). Chromatography of the residue (120.3 mg) on a silica gel (10 g) column with dichloromethane–methanol (200 : 1) gave **5a** (71.3 mg, 70.7%) as a colorless amorphous powder ($[\alpha]_D^{20}$ −2.0° (c=1.0, methanol)), whose spectra (IR ($CHCl_3$): 1675, 1620 cm^{-1}, ^{1}H-NMR δ: 1.55 (3H, d, J=6.9 Hz, 6-CH_3), 2.23 (3H, s, ArCH_3), 3.04 (3H, s, NCH_3), 3.55, 3.72, 3.80, 3.85 (each 3H, s, OCH_3), 4.03 (1H, q, J=6.9 Hz, 6-H), 4.04 (1H, d, J=14.8 Hz, NCH), 5.14 (1H, d, J=14.8 Hz, NCH), 6.59 (1H, s, ArH), 6.69 (2H, d, J=8.6 Hz, 2 × ArH), 6.82 (2H, d, J=8.6 Hz, 2 × ArH), 7.19 (1H, s, C=CH) were identical with those of a racemic sample (see above).

(−)-6*S*-(*Z*)-3-(2,4,5-Trimethoxy-3-methylbenzylidene)-1,6-dimethylpiperazine-2,5-dione (7a) Concentrated H_2SO_4 (0.15 ml) was added to a stirred solution of (−)-**5a** (131.7 mg, 0.29 mmol) in TFA (3 ml), and the resulting solution was stirred for 24 h at room temperature. The reaction mixture was poured into water (20 ml), made alkaline with concentrated NH_4OH, and extracted with dichloromethane (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid (89.2 mg), recrystallization of which from ethyl acetate-ether gave (−)-**7a** (82.4 mg, 85.0%) as colorless prisms, mp 155.5—157 °C and $[\alpha]_D^{20}$ −6.7° (c=1.0, methanol), whose spectra were also identical with those of a racemic sample (see above).

3*SR*,6*SR*-3-(2,4,5-Trimethoxy-3-methylbenzyl)-1,6-dimethylpiperazine-2,5-dione (13) A solution of **7a** (1.002 g, 3 mmol) in ethanol (30 ml) was hydrogenated over 20% palladium on carbon (500 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethanol (200 ml). The combined filtrates were evaporated and the residue was diluted with water (100 ml), and extracted with chloroform (50 ml × 3). The combined extracts were washed with water (50 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave **13** (693.0 mg, 68.3%) as colorless prisms, mp 127.5—129 °C. IR (KBr): 3210, 3090, 1675, 1645 cm^{-1}. ^{1}H-NMR δ: 1.26 (3H, d, J=7.3 Hz, 6-CH_3), 2.21 (3H, s, ArCH_3), 2.95 (1H, dd, J=13.5, 6.3 Hz, 3-CH), 2.97 (3H, s, NCH_3), 3.29 (1H, dd, J=13.5, 4.0 Hz, 3-CH), 3.67, 3.77, 3.81 (each 3H, s, OCH_3), 4.09 (1H, q, J=7.3 Hz, 6-H), 4.29 (1H, m, 3-H), 4.94 (1H, br s, NH), 6.54 (1H, s, ArH). MS m/z (%): 336 (M^+, 27), 196 (13), 195 (100), 165 (15). *Anal.* Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.45; H, 7.22; N, 8.14.

3*SR*,6*SR*-4-Isopropyloxycarbonyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,6-dimethylpiperazine-2,5-dione (14) A solution of **13** (693 mg, 2.05 mmol), triethylamine (857 μl, 6.15 mmol), and 4-(dimethylamino)-pyridine (DMAP) (750.3 mg, 6.15 mmol) in dry dichloromethane (50 ml) was cooled with ice-water, and isopropyl chloroformate (1.398 ml, 12.3 mmol) was added dropwise to it over 15 min. The solution was then stirred at room temperature for 15 h. The organic layer was washed with 1 N HCl (100 ml), and then water (50 ml), dried, and concentrated *in vacuo* to give a residue (952 mg). Chromatography on a silica gel (40 g) column with dichloromethane gave a solid, recrystallization of which from ethyl acetate–ether gave **14** (689.7 mg, 79.7%) as colorless prisms, mp 94—96 °C. IR (KBr): 1770, 1720, 1675 cm^{-1}. ^{1}H-NMR δ: 0.98 (3H, d, J=7.3 Hz, 6-CH_3), 1.26, 1.31 (each 3H, d, J=6.3 Hz, OCHC$\underline{H}_3$), 2.19 (3H, s, ArCH_3), 2.89 (3H, s, NCH_3), 3.10 (1H, dd, J=13.9, 5.6 Hz, 3-CH), 3.43 (1H, dd, J=13.9, 5.1 Hz, 3-CH), 3.62, 3.74, 3.80 (each 3H, s, OCH_3), 3.94 (1H, q, J=7.3 Hz, 6-H), 5.01 (1H, sept, J=6.3 Hz, OCH), 5.06 (1H, dd, J=5.6, 5.1 Hz, 3-H), 6.52 (1H, s, ArH). MS m/z (%): 422 (M^+, 25), 196 (13), 195 (100). *Anal.* Calcd for $C_{21}H_{30}N_2O_7$: C, 59.70; H, 7.16; N, 6.63. Found: C, 59.64; H, 7.08; N, 6.61.

3-(2,4,5-Trimethoxy-3-methylbenzyl)-3,4-dihydro-4-isopropyloxycarbonyl-1,6-dimethyl-2-pyrazinone (16). Method A A stirred solution of **14** (126.6 mg, 3 mmol) in dry THF (9 ml) was cooled in ice-water, and lithium tri-*tert*-butoxyaluminum hydride (305.1 mg, 12 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water (2 ml) and then filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereomeric mixture of the alcohol **15** (125.6 mg), which was used for the next step without further purification. A solution of the above mixture in formic acid (3.75 ml) was heated for 30 min at 70 °C and then diluted with water (10 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (125.6 mg). Chromatography on a silica gel (4 g) column with hexane–ethyl acetate (2 : 1) gave **16** (96.5 mg, 79.2%) as a colorless amorphous powder.

Method B Reduction of **14** (168.8 mg, 0.4 mmol) with lithium tri-*tert*-butoxyaluminum hydride (406.8 mg, 1.6 mmol) as described above afforded a crude diastereomeric mixture of the alcohol **15** (170.0 mg). A solution of the above mixture and triethylamine (0.1 μl, 0.717 mmol) in dichloromethane (16 ml) was cooled in ice-water, and methanesulfonyl chloride (55.7 μl, 0.719 mmol) was added dropwise to it over 10 min. The mixture was heated under reflux for 24 h, after which it was washed with 1 N HCl (16 ml) and then with water (10 ml), dried, and concentrated *in vacuo* to give a residue (178.4 mg). Chromatography on a silica gel (4 g) column with hexane–ethyl acetate (2 : 1) gave **16** (158.3 mg, 97.5%) as a colorless amorphous powder.

Compound **16:** IR ($CDCl_3$): 1690, 1665, 1655 cm^{-1}. ^{1}H-NMR δ: This compound was a mixture of two rotational isomers, ratio, 3 : 2 (major isomer) 0.80, 1.09 (3H, d, J=6.3 Hz, OCHC$\underline{H}_3$), 1.97 (3H, d, J=1.0 Hz, 6-CH_3), 2.19 (3H, s, ArCH_3), 2.72 (1H, dd, J=13.2, 9.9 Hz, 3-CH), 2.97 (1H, dd, J=13.2, 3.6 Hz, 3-CH), 3.14 (3H, s, NCH_3), 3.69, 3.76, 3.80 (each 3H, s, OCH_3), 4.65 (1H, sept, J=6.3 Hz, OCH), 4.92 (1H, dd, J=9.9, 3.6 Hz, 3-H), 6.15 (1H, br s, 5-H), 6.41 (1H, s, ArH); (minor isomer) 1.17, 1.23 (3H, d, J=6.3 Hz, OCHC$\underline{H}_3$), 1.80 (3H, d, J=1.0 Hz, 6-CH_3), 2.18 (3H, s, ArCH_3), 2.81 (1H, dd, J=13.5, 7.6 Hz, 3-CH), 3.09 (1H, dd, J=13.5, 3.6 Hz, 3-CH), 3.14 (3H, s, NCH_3), 3.66, 3.75, 3.80 (each 3H, s, OCH_3), 4.88 (1H, sept, J=6.3 Hz, OCH), 5.06 (1H, dd, J=7.6, 3.6 Hz, 3-H), 5.88 (1H, br s, 5-H), 6.50 (1H, s, ArH). ^{13}C-NMR δ: (major isomer) 9.6 (q, ArCH_3), 16.0 (q, 6-CH_3), 21.3 (q, CHCH_3), 22.0 (q, CH$\underline{C}H_3$), 28.8 (q, NCH_3), 30.0 (t, 3-CH_2), 56.0 (q, OCH_3), 57.8 (d, C-3), 60.0 (q, OCH_3), 60.7 (q, OCH_3), 69.5 (d, OCH), 106.1 (q, C-5), 111.6 (d), 121.2 (s), 124.3 (s), 125.3 (s), 146.9 (s), 148.9 (s), 151.4 (s), 152.8 (s), 166.2 (s, C-2); (minor isomer) 9.6 (q, ArCH_3), 15.8 (q, 6-CH_3), 21.9 (q, CH$\underline{C}H_3$), 21.9 (q, CH$\underline{C}H_3$), 28.6 (q, NCH_3), 30.3 (t, 3-CH_2), 55.9 (q, OCH_3), 56.7 (d, C-3), 60.0 (q, OCH_3), 60.6 (q, OCH_3), 69.6 (d, OCH), 106.2 (q, C-5), 111.5 (d), 119.6 (s), 124.2 (s), 125.0 (s), 146.7 (s), 148.6 (s), 151.6 (s), 152.2 (s), 166.2 (s, C-2). MS m/z (%): 406 (M^+, 72), 211 (52), 195 (43), 169 (20), 167 (12), 125 (100), 43 (18). High-resolution MS Calcd for $C_{21}H_{30}N_2O_6$: 406.2104. Found: 406.2102.

Isopropyl 1,2,3,4,5,6-Hexahydro-7,9,10-trimethoxy-2,3,8-trimethyl-(1α,2α,5α)-4-oxo-1,5-imino-3-benzazocine-11-carboxylate (17a) and

Isopropyl 1,2,3,4,5,6-Hexahydro-7,9,10-trimethoxy-2,3,8-trimethyl-(1α,2β,5α)-4-oxo-1,5-imino-3-benzazocine-11-carboxylate (17b). From 16 A solution of **16** (28.4 mg, 0.07 mmol) in TFA (0.9 ml) was heated under reflux for 24 h and then diluted with water (10 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (28.2 mg). Chromatography on a silica gel (2 g) column with hexane–ethyl acetate (5 : 1) gave **17** (25.0 mg, 98.0%) as an inseparable diastereomeric mixture.

From 15 A solution of **15** (169.6 mg, 0.4 mmol) in TFA (5 ml) was heated under reflux for 24 h, and then diluted with water (10 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (142.6 mg). Chromatography on a silica gel (6 g) column with hexane–ethyl acetate (5 : 1) as an eluent gave **17** (82.3 mg, 50.7%) as an inseparable diastereomeric mixture.

Compound **17**: IR ($CDCl_3$): 1705, 1650 cm^{-1}. The signals in the ^{1}H-NMR and ^{13}C-NMR spectra of the diastereomeric mixture of **17a** and **17b** (ratio *ca.* 1 : 1) were not split, which indicated they were mixtures of rotational isomers, (ratio 3 : 2). MS *m/z* (%): 406 (M^+, 98), 322 (10), 321 (57), 320 (59), 319 (22), 307 (20), 306 (100), 279 (65), 278 (60), 264 (17), 235 (14), 234 (87), 204 (21), 43 (14). High-resolution MS Calcd for $C_{21}H_{30}N_2O_6$: 406.2104. Found: 406.2100.

1,2,3,4,5,6-Hexahydro-7,9,10-trimethoxy-2,3,8-trimethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (19a) and 1,2,3,4,5,6-hexahydro-7,9,10-trimethoxy-2,3,8-trimethyl-(1α,2β,5α)-1,5-imino-3-benzazocin-4-one(19b). From a Mixture of 17a and 17b Concentrated H_2SO_4 (0.18 ml) was added to a stirred solution of a mixture of **17a** and **17b** (60.1 mg, 0.148 mmol) in TFA (3.5 ml). The resulting solution was stirred at room temperature for 2 h, poured into water (10 ml), made alkaline with concentrated NH_4OH, and extracted with dichloromethane (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a residue (52.0 mg). Chromatography on a silica gel (4 g) column with dichloromethane–methanol (50 : 1—25 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **19a** (20.1 mg, 42.4%) as colorless needles, mp 137.5—139 °C. Further elution with dichloromethane–methanol (25 : 1—10 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **19b** (18.2 mg, 38.4%) as colorless prisms, mp 139.5—141 °C.

From 15 The same procedure as described above but using **15** (212 mg, 0.5 mmol) in concentrated H_2SO_4 (0.6 ml) and TFA (13 ml) gave **19a** (80.9 mg, 50.5%) and **19b** (66.7 mg, 41.7%).

From 16 The same procedure as described above but using **16** (790.7 mg, 1.948 mmol) in concentrated H_2SO_4 (1.0 ml) and TFA (20 ml) gave **19a** (304.3 mg, 48.8%) and **19b** (273.9 mg, 44.0%).

Compound **19a**: IR ($CHCl_3$) 3300, 1635, 1620 cm^{-1}. ^{1}H-NMR δ: 1.15 (3H, d, J=6.7 Hz, 2-CH_3), 1.97 (1H, br s, NH), 2.19 (3H, s, 8-CH_3), 2.86 (3H, s, 3-CH_3), 2.96 (1H, dd, J=18.0, 7.3 Hz, 6-Hα), 3.09 (1H, dd, J=18.0, 1.0 Hz, 6-Hβ), 3.68, 3.79, 3.80 (each 3H, s, OCH_3), 3.91 (1H, dq, J=6.7, 5.2 Hz, 2-H), 3.99 (1H, dd, J=7.3, 1.0 Hz, 5-H), 4.45 (1H, d, J=5.2 Hz, 1-H). ^{13}C-NMR δ: 9.3 (q, 8-CH_3), 16.0 (q, 2-CH_3), 28.0 (t, C-6), 29.7 (q, 3-CH_3), 49.2 (d, C-1), 52.5 (d, C-5), 59.5 (d, C-2), 59.8 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 122.6 (s), 124.7 (s), 124.9 (s), 146.5 (s), 149.6 (s), 152.6 (s), 171.2 (s, C-4). MS *m/z* (%): 320 (M^+, 17), 235 (24), 234 (100), 204 (11). *Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.69; H, 7.56; N, 8.55.

Compound **19b**: IR (KBr) 3320, 1635 cm^{-1}. ^{1}H-NMR δ: 1.48 (3H, d, J=6.4 Hz, 2-CH_3), 2.01 (1H, br s, NH), 2.18 (3H, s, 8-CH_3), 2.82 (3H, s, 3-CH_3), 2.91 (1H, dd, J=17.4, 6.7 Hz, 6-Hα), 3.08 (1H, dd, J=17.4, 1.2 Hz, 6-Hβ), 3.36 (1H, dq, J=6.4, 1.0 Hz, 2-H), 3.67, 3.80, 3.88 (each 3H, s, OCH_3), 3.90 (1H, dd, J=6.4, 1.2 Hz, 5-H), 4.07 (1H, d, J=1.0 Hz, 1-H). ^{13}C-NMR δ: 9.3 (q, 8-CH_3), 18.6 (q, 2-CH_3), 28.3 (t, C-6), 33.1 (q, 3-CH_3), 50.8 (d, C-1), 52.5 (d, C-5), 59.9 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 61.1 (d, C-2), 122.6 (s), 124.5 (s), 128.5 (s), 145.5 (s), 149.7 (s), 152.5 (s), 170.5 (s, C-4). MS *m/z* (%): 320 (M^+, 22), 235 (26), 234 (100). *Anal.* Calcd for $C_{17}H_{24}N_2O_4 \cdot 1/10\ H_2O$: C, 63.37; H, 7.57; N, 8.69. Found: C, 63.30; H, 7.55; N, 8.63.

1,2,3,4,5,6-Hexahydro-7,9,10-trimethoxy-2,3,8,11-tetramethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (20a) Formaldehyde (37% solution in water, 7.5 ml) was added to a stirred solution of **19a** (267.2 mg, 0.835 mmol) in formic acid (8.7 ml) at 60 °C. After having been stirred at 70 °C for 1 h, the reaction mixture was poured into water (30 ml) and extracted with chloroform (45 ml × 3). The combined extracts were washed with 5% $NaHCO_3$ (45 ml), dried, and concentrated *in vacuo* to give the residue (395 mg). Chromatography of this on a silica gel (20 g) column with 40 : 1 dichloromethane–methanol gave **20a** (261.3 mg, 93.7%) as a colorless amorphous powder. IR ($CHCl_3$) 1645 cm^{-1}. ^{1}H-NMR δ: 1.12 (3H, d, J=6.9 Hz, 2-CH_3), 2.19 (3H, s, 8-CH_3), 2.44 (3H, s, 11-CH_3), 2.86 (3H, s, 3-CH_3), 2.89 (1H, d, J=18.2 Hz, 6-Hβ), 3.03 (1H, dd, J=18.2, 6.9 Hz, 6-Hα), 3.68 (1H, dd, J=5.3, 1.3 Hz, 5-H), 3.69, 3.78, 3.79 (each 3H, s, OCH_3), 4.00 (1H, dq, J=6.9, 5.3 Hz, 2-H), 4.15 (1H, dd, J=5.3, 1.3 Hz, 1-H). ^{13}C-NMR δ: 9.2 (q, 8-CH_3), 15.4 (q, 2-CH_3), 22.9 (t, C-6), 29.6 (q, 3-CH_3), 39.9 (q, 11-CH_3), 55.6 (d, C-1), 56.5 (d, C-2), 58.4 (d, C-5), 59.8 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (q, OCH_3), 121.9 (s), 122.7 (s), 124.5 (s), 147.2 (s), 149.7 (s), 152.2 (s), 171.0 (s, C-4). MS *m/z* (%): 334 (M^+, 17), 249 (26), 248 (100), 218 (11). High-resolution MS Calcd for $C_{18}H_{26}N_2O_4$: 334.1893. Found: 334.1890.

1,2,3,4,5,6-Hexahydro-7,9,10-trimethoxy-2,3,8,11-tetramethyl-(1α,2β,5α)-1,5-imino-3-benzazocin-4-one (20b) Formaldehyde (37% solution in water, 5.0 ml) was added to a stirred solution of **19b** (226.3 mg, 0.707 mmol) in formic acid (5.8 ml) at 60 °C. After having been stirred at 70 °C for 1 h, the reaction mixture was poured into water (30 ml) and extracted with chloroform (30 ml × 3). The combined extracts were washed with 5% $NaHCO_3$ (30 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave **20b** (226.3 mg, 95.8%) as colorless prisms, mp 110.5—112 °C. IR (KBr) 1665 cm^{-1}. ^{1}H-NMR δ: 1.49 (3H, d, J=6.3 Hz, 2-CH_3), 2.19 (3H, s, 8-CH_3), 2.36 (3H, s, 11-CH_3), 2.77 (1H, d, J=18.1 Hz, 6-Hβ), 2.80 (3H, s, 3-CH_3), 2.98 (1H, dd, J=18.1, 6.6 Hz, 6-Hα), 3.25 (1H, q, J=6.3 Hz, 2-H), 3.68 (3H, s, OCH_3), 3.68 (1H, d, J=6.6 Hz, 5-H), 3.70 (1H, s, 1-H), 3.81, 3.88 (each 3H, s, OCH_3). ^{13}C-NMR δ: 9.2 (q, 8-CH_3), 18.5 (q, 2-CH_3), 19.6 (t, C-6), 32.8 (q, 3-CH_3), 39.5 (q, 11-CH_3), 57.1 (d, C-1), 58.4 (d, C-5), 59.8 (q, OCH_3), 59.8 (q, OCH_3), 60.2 (q, OCH_3), 61.4 (d, C-2), 121.7 (s), 124.2 (s), 125.4 (s), 146.7 (s), 149.7 (s), 151.9 (s), 170.4 (s, C-4). MS *m/z* (%): 334 (M^+, 15), 249 (28), 248 (100), 218 (17). *Anal.* Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.37; H, 7.86; N, 8.27.

1,2,3,4,5,6-Hexahydro-7-hydroxy-9,10-dimethoxy-2,3,8,11-tetramethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (21a) A dichloromethane solution of boron tribromide (1.0 M, 1.33 ml, 1.33 mmol) was added to a stirred solution of **20a** (246.5 mg, 0.738 mmol) in dry dichloromethane (20 ml) at −78 °C. The reaction mixture was kept at the same temperature for 20 min, and at 0 °C for 1 h, then poured into ice-water (10 g). The pH was brought to 7—8 with 5% $NaHCO_3$ and the solution was extracted with dichloromethane (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from methanol gave **21a** (203.3 mg, 86.1%) as colorless prisms, mp 245—246 °C. The combined aqueous layer was acidified with 1 N HCl (pH 3—4) and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from chloroform–ether gave **22a** (11.4 mg, 5.3%) as pale yellow prisms, mp 203—206 °C (dec.).

Compound **21a**: IR (KBr) 3500—3100, 1650 cm^{-1}. ^{1}H-NMR δ: 1.13 (3H, d, J=6.6 Hz, 2-CH_3), 2.17 (3H, s, 8-CH_3), 2.41 (3H, s, 11-CH_3), 2.86 (3H, s, 3-CH_3), 2.91 (2H, d, J=4.0 Hz, 6-H_2), 3.75 (3H, s, OCH_3), 3.75 (1H, d, J=4.0 Hz, 5-H), 3.78 (3H, s, OCH_3), 4.00 (1H, dq, J=6.6, 5.3 Hz, 2-H), 4.14 (1H, d, J=5.3 Hz, 1-H), 6.20—7.20 (1H, br s, OH). ^{13}C-NMR δ: 9.0 (q, 8-CH_3), 15.4 (q, 2-CH_3), 22.3 (t, C-6), 29.9 (q, 3-CH_3), 39.8 (q, 11-CH_3), 55.6 (d, C-1), 57.2 (d, C-2), 58.3 (d, C-5), 60.2 (q, OCH_3), 60.4 (q, OCH_3), 114.7 (s), 118.2 (s), 121.4(s), 144.7 (s), 148.5 (s), 149.7 (s), 171.4 (s, C-4). MS *m/z* (%): 320 (M^+, 17), 235 (23), 234 (100). *Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 63.74; H, 7.55; N, 8.74. Found: C, 63.59; H, 7.55; N, 8.65.

Compound **22a**: IR (KBr) 3500—3050, 1660, 1640, 1625 cm^{-1}. ^{1}H-NMR δ: 1.08 (3H, d, J=6.3 Hz, 2-CH_3), 1.95 (3H, s, 8-CH_3), 2.38 (3H, s, 11-CH_3), 2.80 (2H, d, J=3.6 Hz, 6-H_2), 2.89 (3H, s, 3-CH_3), 3.67 (1H, dd, J=3.6, 1.3 Hz, 5-H), 4.01 (1H, dq, J=6.3, 5.9 Hz, 2-H), 4.02 (1H, dd, J=5.9, 1.3 Hz, 1-H), 7.07 (1H, br s, OH). ^{13}C-NMR δ: 8.0 (q, 8-CH_3), 17.1 (q, 2-CH_3), 23.8 (t, C-6), 29.6 (q, 3-CH_3), 39.7 (q, 11-CH_3), 54.0 (d, C-1), 55.9 (d, C-2), 57.9 (d, C-5), 117.7 (s), 133.8 (s), 144.8 (s), 150.8 (s), 169.9 (s, C-4), 182.4 (s), 185.6 (s). MS *m/z* (%): 290 (M^+, 68), 206 (18), 205 (100), 176 (10). *Anal.* Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.43; H, 6.20; N, 9.56.

1,2,3,4,5,6-Hexahydro-7-hydroxy-9,10-dimethoxy-2,3,8,11-tetramethyl-(1α,2β,5α)-1,5-imino-3-benzazocin-4-one (21b) A dichloromethane solution of boron tribromide (1.0 M, 984 μl, 0.984 mmol) was added to a stirred solution of **20b** (182.5 mg, 0.546 mmol) in dry dichloromethane

(15 ml) at −78 °C. The reaction mixture was kept at the same temperature for 20 min, and at 0 °C for 1 h, then poured into ice-water (10 g). The pH was brought to 7—8 with 5% $NaHCO_3$ and extracted with dichloromethane (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from methanol gave **21b** (161.9 mg, 92.6%) as colorless prisms, mp 244—245.5 °C. The combined aqueous layer was acidified with 1 N HCl (pH 3—4) and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate gave **22b** (11.7 mg, 7.4%) as pale yellow prisms, mp 230—232 °C.

Compound **21b**: IR (KBr) 3500—3100, 1640 cm^{-1}. ^{1}H-NMR δ: 1.50 (3H, d, J=6.6 Hz, 2-CH_3), 2.18 (3H, s, 8-CH_3), 2.35 (3H, s, 11-CH_3), 2.80 (1H, d, J=17.5 Hz, 6-Hβ), 2.82 (3H, s, 3-CH_3), 2.89 (1H, dd, J=17.5, 6.3 Hz, 6-Hα), 3.29 (1H, q, J=6.6 Hz, 2-H), 3.73 (2H, br s, 5-H, 1-H), 3.79, 3.84 (each 3H, s, OCH_3), 6.87 (1H, br s, OH). ^{13}C-NMR δ: 9.1 (q, 8-CH_3), 18.6 (q, 2-CH_3), 19.7 (t, C-6), 33.1 (q, 3-CH_3), 39.5 (q, 11-CH_3), 57.2 (d, C-1), 58.4 (d, C-5), 60.1 (q, OCH_3), 60.5 (q, OCH_3), 61.7 (d, C-2), 114.8 (s), 118.0 (s), 124.3(s), 143.8 (s), 148.3 (s), 149.7 (s), 170.8 (s, C-4). MS m/z (%): 320 (M^+, 15), 235 (26), 234 (100). *Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 63.74; H, 7.55; N, 8.74. Found: C, 63.48; H, 7.63; N, 8.54.

Compound **22b**: IR (KBr) 3600—3350, 1655, 1620 cm^{-1}. ^{1}H-NMR δ: 1.49 (3H, d, J=6.3 Hz, 2-CH_3), 1.95 (3H, s, 8-CH_3), 2.32 (3H, s, 11-CH_3), 2.65 (1H, dd, J=20.8, 2.0 Hz, 6-Hβ), 2.76 (1H, ddd, J=20.8, 5.3, 1.3 Hz, 6-Hα), 2.84 (3H, s, 3-CH_3), 3.22 (1H, dq, J=6.3, 1.0 Hz, 2-H), 3.58 (1H, dd, J=1.3, 1.0 Hz, 1-H), 3.69 (1H, ddd, J=5.3, 2.0, 1.0 Hz, 5-H), 7.10—7.20 (1H, br s, OH). ^{13}C-NMR δ: 8.0 (q, 8-CH_3), 18.3 (q, 2-CH_3), 20.4 (t, C-6), 32.7 (q, 3-CH_3), 39.4 (q, 11-CH_3), 55.6 (d, C-1), 58.0 (d, C-5), 59.0 (d, C-2), 117.9 (s), 134.4 (s), 143.4(s), 151.0 (s), 169.4 (s, C-4), 182.5 (s), 185.9 (s). MS m/z (%): 290 (M^+, 49), 206 (17), 205 (100), 204 (27), 177 (10), 176 (12). *Anal.* Calcd for $C_{15}H_{18}N_2O_4 \cdot 1/10\ H_2O$: C, 61.67; H, 6.28; N, 9.59. Found: C, 61.70; H, 6.29; N, 9.31.

1,2,3,4,5,6,7,10-Octahydro-9-methoxy-2,3,8,11-tetramethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4,7,10-trione (23a) A solution of **21a** (235.1 mg, 0.735 mmol) in 8 N HNO_3 (7.35 ml) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (40 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (30 ml × 3). The combined extracts were washed with water (30 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ether gave **23a** (180.9 mg, 81.0%) as pale yellow prisms, mp 108—109.5. IR (KBr) 1670, 1630 cm^{-1}. ^{1}H-NMR δ: 1.06 (3H, d, J=6.9 Hz, 2-CH_3), 1.96 (3H, s, 8-CH_3), 2.37 (3H, s, 11-CH_3), 2.68 (1H, d, J=20.8 Hz, 6-Hβ), 2.80 (1H, dd, J=20.8, 6.3 Hz, 6-Hα), 2.89 (3H, s, 3-CH_3), 3.65 (1H, d, J=6.3 Hz, 5-H), 3.97 (3H, s, OCH_3), 4.01 (1H, dq, J=6.9, 5.0 Hz, 2-H), 4.12 (1H, d, J=5.0 Hz, 1-H). ^{13}C-NMR δ: 8.6 (q, 8-CH_3), 17.2 (q, 2-CH_3), 23.2 (t, C-6), 29.6 (q, 3-CH_3), 39.6 (q, 11-CH_3), 53.6 (d, C-1), 56.0 (d, C-2), 57.9 (d, C-5), 60.8 (q, OCH_3), 129.0 (s), 136.4 (s), 141.5(s), 155.8 (s), 167.0 (s, C-4), 182.5 (s), 186.3 (s). MS m/z (%): 304 (M^+, 100), 220 (12), 219 (36), 218 (56), 204 (56), 202 (12), 201 (23), 190 (19), 176 (16). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.11; H, 6.66; N, 9.13.

1,2,3,4,5,6,7,10-Octahydro-9-methoxy-2,3,8,11-tetramethyl-(1α,2β,5α)-1,5-imino-3-benzazocin-4,7,10-trione (23b) A solution of **21b** (161.9 mg, 0.506 mmol) in 8 N HNO_3 (5.12 ml) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (30 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate gave **23b** (148.0 mg, 96.2%) as pale yellow needles, mp 191—193 °C (dec.). IR (KBr) 1675, 1642, 1620 cm^{-1}. ^{1}H-NMR δ: 1.48 (3H, d, J=6.6 Hz, 2-CH_3), 1.96 (3H, s, 8-CH_3), 2.32 (3H, s, 11-CH_3), 2.60 (1H, d, J=19.8 Hz, 6-Hβ), 2.74 (1H, ddd, J=19.8, 5.6, 1.0 Hz, 6-Hα), 2.83 (3H, s, 3-CH_3), 3.12 (1H, q, J=6.6 Hz, 2-H), 3.58 (1H, s, 1-H), 3.66 (1H, d, J=5.6 Hz, 5-H), 4.02 (3H, s, OCH_3). ^{13}C-NMR δ: 8.7 (q, 8-CH_3), 18.3 (q, 2-CH_3), 20.1 (t, C-6), 32.7 (q, 3-CH_3), 39.4 (q, 11-CH_3), 55.8 (d, C-1), 57.9 (d, C-5), 59.1 (d, C-2), 60.9 (q, OCH_3), 129.4 (s), 136.7 (s), 140.5 (s), 155.3 (s), 169.4 (s, C-4), 182.9 (s), 186.6 (s). MS m/z (%): 304 (M^+, 100), 219 (47), 218 (65), 205 (13), 204 (77), 202 (17), 201 (38), 190 (29), 176 (24). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.84; H, 6.66; N, 9.22.

1,2,3,4,5,6,7,10-Octahydro-6-hydroxy-9-methoxy-2,3,8,11-tetramethyl-(1α,2α,5α,6β)-1,5-imino-3-benzazocin-4,7,10-trione (24a) A solution of **23a** (30.4 mg, 0.1 mmol) and selenium oxide (12.2 mg, 0.11 mmol) in dioxane (3 ml) was heated at reflux for 5 h. The reaction mixture was diluted with water (20 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (15 ml × 3). The combined extracts were washed with water (15 ml), dried, and concentrated *in vacuo* to give a residue (28.3 mg). Chromatography of this on a silica gel (8 g) column with dichloromethane–methanol (100 : 1) gave a solid, recrystallization of which from acetone–ether gave **25a** (3.5 mg, 10.9%) as pale yellow prisms, mp 106.5—108 °C. Further elution with dichloromethane–methanol (80 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **24a** (20.8 mg, 65.0%) as orange prisms, mp 164.5—166 °C.

Compound **24a**: IR (KBr) 3330, 1670, 1645, 1630 cm^{-1}. ^{1}H-NMR δ: 1.03 (3H, d, J=6.6 Hz, 2-CH_3), 1.98 (3H, s, 8-CH_3), 2.62 (3H, s, 11-CH_3), 2.89 (3H, s, 3-CH_3), 2.97 (1H, d, J=5.3 Hz, OH), 3.70 (1H, s, 5-H), 3.99 (3H, s, OCH_3), 4.03 (1H, dq, J=6.6, 5.3 Hz, 2-H), 4.18 (1H, dd, J=5.3, 1.3 Hz, 1-H), 4.75 (1H, dd, J=5.6, 1.3 Hz, 6-H). ^{13}C-NMR δ: 8.6 (q, 8-CH_3), 16.9 (q, 2-CH_3), 29.7 (q, 3-CH_3), 41.1 (q, 11-CH_3), 52.7 (d, C-2), 53.8 (d, C-1), 60.9 (q, OCH_3), 63.7 (d, C-6), 65.9 (d, C-5), 129.3 (s), 137.7 (s), 140.1 (s), 156.0 (s), 167.4 (s, C-4), 182.6 (s), 187.1 (s). MS m/z (%): 320 (M^+, 62), 235 (15), 234 (23), 220 (19), 219 (21), 218 (100). *Anal.* Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 59.71; H, 6.29; N, 8.63.

Compound **25a**: IR (KBr) 3560, 3450—2500, 1650, 1615 cm^{-1}. ^{1}H-NMR δ: 1.22 (3H, d, J=6.6 Hz, 2-CH_3), 2.21 (3H, s, 8-CH_3), 2.50 (3H, s, 11-CH_3), 2.92 (3H, s, 3-CH_3), 3.87 (3H, s, OCH_3), 3.93 (1H, d, J=1.7 Hz, 5-H), 4.14 (1H, dq, J=6.6, 5.3 Hz, 2-H), 4.46 (1H, dd, J=5.3, 1.7 Hz, 1-H), 5.61 (1H, s, OH), 11.82 (1H, s, OH). ^{13}C-NMR δ: 8.9 (q, 8-CH_3), 15.2 (q, 2-CH_3), 30.3 (q, 3-CH_3), 40.9 (q, 11-CH_3), 56.1 (d, C-1), 56.8 (d, C-2), 61.2 (q, OCH_3), 71.9 (d, C-5), 109.1 (s), 117.9 (s), 118.9 (s), 139.0 (s), 153.3 (s), 156.2 (s), 163.4 (s, C-4), 196.9 (s, C-6). MS m/z (%): 320 (M^+, 65), 236 (19), 235 (100), 234 (16), 220 (24), 217 (14). *Anal.* Calcd for $C_{16}H_{20}N_2O_5 \cdot H_2O$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.79; H, 6.60; N, 8.13.

1,2,3,4,5,6,7,10-Octahydro-6-hydroxy-9-methoxy-2,3,8,11-tetramethyl-(1α,2β,5α,6β)-1,5-imino-3-benzazocin-4,7,10-trione (24b) A solution of **23b** (42.0 mg, 0.138 mmol) and selenium oxide (16.9 mg, 0.152 mmol) in dioxane (3.5 ml) was heated at reflux for 24 h. The reaction mixture was diluted with water (25 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a residue (78.1 mg). Chromatography of this on a silica gel (8 g) column with dichloromethane–methanol (80 : 1) gave a solid, recrystallization of which from acetone–chloroform gave **24b** (20.9 mg, 66.0%) as orange prisms, mp 199—201 °C (dec.). IR (KBr) 3390, 1660, 1635, 1615 cm^{-1}. ^{1}H-NMR δ: 1.49 (3H, d, J=6.6 Hz, 2-CH_3), 1.98 (3H, s, 8-CH_3), 2.58 (3H, s, 11-CH_3), 2.80 (3H, s, 3-CH_3), 3.10 (1H, d, J=4.0 Hz, OH), 3.12 (1H, dq, J=6.6, 1.0 Hz, 2-H), 3.69 (1H, dd, J=1.0, 0.5 Hz, 1-H), 3.82 (1H, dd, J=1.0, 0.5 Hz, 5-H), 4.05 (3H, s, OCH_3), 4.60 (1H, dd, J=4.0, 1.0 Hz, 6-H). ^{13}C-NMR δ: 8.6 (q, 8-CH_3), 18.3 (q, 2-CH_3), 32.8 (q, 3-CH_3), 41.8 (q, 11-CH_3), 56.1 (d, C-1), 58.3 (d, C-2), 61.0 (q, OCH_3), 62.3 (d, C-6), 65.6 (d, C-5), 129.4 (s), 136.8 (s), 138.8 (s), 155.7 (s), 167.3 (s, C-4), 183.3 (s), 187.6 (s). MS m/z (%): 320 (M^+, 100), 305 (24), 289 (15), 235 (20), 234 (29), 220 (37), 219 (19), 218 (81), 205 (10). *Anal.* Calcd for $C_{16}H_{20}N_2O_5 \cdot 1/2\ H_2O$: C, 58.35; H, 6.43; N, 8.51. Found: C, 58.40; H, 6.14; N, 8.39.

1,2,3,4,5,6,7,10-Octahydro-6,9-dimethoxy-2,3,8,11-tetramethyl-(1α,2α,5α,6β)-1,5-imino-3-benzazocin-4,7,10-trione (26a) A solution of **23a** (30.4 mg, 0.1 mmol) and selenium oxide (33.3 mg, 0.3 mmol) in methanol (8 ml) was heated at reflux for 24 h. The reaction mixture was diluted with water (25 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a residue (38.7 mg). Chromatography of this on a silica gel (8 g) column with dichloromethane–methanol (100 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **26a** (25.6 mg, 76.6%) as pale yellow prisms, mp 113.5—115 °C. IR (KBr) 1660, 1645, 1620 cm^{-1}. ^{1}H-NMR δ: 1.02 (3H, d, J=6.9 Hz, 2-CH_3), 1.99 (3H, s, 8-CH_3), 2.61 (3H, s, 11-CH_3), 2.88 (3H, s, 3-CH_3), 3.59 (3H, s, OCH_3), 3.66 (1H, dd, J=1.7, 1.5 Hz, 5-H), 3.95 (3H, s, OCH_3), 4.03 (1H, dq, J=6.9, 5.3 Hz, 2-H), 4.18 (1H, dd, J=5.3, 1.3 Hz, 1-H), 4.21 (1H, d, J=1.7 Hz, 6-H). ^{13}C-NMR δ: 8.8 (q, 8-CH_3), 16.7 (q, 2-CH_3), 29.6 (q, 3-CH_3), 41.2 (q, 11-CH_3), 52.7 (d, C-2), 53.2 (d, C-1), 59.0 (q, OCH_3), 60.9 (q, OCH_3), 63.3 (d, C-5), 72.2 (d, C-6), 130.1 (s), 138.2 (s), 139.3 (s), 155.6 (s), 167.3

(s, C-4), 182.6 (s), 185.8 (s). MS *m/z* (%): 334 (M^+, 22), 219 (15), 218 (100). *Anal.* Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.79; H, 6.62; N, 8.32.

1,2,3,4,5,6,7,10-Octahydro-6,9-dimethoxy-2,3,8,11-tetramethyl-(1α, 2β,5α,6β)-1,5-imino-3-benzazocin-4,7,10-trione (26b) A solution of **23b** (24.4 mg, 0.08 mmol) and selenium oxide (26.7 mg, 0.24 mmol) in methanol (8 ml) was heated at reflux for 96 h. The reaction mixture was diluted with water (25 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml × 3). The combined extracts were washed with water (20 ml), dried, and concentrated *in vacuo* to give a residue (25.8 mg). Chromatography of this on a silica gel (8 g) column with dichloromethane–methanol (200 : 1) gave a solid, recrystallization of which from ether gave **26b** (16.3 mg, 60.8%) as pale yellow prisms, mp 179—181 °C. Further elution with dichloromethane–methanol (80 : 1) gave a solid, recrystallization of which from acetone–chloroform gave **24b** (4.6 mg, 17.9%) as orange prisms, whose spectra were identical with those of an authentic sample (see above).

Compound **26b**: IR (KBr) 1660, 1640, 1615 cm^{-1}. ^{1}H-NMR δ: 1.48 (3H, d, J=6.3 Hz, 2-CH_3), 1.99 (3H, s, 8-CH_3), 2.56 (3H, s, 11-CH_3), 2.79 (3H, s, 3-CH_3), 3.09 (1H, dq, J=6.3, 1.0 Hz, 2-H), 3.59 (3H, s, OCH_3), 3.70 (1H, br s, 1-H), 3.81 (1H, br s, 5-H), 4.00 (3H, s, OCH_3), 4.06 (1H, d, 1.0 Hz, 6-H). ^{13}C-NMR δ: 8.9 (q, 8-CH_3), 18.3 (q, 2-CH_3), 32.8 (q, 3-CH_3), 41.8 (q, 11-CH_3), 56.0 (d, C-1), 58.4 (d, C-2), 58.9 (q, OCH_3), 60.9 (q, OCH_3), 62.6 (d, C-5), 70.7 (d, C-6), 130.3 (s), 137.4 (s), 138.0 (s), 155.3 (s), 167.0 (s, C-4), 183.4 (s), 186.0 (s). MS *m/z* (%): 334 (M^+, 27), 219 (17), 218 (100). *Anal.* Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.98; H, 6.66; N, 8.27.

Attempted Condensation of Acetate (+)-27 with Benzaldehyde 9. Method A Condensation of (+)-**27** (36.8 mg, 0.2 mmol) and **9** (42.0 mg, 0.2 mmol) with a solution of potassium *tert*-butoxide (22.5 mg, 0.2 mmol) in *tert*-butyl alcohol (0.4 ml) in dry DMF (0.8 ml) at room temperature for 24 h gave a residue (47.6 mg). Chromatography of this on a silica gel (6 g) column with benzene–ethyl acetate (9 : 1) gave **9** (11.3 mg, 26.9% recovery) and further elution with benzene–ethyl acetate (2 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **7a** (3.1 mg, 4.6%) as colorless prisms. Further elution with ethyl acetate gave a solid, recrystallization of which from ether gave **28** (6.6 mg, 8.4%) as colorless needles, mp 134.5—136 °C (stereochemistry yet to be determined). IR (KBr) 3600—3150, 1745, 1690, 1655 cm^{-1}. ^{1}H-NMR δ: 1.69 (3H, s, 3-CH_3), 2.14 (3H, s, $COCH_3$), 2.20 (3H, s, $ArCH_3$), 3.05 (1H, d, J=17.2 Hz, 6-H), 3.14 (3H, s, 1-CH_3), 3.70 (1H, d, J=17.2 Hz, 6-H), 3.79, 3.80, 3.80 (each 3H, s, OCH_3), 6.08 (1H, br s, OH), 6.39 (1H, s, CHOH), 6.53 (1H, s, ArH). ^{13}C-NMR δ: 9.7 (q, $ArCH_3$), 20.1 (q, $COCH_3$), 21.1 (q, 3-CH_3), 29.9 (q, NCH_3), 45.0 (t, C-6), 56.2 (q, OCH_3), 60.4 (q, OCH_3), 60.7 (q, OCH_3), 67.0 (s, C-3), 73.6 (d, CHOH), 109.2 (d), 123.0 (s), 125.4 (s), 149.0 (s), 149.1 (s), 150.5 (s), 165.4 (s, CO), 167.1 (s, CO), 167.1 (s, CO). MS *m/z* (%): 394 (M^+, 1), 253 (43), 212 (13), 211 (100), 142 (13). High-resolution MS Calcd for $C_{19}H_{26}N_2O_7$: 394.1740. Found: 394.1740.

Method B The same procedure as described above, but using a solution of potassium *tert*-butoxide (44.9 mg, 0.4 mmol) in *tert*-butyl alcohol (0.8 ml) gave a residue (57.5 mg). Chromatography of this on a silica gel (10 g) column with benzene–ethyl acetate (9 : 1) gave **9** (13.6 mg, 32.4% recovery) and further elution with benzene–ethyl acetate (2 : 1) gave a solid, recrystallization of which from ethyl acetate–ether gave **7a** (7.3 mg, 10.9%) as colorless prisms, mp 157—157.5 °C, $[\alpha]_D^{20}$ ±0° (c=1.0, methanol). ^{1}H-NMR δ: 1.54 (3H, d, J=6.9 Hz, 6-CH_3), 2.23 (3H, s, $ArCH_3$), 3.09 (3H, s, NCH_3), 3.62, 3.83, 3.83 (each 3H, s, OCH_3), 4.05 (1H, q, J=6.9 Hz, 6-H), 6.64 (1H, s, ArH), 6.89 (1H, s, C=CH), 9.28 (1H, br s, NH), the spectra of which were identical with those of an authentic sample (see above).

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References and Notes

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3) Saito N., Harada S., Inouye I., Yamaguchi K., Kubo A., *Tetrahedron*, **30**, 8231—8246 (1995).
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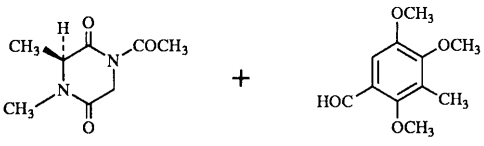
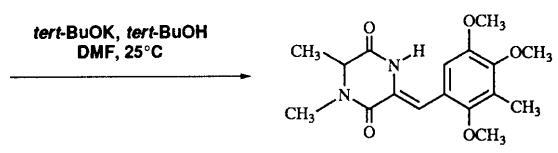
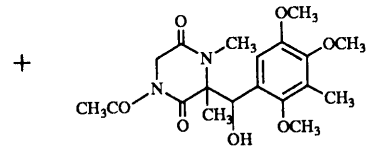
5) *a*) Kurihara H., Mishima H., *Heterocycles*, **17**, 191—199 (1982); *b*) *Idem*, *Tetrahedron Lett.*, **23**, 3639—3640 (1982); *c*) Kurihara H., Mishima H., Arai M., *Heterocycles*, **24**, 1549—1555 (1986).
6) Saito N., Kubo A., Mikami Y., Yazawa K., Arai T., Abstracts of Papers, The AFMC International Medicinal Chemistry Symposium 95. Tokyo, September 1995, P1T044.
7) Reaction of **2** with sodium hydride (1.1 eq) and methyl iodide (1.1 eq) in THF is slow, but heating under reflux for 3 h gave **3** in 93.0% yield (see Experimental).
8) Methylation of **3** with sodium hydride (1 eq) and methyl iodide (3 eq) in DMF under reflux for 3 h gave **5a** and **6** in 39.9% and 2.9% yields, respectively (21.9% of **3** recovered). Methylation of **2** with sodium hydride (2.1 eq) and methyl iodide (10 eq) in DMF under reflux for 14 h gave **3**, **5a**, and **6** in 24.1%, 35.3%, and 1.0% yields, respectively.
9) Kanmera T., Lee S., Aoyagi H., Izumiya N., *Tetrahedron Lett.*, **1979**, 4483—4486.
10) $[\alpha]_D^{20}$ +60.1° (c=1.0, methanol). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR δ: 1.54 (3H, d, J=7.2 Hz, 3-CH_3), 2.57, 2.59 (each 3H, s, $COCH_3$), 4.04 (1H, d, J=18.5 Hz, 6-H), 5.14 (1H, d, J=18.5 Hz, 6-H), 5.25 (1H, q, J=7.3 Hz, 3-H). ^{13}C-NMR δ: 17.7 (q, 3-CH_3), 26.8 (q, $COCH_3$), 26.9 (q, $COCH_3$), 46.4 (t, C-6), 53.9 (d, C-3), 165.7 (s, CO), 168.6 (s, CO), 170.9 (s, CO), 171.2 (s, CO). MS *m/z* (%): 212 (M^+, 46), 170 (100), 169 (70), 128 (26), 127 (41), 85 (45), 72 (20), 43 (97). High-resolution MS Calcd for $C_9H_{12}N_2O_4$: 212.0797. Found: 212.0794.
11) Chai C. L. L., Hay D. B., King A. R., *Aust. J. Chem.*, **49**, 605—610 (1996).
12) A preliminary experiment was carried out by employing the readily available compound **27**, which was prepared in 50% yield from 1,6-dimethylpiperazine-2,5-dione; mp 79—81 °C (lit.[11] 81—82 °C). $[\alpha]_D^{20}$ +25.1° (c=1.0, methanol). ^{1}H-NMR δ: 1.54 (3H, d, J=7.3 Hz, 3-CH_3), 2.57 (3H, s, $COCH_3$), 3.00 (3H, s, NCH_3), 3.98 (1H, d, J=18.2 Hz, 6-H), 4.07 (1H, q, J=7.3 Hz, 3-H), 4.77 (1H, d, J=18.2 Hz, 6-H). Condensation of (+)-**27** with **9** in the presence of potassium *tert*-butoxide (1 eq) in DMF gave **7a** in only 4.6% yield along with the C-6 alkylated compound **28** (8.4%) and recovered **9** (26.9%). Clearly, unfavorable anion formation at the C-6 position of **27** had occurred. Treatment of (+)-**27** and **9** with 2 eq of sodium *tert*-butoxide in DMF at 25 °C for 24 h gave **7a** (10.9%) as a racemic form (see Experimental).



27 **9**

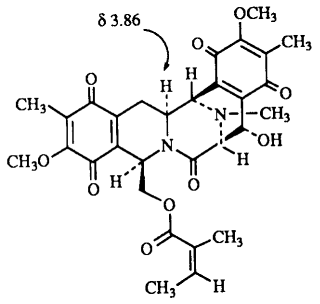


7a



28

13) This compound was a 3:2 mixture of two rotational isomers.
14) *a*) Saito N., Yamauchi R., Nishioka H., Ida S., Kubo A., *J. Org. Chem.*, **54**, 5391—5395 (1989); *b*) Saito N., Tashiro K., Maru Y., Yamaguchi K., Kubo A., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 53—69.
15) The H-2 proton of compound **19a** appears to have a similar chemical shift and coupling constants to that of renieramycin C (δ: 3.86; $J_{1,2}=3.5$ Hz), which was isolated in minute quantity from a bright blue marine sponge, *Reniera* sp.; Frincke J. M., Faulkner D. J., *J. Am. Chem. Soc.*, **104**, 265—269 (1982).



renieramycin C

16) The NOE difference experiments on **25a** indicated magnetization transfer from 10-OH (δ: 5.61) to H-1 (2%), 2-CH_3 (4%), and 9-OCH_3 (6%).
17) Treating **23a** with selenium oxide in dioxane under reflux for 24 h afforded **24a** and **25a** in 2.2% and 19.2% yields, respectively. The intramolecular redox reaction of **25a** probably produced **26a**.[1b]
18) An H-6 proton is orthogonal to the H-5 proton.