Synthesis of Saframycins. X.[1] Transformation of (−)-Saframycin A to (−)-Saframycin Mx Type Compound with the Structure Proposed for Saframycin E

Naoki SAITO, Shunji HARADA, Masayo NISHIDA, Izumi INOUYE, and Akinori KUBO*

Meiji College of Pharmacy, 1–35–23 Nozawa, Setagaya-ku, Tokyo 154, Japan.
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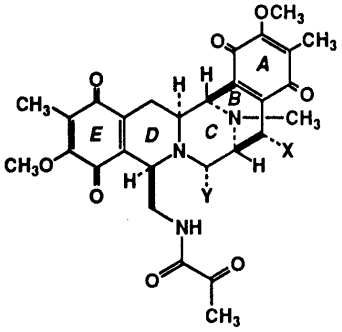
Treatment of (−)-saframycin A (1a) with selenium oxide in acetic acid afforded (−)-saframycin G (1g), and a catalytic reduction and regioselective oxidation sequence afforded the saframycin Mx type compound (3). We applied this methodology to the transformation of (±)-5-hydroxysaframycin B (11) to the hydroquinone (1e). Acetylation of 1e with acetic anhydride in pyridine gave the triacetate (13), which is identical with the triacetyl derivative of natural saframycin E.

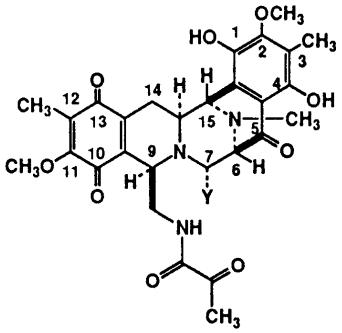
Key words synthesis; saframycin; transformation; regioselective oxidation; hydroquinone

Saframycin is a class of antibiotics with activity against gram-positive bacteria and also against several kinds of tumor.[2] Among this group, the monoquinone-type antibiotics, such as saframycins D (**1d**) and F (**1f**), and saframycins Mx 1 (**2a**) and Mx 2 (**2b**) have a quinone moiety at ring E and a highly substituted benzene ring A with a variety of oxidation levels. Our interest in the relationship of the various skeletal structures of saframycins has let us to conduct a series of chemical transformations.[3] We recently reported the transformation of saframycin A (**1a**) to the saframycin Mx type compound (**3**) through saframycin G (**1g**).[4] Saframycin E (**1e**) is an antitumor antibiotic discovered in the culture broth of *Streptomyces lavendulae* No. 314 in 1977.[5] The structure of **1e** has not been established yet because of its instability; repeated attempts to isolate **1e** have been unsuccessful. Based on a comparison of the chemical properties and spectral data reported for natural saframycin E with those of compound **3**, we proposed that saframycin E has the structure **1e**. In this paper, we present a full account of our transformation of **1a** to **3** and the first synthesis of (±)-**1e** from (±)-saframycin B (**1b**).

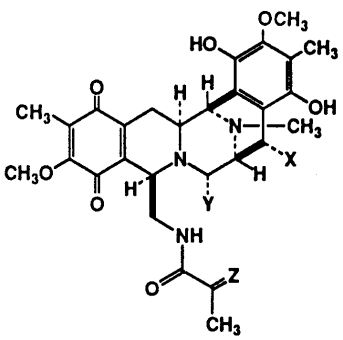
The stability of the hydroquinone ring system at the A ring in saframycin Mxs (**2a, b**) and saframycin D (**1d**) is believed to be due to hydrogen bonding of the oxygen functional group at position **5** and the hydroxyl group at position 4. To confirm the stability of the hydroquinone structure with the oxygen functional group, we studied reduction of the quinone group at the A ring to the corresponding hydroquinone. A preliminary experiment was carried out using the readily available model compounds (**4a—c**) (Chart 1).[3] Although reduction of the quinone (**4a**) seemed to occur quantitatively as judged by thin layer chromatography (TLC) detection, evaporation of this solution resulted in immediate conversion to **4a** in 85.5% yield, probably by air oxidation. On the other hand, treatment of the methoxyquinone (**4b**) under the same conditions resulted in isolation of the hydroquinone (**5b**) in 69.2% yield. Treatment of **5b** with acetic anhydride in acetic acid at 100 °C for 20 h gave the diacetate (**6b**) in 45.8% yield. Hydrogenation of the 5-hydroxyquinone (**4c**)[6] gave the hydroquinone (**5c**) in 60.8% yield. Acetylation of **5c** with acetic anhydride in pyridine gave the triacetate (**6c**) in 63.2% yield. The hydroquinones



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



saframycins:
D (1d): Y = H
F (1f): Y = CN



saframycins:
Mx 1 (2a): X = OCH_3, Y = OH, Z = H, NH_2
Mx 2 (2b): X = OCH_3, Y = H, Z = H, NH_2
3: X = OH, Y = CN, Z = O

Fig. 1

This paper is dedicated to Professor Shin-ichiro Sakai (Chiba University) on the occation of his 65th birthday.

* To whom correspondence should be addressed.

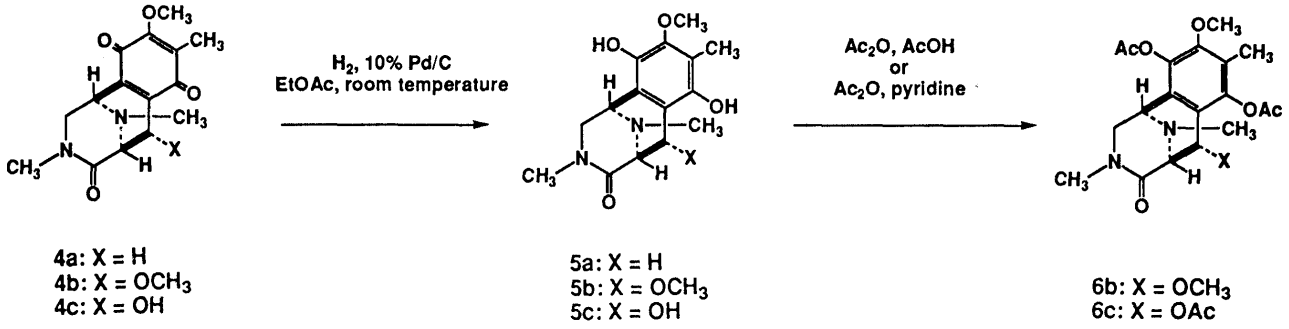


Chart 1

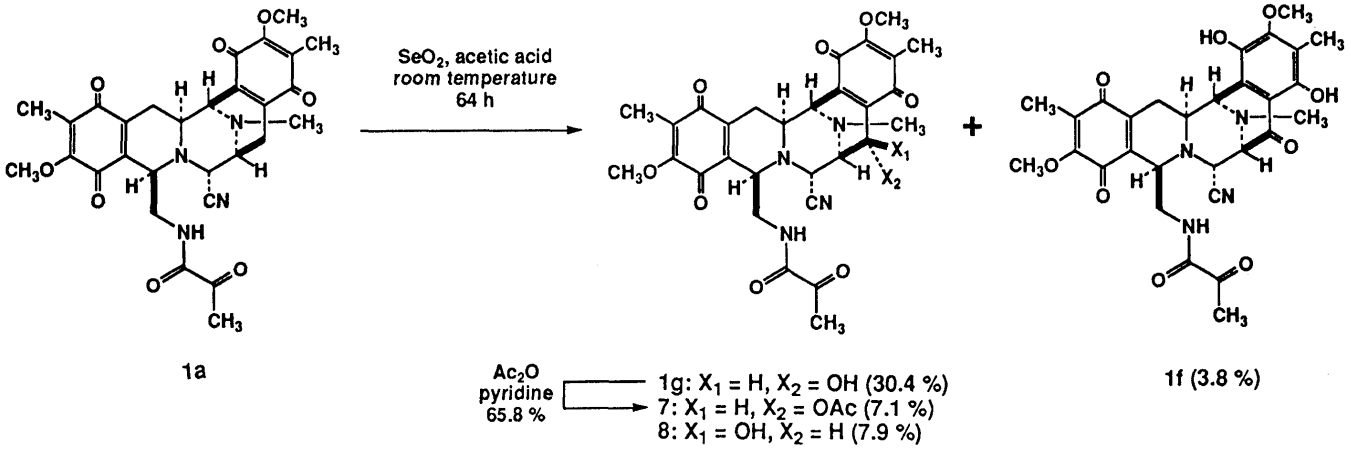


Chart 2

(**5b, c**) were stable in the solid state, but, were easily oxidized to the quinones (**4b, c**) in organic solvents.

Encouraged by the results of these model studies, we applied this strategy to the transformation of (−)-saframycin A (**1a**)[7] to the saframycin Mx type compound (**3**). The introduction of a hydroxyl group into position 5 of **1a** was attempted first using our standard procedure (Chart 2).[3] Unfortunately, no observable reaction occurred when (−)-**1a** was treated with selenium oxide (2 eq) in dioxane for 84 h at room temperature. However, treatment of (−)-**1a** with selenium oxide (10 eq) in acetic acid at room temperature for 64 h afforded (−)-saframycin G (**1g**) in 30.4% yield along with (−)-saframycin G acetate (**7**), (+)-saframycin F (**1f**), and (+)-5-*epi*-saframycin G (**8**) in 7.1%, 3.8%, and 7.9% yields, respectively (Chart 2). The structures of the hydroxyl compounds (**1g** and **8**) were determined on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra; the coupling between H-5 and H-6 was 0.5 Hz for **1g**, while that for the 5-*epimer* (**8**) was 7.3 Hz.[8] Acetylation of **1g** with acetic anhydride in pyridine at room temperature for 1 h afforded the acetate (**7**) in 65.8% yield. The synthetic saframycins F and G were identical with the natural products[9] as judged from ^{1}H-NMR, ^{13}C-NMR, infrared (IR), ultraviolet (UV), mass spectrum (MS), and TLC comparisons.

We then investigated the conversion of **1g** into the hydroquinone (**3**) (Chart 3). Unlike a model of the ABC ring system, the saframycin system has the potential to form hydroquinone isomers, thereby creating a regiochemical problem in the reduction and/or oxidation steps. However, we hoped that this oxidation would be highly regioselective because of the high stability of the hydroquinone forms at the A ring bearing a hydroxyl and methoxyl group at position 5. Treatment of (−)-**1g** with 10% Pd/C in ethyl acetate for 20 min gave the leuco compound (**9**) in quantitative yield. It was difficult to isolate this compound and after removal of the solvent *in vacuo*, **9** was treated with SiO_2 in ethyl acetate at room temperature for 24 h in the presence of oxygen to afford (−)-**3** in 52% yield.[10] This product was very sensitive to light and oxygen, and at above pH 7 was quickly oxidized to afford the bis-quinone (**1g**) in 68.1% yield. A 400 MHz ^{1}H-NMR analysis allowed assignment of the signals of **3**. Diagnostic homoallylic coupling between H-9 and H-14β through five bonds was observed.[11] Acetylation of **3** with acetic anhydride in pyridine gave the triacetate (**10**) in 45.8% yield. Thus, we achieved transformation of (−)-**1a** to the (−)-saframycin Mx type compound (**3**) *via* (−)-**1g**.

Finally, this strategy was successfully applied to the transformation of (±)-saframycin B (**1b**) to (±)-saframycin E (**1e**). The properties of saframycin E (**1e**) have been reported to be as follows: yellow powder, mp 146—148 °C, $[\alpha]_D$ −37.3° (c=0.53 MeOH); molecular formula $C_{28}H_{33}N_3O_9$, UV λ_{max} nm (log ε): 272 (4.10), 368 (2.98), and IR ν_{max}^{KBr}: 3380, 1720, 1685, 1655, 1620 cm^{-1}. Because **1e** is insoluble in chloroform, its ^{1}H-NMR spectrum was obtained in pyridine d_5 at 100 MHz: δ 1.83 (3H, s), 2.17 (3H, s), 2.48 (3H, s), 2.48 (3H, s), 3.82 (3H, s), 3.95 (3H, s), 5.22 (1H, s). To produce more stable derivatives of **1e**, chemical modification was carried out by Arai and co-workers.[5] Treatment of **1e** with acetic

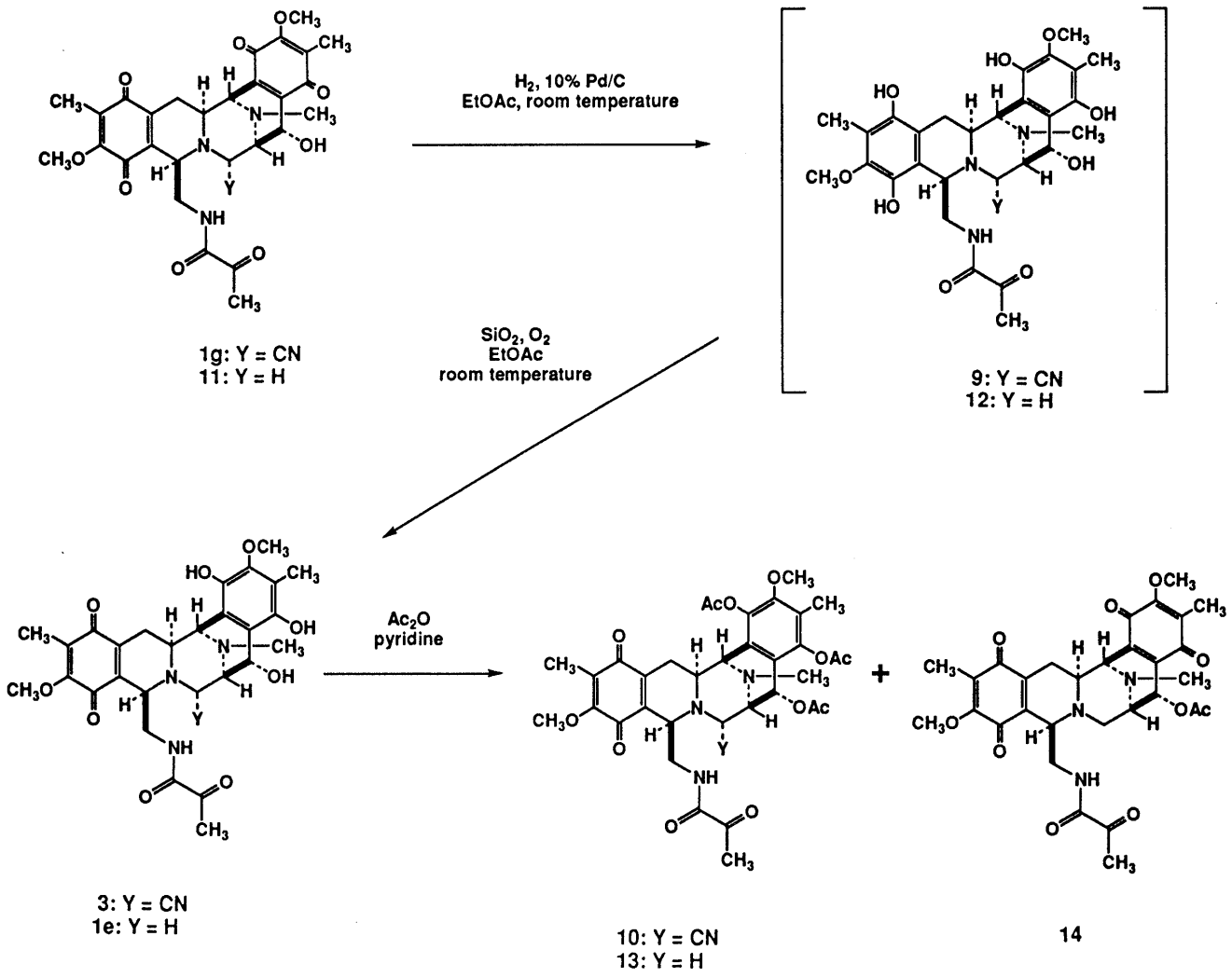


Chart 3

anhydride in pyridine gave its triacetyl derivative in 50% yield. This substance was obtained as yellow needles, mp 194—198 °C, $C_{34}H_{39}N_3O_{12}$, and the spectral data were as follows: MS *m/z* (%) 681 (M^+, 8), 581 (74), 304 (100), 262 (62), 220 (42), 218 (60); IR $\nu_{max}^{CHCl_3}$: 3380, 1760, 1725, 1675, 1660 cm^{-1}; UV λ_{max} nm (log ε): 266 (3.98), 370 (2.97). The 100 MHz ^{1}H-NMR spectrum in $CDCl_3$ of this substance has been reported, and assignments of nine methyl groups have been made: two aromatic methyls (δ 1.92 and 2.12), four acetyl methyls (δ 2.12, 2.20, 2.29, and 2.46), an *N*-methyl (δ 2.48), and two methoxyls (δ 3.84 and 4.16). Comparison of ^{1}H-NMR and ^{13}C-NMR spectral data of saframycin E (**1e**) with those of compound **3** indicated that saframycin E (**1e**) is the 7-descyano derivative of **3**. The starting material (**11**) was obtained from (±)-**1b** by treatment with selenium oxide in dioxane in 40% yield.[3] Hydrogenation of **11** with 10% Pd/C in ethyl acetate for 1 h gave the leuco compound (**12**). This also could not be isolated and, after removal of the solvent, treatment of **12** with SiO_2 in ethyl acetate in the presence of oxygen for 24 h afforded (±)-**1e** in 62.4% overall yield. Unfortunately, direct comparisons of the synthetic **1e** with the natural product have not been possible. Acetylation of **1e** with acetic anhydride in pyridine gave the triacetate (**13**) and the bis-quinone (**14**) in 56.1% and 11.2% yields, respectively. The synthetic **13** was identical with the triacetyl derivative[5] of natural saframycin E (comparisons of UV, IR, MS, and ^{1}H-NMR data, and TLC behavior). The structure of the triacetate (**13**) was supported by ^{13}C-NMR spectral data. Compound (**14**) was obtained from **11** by treatment with acetic anhydride in pyridine, in 78.6% yield.

In summary, we have succeeded in the first total synthesis of (±)-saframycin E (**1e**) from (±)-saframycin B (**1b**). Efforts to achieve the total synthesis of saframycin Mxs are in progress.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Optical rotation $[\alpha]_D$ measurements were made on a Horiba-SEPA-200 automatic digital polarimeter at 20 °C. UV spectra were determined in methanol with a Hitachi 340 spectrometer. IR spectra were obtained with a Hitachi 260-10 spectrophotometer and ^{1}H-NMR spectra were recorded at 270 MHz and 400 MHz with a JEOL JNM-EX 270 and a JNM-GX400 spectrometer. ^{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 are recorded in δ_H values relative to internal $(CH_3)_4Si$ as a standard. Mass spectra were recorded on a JMS-DX 302 mass spectrometer. Elemental analyses were obtained by a Perkin–Elmer Model 240B elemental analyzer. All reactions were conducted under an argon

atmosphere. Dry solvents and reagents were obtained using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts. Removal of the solvent was done with a rotary evaporator and, finally, under high vacuum. Column chromatography was performed with E. Merck Silica gel 60 (70—230 mesh).

Reduction of 4a A solution of **4a** (29.0 mg, 0.1 mmol) in ethyl acetate (4 ml) was hydrogenated over 10% palladium on carbon (10 mg) at 1 atm for 30 min to provide a colorless solution which showed one spot on TLC (*Rf* 0.1, acetone–chloroform, 4 : 5). The catalyst was removed by filtration and washed with ethyl acetate (40 ml). At this stage, the colorless solution became pale yellow, and this solution showed one spot on TLC (*Rf* 0.35, acetone–chloroform, 4 : 5). The combined filtrates were concentrated *in vacuo* to restore **4a** (24.8 mg, 85.5%) as a pale yellow solid.

1,2,3,4,5,6-Hexahydro-7,10-dihydroxy-6,9-dimethoxy-3,8,11-trimethyl-4-oxo-1,5-imino-3-benzazocine (5b) A solution of **4b** (48.0 mg, 0.15 mmol) in ethyl acetate (4 ml) was hydrogenated over 10% palladium on carbon (10 mg) at 1 atm for 30 min. The catalyst was removed by filtration and washed with ethyl acetate (40 ml). The combined filtrates were concentrated *in vacuo* to give **5b** (60.0 mg) as a solid. Recrystallization of this solid from chloroform–ethyl acetate afforded pure **5b** (33.4 mg, 69.2%) as colorless prisms, mp 210—212 °C. IR ν_{max}^{KBr}: 3510, 3400—3020, 2940, 1645, 1620 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 237 (3.39), 293 (3.60). ^{1}H-NMR δ: 2.20 (3H, s, $ArCH_3$), 2.61 (3H, s, NCH_3), 2.86 (3H, s, NCH_3), 3.20 (1H, d, J=12.2 Hz, H-2α), 3.59 (3H, s, 6-OCH_3), 3.78 (3H, s, 9-OCH_3), 3.81 (1H, dd, J=0.7, 0.5 Hz, H-5), 3.93 (1H, dd, J=12.2, 5.0 Hz, H-2β), 4.23 (1H, dd, J=5.0, 0.5 Hz, H-1), 4.45 (1H, d, J=0.7 Hz, H-6), 5.66 and 6.24 (each 1H, s, D_2O exchangeable, OH). ^{13}C-NMR δ: 9.1 (q, CH_3), 34.2 and 40.8 (each q, NCH_3), 50.0 (t, C^2), 50.7 (d, C^1), 55.8 and 60.9 (each q, OCH_3), 61.8 (d, C^5), 75.2 (d, C^6), 114.5 (s), 117.7 (s), 119.9 (s), 138.4 (s), 145.7 (s), 147.6 (s), 167.7 (s, CO). MS *m/z* (relative intensity): 322 (M^+, 67), 320 (14), 290 (75), 259 (89), 250 (100), 220 (76), 218 (40), 205 (29), 204 (20). *Anal.* Calcd for $C_{16}H_{22}N_2O_5\cdot 3/4H_2O$: C, 57.22; H, 7.05; N, 8.34. Found: C, 57.01; H, 6.75; N, 8.17.

7,10-Diacetoxy-1,2,3,4,5,6-hexahydro-6,9-dimethoxy-3,8,11-trimethyl-4-oxo-1,5-imino-3-benzazocine (6b) Acetic anhydride (0.2 ml) was added to a solution of **5b** (13.0 mg, 0.0404 mmol) in acetic acid (0.5 ml), and the mixture was heated at 100 °C for 20 h. It was then diluted with water (10 ml), made alkaline with 10% Na_2CO_3, and extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue (19.1 mg) was subjected to chromatography (silica gel, 6 g, 50 : 1 dichloromethane–methanol) to give **6b** (11.7 mg, 45.8%) as a pale yellow amorphous powder. IR $\nu_{max}^{CHCl_3}$: 1760, 1655, 1645, 1640 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 220 (3.01), 264 (2.23). ^{1}H-NMR δ: 2.09 (3H, s, $ArCH_3$), 2.32 and 2.36 (each 3H, s, $COCH_3$), 2.62 (3H, s, NCH_3), 2.81 (3H, s, NCH_3), 2.93 (1H, d, J=12.2 Hz, H-2α), 3.52 (3H, s, 6-OCH_3), 3.73 (1H, br s, H-5), 3.74 (3H, s, 9-OCH_3), 3.90 (1H, dd, J=12.2, 5.0 Hz, H-2β), 4.05 (1H, dd, J=5.0, 0.5 Hz, H-1), 4.27 (1H, d, J=0.7 Hz, H-6). MS *m/z* (relative intensity): 406 (M^+, 47), 376 (31), 335 (14), 334 (100), 304 (48), 292 (45), 262 (34). High-resolution MS Calcd for $C_{20}H_{26}N_2O_7$: 406.1716. Found: 406.1716.

1,2,3,4,5,6-Hexahydro-6,7,10-trihydroxy-9-methoxy-3,8,11-trimethyl-4-oxo-1,5-imino-3-benzazocine (5c) A solution of **4c** (45.9 mg, 0.15 mmol) in ethanol (4 ml) was hydrogenated over 10% palladium on carbon (10 mg) at 1 atm for 4 h. The catalyst was removed by filtration and washed with ethyl acetate (40 ml). The combined filtrates were concentrated *in vacuo* to give **5c** (61.4 mg) as a solid. Recrystallization of this solid from methanol afforded pure **5c** (28.1 mg, 60.8%) as colorless prisms, mp 221—223 °C (dec.). IR ν_{max}^{KBr}: 3600—3020, 1645, 1620 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 224 (3.83), 290 (3.64), 294 (3.63). ^{1}H-NMR (1 : 1 $CDCl_3$–CD_3OD) δ: 2.18 (3H, s, $ArCH_3$), 2.67 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 3.23 (1H, d, J=12.9 Hz, H-2α), 3.57 (1H, br s, H-5), 3.74 (3H, s, 9-OCH_3), 4.00 (1H, dd, J=12.9, 5.0 Hz, H-2β), 4.31 (1H, dd, J=5.0, 1.3 Hz, H-1), 4.86 (1H, d, J=1.3 Hz, H-6). ^{13}C-NMR (1 : 1 $CDCl_3$–CD_3OD) δ: 9.3 (q, CH_3), 34.5 and 41.3 (each q, NCH_3), 49.6 (t, C^2), 51.3 (d, C^1), 60.8 (q, OCH_3), 65.9 (d, C^6), 67.9 (d, C^5), 117.5 (s), 119.1 (s), 120.7 (s), 139.5 (s), 146.7 (s), 147.3 (s), 168.9 (s, CO). MS *m/z* (relative intensity): 308 (M^+, 65), 291 (24), 290 (26), 259 (30), 236 (100), 221 (22), 220 (67). *Anal.* Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.26; H, 6.76; N, 8.94.

6,7,10-Triacetoxy-1,2,3,4,5,6-hexahydro-9-dimethoxy-3,8,11-trimethyl-4-oxo-1,5-imino-3-benzazocine (6c) Acetic anhydride (0.2 ml) was added to a solution of **5c** (24.8 mg, 0.08 mmol) in dry pyridine (0.5 ml), and the mixture was left to stand for 12 h. The reaction mixture 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 (48.6 mg). Recrystallization of this residue from ether afforded **6c** (22.1 mg, 63.2%) as colorless needles, mp 232—234 °C. IR ν_{max}^{KBr}: 1755, 1730, 1650 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 220 (2.78), 264 (1.76). ^{1}H-NMR δ: 2.07 (3H, s, $ArCH_3$), 2.08, 2.25, and 2.37 (each 3H, s, $COCH_3$), 2.63 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.96 (1H, d, J=12.2 Hz, H-2α), 3.59 (1H, br s, H-5), 3.76 (3H, s, OCH_3), 3.93 (1H, dd, J=12.2, 5.0 Hz, H-2β), 4.11 (1H, dd, J=5.0, 1.3 Hz, H-1), 6.08 (1H, d, J=1.3 Hz, H-6). ^{13}C-NMR δ: 10.2 (q, CH_3), 20.4, 20.5, and 21.0 (each q, $COCH_3$), 34.1 (q, NCH_3), 41.3 (q, NCH_3), 49.8 (t, C^2), 50.8 (d, C^1), 60.9 (OCH_3), 64.7 (d, C^6), 64.7 (d, C^5), 120.2 (s), 126.0 (s), 128.1 (s), 138.7 (s), 147.1 (s), 151.1 (s), 165.5 (s, CO), 168.1 (s, CO), 168.6 (s, CO), 169.5 (s, CO). MS *m/z* (relative intensity): 434 (M^+, 58), 375 (30), 363 (22), 362 (100), 320 (25), 304 (78), 262 (28). *Anal.* Calcd for $C_{21}H_{26}N_2O_8\cdot 1/4H_2O$: C, 57.58; H, 6.07; N, 6.40. Found: C, 57.87; H, 6.36; N, 6.10.

Oxidation of (−)-Saframycin A (1a) with Selenium Oxide In Dioxane: A solution of **1a** (16.0 mg, 0.0284 mmol) and selenium oxide (6.3 mg, 0.0568 mmol) in dioxane (2 ml) was stirred for 84 h at room temperature. The reaction mixture was diluted with water (20 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 (21.2 mg). Chromatography on a silica gel (5 g) column with hexane–ethyl acetate (1 : 1) afforded only the starting material (7.0 mg 45.5% recovery) as a pale yellow amorphous powder.

In Acetic Acid: A solution of **1a** (224.8 mg, 0.4 mmol) and selenium oxide (443.8 mg, 4.0 mmol) in acetic acid (20 ml) was stirred for 64 h at room temperature. The reaction mixture was diluted with water (50 ml), made alkaline with NH_4OH, and extracted with chloroform (50 ml × 3). The combined extracts were washed with water (50 ml), dried, and concentrated *in vacuo* to give a residue (240.0 mg). Chromatography on silica gel (50 g) with hexane–ethyl acetate (2 : 3) as the eluent gave a mixture (fraction A). Further elution with hexane–ethyl acetate (1 : 1—1 : 2) gave **1g** (70.3 mg, 30.4%) as a pale yellow solid. Fraction A, which showed three major spots on TLC (*Rf*, 0.5, 0.46, and 0.38, 1 : 1 hexane–ethyl acetate), was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 2 : 1, hexane–ethyl acetate) to afford **1f** (8.8 mg, 3.8%), **7** (17.6 mg, 7.1%), and **8** (18.3 mg, 7.9%).

Saframycin G (1g) A pale yellow solid; $[\alpha]_D$ −46.0° (c=1.0 in MeOH). IR ν_{max}^{KBr}: 3540, 3425, 2255, 1730, 1695, 1665, 1650, 1630 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 264 (4.24), 370 (2.95). ^{1}H-NMR δ: 1.21 (1H, ddd, J=17.3, 11.5, 3.2 Hz, H-14β), 1.92 and 2.00 (each 3H, s, quinone CH_3), 2.26 (3H, s, $COCH_3$), 2.48 (3H, s, NCH_3), 2.86 (1H, dd, J=17.3, 2.9 Hz, H-14α), 3.07 (1H, ddd, J=11.5, 3.0, 2.0 Hz, H-14a), 3.30 (1H, dt, J=14.2, 4.3 Hz, 9-CH), 3.46 (1H, ddd, J=2.6, 1.3, 0.5 Hz, H-6), 3.53 (1H, br s, OH), 3.69 (1H, ddd, J=14.2, 8.6, 1.7 Hz, 9-CH), 3.96 (1H, ddd, J=4.3, 3.2, 1.7 Hz, H-9), 4.03 and 4.06 (each 3H, s, OCH_3), 4.13 (1H, dd, J=3.0, 1.3 Hz, H-15), 4.16 (1H, d, J=2.6 Hz, H-7), 4.33 (1H, d, J=0.5 Hz, H-5), 6.63 (1H, dd, J=8.6, 4.3 Hz, NH). ^{13}C-NMR δ: 8.5 (q, CH_3), 8.7 (q, CH_3), 24.2 (q, $COCH_3$), 24.9 (t, C^{14}), 40.6 (t, 9-CH_2), 42.5 (q, NCH_3), 53.2 (d, C^{14a}), 55.0 (d, C^{15}), 56.1 (d, C^7), 56.5 (d, C^9), 61.1 (q, OCH_3), 61.1 (q, OCH_3), 62.1 (d, C^5), 62.3 (d, C^6), 116.2 (s, CN), 128.3 (s), 129.1 (s), 135.6 (s), 135.6 (s), 140.8 (s), 141.1 (s), 155.9 (s), 156.0 (s), 160.2 (s, CO), 180.7 (s), 182.7 (s), 185.2 (s), 188.3 (s), 196.8 (s, $COCH_3$). MS *m/z* (relative intensity): 578 (M^+, 3), 478 (14), 462 (10), 259 (12), 245 (16), 244 (14), 243 (23), 236 (53), 235 (100), 234 (26), 221 (16), 220 (16), 219 (30), 218 (68), 206 (10), 204 (18), 203 (13), 43 (12). *Anal.* Calcd for $C_{29}H_{30}N_4O_9\cdot H_2O$: C, 58.38; H, 5.41; N, 9.39. Found: C, 58.69; H, 5.40; N, 9.09.

Saframycin G Acetate (7) A pale yellow amorphous powder; $[\alpha]_D$ −40.0° (c=0.8 in MeOH). IR $\nu_{max}^{CHCl_3}$: 3400, 1735, 1720, 1690, 1655, 1645, 1615 cm^{-1}. UV λ_{max} nm ($\log\varepsilon$): 264 (4.14), 372 (3.11). ^{1}H-NMR δ: 1.12 (1H, ddd, J=16.8, 11.6, 3.0 Hz, H-14β), 1.91 and 2.02 (each 3H, s, quinone CH_3), 2.09 (3H, s, $OCOCH_3$), 2.24 (3H, s, $COCH_3$), 2.48 (3H, s, NCH_3), 2.86 (1H, dd, J=16.8, 3.0 Hz, H-14α), 3.09 (1H, ddd, J=11.6, 3.0, 2.0 Hz, H-14a), 3.29 (1H, dt, J=14.2, 4.0 Hz, 9-CH), 3.32 (1H, ddd, J=2.3, 0.5, 0.5 Hz, H-6), 3.77 (1H, ddd, J=14.2, 9.2, 1.7 Hz, 9-CH), 3.99 (1H, ddd, J=4.0, 3.0, 1.7 Hz, H-9), 4.03 and 4.04 (each 3H, s, OCH_3), 4.20 (1H, dd, J=2.0, 0.5 Hz, H-15), 4.30 (1H, d, J=2.3 Hz, H-7), 5.40 (1H, d, J=0.5 Hz, H-5), 6.58 (1H, dd, J=9.2, 4.0 Hz, NH). ^{13}C-NMR δ: 8.7 (q, CH_3), 8.9 (q, CH_3), 20.8 (q, $OCOCH_3$), 24.3 (q, $COCH_3$), 24.7 (t, C^{14}), 40.8 (t, 9-CH_2), 42.4 (q, NCH_3), 53.4 (d, C^{14a}), 54.5 (d, C^{15}), 55.4 (d, C^7), 56.5 (d, C^9), 61.0 (q, OCH_3), 61.1 (q, OCH_3),

61.2 (d, C^5), 61.6 (d, C^6), 115.9 (s, CN), 128.1 (s), 130.5 (s), 135.7 (s), 137.8 (s), 138.4 (s), 140.7 (s), 155.5 (s), 156.0 (s), 160.2 (s, CO), 169.9 (s, O<u>C</u>OCH$_3$), 180.6 (s), 182.4 (s), 184.9 (s), 185.2 (s), 196.8 (s, <u>C</u>OCH$_3$). MS *m/z* (relative intensity): no M^+, 562 (3), 520 (4), 462 (7), 257 (6), 243 (8), 235 (15), 220 (32), 219 (28), 218 (100), 43 (21). FAB-MS *m/z*: 621 ($M^+ + 1$).

Saframycin F (1f) A pale yellow solid; $[\alpha]_D$ +135.7° (c=0.6 in MeOH). IR $\nu_{max}^{CHCl_3}$: 3400, 1725, 1680, 1655, 1640, 1620 cm^{-1}. UV λ_{max} nm (log ε): 244 (4.02), 276 (4.07), 374 (3.61). ^{1}H-NMR δ: 1.54 (1H, ddd, J=18.2, 11.2, 2.6 Hz, H-14β), 1.97 (3H, s, 12-CH$_3$), 2.17 (3H, s, COCH$_3$), 2.25 (3H, s, 3-CH$_3$), 2.48 (3H, s, NCH$_3$), 3.07 (1H, dt, J=13.9, 3.3 Hz, 9-CH), 3.08 (1H, dd, J=18.2, 3.0 Hz, H-14α), 3.33 (1H, dt, J=11.2, 3.0 Hz, H-14a), 3.48 (1H, dd, J=2.7, 1.3 Hz, H-6), 3.71 (1H, ddd, J=13.9, 9.2, 1.7 Hz, 9-CH), 3.94 (3H, s, 2-OCH$_3$), 3.99 (1H, ddd, J=3.3, 2.6, 1.7 Hz, H-9), 4.03 (3H, s, 11-OCH$_3$), 4.27 (1H, s, H-7), 4.38 (1H, dd, J=3.0, 1.3 Hz, H-15), 5.74 (1H, s, OH), 6.14 (1H, dd, J=9.2, 3.3 Hz, NH), 11.53 (1H, s, OH). ^{13}C-NMR δ: 8.7 (q, CH$_3$), 9.0 (q, CH$_3$), 23.8 (t, C^{14}), 24.3 (q, CO<u>C</u>H$_3$), 40.8 (t, 9-CH$_2$), 42.6 (q, NCH$_3$), 53.4 (d, C^{14a}), 54.3 (d, C^7), 56.2 (d, C^9), 56.5 (d, C^{15}), 61.1 (q, OCH$_3$), 61.3 (q, OCH$_3$), 66.2 (d, C^6), 111.7 (s), 115.8 (s, CN), 117.0 (s), 119.3 (s), 127.9 (s), 135.5 (s), 139.8 (s), 141.7 (s), 154.0 (s), 155.3 (s), 156.1 (s), 160.2 (s, CO), 180.6 (s), 185.7 (s), 195.8 (s, <u>C</u>OCH$_3$), 198.8 (s, C^5). MS *m/z* (relative intensity): no M^+, 480 (5), 243 (8), 236 (53), 235 (100), 220 (9). FAB-MS *m/z* 579 ($M^+ + 1$).

5-*epi*-Saframycin G (8) A pale yellow amorphous powder; $[\alpha]_D$ +28.7° (c 0.87 in MeOH). IR $\nu_{max}^{CHCl_3}$: 3530, 3380, 1735, 1685, 1650, 1630, 1610 cm^{-1}. UV λ_{max} nm (log ε): 264 (4.16), 360 (2.89). ^{1}H-NMR δ: 1.14 (1H, ddd, J=17.5, 11.6, 2.8 Hz, H-14β), 1.90 and 2.03 (each 3H, s, quinone CH$_3$), 2.23 (3H, s, COCH$_3$), 2.48 (3H, s, NCH$_3$), 2.81 (1H, dd, J=17.5, 2.3 Hz, H-14α), 3.23 (1H, dt, J=11.6, 3.0 Hz, H-14a), 3.29 (1H, dt, J=14.2, 3.6 Hz, 9-CH), 3.48 (1H, ddd, J=7.3, 2.7, 1.0 Hz, H-6), 3.83 (1H, d, J=2.9 Hz, OH), 3.89 (1H, ddd, J=14.2, 8.6, 1.3 Hz, 9-CH), 3.98 (1H, ddd, J=3.6, 2.8, 2.6 Hz, H-9), 4.00 (1H, dd, J=3.0, 1.0 Hz, H-15), 4.02 and 4.06 (each 3H, s, OCH$_3$), 4.64 (1H, d, J=2.7 Hz, H-7), 5.09 (1H, dd, J=7.3, 2.9 Hz, H-5), 7.06 (1H, dd, J=8.6, 3.6 Hz, NH). ^{13}C-NMR δ: 8.5 (q, CH$_3$), 8.6 (q, CH$_3$), 24.4 (t, C^{14}), 24.8 (q, CO<u>C</u>H$_3$), 41.6 (t, 9-CH$_2$), 41.8 (q, NCH$_3$), 51.2 (d, C^7), 52.9 (d, C^{14a}), 55.7 (d, C^{15}), 56.2 (d, C^9), 58.1 (d, C^6), 60.5 (d, C^5), 61.1 (q, OCH$_3$), 61.1 (q, OCH$_3$), 117.2 (s, CN), 127.7 (s), 129.8 (s), 136.1 (s), 137.5 (s), 139.9 (s), 140.0 (s), 155.8 (s), 156.3 (s), 160.2 (s, CO), 180.8 (s), 182.7 (s), 185.5 (s), 188.7 (s), 196.9 (s, <u>C</u>OCH$_3$). MS *m/z* (relative intensity): 578 (M^+, 1), 478 (6), 453 (12), 259 (13), 257 (17), 243 (14), 236 (49), 235 (100), 234 (14), 220 (23), 218 (14), 206 (17). High-resolution MS Calcd for $C_{29}H_{30}N_4O_9$: 578.2013. Found: 578.2015.

Acetylation of Saframycin G (1g) Acetic anhydride (0.1 ml) was added to a solution of **1g** (21.1 mg, 0.0365 mmol) in dry pyridine (1.0 ml), and the reaction mixture was left to stand at room temperature for 22 h. After being diluted with water (5 ml), the mixture was extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue (21.6 mg) was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent: 1 : 1, hexane–ethyl acetate) to afford **7** (14.9 mg, 65.8%) as a pale yellow solid, which was identical with **7** prepared as above.

***N*-[(7-Cyano-6,7,9,10,13,14,14a,15-octahydro-1,4,5-trihydroxy-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-5β,6α,7α,9α,14aα,15α-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (3)** A solution of **1g** (72.6 mg, 0.126 mmol) in ethyl acetate (10 ml) was hydrogenated over 10% palladium on carbon (20 mg) at 1 atm for 20 min. The catalyst was removed by filtration and washed with ethyl acetate (60 ml). The combined filtrates were concentrated *in vacuo* to give the unstable bis-hydroquinone (**9**, 68.9 mg). ^{1}H-NMR δ: (2 : 1, $CDCl_3$–CD_3OD): 1.81 (1H, dd, H-14β), 2.18 (6H, s, 2 × ArCH$_3$), 2.21 (3H, s, COCH$_3$), 2.40 (3H, s, NCH$_3$), 3.11—3.16 (2H, m), 3.36 (2H, br), 3.58 (1H, m), 3.71 and 3.78 (each 3H, s, OCH$_3$), 4.08 (2H, br s), 4.24 (1H, br s), 4.53 (1H, s, H-5), 6.52 (1H, br d, NH). ^{13}C-NMR δ (2 : 1 $CDCl_3$–CD_3OD): 9.3 (q), 9.5 (q), 24.3 (q), 25.8 (t), 41.0 (t), 42.5 (q), 56.1 (d), 57.0 (d), 57.1 (d), 57.4 (d), 60.6 (q), 60.8 (q), 64.0 (d), 64.9 (d), 116.6 (s), 117.4 (s), 117.8 (s), 117.9 (s), 118.0 (s), 118.5 (s), 119.7 (s), 139.4 (s), 140.3 (s), 144.3 (s), 144.3 (s), 146.3 (s), 146.8 (s), 160.6 (s), 195.9 (s). This was used for the next step without further purification. Silica gel (200 mg) was added to a solution of **9** in ethyl acetate (15 ml), and the mixture was stirred in an oxygen atmosphere at room temperature for 24 h. The reaction mixture was filtered and then washed with ethyl acetate (60 ml). The combined filtrates were concentrated *in vacuo* to give a solid (67.0 mg), recrystallization of which from ethyl acetate afforded pure **3** (37.9 mg, 52.0%) as pale yellow needles, mp 170—172 °C (dec.). $[\alpha]_D$ −28.0° (c=1.0 in MeOH). IR ν_{max}^{KBr}: 3700—3050, 2250, 1735, 1695, 1665, 1645, 1630 cm^{-1}. UV λ_{max} nm (log ε): 270 (3.95), 294 (3.80), 360 (2.34). ^{1}H-NMR δ: 1.57 (1H, ddd, J=18.3, 11.5, 2.7 Hz, H-14β), 1.93 (3H, s, 12-CH$_3$), 2.22 (3H, s, 3-CH$_3$), 2.23 (3H, s, COCH$_3$), 2.49 (3H, s, NCH$_3$), 3.08 (1H, ddd, J=11.5, 2.9, 2.7 Hz, H-14a), 3.09 (1H, dd, J=18.3, 2.9 Hz, H-14α), 3.46—3.53 (3H, m, H-6 and 9-CH$_2$), 3.76 (3H, s, 2-OCH$_3$), 3.93 (1H, br s, H-9), 4.01 (3H, s, 11-OCH$_3$), 4.22 (1H, dd, J=2.7, 0.5 Hz, H-15), 4.23 (1H, d, J=2.4 Hz, H-7), 4.61 (1H, s, H-5), 5.50 (1H, s, OH), 6.30 (1H, dd, J=7.9, 4.3 Hz, NH), 6.63 (1H, s, OH). ^{13}C-NMR δ: 7.8 (q, 3-CH$_3$), 8.4 (q, 12-CH$_3$), 23.5 (q, COCH$_3$), 24.0 (t, C^{14}), 39.7 (t, 9-CH$_2$), 41.9 (q, NCH$_3$), 54.2 (d, C^{14a}), 55.8 (d, C^{15}), 56.0 (d, C^9), 56.0 (d, C^7), 59.8 (q, 2-OCH$_3$), 60.3 (q, 11-OCH$_3$), 63.1 (d, C^5), 63.7 (d, C^6), 114.4 (s), 116.7 (s, CN), 117.7 (s), 127.7 (s), 127.7 (s), 135.1 (s), 140.2 (s), 142.3 (s), 145.4 (s), 145.7 (s), 155.5 (s), 160.4 (s, CO), 180.7 (s, C^{10}), 185.6 (s, C^{13}), 194.9 (s, CO). MS *m/z* (relative intensity): no M^+, 553 (5), 480 (7), 464 (20), 462 (15), 455 (15), 453 (18), 317 (8), 260 (19), 259 (30), 257 (11), 245 (47), 244 (33), 243 (100), 236 (33), 235 (50), 234 (14), 230 (13), 229 (21), 221 (24), 220 (90), 219 (22), 218 (38), 217 (11), 216 (19), 206 (15), 205 (18), 204 (33), 203 (15), 202 (12), 201 (12), 190 (13), 176 (11), 43 (15). *Anal.* Calcd for $C_{29}H_{32}N_4O_9 \cdot 3/4H_2O$: C, 58.63; H, 5.68; N, 9.43. Found: C, 58.91; H, 5.82; N, 8.96.

Oxidation of 3 A solution of **3** (11.3 mg, 0.0195 mmol) in ethyl acetate (2 ml) and 5% $NaHCO_3$ was stirred in air at room temperature. After being diluted with water (5 ml), the mixture was extracted with ethyl acetate (5 ml × 3). The combined extracts were washed with water (10 ml), dried and concentrated *in vacuo*. The residue (9.7 mg, 68.1%) was identical with saframycin G **1g**.

Acetylation of 3 Acetic anhydride (0.2 ml) was added to a solution of **3** (19.2 mg, 0.0331 mmol) in dry pyridine (0.5 ml), and the mixture was left to stand at room temperature for 2 h. After being diluted with water (10 ml), the mixture was extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue (27.5 mg) was subjected to chromatography (silica gel, 6 g, 1 : 1, hexane–ethyl acetate) to give **10** (10.7 mg, 45.8%) as a pale yellow amorphous powder.

***N*-[(1,4,5-Triacetoxy-7-cyano-6,7,9,10,13,14,14a,15-octahydro-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-5β,6α,7α,9α,14aα,15α-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (10)** $[\alpha]_D$ −63.4° (c=1.0 in MeOH). IR $\nu_{max}^{CHCl_3}$: 3355, 1765, 1750, 1725, 1675, 1655, 1630, 1610 cm^{-1}. UV λ_{max} nm (log ε): 266 (3.94), 280 sh (3.85), 370 (2.70). ^{1}H-NMR δ: 1.34 (1H, ddd, J=17.2, 11.5, 2.6 Hz, H-14β), 1.91 (3H, s, 12-CH$_3$), 2.09 (3H, s, COCH$_3$), 2.12 (3H, s, OAc), 2.19 (3H, s, 3-CH$_3$), 2.26 (3H, s, OAc), 2.44 (3H, s, OAc), 2.51 (3H, s, NCH$_3$), 2.89 (1H, dd, J=17.2, 2.6 Hz, H-14α), 2.97 (1H, dt, J=13.9, 3.3 Hz, 9-CH), 3.12 (1H, dt, J=11.5, 2.6 Hz, H-14a), 3.33 (1H, br s, H-6), 3.74 (1H, ddd, J=13.2, 8.9, 1.7 Hz, 9-CH), 3.82 (3H, s, 2-OCH$_3$), 3.85 (1H, d, J=2.3 Hz, H-15), 3.93 (1H, br s, H-9), 4.08 (3H, s, 11-OCH$_3$), 4.16 (1H, d, J=2.0 Hz, H-7), 5.49 (1H, s, H-5), 6.95 (1H, dd, J=8.9, 3.3 Hz, NH). ^{13}C-NMR δ: 8.5 (q, 3-CH$_3$), 9.8 (q, 12-CH$_3$), 20.6 (q, OCO<u>C</u>H$_3$), 20.7 (q, OCO<u>C</u>H$_3$), 20.8 (q, OCO<u>C</u>H$_3$), 23.6 (t, C^{14}), 24.4 (q, CO<u>C</u>H$_3$), 42.0 (t, 9-CH$_2$), 42.6 (q, NCH$_3$), 54.2 (d, C^{14a}), 56.3 (d, C^7), 56.9 (d, C^9), 57.1 (d, C^{15}), 60.9 (q, 2-OCH$_3$), 61.0 (q, 11-OCH$_3$), 61.4 (d, C^6), 62.7 (d, C^5), 116.1 (s, CN), 122.0 (s), 123.0 (s), 126.3 (s), 127.0 (s), 136.2 (s), 139.4 (s), 140.1 (s), 145.4 (s), 151.2 (s), 156.6 (s), 161.3 (s, CO), 168.5 (s, O<u>C</u>OCH$_3$), 169.8 (s, O<u>C</u>OCH$_3$), 170.4 (s, O<u>C</u>OCH$_3$), 180.3 (s, C^{10}), 185.8 (s, C^{13}), 195.7 (s, CO). MS *m/z* (relative intensity): 706 (M^+, 3), 606 (53), 402 (26), 359 (7), 305 (19), 304 (100), 262 (33), 220 (19), 219 (10), 218 (24). High-resolution MS Calcd for $C_{35}H_{38}N_4O_{12}$: 706.2486. Found: 706.2504.

***N*-[(6,7,9,10,13,14,14a,15-Octahydro-1,4,5-trihydroxy-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-5β,6α,9α,14aα,15α-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (Saframycin E, 1e)** A solution of **11** (22.2 mg, 0.04 mmol) in ethyl acetate (5 ml) was hydrogenated over 10% palladium on carbon (10 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethyl acetate (60 ml). The combined filtrates were concentrated *in vacuo* to give a colorless solid (**12**, 28.1 mg), which was used for the next step without further purification. Silica gel (100 mg) was added to a solution of **12** in ethyl acetate (5 ml), and the mixture was stirred in an oxygen atmosphere at room temperature for 24 h. The reaction mixture was filtered and then washed with ethyl acetate (60 ml). The combined filtrates

were concentrated *in vacuo* to give a solid (26.7 mg), recrystallization of which from ethyl acetate–ether afforded pure **1e** (13.9 mg, 62.4%) as pale yellow needles, mp 175—178 °C (dec.). IR ν_{max}^{KBr}: 3700—3050, 1720, 1670, 1655, 1630, 1605 cm^{-1}. UV λ_{max} nm (log ε): 272 (4.01), 280sh (4.00), 368 (2.91). ^{1}H-NMR δ: 1.48 (1H, ddd, J=18.2, 10.6, 3.0 Hz, H-14β), 1.89 (3H, s, 12-CH$_3$), 2.13 (3H, s, 3-CH$_3$), 2.14 (3H, s, COCH$_3$), 2.65 (3H, s, NCH$_3$), 2.81 (1H, ddd, J=10.6, 2.6, 2.3 Hz, H-14a), 2.92 (1H, dd, J=18.2, 2.6 Hz, H-14α), 2.94 (1H, dd, J=10.9, 1.0 Hz, H-7), 3.05 (1H, dd, J=10.9, 1.2 Hz, H-7), 3.24 (1H, ddd, J=14.2, 4.3, 4.3 Hz, 9-CH), 3.25 (1H, br s, H-6), 3.57 (1H, ddd, J=14.2, 7.9, 1.0 Hz, 9-CH), 3.57 (1H, br s, H-9), 3.75 (3H, s, 2-OCH$_3$), 4.00 (3H, s, 11-OCH$_3$), 4.14 (1H, dd, J=2.3, 0.5 Hz, H-15), 4.63 (1H, s, H-5), 6.29 (1H, dd, J=7.9, 4.3 Hz, NH). ^{13}C-NMR δ: 8.6 (q, 3-CH$_3$), 9.0 (q, 12-CH$_3$), 24.3 (q, COCH$_3$), 24.7 (t, C^{14}), 40.7 (q, NCH$_3$), 40.8 (t, 9-CH$_2$), 52.3 (t, C^7), 52.9 (d, C^{14a}), 56.4 (d, C^{15}), 58.2 (d, C^9), 60.6 (q, 2-OCH$_3$), 61.0 (q, 11-OCH$_3$), 62.6 (d, C^6), 68.4 (d, C^5), 118.3 (s), 118.6 (s), 119.0 (s), 127.9 (s), 136.3 (s), 138.9 (s), 142.9 (s), 145.4 (s), 146.9 (s), 156.1 (s), 160.4 (s, CO), 181.4 (s, C^{10}), 186.1 (s, C^{13}), 195.6 (s, CO). FAB-MS m/z: 556 (M$^+$+1). *Anal.* Calcd for $C_{28}H_{33}N_3O_9 \cdot H_2O$: C, 58.63; H, 6.15; N, 7.33. Found: C, 58.19; H, 5.86; N, 7.14.

Acetylation of (±)-Saframycin E (1e) Acetic anhydride (0.2 ml) was added to a solution of **1e** (16.2 mg, 0.0292 mmol) in dry pyridine (0.5 ml), and the mixture was left to stand at room temperature for 2 h. After being diluted with water (20 ml), the mixture was extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give a residue (21.1 mg). Chromatography on a silica gel (8 g) column with dichloromethane–methanol (200 : 1) afforded **14** (2.2 mg, 11.2%) as a solid, whose spectra were identical with those of an authentic sample obtained from **11** (*vide infra*). Further elution with dichloromethane–methanol (100 : 1) afforded **13** (12.6 mg, 56.1%) as a solid.

***N*-[(1,4,5-Triacetoxy-6,7,9,10,13,14,14a,15-octahydro-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-5β,6α,9α,14aα,15α-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (13)** Pale yellow needles from ether, mp 228—231 °C (dec.). IR ν_{max}^{KBr}: 3670—3300, 3390, 1775, 1755, 1725, 1680, 1665, 1640, 1625 cm^{-1}. ($CHCl_3$): 3365, 1755, 1725, 1675, 1655, 1635, 1615 cm^{-1}. UV λ_{max} nm (log ε): 266 (3.93), 280sh (3.83), 370 (2.65). ^{1}H-NMR δ: 1.36 (1H, ddd, J=17.5, 11.2, 2.8 Hz, H-14β), 1.89 (3H, s, 12-CH$_3$), 2.08 (3H, s, COCH$_3$), 2.09 (3H, s, OAc), 2.18 (3H, s, 3-CH$_3$), 2.26 (3H, s, OAc), 2.43 (3H, s, OAc), 2.46 (3H, s, NCH$_3$), 2.66 (1H, dt, J=11.2, 2.6 Hz, H-14a), 2.79 (1H, dd, J=17.5, 2.6 Hz, H-14α), 2.81 (1H, dd, J=10.9, 2.6 Hz, H-7), 3.02 (1H, ddd, J=13.2, 4.0, 3.6 Hz, 9-CH), 3.07 (1H, br s, H-6), 3.13 (1H, dd, J=10.9, 2.0 Hz, H-7), 3.62 (1H, br s, H-9), 3.68 (1H, ddd, J=13.2, 9.2, 1.7 Hz, 9-CH), 3.77 (1H, dd, J=2.6, 0.5 Hz, H-15), 3.81 (3H, s, 2-OCH$_3$), 4.07 (3H, s, 11-OCH$_3$), 5.57 (1H, s, H-5), 6.96 (1H, dd, J=9.2, 4.0 Hz, NH). ^{13}C-NMR δ: 8.5 (q, 3-CH$_3$), 9.8 (q, 12-CH$_3$), 20.7 (q, OCOCH$_3$), 20.8 (q, OCOCH$_3$), 21.0 (q, OCOCH$_3$), 24.3 (t, C^{14}), 24.5 (q, COCH$_3$), 42.0 (t, 9-CH$_2$), 42.4 (q, NCH$_3$), 56.5 (t, C^7), 57.7 (d, C^{14a}), 58.0 (d, C^{15}), 58.3 (d, C^9), 59.5 (d, C^6), 60.9 (q, 2-OCH$_3$), 61.0 (q, 11-OCH$_3$), 64.6 (d, C^5), 123.4 (s), 124.2 (s), 125.5 (s), 126.7 (s), 137.3 (s), 140.0 (s), 140.2 (s), 145.4 (s), 150.8 (s), 156.9 (s), 161.3 (s, CO), 168.6 (s, OCOCH$_3$), 170.6 (s, OCOCH$_3$), 170.6 (s, OCOCH$_3$), 181.1 (s, C^{10}), 186.3 (s, C^{13}), 195.7 (s, CO). MS m/z (relative intensity): 681 (M$^+$, 8), 581 (100), 317 (11), 304 (47), 262 (24), 232 (14), 220 (14), 218 (20). *Anal.* Calcd for $C_{34}H_{39}N_3O_{12}$: C, 59.91; H, 5.77; N, 6.16. Found: C, 59.68; H, 5.87; N, 5.92.

Acetylation of 11 Acetic anhydride (0.2 ml) was added to a solution of **11** (11.0 mg, 0.02 mmol) in dry pyridine (0.5 ml), and the mixture was left to stand at room temperature for 2 h. After being diluted with water (10 ml), the mixture was extracted with chloroform (10 ml × 3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue (11.4 mg) was subjected to chromatography (silica gel, 5 g, 1 : 200, methanol–dichloromethane) to give **14** (9.3 mg, 78.6%) as a solid.

***N*-[(5-Acetoxy-1,5,6,7,9,10,13,14,14a,15-decahydro-2,11-dimethoxy-3,12,16-trimethyl-1,4,10,13-tetraoxo-5β,6α,9α,14aα,15α-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (14)** Pale yellow prisms from ethyl acetate–ether, mp 172—175 °C (dec.). IR ν_{max}^{KBr}: 3700—3200, 3460, 1740, 1700, 1670, 1645, 1625 cm^{-1}. UV λ_{max} nm (log ε): 266 (4.32), 370 (3.11). ^{1}H-NMR δ: 1.17 (1H, ddd, J=16.8, 10.6, 3.0 Hz, H-14β), 1.89 (3H, s, quinone CH$_3$), 2.03 (3H, s, quinone CH$_3$), 2.07 (3H, s, OAc), 2.22 (3H, s, COCH$_3$), 2.44 (3H, s, NCH$_3$), 2.70 (1H, dd, J=16.8, 2.6 Hz, H-14α), 2.72 (1H, ddd, J=10.6, 2.6, 2.0 Hz, H-14a), 2.76 (1H, dd, J=10.9, 3.0 Hz, H-7), 3.09 (1H, br s, H-6), 3.18—3.24 (2H, m, H-7 and 9-CH), 3.66 (1H, br s, H-9), 3.78 (1H, ddd, J=13.9, 10.2, 2.3 Hz, 9-CH), 4.01 (3H, s, OCH$_3$), 4.02 (3H, s, OCH$_3$), 4.15 (1H, dd, J=2.0, 0.5 Hz, H-15), 5.50 (1H, s, H-5), 6.72 (1H, dd, J=10.2, 4.0 Hz, NH). ^{13}C-NMR δ: 8.6 (q, CH$_3$), 8.8 (q, CH$_3$), 21.0 (q, OCOCH$_3$), 24.3 (q, COCH$_3$), 25.4 (t, C^{14}), 40.6 (t, 9-CH$_2$), 42.0 (q, NCH$_3$), 55.1 (t, C^7), 55.2 (d, C^{15}), 56.0 (d, C^{14a}), 57.9 (d, C^9), 59.6 (d, C^6), 60.9 (q, CH$_3$), 61.0 (q, OCH$_3$), 63.2 (d, C^5), 127.6 (s), 130.4 (s), 136.1 (s), 138.8 (s), 139.1 (s), 141.2 (s), 155.6 (s), 156.3 (s), 160.1 (s, CO), 169.9 (s, OCOCH$_3$), 181.2, 182.8, 185.4, and 185.6 (each s, quinone CO), 196.7 (s, CO). FAB-MS m/z: 596 (M$^+$+1). *Anal.* Calcd for $C_{30}H_{33}N_3O_{10}$: C, 60.49; H, 5.59; N, 7.06. Found: C, 60.48; H, 5.71; N, 6.89.

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References and Notes

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7) Saframycin A (**1a**) was kindly supplied by Professor Arai T., Department of Experimental Chemotherapy, Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University and it was further purified by preparative thin layer chromatography on silica gel plates (solvent 1 : 1, benzene–ethyl acetate) to afford pure **1a** as a pale yellow amorphous powder. This sample showed $[\alpha]_D$ −57.8° (c=1.0, MeOH) and its ^{1}H-NMR, ^{13}C-NMR, IR, UV, MS, and TLC data were identical with reported values, except for its optical rotation, $[\alpha]_D$ +18.2° (c=0.9, MeOH) see: Arai T., Takahashi K., Nakahara S., Kubo A., *Experientia*, **36**, 1205 (1980).
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10) In terms of mitomycin chemistry, the leuco form of mitomycin F reacts with silica gel in the presence of oxygen to afford 9-*epi*-mitomycin B. See: Egbertson M., Danishefsky S. J., Schulte G., *J. Org. Chem.*, **52**, 4424 (1987) and references cited therein.
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