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SYNTHESIS OF SAFRAMYCINS. IX. AN EFFICIENT SYNTHESIS OF THE ABC RING OF SAFRACINS.

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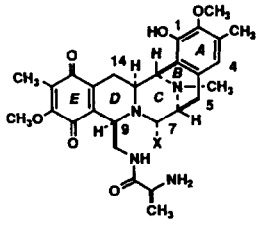
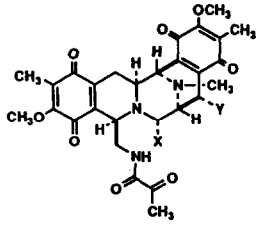
Abstract: 1,2,3,4,5,6-Hexahydro-10-hydroxy-1,5-imino-9-methoxy-3,8,11-trimethyl-3-benzazocine **3b** embodying all of the skeletal features of the ABC ring of safracins has been synthesized from compound **4a** *via* a direct regioselective bromination, followed by the sequence reduction, metal-halogen interchange, and reaction of the organometallic intermediate with nitrobenzene. And the conversion of **3b** to a quinone **21b** is also described.

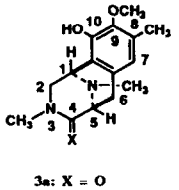
Sometime ago we became interested in safracins A **1a** and B **1b**, which were first isolated by the Yoshitomi Laboratories group from *Pseudomonas fluorescens* A2-2 in 1983,[1] as attractive synthetic targets because they were plausible and important biogenetic intermediates of saframycins **2a-c**.[2] We recently have reported preparation of the ABC ring model compound **3a** of safracins involving nitration of **4a**, followed by hydrogenation to an amine **5** and subsequent diazotization of the amine **5** in the usual manner which gave the phenol **3a**.[3] A more efficient synthetic method was required, however, because the overall yield of **3a** in this route was rather low and this sequence could not be applied for the total synthesis of **1a**. This paper describes an efficient synthesis of **3b** using aromatic hydroxylation of bromide **10b** and the conversion of **3b** to a quinone **21b** which embodies all of the skeletal features of the "right half" of saframycin B **2b**.[4]



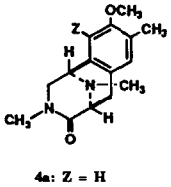
safracin A (1a): X = H
safracin B (1b): X = OH



saframycin A (2a): X = CN, Y = H
saframycin B (2b): X = Y = H
saframycin C (2c): X = H, Y = OCH_3



3a: X = O
3b: X = H_2

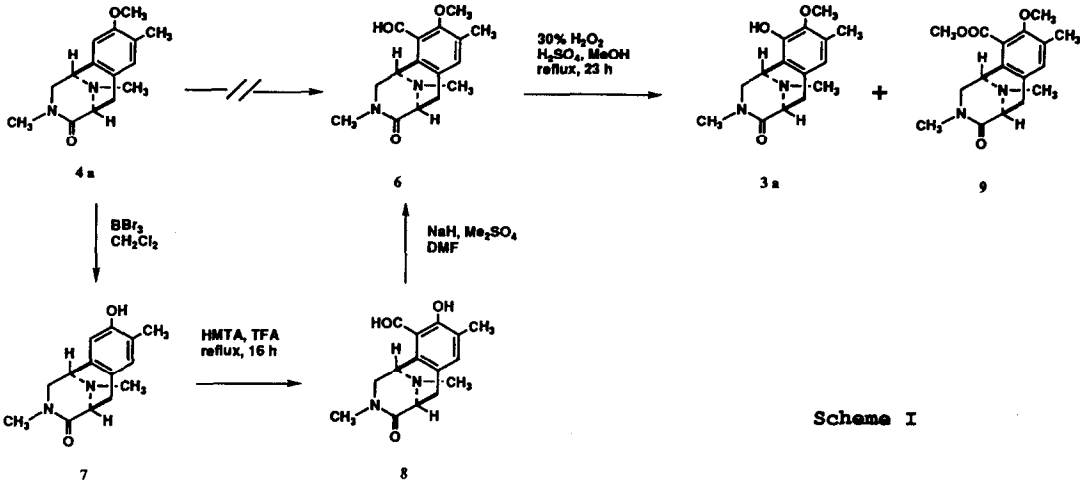


4a: Z = H
5: Z = NH_2

Chart I

Results and Discussion

The challenge addressed was the introduction of a hydroxy group into the C-10 position[5] of the hexahydro-1,5-imino-3-benzazocine skeleton by means of Baeyer-Villiger reaction (**Scheme I**). Numerous efforts for the direct formylation of **4a**[3] employing usual reagents (Cl_2CHOCH_3-$TiCl_4$, hexamethylenetetramine-trifluoroacetic acid, $POCl_3$-dimethylformamide (DMF)) were totally unsuccessful, only the starting material was recovered. Accordingly, the sequence of reactions was studied. Treatment of **4a** with boron tribromide at -20°C for 1 h afforded the phenol **7** in 75% yield.[3] This material was then converted into the aldehyde **8** according to the procedure of Pandit[6] in 97% yield. Methylation of **8** with dimethyl sulfate in the presence of sodium hydride in DMF at room temperature for 1 h afforded **6** in 81% yield. To prevent the formation of any unwanted *N*-oxides[7] during Baeyer-Villiger reaction, the Matsumoto protocol was used.[8] Treating **6** and 30% hydrogen peroxide in methanol with sulfuric acid under reflux for 23 h gave the phenol **3a** in 7% yield and the ester **9** in 59% yield.[9]

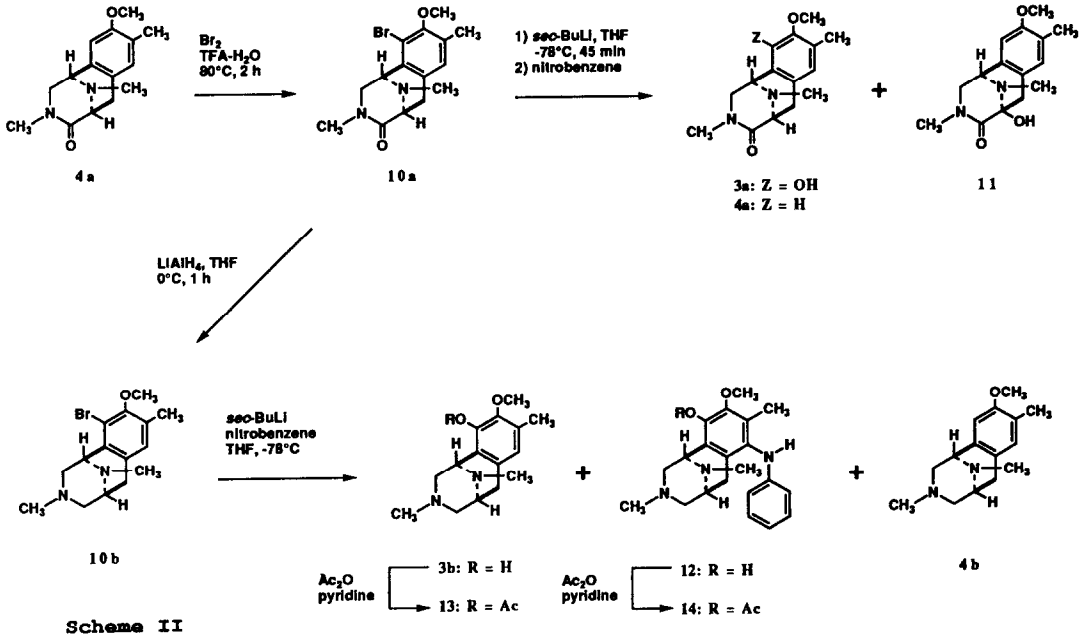


Scheme I

The yield of this process was disappointingly low because of the occurrence of unwanted hydrogen migration and proved exceedingly troublesome. This prompted us to examine the introduction of a hydroxy group which required a different approach (**Scheme II**).

Wiriyachitra and Cava[11] reported some isoquinoline alkaloids can be hydroxylated through the corresponding aryl bromides by a method based on a reaction first noted by Buck and Köbrich[10]. Treatment of **4a** with bromine in aqueous trifluoroacetic acid at 80°C for 2 h gave the bromide **10a** in 86% yield. We were surprised to find that treatment of **10a** with *sec*-BuLi in THF at -78°C followed by oxidation with nitrobenzene gave the expected phenol **3a** in only 5% yield. The major products **11** and **4a** were obtained in 21% and 19% yields, respectively. The structure of **11** was supported by the ^{13}C NMR spectrum, which showed a peak at δ 83.9 (singlet) assigned to the carbon at C-5 position. The ^1H NMR spectrum also showed two doublet signals at δ 2.86 and 3.00 assigned to the methylene proton at C-6 position. Obviously, an unfavorable lithium-hydrogen exchange at C-5 position had occurred. We assumed that the methine proton enjoyed resonance

stabilization from an adjacent amide carbonyl group. Furthermore, treatment of **4a** with *sec*-BuLi in THF at -78°C followed by oxidation with nitrobenzene afforded **11** in 53% yield.[12] The prohibition of undesired reaction would probably best be accomplished using the amine **10b** which was obtained by reduction of **10a** with lithium aluminum hydride in 77% yield. Treatment of **10b** with *sec*-BuLi in THF at -78°C followed by oxidation with nitrobenzene gave the phenol (**3b**) in 34% yield along with **4b** in 45% yield. After extensive investigation of the reaction conditions, the following procedure was found to be best in terms of product yield and reproducibility of the reaction: Treatment of **10b** with 15 equiv of nitrobenzene in THF at -78°C in the presence of 20 equiv of *sec*-BuLi provided the phenols **3b** and **12** in 53% and 3% yields, respectively (along with 24% of **4b**).[13]



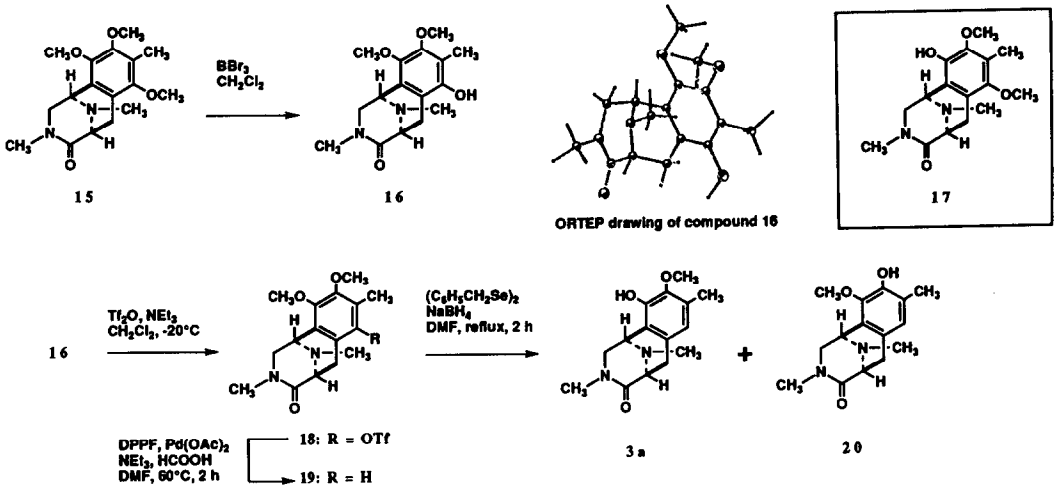
4a **10a** **3a: Z = OH** **4a: Z = H** **11**

10b **4b**

Scheme II

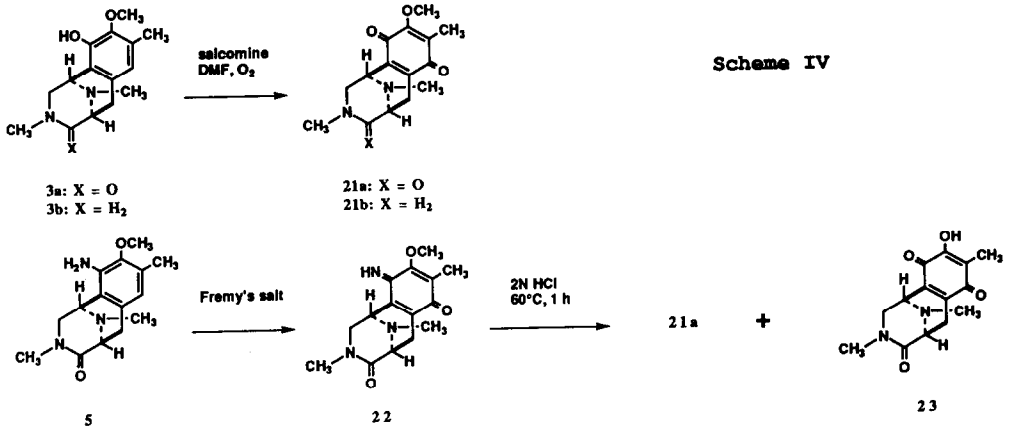
Next, we turned our attention to preparing the phenol **3a** from a polymethoxyarene **15** which was the key intermediate of the ABC ring model of saframycins.[4a] Previously we reported that the partial demethylation of **15** with boron tribromide in dichloromethane at -78°C for 1 h afforded the phenol **17** (**Scheme III**).[4b] The preferential cleavage of the more hindered ether group has already been documented for boron tribromide,[14] and it thus seemed reasonable that the structure of the phenol would be **17**. We are now convinced that the phenol has a structure of **16** and this was confirmed by X-ray crystallographic analysis. We then investigated the conversion of **16** into the phenol **3a**. Acylation of **16** with trifluoromethanesulfonic anhydride gave the triflate **18** in 87% yield. Treatment of **18** with formic acid, triethylamine, palladium acetate, and 1,1-bis(dipenylphosphino)ferrocene (DPPF) in DMF at 60°C for 2 h[15] afforded the deoxygated product **19** in 89% yield. The structure of **19** was supported by the ^{1}H NMR spectrum, and irradiation of the aromatic proton at δ 6.68 caused an nuclear Overhauser enhancement (NOE) of the methyl signal at δ 2.22 (4%). After numerous

efforts under various of conditions,[16] the *O*-demethylation of **19** with sodium benzylselenoate was achieved. Treatment of **19** with sodium benzylselenoate which was prepared *in situ* by the reaction of excess sodium borohydride and dibenzyl diselenide[18] in DMF under reflux for 2 h gave the phenols **3a** and **20** in 28% and 17% yields (38% yield of **19** was recovered). Interestingly, treatment of **19** with boron tribromide in dichloromethane at -78°C afforded the single product **20** in 30% yield. Thus, we efficiently synthesized the phenol **3a** from **15** which was the key intermediate of the ABC ring model of saframycins.



Scheme III

With the ABC ring models of safracins **3a** and **3b** in hand, we then turned our attention to the conversion of the phenols **3a,b** into the *p*-quinones **21a,b** as a model conversion of safracins to saframycins (**Scheme IV**). Treatment of **3a** with bis(salicylidene)ethylene-diiminocobalt (II) (salcomine)[19] in DMF at room temperature for 5 h afforded **21a** in 64% yield. Similarly, salcomine oxidation of **3b** provided **21b** in 55% yield. These quinones **21a,b** were identical in all respects with authentic samples.[4a]



Scheme IV

On the other hand, oxidation of the amine **5** with Fremy's salt gave the imine **22** in 97.5% yield. Treatment of **22** with aqueous hydrochloric acid gave the quinones **21a** and **23** in 50% and 40% yields, respectively.[20]

In summary, we have succeeded in synthesizing the ABC ring system of safracins from **4a** and **15**. The results described herein are being applied to the total synthesis of safracin A (**1a**) which is currently being undertaken in our laboratory.

Experimental Section

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. UV spectra were determined in methanol with a Hitachi 340 spectrometer. IR spectra were obtained with a Hitachi 260-10 spectrophotometer and ^{1}H-NMR spectra were recorded at 270MHz with a JEOL JNM-EX 270 spectrometer. ^{13}C-NMR were recorded at 67.5MHz (multiplicity determined from off-resonance decoupled or INEPT spectra). NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to internal $(CH_3)_4Si$ 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, and 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).

10-Formyl-1,2,3,4,5,6-hexahydro-9-hydroxy-1,5-imino-3,8,11-trimethyl-4-oxo-3-benzazocine (8). A suspension of the phenol (**7**[3]: 49.2 mg, 0.2 mmol) and hexamethylenetetramine (280.9 mg, 2 mmol) in trifluoroacetic acid (9 mL) was heated under reflux for 16 h. The reaction mixture was diluted with water (30 mL), made alkaline with powdered $NaHCO_3$, and extracted with dichloromethane (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (63.2 mg). Chromatography on a silica gel (10 g) column with dichloromethane-methanol (50:1 - 40:1) afforded **8** (53.2 mg, 97.1 %) as a solid, which was recrystallized from methanol to give pale yellow needles: mp 202-203°C; IR (KBr) 3600-3300, 1635 cm^{-1}; UV λ_{max} (log ε) 220 (4.16), 271 (3.96), 354 (3.55) nm; ^{1}H NMR δ 2.21 (3H, s, $ArCH_3$), 2.52 (3H, s, NCH_3), 2.77 (1H, d, *J* = 17.2 Hz, 6-Hβ), 2.87 (3H, s, NCH_3), 3.15 (1H, d, *J* = 11.6 Hz, 2-Hβ), 3.17 (1H, dd, *J* = 17.2, 6.3 Hz, 6-Hα), 3.66 (1H, d, *J* = 6.3 Hz, 5-H), 4.10 (1H, dd, *J* = 11.6, 5.0 Hz, 2-Hα), 4.56 (1H, d, *J* = 5.0 Hz, 1-H), 7.13 (1H, s, 7-H), 10.23 (1H, s, CHO), 12.26 (1H, s, OH); ^{13}C NMR δ 15.0 (q, $ArCH_3$), 27.0 (t, 6-C), 33.8 (q, NCH_3), 40.1 (q, NCH_3), 51.0 (d, 1-C), 55.1 (t, 2-C), 58.6 (d, 5-C), 115.4 (s), 123.2 (s), 126.9 (s), 134.3 (s), 139.2 (d, 7-C), 161.4 (s), 169.8 (s, CO), 192.9 (s, CHO); MS, *m/z* (relative intensity) 274 (M^+, 22), 203 (19), 202 (100). Anal. Calcd for $C_{15}H_{18}N_2O_3 \cdot 1/10H_2O$: C, 65.25; H, 6.64; N, 10.15. Found: C, 65.12; H, 6.65; N, 10.00.

10-Formyl-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (6). Sodium hydride (60% oil dispersion, washed with dry hexane three times, 28.8 mg, 1.2 mmol) was added to a stirred solution of **8** (164.4 mg, 0.6 mmol) in dry DMF (10 mL), and the resulting solution was stirred for 30 min at room temperature. Dimethyl sulfate (108.4 μL, 1.2 mmol) in dry DMF (2 mL) was added, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was diluted with ethyl acetate (20 mL), and extracted with 1N HCl (20

mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (145.3 mg). Chromatography on a silica gel (15 g) column with dichloromethane-methanol (50:1) afforded **6** (139.5 mg, 80.7 %) as a solid, which was recrystallized from ethyl acetate to give colorless needles: mp 154-156°C; IR (KBr) 1685, 1655 cm^{-1}; UV λ_{max} (log ε) 210 (4.38), 259 (3.96), 314 (3.51) nm; ^1H NMR δ 2.31 (3H, s, $ArCH_3$), 2.47 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.86 (1H, d, J = 17.2 Hz, 6-Hβ), 3.10 (1H, d, J = 12.5 Hz, 2-Hβ), 3.21 (1H, dd, J = 17.2, 6.9 Hz, 6-Hα), 3.61 (1H, d, J = 6.9 Hz, 5-H), 3.85 (3H, s, OCH_3), 4.05 (1H, dd, J = 12.5, 5.3 Hz, 2-Hα), 4.72 (1H, d, J = 5.3 Hz, 1-H), 7.22 (1H, s, 7-H), 10.51 (1H, s, CHO); ^{13}C NMR δ 15.4 (q, $ArCH_3$), 28.2 (t, 6-C), 33.9 (q, NCH_3), 40.2 (q, NCH_3), 52.5 (d, 1-C), 54.0 (t, 2-C), 58.4 (d, 5-C), 63.2 (q, OCH_3), 125.6 (s), 129.4 (s), 131.1 (s), 135.8 (s), 138.3 (d, 7-C), 163.0 (s), 170.0 (s, CO), 193.0 (s, CHO); MS, *m/z* (relative intensity) 288 (M^+, 18), 217 (22), 216 (100). Anal. Calcd for $C_{16}H_{20}N_2O_3 \cdot 1/10H_2O$: C, 66.23; H, 7.02; N, 9.66. Found: C, 66.18; H, 6.96; N, 9.62.

Baeyer-Villiger oxidation of 6. A solution of **6** (28.8 mg, 0.1 mmol), concentrated H_2SO_4 (7 μL) in methanol (1 mL) was cooled with ice-water, and 30% hydrogen peroxide (20 μL) was added dropwise over 5 min. The reaction mixture was heated under reflux for 23 h. The reaction mixture was diluted with water (10 mL), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo to give the residue (29.2 mg). Chromatography on a silica gel (8 g) column with dichloromethane-methanol (100:1 - 50:1) afforded **9** (18.6 mg, 58.5 %) as a solid, which was recrystallized from ether to give colorless needles. Further elution with dichloromethane-methanol (40:1) gave **3a** (1.8 mg, 6.5 %) as colorless prisms, mp 217-218.5°C, which were identical in all respects with the authentic sample described earlier.[3)]

1,2,3,4,5,6-Hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine-10-carboxylic Acid Methyl Ester (9): mp 132-133.5°C; IR (KBr) 1725, 1650 cm^{-1}; UV λ_{max} (log ε) 212 (4.28), 272 (3.18), 314 (3.30) nm; ^1H NMR δ 2.26 (3H, s, $ArCH_3$), 2.46 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 2.84 (1H, d, J = 17.2 Hz, 6-Hβ), 3.17 (1H, dd, J = 17.2, 6.6 Hz, 6-Hα), 3.28 (1H, dd, J = 14.5, 4.0 Hz, 2-Hβ), 3.62 (1H, d, J = 6.6 Hz, 5-H), 3.76 (3H, s, OCH_3), 3.86 (1H, d, J = 14.5 Hz, 2-Hα), 3.89 (1H, d, J = 4.0 Hz, 1-H), 3.94 (3H, s, OCH_3), 7.00 (1H, s, 7-H); ^{13}C NMR δ 15.8 (q, $ArCH_3$), 27.4 (t, 6-C), 33.8 (q, NCH_3), 40.0 (q, NCH_3), 52.4 (q, OCH_3), 53.5 (d, 1-C), 54.0 (t, 2-C), 58.9 (d, 5-C), 61.6 (q, OCH_3), 126.6 (s), 128.5 (s), 130.6 (s), 130.7 (s), 133.3 (d, 7-C), 154.3 (s), 168.5 (s, CO), 169.9 (s, NHCO); MS, *m/z* (relative intensity) 318 (M^+, 19), 247 (21), 246 (100). Anal. Calcd for $C_{17}H_{20}N_2O_4 \cdot 1/10H_2O$: C, 63.77; H, 6.99; N, 8.75. Found: C, 63.76; H, 6.92; N, 8.65.

10-Bromo-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (10a). A carbon tetrachloride solution of bromine (1.0 M, 4.5 mL, 4.5 mmol) was added to a stirred solution of **4a** (780 mg, 3 mmol) in trifluoroacetic acid (5 mL) and water (2 mL) at 80°C for 10 min, and the mixutre was heated at 80°C for 2 h. The reaction mixture was diluted with ether (30 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (997.9 mg). Chromatography on a silica gel (50 g) column with dichloromethane-methanol (100:3) afforded **10a** (874.5 mg, 85.9 %) as a solid, which was recrystallized from ethyl acetate-ether to give colorless prisms: mp 117.5-119°C; IR (KBr) 1650 cm^{-1}; UV λ_{max} (log ε) 220 (4.11), 273 (3.01), 282

(3.05) nm; ^{1}H NMR δ 2.30 (3H, s, $ArCH_3$), 2.48 (3H, s, NCH_3), 2.83 (1H, d, *J* = 17.2 Hz, 6-Hβ), 2.85 (3H, s, NCH_3), 3.19 (1H, dd, *J* = 17.2, 6.9 Hz, 6-Hα), 3.26 (1H, d, *J* = 11.9 Hz, 2-Hβ), 3.63 (1H, d, *J* = 6.9 Hz, 5-H), 3.79 (3H, s, OCH_3), 3.92 (1H, dd, *J* = 11.9, 5.0 Hz, 2-Hα), 4.20 (1H, d, *J* = 5.0 Hz, 1-H), 6.91 (1H, s, 7-H); ^{13}C NMR δ 16.4 (q, $ArCH_3$), 27.6 (t, 6-C), 33.9 (q, NCH_3), 40.0 (q, NCH_3), 52.7 (t, 2-C), 55.9 (d, 1-C), 59.0 (d, 5-C), 60.1 (q, OCH_3), 118.5 (s), 130.3 (s), 130.6 (d, 7-C), 131.9 (s), 132.3 (s), 154.0 (s), 170.0 (s, CO); MS, *m/z* (relative intensity) 340 (M^++2, 25), 338 (M^+, 27), 269 (18), 268 (99), 267 (20), 266 (100). Anal. Calcd for $C_{15}H_{19}N_2O_2Br$: C, 53.11; H, 5.65; N, 8.17. Found: C, 53.01; H, 5.59; N, 8.17.

Hydroxylation of 10a. A solution of the bromide (**10a**: 33.9 mg, 0.1 mmol) in dry THF (2.9 mL) was added to a solution of *sec*-BuLi (1.08 M, 463 μL, 0.5 mmol) in cyclohexane and dry THF (1.1 mL) and the mixture was allowed to stir for 45 min at -78°C. To this mixture at the same temperature, nitrobenzene (83.4 μl, 0.81 mmol) was added quickly. After being kept at the same temperature for 1 h, the solution was brought to room temperature over 1 h. The reaction mixture was diluted with ether (10 mL) and extracted with 1N HCl (10 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo to give the residue (28.1 mg). This material was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 15:1 dichloromethane-methanol) to afford the phenol (**3a**: 1.5 mg, 5.4 %), the alcohol (**11**: 5.9 mg, 21.3 %), and **4a** (4.8 mg, 18.5 %).

1,2,3,4,5,6-Hexahydro-5-hydroxy-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (11). A solution of **4a** (78.0 mg, 0.3 mmol) in dry THF (3 mL) was added to a solution of *sec*-BuLi (1.08 M, 1.39 mL, 1.5 mmol) in cyclohexane and dry THF (3 mL) and the mixture was stirred for 45 min at -78°C. To this mixture at the same temperature, nitrobenzene (309 μl, 3.0 mmol) was added quickly. After being kept at the same temperature for 1 h, the solution was brought to room temperature over 1 h. The reaction mixture was diluted with ether (20 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (67.1 mg). This material was subjected to chromatography (silica gel, 10 g; elution with 50:1 dichloromethane-methanol) to give the alcohol **11** (43.6 mg, 52.7 %) as a solid, which was recrystallized from methanol to give colorless needles: mp 258-260°C; IR (KBr) 3750-3350, 1670, 1630 cm^{-1}; UV λ_{max} (log ε) 220 (3.97), 230 (3.71), 278 (3.44), 286 (3.44) nm; ^{1}H NMR δ 2.18 (3H, s, $ArCH_3$), 2.45 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.86 (1H, d, *J* = 17.2 Hz, 6-Hβ), 3.00 (1H, d, *J* = 17.2 Hz, 6-Hα), 3.09 (1H, d, *J* = 10.9 Hz, 2-Hβ), 3.82 (3H, s, OCH_3), 3.99 (1H, dd, *J* = 10.9, 4.9 Hz, 2-Hα), 4.05 (1H, d, *J* = 4.9 Hz, 1-H), 6.56 (1H, s, 7-H), 6.84 (1H, s, 10-H); ^{13}C NMR δ 15.9 (q, $ArCH_3$), 32.4 (t, 6-C), 34.6 (q, NCH_3), 34.9 (q, NCH_3), 55.4 (q, OCH_3), 56.0 (t, 2-C), 59.7 (d, 1-C), 83.9 (s, 5-C), 108.1 (d, 10-C), 124.5 (s), 126.5 (s), 130.7 (d, 7-C), 130.8 (s), 156.7 (s), 170.9 (s, CO); MS, *m/z* (relative intensity) 276 (M^+, 15), 205 (25), 204 (100). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 64.99; H, 7.30; N, 10.16.

10-Bromo-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-3-benzazocine (10b). Lithium aluminum hydride (151.6 mg, 2.15 mmol) was added to a stirred solution of **10a** (729.4 mg, 2.15 mmol) in dry THF (40 mL) at 0°C, and then stirring was continued at 0°C for 1 h. After being quenched at 0°C by the addition of water, the mixture was filtered and the filter cake was carefully washed with

chloroform (100 mL). The combined filtrates were concentrated in vacuo. The residue was diluted with ethyl acetate (50 mL), and extracted with 1N HCl (30 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (717.1 mg). Chromatography on a silica gel (40 g) column with ethyl acetate-methanol (40:1) afforded **10b** (502.4 mg, 77.2 %) as a solid, which was recrystallized from ether to give colorless needles: mp 60-61°C; IR (KBr) 2990, 2970, 2940, 2905, 2890, 2840, 2790, 2730, 1655, 1470, 1450, 1440, 1375, 1365, 1310, 1285, 1235, 1200, 1175, 1130, 1080, 1055, 1025, 1000, 985, 950 cm^{-1}; UV λ_{max} (log ε) 220 (4.10), 240sh (3.83), 273 (3.04), 282 (3.10) nm; ^1H NMR δ 2.13 (3H, s, NCH_3), 2.28 (3H, s, $ArCH_3$), 2.30 (3H, s, NCH_3), 2.37 (1H, dd, *J* = 10.6, 3.0 Hz, 2-Hα), 2.45 (1H, dd, *J* = 10.6, 2.3 Hz, 4-Hα), 2.54 (1H, dd, *J* = 20.5, 3.6 Hz, 6-Hβ), 2.75 (1H, ddd, *J* = 10.6, 1.0, 1.0 Hz, 4-Hβ), 2.89 (1H, ddd, *J* = 10.6, 1.0, 1.0 Hz, 2-Hβ), 3.09 (1H, dd, *J* = 20.5, 7.6 Hz, 6-Hα), 3.09 (1H, dddd, *J* = 7.6, 3.6, 2.3, 1.0 Hz, 5-H), 3.79 (3H, s, OCH_3), 4.03 (1H, br s, 1-H), 6.87 (1H, s, 7-H); ^{13}C NMR δ 16.4 (q, $ArCH_3$), 26.5 (t, 6-C), 41.1 (q, NCH_3), 46.5 (q, NCH_3), 52.9 (d, 5-C), 58.5 (d, 1-C), 58.6 (t, 2-C), 60.0 (q, OCH_3), 62.6 (t, 4-C), 118.4 (s), 129.4 (d, 7-C), 130.4 (s), 132.7 (s), 133.7 (s), 152.9 (s); MS, *m/z* (relative intensity) 326 (M^++2, 5), 324 (M^+, 5), 269 (18), 268 (99), 267 (15), 266 (100). Anal. Calcd for $C_{15}H_{21}N_2OBr \cdot 1/5H_2O$: C, 54.79; H, 6.56; N, 8.52. Found: C, 54.80; H, 6.57; N, 8.41.

Hydroxylation of 10b. (**Method A**): A solution of the bromide (**10b**: 65.1 mg, 0.2 mmol) in dry THF (5 mL) was added to a solution of *sec*-BuLi (1.08 M, 1.93 mL, 2.08 mmol) in cyclohexane and dry THF (5 mL) and the mixture was allowed to stir for 45 min at -78°C. To this mixture at the same temperature, nitrobenzene (164.7 μl, 1.6 mmol) was added quickly. After being kept at the same temperature for 1 h, the solution was brought to room temperature over 1 h. The reaction mixture was diluted with ether (20 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo to give the residue (111.4 mg). Chromatography on a silica gel (10 g) column with dichloromethane-methanol (100:3) afforded **4b** (21.9 mg, 44.5 %) as a solid, which was recrystallized from ethyl acetate-ether to give colorless needles. Further elution with dichloromethane-methanol (20:1 - 10:1) gave **3b** (17.7 mg, 33.8 %) as a solid, which was recrystallized from methanol to give colorless prisms. (**Method B**). A solution of *sec*-BuLi (1.08 M, 3.70 mL, 4.0 mmol) in cyclohexane was added quickly to a stirred solution of **10b** (65.1 mg, 0.2 mmol) and nitrobenzene (309 μL, 3.0 mmol) in dry THF (10 mL) at -78°C. After being kept at the same temperature for 4 h, the solution was brought to -30°C for 30 min. The reaction mixture was diluted with ether (20 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo to give the residue (133.1 mg). Chromatography on a silica gel (10 g) column with dichloromethane-methanol (50:1) afforded the starting material **10b** (15.0 mg, 23.0 %) and dichromethne-methanol (100:3) afforded **4b** (12.0 mg, 24.4 %) as a solid, which was recrystallized from ethyl acetate-ether to give colorless needles. Further elution with dichloromethane-methanol (20:1 - 10:1) gave the residue (32.0 mg), which showed two major spots on TLC (Rf 0.11 and 0.09, 9:1 chloroform-methanol). This material was subjected to chromatography on a silica gel, 6 g) column with ethyl acetate-methanol (20:1) and afforded **12** (2.4 mg, 3.4 %), and with ethyl acetate-methanol (10:1 - 3:1) afforded **3b** (27.5 mg, 52.5 %) as a solid, which was recrystallized from acetone to give colorless prisms.

1,2,3,4,5,6-Hexahydro-10-hydroxy-1,5-imino-9-methoxy-3,8,11-trimethyl-3-benzazocine (3b). mp 184.5-185°C; IR (KBr) 3000, 2930, 2880, 2800, 2615, 1585, 1495, 1465, 1445, 1435, 1415, 1375, 1350, 1325, 1295, 1255, 1230, 1175, 1130, 1080, 1060, 1045, 1025, 1000, 982, 945, 860, 845, 835, 785, 745 cm^{-1}; UV λ_{max} (log ε) 222 (3.98), 272 (3.89), 280 (3.93) nm; ^1H NMR δ 2.14 (3H, s, NCH_3), 2.24 (3H, s, $ArCH_3$), 2.33 (3H, s, NCH_3), 2.41 (1H, dd, *J* = 10.6, 3.0 Hz, 2-Hα), 2.47 (1H, dd, *J* = 10.9, 2.9 Hz, 4-Hα), 2.54 (1H, d, *J* = 17.2 Hz, 6-Hβ), 2.76 (1H, d, *J* = 10.9 Hz, 4-Hβ), 2.86 (1H, ddd, *J* = 10.6, 2.0, 2.0 Hz, 2-Hβ), 3.07 (1H, dd, *J* = 17.2, 7.6 Hz, 6-Hα), 3.10 (1H, ddd, *J* = 7.6, 2.0, 1.0 Hz, 5-H), 3.76 (3H, s, OCH_3), 4.04 (1H, br s, 1-H), 6.47 (1H, s, 7-H); ^{13}C NMR δ 15.8 (q, $ArCH_3$), 26.4 (t, 6-C), 41.0 (q, NCH_3), 46.6 (q, NCH_3), 52.9 (d, 5-C), 53.0 (d, 1-C), 59.2 (t, 2-C), 60.7 (q, OCH_3), 62.7 (t, 4-C), 120.3 (s), 121.0 (d, 7-C), 128.0 (s), 131.6 (s), 142.8 (s), 145.4 (s); MS, *m/z* (relative intensity) 262 (M^+, 10), 205 (15), 204 (100), 189 (13), 173 (6). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.60; H, 8.70; N, 10.67.

1,2,3,4,5,6-Hexahydro-10-hydroxy-1,5-imino-9-methoxy-3,8,11-trimethyl-7-phenylamino-3-benzazocine (12). mp 212-214°C; IR (KBr) 3310, 2950, 2910, 2805, 2602, 1515, 1500, 1460, 1438, 1415, 1385, 1370, 1350, 1322, 1302, 1265, 1255, 1238, 1178, 1118, 1085, 1060, 1045, 1012, 998, 975, 950, 860, 790, 745 cm^{-1}; UV λ_{max} (log ε) 246 (4.10), 268sh (3.96), 302sh (3.40) nm; ^1H NMR δ 2.13 (3H, s, $ArCH_3$), 2.15 (3H, s, NCH_3), 2.30 (3H, s, NCH_3), 2.43 (1H, dd, *J* = 10.6, 3.0 Hz, 2-Hα), 2.44 (1H, dd, *J* = 10.9, 3.6 Hz, 4-Hα), 2.47 (1H, d, *J* = 18.1 Hz, 6-Hβ), 2.71 (1H, ddd, *J* = 10.9, 1.0, 1.0 Hz, 4-Hβ), 2.83 (1H, dd, *J* = 18.1, 7.6 Hz, 6-Hβ), 2.89 (1H, ddd, *J* = 10.6, 1.0, 1.0 Hz, 2-Hβ), 3.07 (1H, br d, 5-H), 3.78 (3H, s, OCH_3), 4.12 (1H, br s, 1-H), 5.02 (1H, br s, NH), 6.46 (2H, dd, *J* = 8.6, 1.0 Hz, ArH x 2), 6.71 (1H, t like, ArH), 7.13 (2H, dd, *J* = 8.6, 7.3 Hz, ArH x 2); ^{13}C NMR δ 11.4 (q, $ArCH_3$), 23.8 (t, 6-C), 41.0 (q, NCH_3), 46.5 (q, NCH_3), 52.7 (d, 5-C), 53.0 (d, 1-C), 59.1 (t, 2-C), 60.9 (q, OCH_3), 62.5 (t, 4-C), 112.6 (d), 117.6 (s), 120.5 (d), 127.7 (s), 128.8 (s), 129.4 (d), 131.0 (s), 143.2 (s), 144.2 (s), 146.9 (s); MS, *m/z* (relative intensity) 353 (M^+, 15), 296 (23), 295 (100), 280 (14). Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.36; H, 7.97; N, 11.64.

1,2,3,4,5,6-Hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-3-benzazocine (4b). A stirred solution of **4a** (260 mg, 1.0 mmol) in dry THF (30 mL) was cooled with ice-water, a THF solution of aluminum hydride (0.5 M, 12 mL, 6 mmol) was added dropwise over 10 min, and then stirring was continued at 0°C for 1 h. After being quenched by the addition of methanol, the reaction mixture was concentrated in vacuo. The residue (302.1 mg) was subjected to chromatography (silica gel, 16 g; elution with 100:3 - 20:1 dichloromethane-methanol) to give **4b** (211.5 mg, 86.0 %) as a solid, which was recrystallized from ethyl acetate-ether to give colorless prisms: mp 88-89.5°C; IR (KBr) 3010, 2970, 2940, 2900, 2830, 2790, 2760, 1615, 1505, 1455, 1415, 1375, 1360, 1350, 1330, 1310, 1295, 1275, 1260, 1230, 1215, 1170, 1150, 1105, 1080, 1065, 1050, 1035, 1010, 1000, 950, 920, 880, 855, 845, 820, 785, 760, 740 cm^{-1}; UV λ_{max} (log ε) 220 (3.94), 238sh (3.75), 282 (3.49), 288 (3.48) nm; ^1H NMR δ 2.13 (3H, s, NCH_3), 2.16 (3H, s, $ArCH_3$), 2.34 (3H, s, NCH_3), 2.44 (2H, dd, *J* = 10.6, 3.0 Hz, 2-Hα and 4-Hα), 2.54 (1H, d, *J* = 16.8 Hz, 6-Hβ), 2.75-2.81 (2H, m, 4-Hβ and 2-Hβ), 3.05 (1H, dd, *J* = 16.8, 7.6 Hz, 6-Hα), 3.09 (1H, br s, 5-H), 3.60 (1H, br s, 1-H), 3.79 (3H, s, OCH_3), 6.47 (1H, s, 7-H), 6.85 (1H, s, 10-H); ^{13}C NMR δ 16.0 (q, $ArCH_3$), 26.2 (t, 6-C), 41.2 (q, NCH_3), 46.6 (q, NCH_3), 53.3 (d, 5-C), 55.4 (q, OCH_3), 59.1 (d, 1-C), 61.5 (t, 2-C), 62.9 (t, 4-C), 108.6 (d, 10-C), 124.7 (s), 126.6 (s), 129.8 (d, 7-C), 134.0 (s), 155.7 (s); MS,

m/z (relative intensity) 246 (M^+, 10), 189 (15), 188 (100), 173 (7). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.94; H, 9.11; N, 11.35.

10-Acetoxy-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-3-benzazocine (13). Acetic anhydride (0.2 mL) was added to a solution of **3b** (34.7 mg, 0.132 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (5 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give the residue (28.2 mg). This material was subjected to chromatography on a silica gel (6 g) column with dichloromethane-methanol (100:1 - 50:1) to afford **13** (20.5 mg, 50.9 %) as a solid, which was recrystallized from ether-hexane to give colorless needles: mp 117-119°C; IR (KBr) 1765 cm^{-1}; UV λ_{max} (log ε) 220 (4.01), 270 (3.96), 278 (3.96) nm; ^1H NMR δ 2.13 (3H, s, NCH_3), 2.25 (3H, s, $ArCH_3$), 2.28 (3H, s, NCH_3), 2.33 (3H, s, $COCH_3$), 2.39 (1H, dd, *J* = 10.6, 3.0 Hz, 2-Hα), 2.45 (1H, dd, *J* = 10.6, 2.0 Hz, 4-Hα), 2.57 (1H, d, *J* = 16.8 Hz, 6-Hβ), 2.72 (1H, dd, *J* = 10.6, 2.0 Hz, 2-Hβ), 2.76 (1H, d, *J* = 10.6, Hz, 4-Hβ), 3.08 (1H, dd, *J* = 16.8, 7.6 Hz, 6-Hα), 3.11 (1H, br, 5-H), 3.70 (1H, br s, 1-H), 3.72 (3H, s, OCH_3), 6.82 (1H, s, 7-H); ^{13}C NMR δ 15.8 (q, $ArCH_3$), 20.5 (q, $COCH_3$), 26.1 (t, 6-C), 40.9 (q, NCH_3), 46.4 (q, NCH_3), 52.7 (d, 5-C), 53.7 (d, 1-C), 59.6 (t, 2-C), 60.4 (q, OCH_3), 62.6 (t, 4-C), 126.6 (s), 127.6 (d, 7-C), 129.9 (s), 131.3 (s), 141.3 (s), 147.6 (s), 169.1 (CO); MS, *m/z* (relative intensity) 304 (M^+, 13), 247 (20), 246 (100), 205 (10), 204 (68). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.85; H, 8.29; N, 9.09.

10-Acetoxy-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-7-phenylamino-3-benzazocine (14). Acetic anhydride (0.2 mL) was added to a solution of **12** (12.8 mg, 0.0363 mmol) in dry pyridine (0.5 mL), and the mixture was left to stand at room temperature for 1 h. After being diluted with water (5 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give the residue (19.2 mg). This material was subjected to chromatography on a silica gel (6 g) column with dichloromethane-methanol (100:1 - 50:1) to afford **14** (12.9 mg, 90.1 %) as a solid, which was recrystallized from ether-hexane to give colorless needles: mp 151.5-153°C; IR (KBr) 3380, 1762, 1605 cm^{-1}; UV λ_{max} (log ε) 241 (4.11), 276 (3.91) nm; ^1H NMR δ 2.13 (6H, s, NCH_3 and $ArCH_3$), 2.26 (3H, s, NCH_3), 2.36 (3H, s, $COCH_3$), 2.38-2.44 (2H, m, 4-Hα and 2-Hα), 2.47 (1H, d, *J* = 18.2 Hz, 6-Hβ), 2.69 (1H, ddd, *J* = 10.6, 1.0, 1.0 Hz, 2-Hβ), 2.73 (1H, ddd, *J* = 10.0, 1.0, 1.0 Hz, 4-Hβ), 2.84 (1H, dd, *J* = 18.2, 7.6 Hz, 6-Hβ), 3.07 (1H, br d, 5-H), 3.74 (1H, s like, 1-H), 3.74 (3H, s, OCH_3), 5.11 (1H, br s, NH), 6.52 (2H, d, *J* = 8.6, 1.0 Hz, ArH x 2), 6.71 (1H, t, *J* = 8.3 Hz, ArH), 7.16 (2H, t, *J* = 8.3 Hz, ArH x 2); ^{13}C NMR δ 11.5 (q, $ArCH_3$), 20.6 (q, $COCH_3$), 23.7 (t, 6-C), 40.9 (q, NCH_3), 46.3 (q, NCH_3), 52.6 (d, 5-C), 53.8 (d, 1-C), 59.5 (t, 2-C), 60.7 (q, OCH_3), 62.5 (t, 4-C), 113.2 (d), 118.2 (d), 127.0 (s), 128.8 (s), 129.3 (s), 130.2 (s), 134.9 (s), 139.7 (s), 145.9 (s), 148.2 (s), 169.2 (CO); MS, *m/z* (relative intensity) 395 (M^+, 15), 338 (25), 337 (100), 296 (11), 295 (53). Anal. Calcd for $C_{23}H_{29}N_3O_3 \cdot 1/5H_2O$: C, 69.22; H, 7.43; N, 10.53. Found: C, 69.39; H, 7.74; N, 10.23.

X-ray structure determination of 16. Crystals of **16** ($C_{16}H_{22}N_2O_4$)[4a] belong to triclinic space group $P\bar{1}$, with cell constants *a* = 8.6585 (179) Å, *b* = 13.1325 (211) Å, *c* = 7.5576 (116) Å, Z = 2, d_c = 1.314 cm^{-1}. X-ray intensities were measured at 296 K with an AFC-5 (Rikagu Denki) type diffractometer using graphite-monochromated Cu Kα radiation, ω–2θ scan mode, $3° \leq 2\theta \leq 120°$, number of reflexcions measured 2228, number of reflections with F (o) > 3 δ (Fo) 2138. The structure was solved by direct methods.

Refinements were done by a local block-diagonal version of UNICS III system (Open program Tokyo University). Hydrogen atoms were found from the difference in Fourier syntheses. The final *R* factor was 9.83 %. The drawing of the molecule was made by ORTEP.

1,2,3,4,5,6-Hexahydro-7-hydroxy-1,5-imino-9,10-dimethoxy-3,8,11-trimethyl-4-oxo-3-benzazocine Trifluoromethanesulfonate (18). Trifluoromethanesulfonic anhydride (53.2 μL, 32.0 mmol) was added to a stirred solution of **16** (54.4 mg, 0.18 mmol) and triethylamine (88.8 μL, 65.0 mmol) in dry dichloromethane (3 mL) at -20°C. After being kept at the same temperature for 30 min, the reaction mixture was poured into 5% $NaHCO_3$ and the phases were separated. The aqueous layer was extracted with dichloromethane (10 mL x 2). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (94.4 mg). Chromatography on a silica gel (10 g) column with dichloromethane-methanol (100:1 - 80:1) afforded **18** (67.7 mg, 87.0 %) as a solid, which was recrystallized from acetone to give colorless prisms: mp 138-140°C; IR (KBr) 1665 cm^{-1}; UV λ_{max} (log ε) 221 (4.38) nm; ^1H NMR δ 2.27 (3H, s, $ArCH_3$), 2.50 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.92 (1H, d, *J* = 17.8 Hz, 6-Hβ), 3.07 (1H, d, *J* = 11.9 Hz, 2-Hβ), 3.17 (1H, dd, *J* = 17.8, 6.6 Hz, 6-Hα), 3.68 (1H, d, *J* = 6.6 Hz, 5-H), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.96 (1H, dd, *J* = 11.9, 4.6 Hz, 2-Hα), 4.15 (1H, d, *J* = 4.6 Hz, 1-H); ^{13}C NMR δ 10.7 (q, $ArCH_3$), 23.5 (t, 6-C), 34.0 (q, NCH_3), 40.0 (q, NCH_3), 51.3 (d, 1-C), 53.4 (t, 2-C), 58.1 (d, 5-C), 60.3 (q, OCH_3), 60.4 (q, OCH_3), 123.3 (s), 126.5 (s), 141.0 (s), 149.5 (s), 149.9 (s), 169.4 (s, CO); MS, *m/z* (relative intensity) 438 (M^+, 18), 367 (21), 366 (56), 306 (22), 305 (100), 234 (25), 233 (41), 218 (35). Anal. Calcd for $C_{17}H_{21}N_2O_6F_3S$: C, 46.57; H, 4.83; N, 6.39. Found: C, 46.71; H, 4.85; N, 6.42.

1,2,3,4,5,6-Hexahydro-1,5-imino-9,10-dimethoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (19). Formic acid (71 μL, 0.64 mmol) was added to a mixture of **18** (68.6 mg, 0.16 mmol), triethylamine (130 μL, 0.96 mmol), palladium acetate (7.0 mg, 0.03 mmol), and 1,1-bis(dipenylphosphino)-ferrocene (DPPF: 35.0 mg, 0.064 mmol) in dry DMF (1.5 mL) at 0°C for 10 min. The reaction mixture was stirred for 1 h at room temperature, and then heated at 60°C for 2 h. The reaction mixture was poured onto benzene (20 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (84.0 mg). Chromatography on a silica gel (10 g) column with ethyl acetate-methanol (30:1 - 10:1) afforded **19** (40.2 mg, 89.3 %) as a solid, which was recrystallized from ethyl acetate to give colorless prisms: mp 102-104°C; IR (KBr) 1650 cm^{-1}; UV λ_{max} (log ε) 220 (4.32), 269 (3.88), 276 (3.85) nm; ^1H NMR δ 2.22 (3H, s, $ArCH_3$), 2.50 (3H, s, NCH_3), 2.81 (1H, d, *J* = 17.2 Hz, 6-Hβ), 2.85 (3H, s, NCH_3), 3.08 (1H, dd, *J* = 11.6, 1.0 Hz, 2-Hβ), 3.14 (1H, dd, *J* = 17.2, 6.9 Hz, 6-Hα), 3.61 (1H, d, *J* = 6.9 Hz, 5-H), 3.79 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.95 (1H, dd, *J* = 11.6, 4.9 Hz, 2-Hα), 4.13 (1H, d, *J* = 4.9 Hz, 1-H), 6.68 (1H, s, 7-H); ^{13}C NMR δ 15.8 (q, $ArCH_3$), 27.6 (t, 6-C), 34.0 (q, NCH_3), 40.1 (q, NCH_3), 51.2 (d, 1-C), 53.7 (t, 2-C), 59.2 (d, 5-C), 59.9 (q, OCH_3), 60.2 (q, OCH_3), 125.6 (d, 7-C), 126.0 (s), 128.4 (s), 131.5 (s), 149.1 (s), 149.6 (s), 170.2 (s, CO); MS, *m/z* (relative intensity) 290 (M^+, 27), 219 (21), 218 (100). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.54. Found: C, 66.02; H, 7.67; N, 9.54.

Partial Demethylation of 19. 1) **Using Boron Tribromide**: A dichloromethane solution of boron tribromide (1.0 M, 0.3 mL, 0.3 mmol) was added to a stirred solution of **19** (29.0 mg, 0.1 mmol) in dry dichloromethane (3 mL) at -78°C. After being kept at the same temperature for 2 h, and then at 0°C for 1 h, the

reaction mixture was poured into 5% $NaHCO_3$ (10 mL) and the phases were separated. The aqueous layer was extracted with dichloromethane (10 mL x 2). The combined extracts were washed with water, dried, and concentrated in vacuo to give the residue (16.8 mg). Chromatography on a silica gel (5 g) column with dichloromethane-methanol (50:1 - 30:1) afforded **20** (5.8 mg, 29.6 %) as a solid, which was recrystallized from acetone to give colorless prisms: mp 178-180°C; IR (KBr) 3600-3040, 1640, 1620 cm^{-1}; UV λ_{max} (log ε) 218 (4.39), 276 (4.17), 282 (4.18) nm; ^1H NMR δ 2.21 (3H, s, $ArCH_3$), 2.54 (3H, s, NCH_3), 2.80 (1H, d, *J* = 17.1 Hz, 6-Hβ), 2.83 (3H, s, NCH_3), 3.11 (1H, dd, *J* = 17.1, 6.6 Hz, 6-Hα), 3.12 (1H, d, *J* = 11.7 Hz, 2-Hβ), 3.64 (1H, d, *J* = 6.6 Hz, 5-H), 3.82 (3H, s, OCH_3), 3.98 (1H, dd, *J* = 11.7, 4.9 Hz, 2-Hα), 4.10 (1H, d, *J* = 4.9 Hz, 1-H), 5.45 (1H, br s, OH), 6.67 (1H, s, 7-H); ^{13}C NMR δ 15.6 (q, $ArCH_3$), 27.2 (t, 6-C), 34.0 (q, NCH_3), 40.0 (q, NCH_3), 51.4 (d, 1-C), 53.6 (t, 2-C), 59.2 (d, 5-C), 60.8 (q, OCH_3), 124.1 (s), 124.7 (s), 125.2 (s), 126.5 (d, 7-C), 143.8 (s), 145.5 (s), 169.8 (s, CO); MS, *m/z* (relative intensity) 276 (M^+, 29), 205 (20), 204 (100), 189 (24), high-resolution MS calcd for $C_{15}H_{20}N_2O_3$ 276.1473, found 276.1473. 2) **Using Sodium Benzylselenoate:** Sodium borohydride (20 mg, 0.5277 mmol) was added to a stirred solution of dibenzyl diselenide (11.0 mg, 0.068 mmol) in dry DMF (1 mL) at room temperature. After being kept at the same temperature for 15 min, a solution of **19** (29.0 mg, 0.1 mmol) in dry DMF (1 mL) was added quickly. The reaction mixture was heated under reflux for 2 h, and then concentrated in vacuo. The residue was diluted with benzene (20 mL), and extracted with 1N HCl (20 mL x 3). The acidic aqueous layer was made alkaline with NH_4OH and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated in vacuo to give the residue. This material was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent 5:4 dichloromethane-acetone) to afford **3a** (7.6 mg, 27.5 %), **20** (3.4 mg, 16.8 %), and **19** (11.1 mg, 38.3 % recovery).

1,2,3,4,5,6,7,10-Octahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4,7,10-trioxo-3-benzazocine (21a). 1) **Oxidation of the phenol (3a) with salcomine:** Bis(salicylidene)-ethylenediiminocobalt(II) (17.0 mg, 0.052 mmol) was added to a stirred solution of **3a** (27.4 mg, 0.0993 mmol) in dry DMF (3 mL). The dark suspension was stirred under an oxygen atmosphere for 5 h at room temperature. The mixture was filtered through cellulose powder and the filter cake was carefully washed with ethyl acetate. The combined filtrates were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (33.0 mg). The material was then subjected to chromatography on silica gel (8 g) with dichloromethane-methanol (50:1) to afford **21a** (18.4 mg, 63.9 %) as a solid. This material was recrystallized from ethyl acetate-ether to give pale yellow prisms: mp 150-152 °C, whose spectra were identical with those of the authentic sample described earlier.[4a] 2) **Oxidation of the amine (5) with Fremy's salts:** A solution of the amine (5[3]: 55.0 mg, 0.2 mmol) in methanol (0.5 mL) was added quickly to a stirred solution of potassium nitrosodisulfonate (223.6 mg, 0.5 mmol) and aqueous potassium dihydrogen phosphate (0.02 M, 7.5 mL). The mixture was stirred for 1 h, poured into water (10 mL), and extracted with chloroform (10 mL x 3). The combined extracts were washed with water, dried, and concentrated in vacuo to give the imine (**22**: 56.4 mg, 97.5 %) as a solid, which was used in the next step without further purification. An analytical sample was obtained by recrystallization from ethyl acetate: mp 171-173°C; IR (KBr) 3230, 1645, 1620 cm^{-1}; UV λ_{max} (log ε) 268 (4.22), 320 (3.78) nm; ^1H NMR δ 2.00 (3H, s, quinone CH_3), 2.48 (3H, s, NCH_3), 2.76 (1H, d, *J* = 20.1 Hz, 6-Hβ), 2.85 (1H, dd, *J* = 20.1, 4.0 Hz, 6-Hα), 2.89 (3H, s, NCH_3), 3.25 (1H, dd, *J* = 12.2, 1.0 Hz, 2-Hβ), 3.65 (1H, d, *J* = 4.0 Hz, 5-H), 3.86 (3H, s, OCH_3), 3.94 (1H, dd, *J* = 12.2, 5.3 Hz, 2-Hα),

4.34 (1H, d, J = 5.3 Hz, 1-H), 11.08 (1H, s, NH); MS, *m/z* (relative intensity) 289 (M^+, 100), 274 (30), 231 (20), 203 (86). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.07; H, 6.61; N, 14.52. Found: C, 62.07; H, 6.61; N, 14.38.

A solution of the crude **22** (56.4 mg, 0.195 mmol) in 2N HCl (4 mL) was heated at 60°C for 1 h. After being diluted with water (10 mL), the pH was brought to 8-9 with solid $NaHCO_3$ powder, and extracted with chloroform (20 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo to give the residue (35.6 mg). Chromatography on a silica gel (8 g) column with dichloromethane-methanol (100:1 - 80:1) afforded **21a** (29.2 mg, 50.3 %: 2 steps) as a solid, which was identical in all respects with **21a** prepared as above. The pH of the basic aqueous layer was brought to 5-6 with acetic acid, and extracted with chloroform (20 mL x 3). The combined extracts were washed with water, dried, and concentrated in vacuo to give **23** (22.2 mg, 40.2 %) as a solid, which was recrystallized from methanol to give pale yellow needles:

1,2,3,4,5,6,7,10-Octahydro-9-hydroxy-1,5-imino-3,8,11-trimethyl-4,7,10-trioxo-3-benzazocine (23). mp >270°C; IR (KBr) 3350-3050, 1660, 1640, 1625 cm^{-1}; UV λ_{max} (log ε) 268 (4.06), 440 (2.80) nm; ^1H NMR δ 1.95 (3H, s, quinone CH_3), 2.45 (3H, s, NCH_3), 2.79 (2H, d, J = 3.0 Hz, 6-Hα and 6-Hβ), 2.90 (3H, s, NCH_3), 3.04 (1H, d, J = 12.2 Hz, 2-Hβ), 3.65 (1H, td, J = 3.0, 1.0 Hz, 5-H), 3.91 (1H, dd, J = 12.2, 5.3 Hz, 2-Hα), 3.98 (1H, dd, J = 5.3, 1.0 Hz, 1-H); MS, *m/z* (relative intensity) 276 (M^+, 22), 217 (29), 205 (100), 204 (50), 177 (28), 176 (47). Anal. Calcd for $C_{14}H_{16}N_2O_4 \cdot 1/4MeOH$: C, 60.20; H, 6.03; N, 9.85. Found: C, 60.54; H, 6.02; N, 9.45.

1,2,3,4,5,6,7,10-Octahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-7,10-dioxo-3-benzazocine (21b). Bis(salicylidene)ethylenediiminocobalt(II) (27.0 mg, 0.083 mmol) was added to a stirred solution of **3b** (37.7 mg, 0.1439 mmol) in dry DMF (4 mL). The dark suspension was stirred under an oxygen atmosphere for 5 h at room temperature. The mixture was filtered through cellulose powder and the filter cake was carefully washed with ethyl acetate. The combined filtrates were washed with water (20 mL), dried, and concentrated in vacuo to give the residue (42.1 mg). This material was subjected to chromatography on a silica gel (8 g) with dichloromethane-methanol (50:1) to afford **21b** (21.8 mg, 54.9 %) as a solid. This material was recrystallized from ethyl acetate-ether to give pale yellow prisms: mp 106-107 °C, whose spectra were identical with those of the authentic sample described earlier.[4a]

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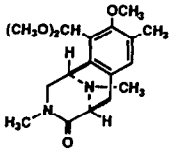

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