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# SYNTHESIS OF 1,2,3,4,5,6,7,10-OCTAHYDRO-1,5-IMINO-7,10-DIOXO-3-BENZAZOCINE-4-CARBONITRILE DERIVATIVE AND EVALUATION OF ANTITUMOR ACTIVITY RELATED TO SAFRAMYCIN AND RENIERAMYCIN ISOQUINOLINEQUINONES

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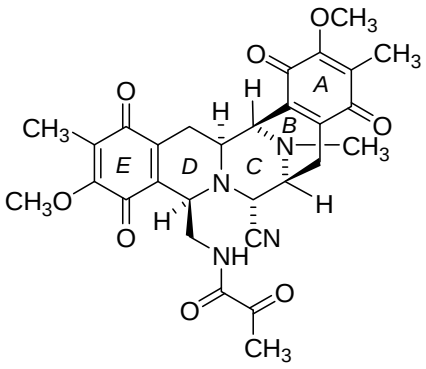
Abstract —3-Benzyl-1,2,3,4,5,6,7,10-octahydro-9-methoxy-8,11-dimethyl-7,10-dioxo-1,5-imino-3-benzazocine-4-carbonitrile (**4**) as a simple model of saframycin A and renieramycin M is prepared and its cytotoxicity tested against three human cancer cell lines.

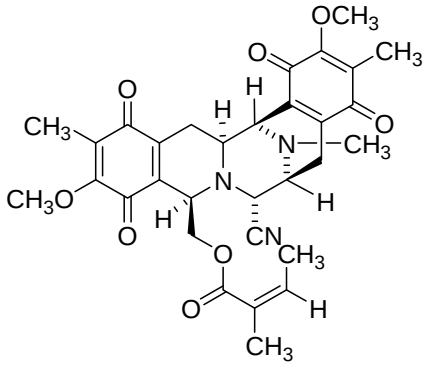
*This paper is dedicated to Professor Steven M. Weinreb (The Pennsylvania State University) on the occasion of his 65$^{th}$ birthday.*

Bistetrahydroisoquinoline natural products such as saframycin A and renieramycin M have generated wide chemical and biological interest because of their exceedingly potent antitumor activity.[1] In 1999, Corey, Schreiber, and co-workers reported that synthetic analog phthalascidin (**1**) displays *in vitro* antitumor activity comparable to ecteinascidin 743, which is a potent antitumor marine natural product currently undergoing phase II/III clinical trials.[2] Later, Myers prepared and evaluated more than 70 derivatives of saframycin A, and they discovered that QAD (**2**) is a more potent inhibitor of human cancer cell proliferation than saframycin A.[3] However, the long and tedious procedure for the total synthesis of these natural products and their analogues is not practical for the producing of amounts of these molecules.[4] Thus, we have been trying to simplify the chemical structures of these molecules while retaining their biological activity. In a previous paper, we reported the practical syntheses of the

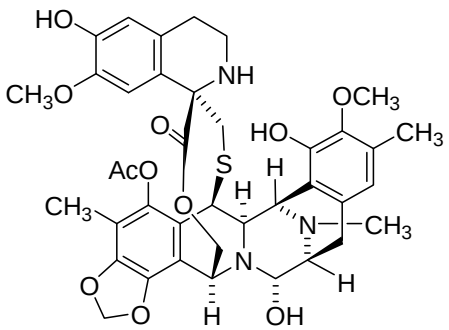
right-hand half modes of these natural products, and these compounds were tested for *in vitro* cytotoxicity against three human cancer cell lines (HCT116 colorectal cancer; QG56 lung cancer; DU145 prostate cancer). The presence of a cyano group at C-4 resulted in increased cytotoxicity and compound (**3**) showed the highest activity.[5] To extend the scope of the synthetic route to the simple model compounds, we selected the *N*-benzyl derivative of octahydro-7,10-dioxo-1,5-imino-3-benzazocine carbonitrile (**4**) *via* **10b** as a new target of the simplified model of saframycins and renieramycins. We report here the preparation of **4** along with its biological activity.



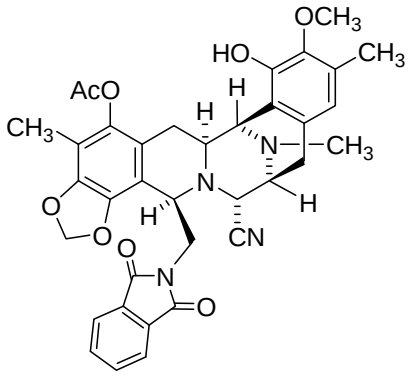
saframycin A



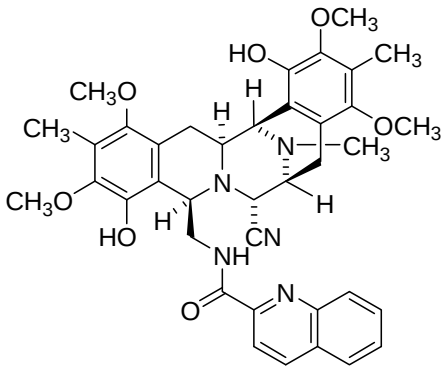
renieramycin M



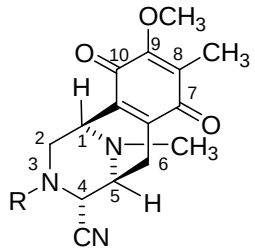
ecteinascidin 743



phthalascidin (**1**)



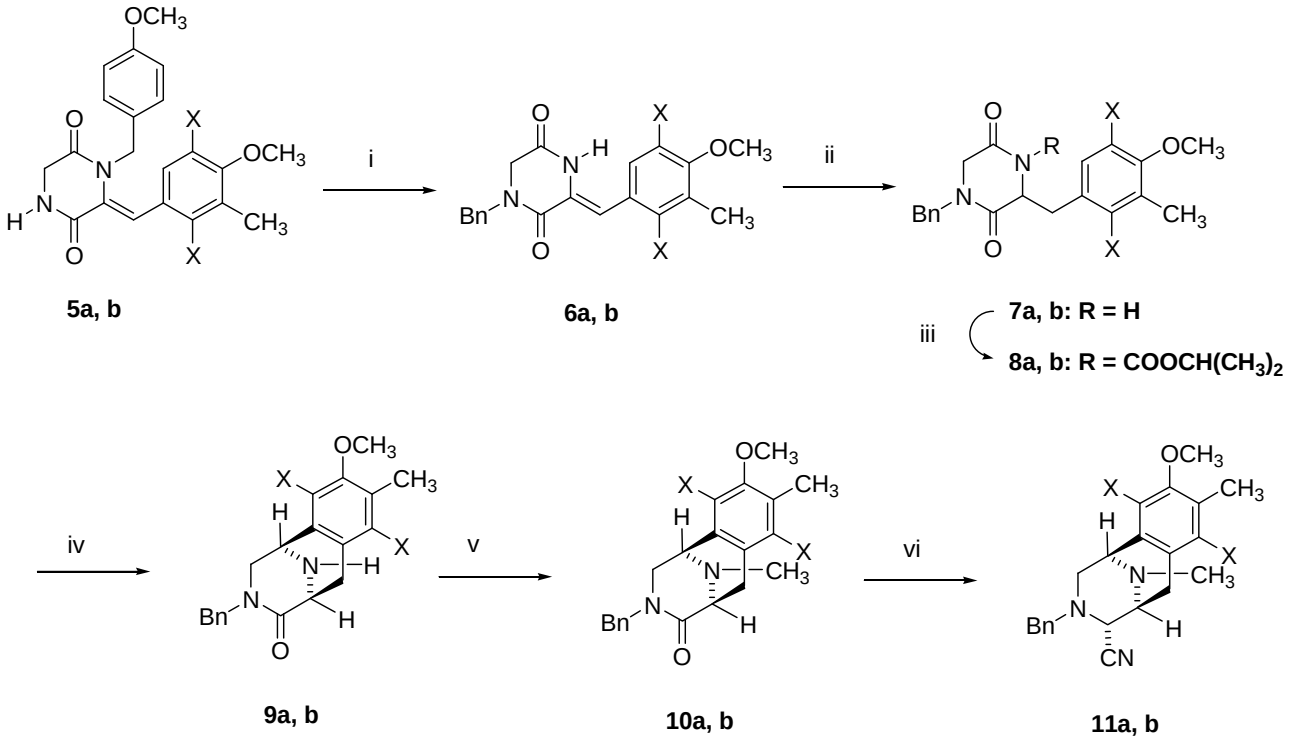
QAD (**2**)



**3**: R = $CH_3$
**4**: R = Bn

Before we prepared our target molecule (**4**), we tried to establish the practical synthesis of 3-benzyl-4-cyano-1,5-imino-3-benzazocine derivative (**11a**). Alkylation of **5a**[6] with benzyl bromide in the presence of sodium hydride afforded the benzyl derivative, the methoxybenzyl group of which was selectively removed under acidic conditions to generate compound (**6a**) in 74% overall yield. Catalytic

hydrogenation of **6a** with hydrogen over 20% palladium on carbon in ethanol gave **7a** in 70% yield. The introduction of an isopropioxycarbonyl group to the amide nitrogen of **7a** was achieved by adding isopropyl chloroformate and base to generate **8a** in 71% yield. Chemoselective reduction of **8a** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran (THF) at 0°C for 1.5 h afforded an unstable alcohol, and this alcohol was subjected to treatment $H_2SO_4$ and trifluoroacetic acid (TFA) at 25°C for 12 h to give **9a** in 82% yield. The reaction involved acid catalyzed ring closure followed by removal of the decarboxyl group. Methylation of **9a** with formaldehyde and formic acid at 70°C for 1 h gave **10a** in 98% yield. The lactam carbonyl of **10a** was reduced cleanly by treatment with 4 equivalents of $LiAlH_2(OC_2H_5)_2$[2b, 7] in THF at -6°C to give the corresponding cyclic aminal, which was subsequently treated with KCN to provide α-aminonitrile (**11a**) in 97% yield. An NOE enhancement between H-6β and H-4 of **11a** revealed the relative stereochemistry at C-4.



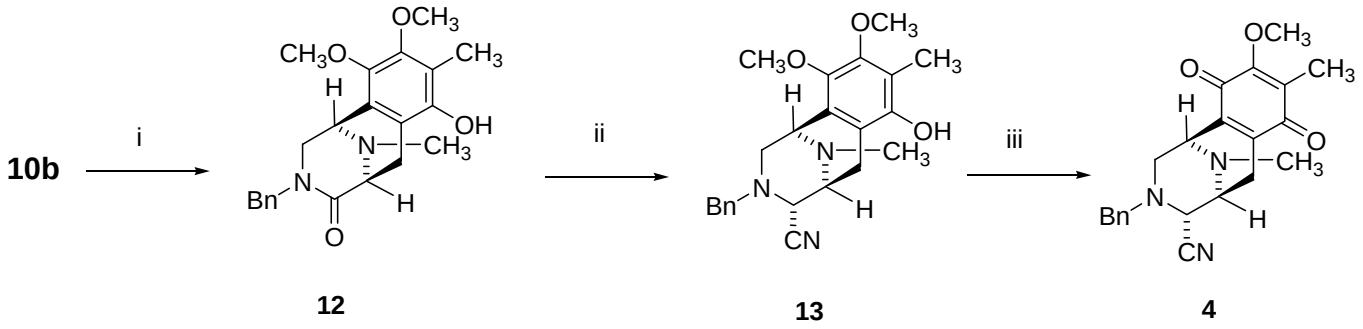

**9a, b** **10a, b** **11a, b**

**Scheme 1**: (a series: X = H; b series: X = $OCH_3$): i) NaH, BnBr, DMF; $H_2SO_4$-TFA; ii) $H_2$, 20% Pd/C, EtOH; iii) $ClCOOCH(CH_3)_2$, $NEt_3$, DMAP, $CH_2Cl_2$; iv) Li(*tert*-BuO)$_3$AlH, THF; $H_2SO_4$, TFA; v) HCHO/HCOOH, 70°C; vi) LiAl $H_2(OC_2H_5)_2$; THF; KCN.

We then investigated the conversion of **5b**[8] into **11b**. Benzylation of **5b**, followed by demethoxybenzylation afforded **6b** in 94% yield. Catalytic hydrogenation of **6b** generated **7b** in 91%

yield, and acylation of **7b** afforded **8b** in 88% yield. Cyclization of **8b** by hydride reduction, followed by $H_2SO_4$-TFA treatment gave **9b** in 74% overall yield. Reductive methylation of **9b** gave **10b** in 98% yield, and transformation of **10b** by partial reduction and KCN treatment furnished **11b** in 89% yield.

Conversion of the trimethoxyarene to the corresponding *p*-quinone was initiated by oxidative demethylation, but oxidative demethylation of **11b** under a variety of conditions was unsuccessful, and only polar polymeric material was generated. This problem was solved by the 3 step conversion from **10b**. Partial demethylation of **10b** with 2 equivalents of boron tribromide in dichloromethane at -78°C gave phenol (**12**) in 83% yield. The hydroxyl group of **12** was assigned to C-7 based upon the observation of an NOE enhancement of the hydroxyl proton (δ 6.61) when 8-$CH_3$ proton was irradiated. Conversion of **12** into α-aminonitrile (**13**) was achieved by hydride reduction, followed by KCN treatment in 73% overall yield. An NOE enhancement between H-6β (δ 2.29, d, $J$ = 17.0 Hz) and H-4 (3.70, d, $J$ = 2 Hz) revealed the relative stereochemistry at C-4 of **13**. Finally, oxidative demethylation of **13** with ceric ammonium nitrate (CAN) in aqueous acetonitrile at 0°C gave **4** in 74% yield.




**Scheme 2**: i) $BBr_3$, $CH_2Cl_2$, -78°C; ii) $LiAlH_2(OC_2H_5)_2$, THF; KCN; iii) CAN, $CH_3CN$-$H_2O$.

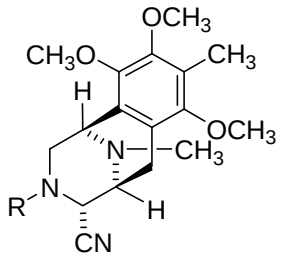
Three ABC ring analogues (**11b**, **13**, **4**) were tested for *in vitro* antitumor activities against HCT116, QG56, and DU145 cell lines.[9] One of the most important findings in this study is that the *N*-benzyl derivative of the simplified model compounds showed stronger cytotoxicity than the corresponding *N*-methyl compounds (**14**, **15**[10], **3**). For good antitumor activity, the quinone moiety at the A ring was also essential. However, it displayed much lower activity than the natural product. The diminishment of the left-hand half portion provides evidence that it might be not a prerequisite for antitumor activity.

In conclusion, we have synthesized a new class of simplified analogs of saframycin A and renieramycin M. Further evaluation of **4** and synthetic efforts aimed at other analogues related to **4** are under way.

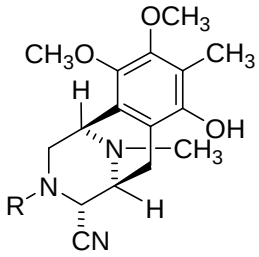
**Table**. *In Vitro* Cytotoxicity of ABC Ring Model Compounds against Several Cancer Cell Lines

| Compounds | HCT116 | QG56 | DU145 |
|---|---|---|---|
| **10b** | 0.39 | 0.55 | 0.38 |
| **13** | 0.15 | 0.27 | 0.15 |
| **4** | 0.017 | 0.027 | 0.023 |
| **14** | > 5 | > 5 | NT |
| **15** | > 5 | > 5 | NT |
| **3** | 0.084 | 0.24 | NT |
| Saframycin A | 0.0004 | 0.0055 | 0.0006 |
| Renieramycin M | 0.0079 | 0.019 | NT |

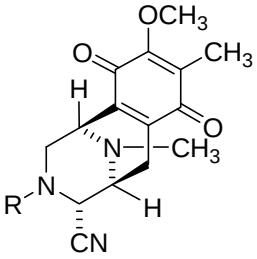
$IC_{50}$ values for HCT116 (colorectal cancer), QG56 (lung cancer) and DU145 (prostate cancer) are shown in μM. NT: not tested.



**11b: R = Bn**
**14: R = $CH_3$**



**13: R = Bn**
**15: R = $CH_3$**



**4: R = Bn**
**3: R = $CH_3$**

## EXPERIMENTAL SECTION

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 260-10 Infrared Fourier transform spectrophotometer. $^1$H NMR spectra were recorded at 300 MHz on a JEOL-AL-300 spectrometer and at 500 MHz on a JEOL-JNM-LA 500 FT NMR spectrometer. $^{13}$C-NMR was recorded at 125 MHz (multiplicity determined distortionless enhancement by polarization transfer (DEPT) spectra). NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in $\delta_H$ values relative to $(CH_3)_4Si$ as the intermal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.

(*Z*)-1-Benzyl-3-(4-methoxy-3-methylbenzylidene)piperazine-2,5-dione (**6a**). Sodium hydride (60% oil dispersion; washed with dry hexane three times, 576.0 mg, 24.0 mmol) was added to a stirred solution of

**5a** (8.16 g, 20.0 mmol) in dry DMF (80 mL) under ice-cooling, and stirring was continued for 30 min at 0°C. A solution of benzyl bromide (1.50 mL, 24.0 mmol) in dry DMF (20 mL) was added quickly, and the reaction mixture was stirred at 25°C for 16 h. The reaction mixture was poured into water (100 mL) and extracted with benzene (100 mL x 3). The combined extracts were washed with saturated aqueous NaCl solution (100 mL), dried, and concentrated *in vacuo* to give a residue that was used in the next step without further purification. Concentrated $H_2SO_4$ (3.5 mL) was added to a stirred solution of the above residue in TFA (70 mL), and the resulting solution was stirred for 15 h at 25°C. The reaction mixture was poured into water (200 mL) and extracted with chloroform (200 mL x 3). The combined extracts were washed with 2 N aqueous NaOH solution (100 mL), dried, and concentrated *in vacuo* to give a solid (13.8 g), the recrystallization of which from ethyl acetate-ether gave **6a** (5.16 g, 74%) as pale yellow prisms, mp 157-158.5°C. $\nu_{max}$ (KBr) 1675, 1620, 1605 $cm^{-1}$; $\delta_H$ 2.22 (3H, s, $ArCH_3$), 3.88 (3H, s, $OCH_3$), 4.04 (2H, s, 6-$H_2$), 4.71 (2H, s, $C_6H_5CH_2N$), 6.86 (1H, d, *J* = 8.3 Hz, 5'-H), 7.06 (1H, s, C-CH), 7.14 (1H, d, *J* = 2.0 Hz, 2'-H), 7.17 (1H, dd, *J* = 8.3, 2.0 Hz, 6'-H), 7.31-7.37 (5H, m, $C_6H_5$), 7.96 (1H, br s, NH); *m/z* (%) 336 ($M^+$, 100), 146 (9), 91 (16). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.40; H, 6.00; N, 8.31.

(*Z*)-1-Benzyl 3-(2,4,5-trimethoxy-3-methylbenzylidene)piperazine-2,5-dione (**6b**). This compound was prepared with the same two-step procedure as that shown above except that **5b** (4.26 g, 10.0 mmol) was used as the starting material. Chromatography of this residue (4.33 g) on a silica gel (100 g) column with benzene-ethyl acetate (5:1) gave **6b** (3.72 g, 94%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 3250, 1690, 1625 $cm^{-1}$; $\delta_H$ 2.23 (3H, s, $ArCH_3$), 3.63 (3H, s, $OCH_3$), 3.83 (6H, s, $OCH_3$ x 2), 4.03 (2H, s, 6-$H_2$), 4.72 (2H, s, $C_6H_5CH_2N$), 6.66 (1H, s, C-CH), 6.98 (1H, s, 6'-H), 7.30-7.41 (5H, m, $C_6H_5$), 9.34 (1H, br s, NH); *m/z* (%) 396 ($M^+$, 44), 366 (23), 365 (100), 274 (11), 91 (30). High-resolution EIMS Calcd for $C_{22}H_{24}N_2O_5$: 396.1685. Found: 396.1686.

1-Benzyl-3-(4-methoxy-3-methylbenzyl)piperazine-2,5-dione (**7a**). A solution of **6a** (6.96 g, 20.0 mmol) in ethanol (50 mL) was hydrogenated over 20% palladium on carbon (4.25 g) at 1 atom for 1.5 h. The catalyst was removed by filtration and washed with ethanol (200 mL) and chloroform (200 mL). The combined filtrates were evaporated and the residue was diluted with water (100 mL) and extracted with chloroform (200 mL x 3). The combined extracts were washed with 5% $NaHCO_3$ solution, dried, and concentrated *in vacuo* to give a solid (7.12 g), the recrystallization of which from acetone give **7a** (4.92 g, 70%) as colorless prisms, mp 170-170.5°C. $\nu_{max}$ (KBr) 3260. 1665, 1620 $cm^{-1}$; $\delta_H$ 2.16 (3H, s, $ArCH_3$), 3.03 (1H, dd, *J* = 13.6, 6.4 Hz, 3-CH), 3.10 (1H, d, *J* = 17.4 Hz, 6-H), 3.12 (1H, dd, *J* = 13.6, 4.2 Hz,

3-CH), 3.56 (1H, d, *J* = 17.4 Hz, 6-H), 3.78 (3H, s, $OCH_3$), 4.28 (1H, m, 3-H), 4.46 (1H, d, *J* = 14.5 Hz, $C_6H_5CHN$), 4.53 (1H, d, *J* = 14.5 Hz, $C_6H_5CHN$), 6.23 (1H, br s, NH), 6.63 (1H, d, *J* = 8.1 Hz, 5'-H), 6.92 (1H, dd, *J* = 8.1, 2.2 Hz, 6'-H), 6.94 (1H, d, *J* = 2.2 Hz, 2'-H), 7.16-7.19 (2H, m), 7.29-7.32 (3H, m); *m/z* (%) 338 ($M^+$, 13), 136 (10), 135 (100), 91 (9). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.97; H; 6.51, N, 8.03.

1-Benzyl-3-(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione (**7b**). This compound was prepared with the same procedure as that described above, but using **6b** (3.16 g, 8.0 mmol) and 20% palladium on carbon (2.0 g) in ethanol (50 mL). Chromatography of the residue (3.22 g) on a silica gel (90 g) column with dichloromethane-methanol (100:1) gave **7b** (2.91 g, 91%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 3384, 1674 $cm^{-1}$; $\delta_H$ 2.21 (3H, s, $ArCH_3$), 3.01 (1H, dd, *J* = 13.8, 8.1 Hz, 3-CH), 3.39 (1H, dd, *J* = 13.9, 4.0 Hz, 3-CH), 3.53 (1H, d, *J* = 17.5 Hz, 6-H), 3.69 (3H, s, $OCH_3$), 3.70 (1H, d, *J* = 17.5 Hz, 6-H), 3.79 (6H, s, $OCH_3$ x 2), 4.35 (1H, m, 3-H), 4.47 (1H, d, *J* = 14.5 Hz, $C_6H_5CHN$), 4.68 (1H, d, *J* = 14.5 Hz, $C_6H_5CHN$), 6.36 (1H, br s, NH), 6.60 (1H, s, 6'-H), 7.20-7.26 (2H, m), 7.29-735 (3H, m); *m/z* (%) 398 ($M^+$, 24), 196 (12), 195 (100), 91 (10). High-resolution EIMS Calcd for $C_{22}H_{26}N_2O_5$: 398.1842. Found: 398.1838.

1-Benzyl-4-isopropyloxycarbonyl-3-(4-methoxy-3-methylbenzyl)piperazine-2,5-dione (**8a**). A solution of **7a** (3.15 g, 9.0 mmol), triethylamine (5.0 mL, 18.0 mmol), and DMAP (4.40 g, 18.0 mmol) in dry dichloromethane (90 mL) was cooled with ice-water, and isopropyl chloroformate (5.4 mL, 36.0 mmol) was added dropwise over 15 min. This mixture was stirred at 25°C for 3 h. The organic layer was washed with 1 N HCl (200 mL) and then with 5% aqueous $NaHCO_3$ solution (200 mL), dried, and concentrated *in vacuo* to give a solid (4.13 g). The recrystallization of which from acetone gave **8a** (2.77 g, 71%) as colorless prisms, mp 113-114°C. $\nu_{max}$ (KBr) 1740, 1720, 1645, 1260 $cm^{-1}$; $\delta_H$ 1.33 (3H, d, *J* = 6.2 Hz, $OCHCH_3$), 1.36 (3H, d, *J* = 6.2 Hz, $OCHCH_3$), 2.06 (3H, s, $ArCH_3$), 2.28 (1H, d, *J* = 18.2 Hz, 6-H), 3.13 (1H, dd, *J* = 14.0, 3.8 Hz, 3-CH), 3.25 (1H, dd, *J* = 14.0, 5.0 Hz, 3-CH), 3.44 (1H, d, *J* = 18.2 Hz, 6-H), 3.71 (3H, s, $OCH_3$), 4.30 (1H, d, *J* = 14.3 Hz, $C_6H_5CHN$), 4.44 (1H, d, *J* = 14.3 Hz, $C_6H_5CHN$), 5.02 (1H,dd, *J* = 4.9, 3.8 Hz, 3-H), 5.13 (1H, sept, *J* = 6.2 Hz, $OCHCH_3$), 6.43 (1H, d, *J* = 8.3 Hz, 5'-H), 6.73 (1H, dd, *J* = 8.3, 2.1 Hz, 6'-H), 6.73 (1H, d, *J* = 2.1 Hz, 2'-H), 7.16-7.20 (2H, m), 7.28-7.35 (3H, m); *m/z* (%) 424 ($M^+$, 23), 135 (100), 91 (9). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.66; H, 6.67; N, 6.48.

1-Benzyl-4-isopropyloxycarbonyl-3-(2,4,5-trimethoxy-3-methylbenzyl)piperazine-2,5-dione (**8b**). This compound was prepared with the same procedure that as described above, but using **7b** (2.59 g, 6.5

mmol), triethylamine (1.8 mL, 13.0 mmol), DMAP (1.59 g, 13.0 mmol), and isopropyl chloroformate (2.94 mL, 26.0 mmol) in dichloromethane (70 mL). Chromatography of the residue (3.88 g) on a silica gel (80 g) column with hexane-ethyl acetate (1:1) gave **8b** (2.75 g, 88%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 1772, 1720, 1662, 1244 $cm^{-1}$; $\delta_H$ 1.31 (3H, d, *J* = 6.3 Hz, OCHC*H*$_3$), 1.34 (3H, d, *J* = 6.3 Hz, OCHC*H*$_3$), 2.15 (3H, s, $ArCH_3$), 2.70 (1H, d, *J* = 18.2 Hz, 6-H), 3.15 (1H, dd, *J* = 13.8, 4.6 Hz, 3-CH), 3.43 (1H, dd, *J* = 13.8, 5.5 Hz, 3-CH), 3.49 (1H, d, *J* = 18.2 Hz, 6-H), 3.61 (3H, s, $OCH_3$), 3.75 (3H, s, $OCH_3$), 3.76 (3H, s, $OCH_3$), 3.98 (1H, d, *J* = 14.4 Hz, $C_6H_5CHN$), 4.86 (1H, d, *J* = 14.4 Hz, $C_6H_5CHN$), 5.05 (1H, sept, *J* = 6.2 Hz, OC*H*$CH_3$), 5.11 (1H,dd, *J* = 5.5, 4.6 Hz, 3-H), 6.46 (1H, s, 6'-H), 7.15-7.18 (2H, m), 7.28-7.31 (3H, m); *m/z* (%) 484 ($M^+$, 36), 196 (12), 195 (100), 91 (8). High-resolution EIMS Calcd for $C_{26}H_{32}N_2O_7$: 484.2210. Found: 484.2211.

3-Benzyl-1,2,3,4,5,6-hexahydro-9-methoxy-8-methyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (**9a**). A solution of **8a** (872.0 mg, 2.0 mmol) in dry THF (30 mL) was cooled in ice-water, and lithium tri-*tert*-butoxyaluminum hydride (2.03 g, 8.0 mmol) was added to it over 5 min. The reaction mixture was stirred for 1.5 h at 0°C, quenched by the addition of water (2 mL), and filtrated through a Celite pad. The filtrate was concentrated *in vacuo* to obtain the crude product (1.15 g) that was used in the next step without further purification. Concentrated $H_2SO_4$ (1 mL) was added to a stirred solution of the above residue in TFA (20 mL), and the mixture was stirred for 12 h at 25°C. The reaction mixture was poured into water (400 mL), made alkaline with $NH_4OH$, and extracted with chloroform (400 mL x 3). The combined extracts were washed with water (400 mL), dried, and concentrated in vacuo to give a solid, the recrystallization of which from ethyl acetate afforded **9a** (546.0 mg, 82%) as colorless prisms, mp 162-163°C. $\nu_{max}$ (KBr) 3350, 1650 $cm^{-1}$; $\delta_H$ 1.90 (1H, s, NH), 2.21 (3H, s, $ArCH_3$), 3.08 (2H, s, 6-$H_2$), 3.10 (1H, dd, *J* = 11.5, 1.4 Hz, 2-Hβ), 3.66 (3H, s, $OCH_3$), 3.76 (1H, dd, *J* = 11.5, 4.2 Hz, 2-Hα), 4.07 (1H, dd, *J* = 4.2, 1.4 Hz, 1-H), 4.19 (1H, d, *J* = 3.8 Hz, 5-H), 4.24 (1H, d, *J* = 15.1 Hz, $C_6H_5CHN$), 4.84 (1H, d, *J* = 15.1 Hz, $C_6H_5CHN$), 6.33 (1H, s, 10-H), 6.72 (2H, d, *J* = 6.6 Hz), 6.92 (1H, s, 7-H), 7.04-7.16 (3H, m); *m/z* (%) 322 ($M^+$, 32), 175 (24), 174 (100), 91 (9). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.34; H, 6.93; N, 8.50.

3-Benzyl-1,2,3,4,5,6-hexahydro-7,9,10-trimethoxy-8-methyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (**9b**). This compound was prepared with the same two step procedure as that described above except that **8b** (1.93 g, 4.0 mmol) was used as the starting material. Recrystallization of the residue (2.03 g) from ethyl acetate-ether gave **9b** (1.13 g, 74%) as colorless prisms, mp 162-163.5°C. $\nu_{max}$ (KBr) 3345, 1665 $cm^{-1}$; $\delta_H$ 1.98 (1H, s, NH), 2.22 (3H, s, $ArCH_3$), 2.90 (1H, dd, *J* = 17.3, 6.3 Hz, 6-Hα), 3.11 (1H, dd, *J* =

11.8, 1.3 Hz, 2-Hβ), 3.23 (1H, dd, *J* = 17.3, 1.5 Hz, 6-Hβ), 3.61 (3H, s, $OCH_3$), 3.64 (3H, s, $OCH_3$), 3.70 (3H, s, $OCH_3$), 3.74 (1H, d, *J* = 11.8 Hz, 2-Hα), 4.04 (1H, d, *J* = 14.9 Hz, $C_6H_5CHN$), 4.07 (1H, br d, *J* = 6.3 Hz, 5-H), 4.42 (1H, d, *J* = 1.3 Hz, 1-H), 5.02 (1H, d, *J* = 14.9 Hz, $C_6H_5CHN$), 6.77 (2H, d, *J* = 6.6 Hz), 7.04-7.08 (3H, m); *m/z* (%) 382 ($M^+$, 30), 235 (23), 234 (100), 204 (12), 91 (7). Anal. Calcd for $C_{22}H_{26}N_2O_4 \cdot 1/2H_2O$: C, 67.44; H, 6.89; N, 7.15. Found: C, 67.42; H, 6.71; N, 6.85.

3-Benzyl-1,2,3,4,5,6-hexahydro-9-methoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (**10a**). Formaldehyde (37% solution in water, 0.4 mL) was added to a stirred solution of **9b** (167.0 mg, 0.5 mmol) in formic acid (0.45 mL) at 60°C. After stirring at 70°C for 1 h, the reaction mixture was poured into water (30 mL) and extracted with chloroform (20 mL x 3). The combined extracts were washed with 5% aqueous $NaHCO_3$ solution (20 mL), dried, and concentrated *in vacuo* to give a residue. Chromatography of this on a silica gel (5 g) column with dichloromethane-methanol (50:1) gave **10a** (170.0 mg, 98%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 1632 $cm^{-1}$; $\delta_H$ 2.21 (3H, s, $ArCH_3$), 2.50 (3H, s, $NCH_3$), 2.87 (1H, d, *J* = 16.8 Hz, 6-Hβ), 3.00 (1H, d, *J* = 10.2 Hz, 2-Hβ), 3.22 (1H, dd, *J* = 16.8, 5.9 Hz, 6-Hα), 3.68 (3H, s, $OCH_3$), 3.74 (1H, d, *J* = 5.9 Hz, 5-H), 3.81 (1H, s, 1-H), 3.82 (1H, d, *J* = 10.2 Hz, 2-Hα), 4.36 (1H, d, *J* = 15.0 Hz, $C_6H_5CHN$), 4.69 (1H, d, *J* = 15.0 Hz, $C_6H_5CHN$), 6.36 (1H, s, 10-H), 6.77 (2H, d, *J* = 6.6 Hz), 6.91 (1H, s, 7-H), 7.05-7.14 (3H, m); $\delta_C$ 15.9 (q, 9-$CH_3$), 27.4 (t, C-6), 40.0 (q, 11-$CH_3$), 48.9 (t, 3-$CH_2C_6H_5$), 52.1 (t, C-2), 55.3 (q, $OCH_3$), 56.1 (d, C-1), 60.0 (d, C-5), 108.4 (d, C-7), 124.2 (s), 126.2 (s), 127.0 (d, C-4'), 127.3 (d, C-3', C-5'), 128.3 (d, C-2', C-6'), 130.8 (d, C-10), 132.7 (s), 136.2 (s, C-1'), 156.5 (s), 170.4 (s, C-4); *m/z* (%) 336 ($M^+$, 22), 189 (19), 188 (100). High-resolution EIMS Calcd for $C_{21}H_{24}N_2O_2$: 336.1838. Found: 336.1842.

3-Benzyl-1,2,3,4,5,6-hexahydro-7,9,10-trimethoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (**10b**). This compound was prepared with the same procedure that as described above, but using **9b** (1.10 g, 0.9 mmol), 37% aqueous formaldehyde solution (2.2 mL), and formic acid (2.6 mL). Chromatography of the residue (1.30 g) on a silica gel (30 g) column with dichloromethane-methanol (50:1) gave **10b** (1.12 g, 98%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 1645 $cm^{-1}$; $\delta_H$ 2.22 (3H, s, $ArCH_3$), 2.52 (3H, s, $NCH_3$), 2.97 (1H, dd, *J* = 11.9, 1.1 Hz, 2-Hβ), 3.07 (1H, d, *J* = 5.3 Hz, 6-Hβ), 3.07 (1H, s, 6-Hα), 3.63 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 3.70 (3H, s, $OCH_3$), 3.72 (1H, this signal overlapped with the methyl signal, 5-H), 3.83 (1H, dd, *J* = 11.9, 4.6 Hz, 2-Hα), 4.07 (1H, dd, *J* = 4.6, 1.1 Hz, 1-H), 4.13 (1H, d, *J* = 14.9 Hz, $C_6H_5CHN$), 4.92 (1H, d, *J* = 14.9 Hz, $C_6H_5CHN$), 6.77-6.81 (2H, m), 7.03-7.13 (3H, m); $\delta_C$ 9.2 (q, 9-$CH_3$), 24.3 (t, C-6), 40.2 (q, 11-$CH_3$), 48.7 (t, 3-$CH_2C_6H_5$), 49.9 (t, C-2), 51.5 (d, C-1), 59.1 (q, $OCH_3$), 59.9 (q, $OCH_3$), 60.0 (q, $OCH_3$), 60.0 (d, C-5), 122.1 (s), 124.2 (s), 126.2

(s), 127.0 (d, C-4'), 127.2 (d, C-3', C-5'), 128.2 (d, C-2', C-6'), 136.5 (s, C-1'), 146.1 (s), 149.8 (s), 152.2 (s), 170.2 (s, C-4); *m/z* (%) 396 ($M^+$, 22), 249 (20), 248 (100), 218 (13). High-resolution EIMS Calcd for $C_{23}H_{28}N_2O_4$: 396.2049. Found: 396.2051.

3-Benzyl-1,2,3,4,5,6-hexahydro-9-methoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocine-4-carbonitrile (**11a**). 1.0 M Lithium diethoxyaluminum hydride in diethyl ether solution was prepared by adding of ethyl acetate (0.244 μL, 2.5 mmol) to a 1.0 M solution of lithium aluminum hydride (2.5 mL, 2.5 mmol) at 0°C and stirring at 0°C for 1 h. A solution of **10a** (210.0 mg, 0.624 mmol) in THF (15 mL) was slowly added to it over 10 min, and the resulting mixture was stirred for 3 h at -6°C. The reaction mixture was quenched with acetic acid (824 mg, 13.0 mmol), and then this solution was treated with a solution of potassium cyanide (244.0 mg, 3.74 mmol) in water (3.0 mL) for 4 h. After diluting with saturated $NaHCO_3$ solution, the mixture was extracted with chloroform (30 mL x 3). The combined extracts were washed with saturated NaCl solution, dried, and concentrated *in vacuo* to give a residue (246.2 mg), the purification of which using column chromatography on silica gel (15 g) with chloroform-methanol (50:1) afforded **11a** (209.9 mg, 97%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 3445, 2916, 2820, 2222, 1508, 1238, 1165 $cm^{-1}$; $\delta_H$ 2.16 (3H, s, $ArCH_3$), 2.27 (1H, d, *J* = 17.1 Hz, 6-Hβ), 2.30 (3H, s, $NCH_3$), 2.60 (1H, d, *J* = 10.8 Hz, 2-Hβ), 2.94 (1H, dd, *J* = 10.8, 2.7 Hz, 2-Hα), 2.99 (1H, dd, *J* = 17.1, 7.8 Hz, 6-Hα), 3.19 (1H, d, *J* = 7.8 Hz, 5-H), 3.45 (1H, d, *J* = 13.8 Hz, $C_6H_5CHN$), 3.53 (1H, d, *J* = 13.8 Hz, $C_6H_5CHN$), 3.57 (1H, br s, 1-H), 3.57 (1H, br s, 4-H), 3.71 (3H, s, $OCH_3$), 6.37 (1H, s, 10-H), 6.79 (1H, s, 7-H), 6.85-6.88 (2H, m), 7.10-7.12 (3H, m); $\delta_C$ 16.2 (q, 9-$CH_3$), 25.0 (t, C-6), 41.6 (q, 11-$CH_3$), 55.2 (t, C-2), 55.3 (q, $OCH_3$), 55.6 (d, C-5), 58.8 (d, C-1), 59.0 (d, C-4), 59.0 (t, 3-$CH_2C_6H_5$), 108.5 (d, C-7), 116.5 (CN), 124.9 (s), 125.7 (s), 127.4 (d, C-4'), 127.4 (d, C-3', C-5'), 128.4 (d, C-2', C-6'), 129.3 (d, C-10), 133.8 (s), 136.8 (s, C-1'), 155.9 (s); *m/z* (%) 347 ($M^+$, 2), 188 (100). High-resolution EIMS Calcd for $C_{22}H_{25}N_3O$: 347.1998. Found: 347.1993.

3-Benzyl-1,2,3,4,5,6-hexahydro-7,9,10-trimethoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocine-4-carbonitrile (**11b**). This compound was prepared with the same procedure that as described above, but using **10b** (219.4 mg, 0.553 mmol) with 4 equivalents of the hydride reagent. Crystallization of the crude product (270.2 mg) from hexane-ether gave **11b** (200.0 mg, 89%) as colorless prisms, mp 116-117°C. $\nu_{max}$ (KBr) 2936, 2831, 2222, 1458, 1408, 1312, 1111, 1072 $cm^{-1}$; $\delta_H$ 2.17 (3H, s, $ArCH_3$), 2.28 (3H, s, $NCH_3$), 2.29 (1H, d, *J* = 18.3 Hz, 6-Hβ), 2.55 (1H, d, *J* = 11.1 Hz, 2-Hβ), 2.90 (1H, dd, *J* = 11.1, 3.3 Hz, 2-Hα), 2.92 (1H, dd, *J* = 18.3, 7.8 Hz, 6-Hα), 3.24 (1H, d, *J* = 7.8 Hz, 5-H), 3.47 (1H, d, *J* = 13.8 Hz, $C_6H_5CHN$), 3.53 (1H, d, *J* = 13.8 Hz, $C_6H_5CHN$), 3.60 (1H, br s, 4-H), 3.65 (3H, s, $OCH_3$), 3.66 (3H, s,

$OCH_3$), 3.73 (3H, s, $OCH_3$), 3.95 (1H, br s, 1-H), 6.87-6.90 (2H, m), 7.04-7.10 (3H, m); $\delta_C$ 9.3 (q, 9-$CH_3$), 20.8 (t, C-6), 41.5 (q, 11-$CH_3$), 52.7 (d, C-1), 53.9 (t, C-2), 55.0 (d, C-5), 58.8 (d, C-4), 59.0 (t, 3-*C*$H_2C_6H_5$), 59.7 (q, $OCH_3$), 60.1 (q, $OCH_3$), 60.4 (q, $OCH_3$), 116.5 (CN), 123.1 (s), 123.3 (s), 126.2 (s), 127.4 (d, C-4'), 128.3 (d, C-3', C-5'), 128.4 (d, C-2', C-6'), 137.0 (s, C-1'), 146.3 (s), 149.4 (s), 151.0 (s); *m/z* (%) 407 ($M^+$, 2), 248 (100), 218 (10). High-resolution EIMS Calcd for $C_{24}H_{29}N_3O_3$: 407.2209. Found: 407.2209.

3-Benzyl-1,2,3,4,5,6-hexahydro-7-hydroxy-9,10-dimethoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocin-4-one (**12**). A dichloromethane solution of boron tribromide (1.0 M, 2.2 mL, 2.2 mmol) was added to a stirred solution of **10b** (439.0 mg, 1.11 mmol) in dichloromethane (40 mL) at -78°C for 10 min. The reaction mixture was kept at the same temperature for 1 h, and at 0°C for 2.5 h, after which it was poured into water (60 mL). After the pH was brought to 7-8 with 5% aqueous $NaHCO_3$ solution, the mixture was extracted with dichloromethane (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated *in vacuo* to give a residue (411.0 mg). Column chromatography on silica gel (45 g) with chloroform-methanol (40:1) gave **12** (351.0 mg 83%) as a colorless amorphous powder. $\nu_{max}$ ($CHCl_3$) 3356, 3009, 2939, 1636, 1458, 1342, 1065 $cm^{-1}$; $\delta_H$ 2.22 (3H, s, $ArCH_3$), 2.29 (1H, d, *J* = 17.0 Hz, 6-Hβ), 2.35 (3H, s, $NCH_3$), 2.65 (1H, d, *J* = 11.0 Hz, 2-Hβ), 2.90 (1H, dd, *J* = 17.0, 8.0 Hz, 6-Hα), 2.93 (1H, dd, *J* = 11.0, 3.0 Hz, 2-Hα), 3.36 (1H, d, *J* = 8.0 Hz, 5-H), 3.55 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.60 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.68 (3H, s, $OCH_3$) 3.80 (3H, s, $OCH_3$), 4.02 (1H, br s, 1-H), 6.61 (1H, br s, OH), 6.92-6.95 (2H, m), 7.14-7.16 (3H, m); $\delta_C$ 9.0 (q, 9-$CH_3$), 23.1 (t, C-6), 39.9 (q, 11-$CH_3$), 49.0 (t, 3-*C*$H_2C_6H_5$), 50.9 (t, C-2), 51.4 (d, C-1), 60.0 (q, $OCH_3$), 60.2 (q, $OCH_3$), 60.2 (d, C-5), 115.4 (s), 118.2 (s), 124.9 (s), 127.1 (d, C-4'), 127.3 (d, C-3', C-5'), 128.4 (d, C-2', C-6'), 136.2 (s, C-1'), 143.4 (s), 148.3 (s), 149.7 (s), 170.4 (s, CO); *m/z* (%) 382 ($M^+$, 28), 234 (100). High-resolution EIMS Calcd for $C_{22}H_{26}N_2O_4$: 382.1893. Found: 382.1893.

3-Benzyl-1,2,3,4,5,6-hexahydro-7-hydroxy-9,10-dimethoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocine-4-carbonitrile (**13**). This compound was prepared with the same procedure that as described above from **10** to **4**, but using **12** (86.2 mg, 0.225 mmol) with 4 equivalents of the hydride reagent. Crystallization of the crude product (270.2 mg) from hexane-ether gave **13** (64.7 mg, 73%) as colorless prisms, mp 166-169°C. $\nu_{max}$ (KBr) 3456, 2330, 1458, 1072 $cm^{-1}$; $\delta_H$ 2.17 (3H, s, $ArCH_3$), 2.29 (1H, d, *J* = 17.0 Hz, 6-Hβ), 2.35 (3H, s, $NCH_3$), 2.65 (1H, d, *J* = 11.0 Hz, 2-Hβ), 2.90 (1H, dd, *J* = 17.0, 8.0 Hz, 6-Hα), 2.93 (1H, dd, *J* = 11.0, 3.0 Hz, 2-Hα), 3.36 (1H, d, *J* = 8.0 Hz, 5-H), 3.55 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.60 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.68 (3H, s, $OCH_3$), 3.70 (1H, d, *J* = 2 Hz, 4-H),

3.80 (3H, s, $OCH_3$), 4.02 (1H, br s, 1-H), 6.92-6.95 (2H, m), 7.14-7.16 (3H, m); $\delta_C$ 8.7 (q, 9-$CH_3$), 20.7 (t, C-6), 41.5 (q, 11-$CH_3$), 52.6 (d, C-1), 53.6 (t, C-2), 54.9 (d, C-5), 59.0 (t, 3-*C*$H_2C_6H_5$), 59.1 (d, C-4), 60.3 (q, $OCH_3$), 60.6 (q, $OCH_3$), 115.2 (s), 116.1 (CN), 116.5 (s), 125.9 (s), 127.3 (d, C-4'), 128.2 (d, C-3', C-5'), 128.3 (d, C-2', C-6'), 136.8 (s, C-1'), 143.6 (s), 146.3 (s), 149.0 (s); *m/z* (%) 393 ($M^+$, 3), 234 (100). High-resolution EIMS Calcd for $C_{23}H_{27}N_3O_3$: 393.2052. Found: 393.2051.

3-Benzyl-9-methoxy-8,11-dimethyl-1,2,3,4,5,6,7,10-octahydro-7,10-dioxo-(1α,2α,5α)-1,5-imino-3-benzazocine-4-carbonitrile (**4**). A solution of CAN (1.943 g, 2.73 mmol) in water (10 mL) was added to a stirred solution of **13** (214.6 mg, 0.545 mmol) in acetonitrile (10 mL) over 10 min, and the mixture was stirred for 1 h at 0°C. The reaction mixture was poured into water (50 mL), pH was brought to 7-8 with 5% aqueous $NaHCO_3$ solution, and the mixture was extracted with chloroform (50 mL x 3). The combined extracts were washed with saturated NaCl solution, dried, and concentrated *in vacuo* to give a residue. Column chromatography on silica gel (10 g) with hexane-ethyl acetate (1:1) gave **4** (151.3 mg, 74%) as a dark yellow powder. $\nu_{max}$ ($CHCl_3$) 3024, 2943, 2230, 1651, 1612, 1308, 1234, 1157 $cm^{-1}$; $\delta_H$ 2.01 (3H, s, $ArCH_3$), 2.05 (1H, d, *J* = 20.9 Hz, 6-Hβ), 2.32 (3H, s, $NCH_3$), 2.58 (1H, ddd, *J* = 11.7, 2.1., 1.2 Hz, 2-Hβ), 2.68 (1H, dd, *J* = 20.9, 7.2 Hz, 6-Hα), 2.95 (1H, dd, *J* = 11.7, 3.0 Hz, 2-Hα), 3.27 (1H, ddd, *J* = 7.2, 2.1, 1.5 Hz, 5-H), 3.54 (1H, d, *J* = 2.1 Hz, 4-H), 3.54 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.66 (1H, d, *J* = 14.0 Hz, $C_6H_5CHN$), 3.72 (1H, br s, 1-H), 4.00 (3H, s, $OCH_3$), 7.12-7.18 (2H, m), 7.21-7.29 (3H, m); $\delta_C$ 8.8 (q, 9-$CH_3$), 20.8 (t, C-6), 41.5 (q, 11-$CH_3$), 51.3 (d, C-1), 51.7 (t, C-2), 54.5 (d, C-5), 57.7 (d, C-4), 58.9 (t, 3-*C*$H_2C_6H_5$), 61.0 (q, $OCH_3$), 115.8 (CN), 127.9 (s), 128.6 (d, C-4'), 128.6 (d, C-3', C-5'), 128.7 (d, C-2', C-6'), 128.7 (s), 136.2 (s, C-1'), 141.0 (s), 155.4 (s), 182.3 (s, CO), 186.9 (s, CO); *m/z* (%) 377 ($M^+$, 11), 219 (100), 204 (26), 176 (12), 91 (25). High-resolution EIMS Calcd for $C_{22}H_{23}N_3O_3$: 377.1739. Found: 377.1742.

1,2,3,4,5,6-Hexahydro-7-hydroxy-9,10-dimethoxy-3,8,11-trimethyl-(1α,2α,5α)-1,5-imino-3-benzazocine-4-carbonitrile (**15**). This compound was prepared with the same procedure that as described above from **10** to **4**, but using **14**[11] (1.394 g, 4.55 mmol) with 4 equivalents of the hydride reagent. Crystallization of the crude product (270.2 mg) from ethyl acetate gave **15** (1.186 g, 82%) as colorless prisms, mp 195-196°C. $\nu_{max}$ (KBr) 3460, 2939, 2226, 1454, 1165, 1115, 1065 $cm^{-1}$; $\delta_H$ 2.04 (3H, s, $ArCH_3$), 2.30 (3H, s, $NCH_3$), 2.43 (1H, d, *J* = 18.0 Hz, 6-Hβ), 2.62 (1H, dd, *J* = 11.1, 1.2 Hz, 2-Hβ), 2.88 (1H, dd, *J* = 11.1, 3.3 Hz, 2-Hα), 2.94 (1H, dd, *J* = 18.0, 8.1 Hz, 6-Hα), 3.42 (1H, dd, *J* = 8.1, 2.1 Hz, 5-H), 3.77 (1H, d, *J* = 2.1 Hz, 4-H), 3.79 (3H, s, $OCH_3$), 3.80 (3H, s, $OCH_3$), 4.01 (1H, br s, 1-H), 4.77 (1H, br s, OH)); $\delta_C$ 8.6 (q, 9-$CH_3$), 20.8 (t, C-6), 41.4 (q, 11-$CH_3$), 43.7 (q, 3-$CH_3$), 52.2 (d, C-1), 54.8 (d,

C-5), 56.0 (t, C-2), 60.2 (q, $OCH_3$), 60.6 (d, C-4), 61.5 (q, $OCH_3$), 115.8 (s), 116.1 (CN), 116.2 (s), 126.0 (s), 143.6 (s), 146.6 (s), 148.9 (s); *m/z* (%) 317 ($M^+$, 4), 234 (100). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.22; H, 7.49; H, 13.01.

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