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Synthesis of Saframycins. XI. Synthetic Studies toward a Total Synthesis of Safracin A

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Abstract: *A synthetic strategy for the preparation of the isoquinolinequinone antibiotic safracin A (**1a**) is outlined. Our initial strategy for the construction of the ABC ring was based on a retrosynthetic analysis. Conversion of **5** in five steps to the imide **16** was followed by a 1,2-reduction with lithium tri-tert-butoxyaluminum hydride to give the allylic alcohol **7a**. This compound was then cyclized to the 1,5-imino-3-benzazocine **8a** and the indeno[1,2-b]pyrazin-2-one **17**. An unwanted isomer **17** was converted to the N-methyl tetracyclic lactam **21**, the structure of which was determined by X-ray crystallography. Conversion of **18** to the pentacyclic pyruvamide **31** was completed in a nine step sequence. Finally, **31** was subjected to a two-step oxidative demethylation to provide the quinones **10a** and **34**. An unsuccessful attempt to introduce a hydroxyl group onto the C-1 position of the quinones **10a** or **34** is also described.*

Safracins A (**1a**) and B (**1b**) were first isolated by the Yoshitomi Laboratories group from *Pseudomonas fluorescens* A2-2 in 1983.[1] The Squibb Laboratories group independently isolated **1b** from *Pseudomonas fluorescens* SC 12695 in the same year.[2] Both safracins were active against the L1210 and P388 leukemia and B16 melanoma mouse tumor lines. The toxic and effective doses of **1a** were much lower than those of **1b**.[3] The absolute configuration of the safracins was elucidated by X-ray crystallography of the 4-brominated derivative of safracin A (**1c**).[4] The safracin structure is similar to that of the saframycins (**2**)[5], however, the pyruvamide side chain and one of the *p*-quinone rings of the saframycins are substituted, respectively, by an alanyl amide side chain and a monophenol ring in the safracins. The Yoshitomi Laboratories group reported the novel transformation of **1a** into the amines **1e** through **1d**.[6] In 1990, ecteinascidin 743 (**3**) and its derivatives with potent *in vivo* antitumor activity were independently isolated from the colonial tunicate *Ecteinascidia turbinata* by Reinhart *et al.*[7a,b] and Wright *et al.*[7c], and the structures assigned to them were similar to those of safracins. It is interesting that these monoquinone-type antibiotics, such as safracins A (**1a**) and B (**1b**), saframycins D (**2d**) and F (**2f**), and saframycin Mxs-1 (**4a**), and -2 (**4b**)[8] have a quinone moiety on E-ring and a highly substituted benzenoid A-ring, along with a variety of oxidation levels within the pentacyclic skeleton (Fig. 1). We became interested in the safracins as attractive synthetic targets because they are plausible biogenetic intermediates of the saframycins and saframycin Mxs. We have reported on the total synthesis of (±)-saframycin B (**2b**)[9a] and the transformation of (±)-**2b** into (±)-saframycins C (**2c**) and D (**2d**).[9b] To extend the scope of

the synthetic route to the saframycin antibiotics, we have focused our attention on the synthesis of safracin A (**1a**). Our initial strategy for its synthesis was based on the retrosynthetic analysis outlined in Scheme 1. To prevent the formation of any unwanted tetrahydroisoquinoline isomer **8b'** from **7b** to **8b**, we planned to introduce the hydroxy group at the C-1 position at a final stage. Previously, we succeeded in the preparation of the ABC ring model compound **6b** of **1a** by bromination of **6a**, followed by amide reduction then subsequent metal-halogen interchange and reaction of the organometallic intermediate with nitrobenzene.[10] In this paper, we describe the total synthesis of the monoquinone compounds **10a** and **34**. An unsuccessful attempt to convert **10a** or **34** into **10b** which is the analogue of **1a** is also described.

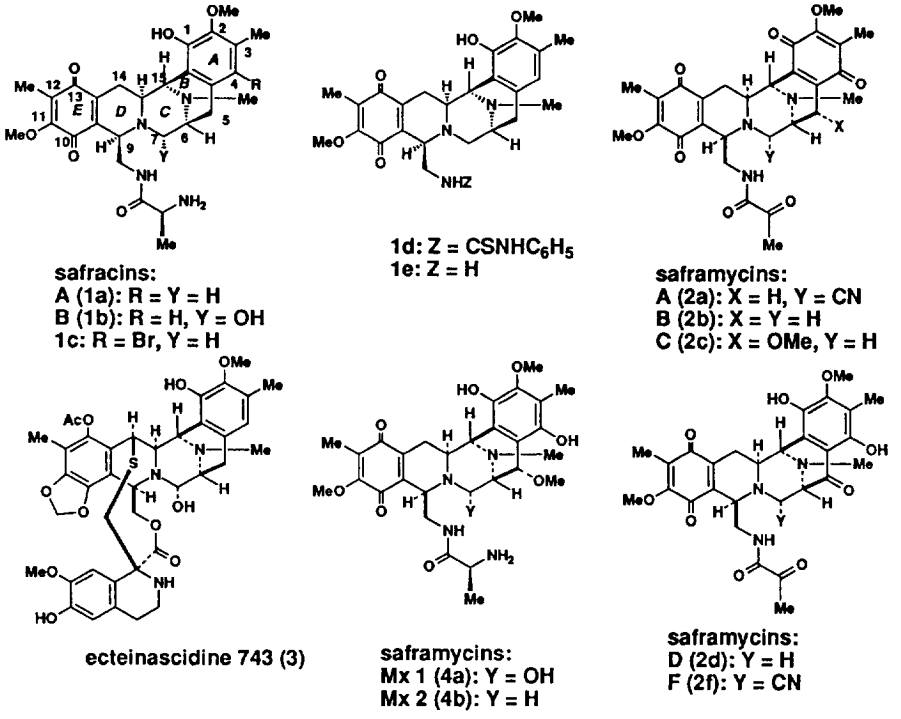


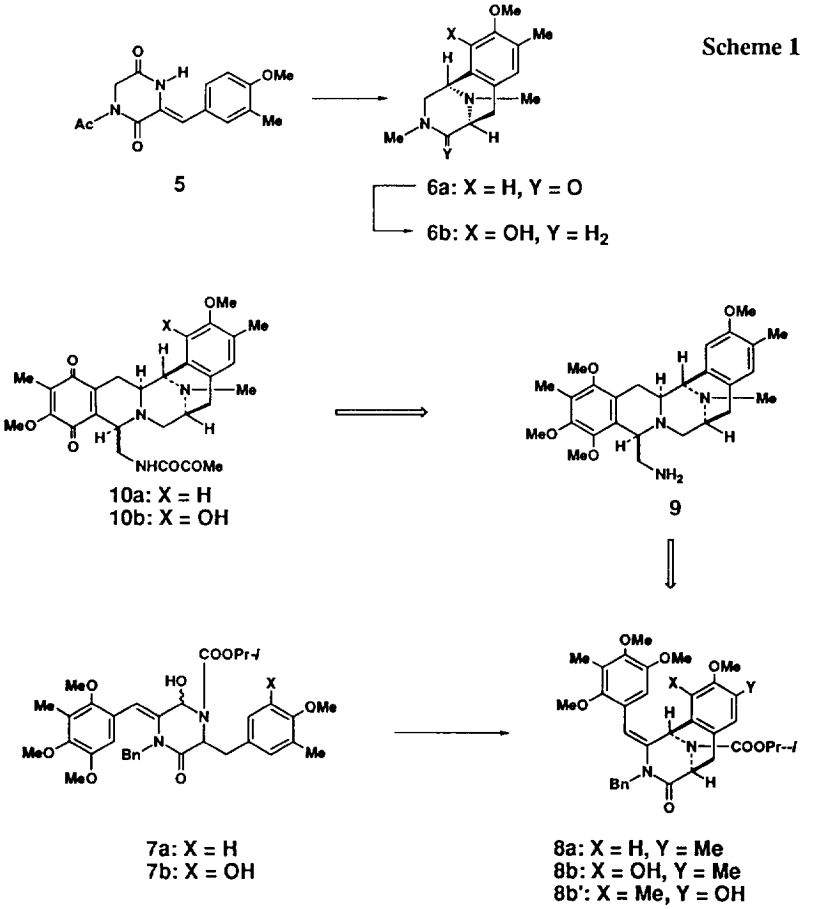
Fig. 1

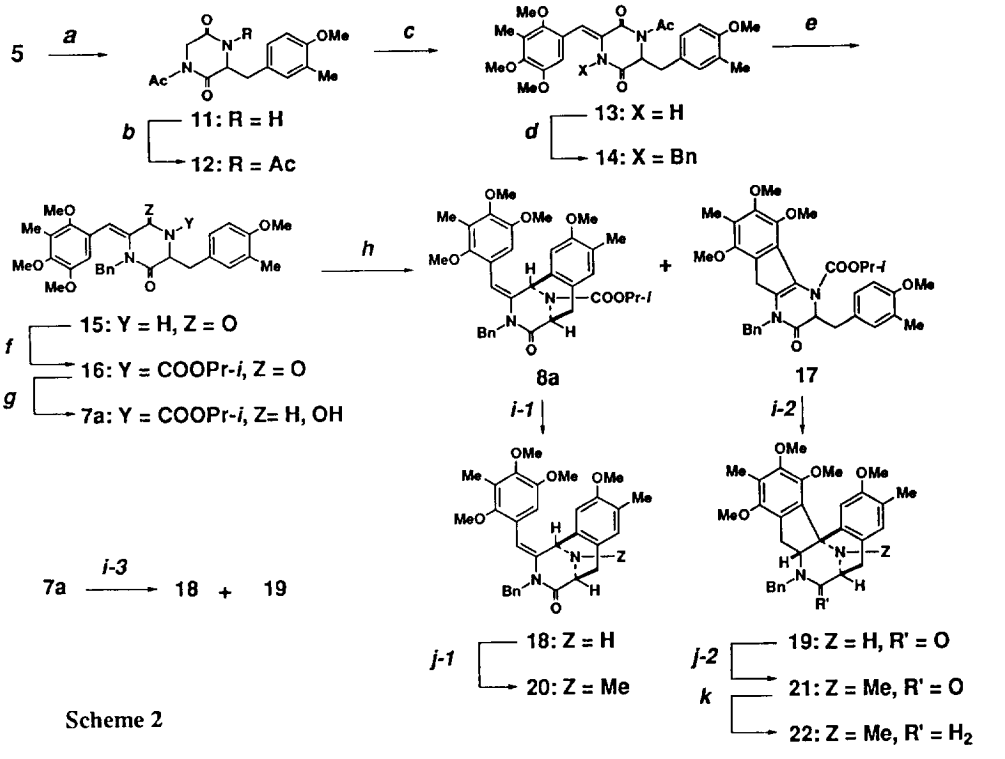
Results and Discussion

Catalytic hydrogenation of readily available olefin **5**[10a] furnished compound **11** in 75% yield (Scheme 2). Acetylation of **11** with acetic anhydride at 100 °C for 22 h afforded the diacetate **12** in 97% yield. Condensation of **12** and 2,4,5-trimethoxy-3-methylbenzaldehyde with potassium *tert*-butoxide gave (*Z*)-arylidenepiperazinedione **13** in 72% yield. Benzylation of **13** with benzyl bromide and sodium hydride in DMF followed by hydrazine hydrate treatment gave the *N*-benzylated derivative **15** in quantitative yield. The piperazine ring of **15** was activated by introduction of a 2-propyloxycarbonyl group to give imide **16** in 93%

yield. Chemoselective reduction of **16** with lithium tri-*tert*-butoxyaluminum hydride in THF afforded a diastereomeric mixture of the alcohol **7a**, which on treatment with formic acid afforded the desired cyclization product **8a** in 64% yield along with the indeno[1,2-*b*]pyrazin-2-one **17** (20%) and precursor **15** (8%).[11] This dehydration/cyclization reaction when run at room temperature with $TiCl_4$ in CH_2Cl_2 gave **8a** (86%) and **17** (4%). On the other hand, treatment of **7a** with BF_3-OEt_2 in CH_2Cl_2 at room temperature afforded **8a** (32%) and **17** (61%). Deprotection of **17** with trifluoroacetic acid and H_2SO_4 gave the secondary amine **19** in 98% yield. Treatment of **8a** under the same conditions gave **18** in 69% yield. Furthermore, treatment of **7a** with trifluoroacetic acid and H_2SO_4 at room temperature for 70 h afforded **18** and **19** in 51% and 9% yields, respectively. Methylation of **18** with formaldehyde and formic acid at 70 °C for 2 h gave the tricyclic lactam **20** in 84% yield. Similar treatment of **19** afforded the pentacyclic lactam **21** in 87% yield. The stereochemical structure of **21** was confirmed by X-ray crystallographic analysis (Fig. 2). The stereochemical course of ring closure from **17** to **19** could be rationalized by ring formation proceeding through the iminium isomer **i** from the convex face (Fig. 3).[12] Reduction of **21** with aluminum hydride at 0 °C for 30 min gave the amine **22** in 91% yield.

Scheme 1

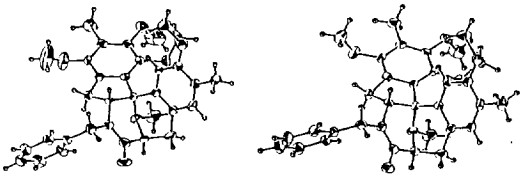




Scheme 2

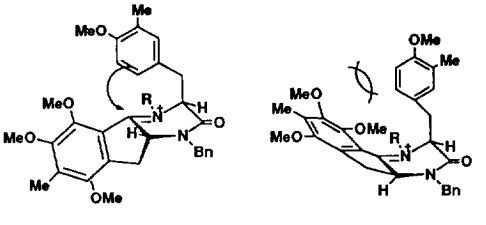
reagents and conditions: a) H_2, 10% Pd/C, DMF-EtOH = 1:1, 75%; b) Ac_2O, 100 °C, 22 h, 97%; c) 2,4,5-trimethoxy-3-methylbenzaldehyde, *tert*-BuOK, *tert*-BuOH, DMF, room temperature, 3 h, 72%; d) NaH, BnBr, DMF, room temperature, 1 h; e) NH_2NH_2-H_2O, DMF, room temperature, 1 h; f) ClCOOPr-*i*, NEt_3, DMAP, CH_2Cl_2, room temperature, 1 h, 93% (3 steps); g) Li(*tert*-BuO)$_3$AlH, THF, 0 °C, 1 h, 100%; h) *Method A*: HCOOH, 70 °C, 2 h (**8a**, 64%; **17**, 20%; **15**, 8%); *Method B*: $TiCl_4$, CH_2Cl_2, room temperature, 1 h (**8a**: 86%; **17**, 4%; **15**, 4%); *Method C*: BF_3OEt_2, CH_2Cl_2, room temperature, 14 h (**8a**, 31%; **17**, 61%, **15**, 6.6%); i-1) TFA-H_2SO_4, room temperature, 19 h, 98%; i-2) TFA-H_2SO_4, room temperature, 40 h, 69%; i-3) TFA-H_2SO_4, room temperature, 70 h (**18**, 51%; **19**, 9%); j-1) 37% HCHO, HCOOH, 70 °C, 2 h, 84.3%; j-2) 37% HCHO-HCOOH, 70 °C, 38 h, 87%; k) AlH_3, THF, 0 °C, 30 min, 91%.

Fig. 2. ORTEP drawing of compound **21** (two molecules are included in an asymmetric unit).



Molecular Structure I Molecular Structure II

Fig. 3



i ii

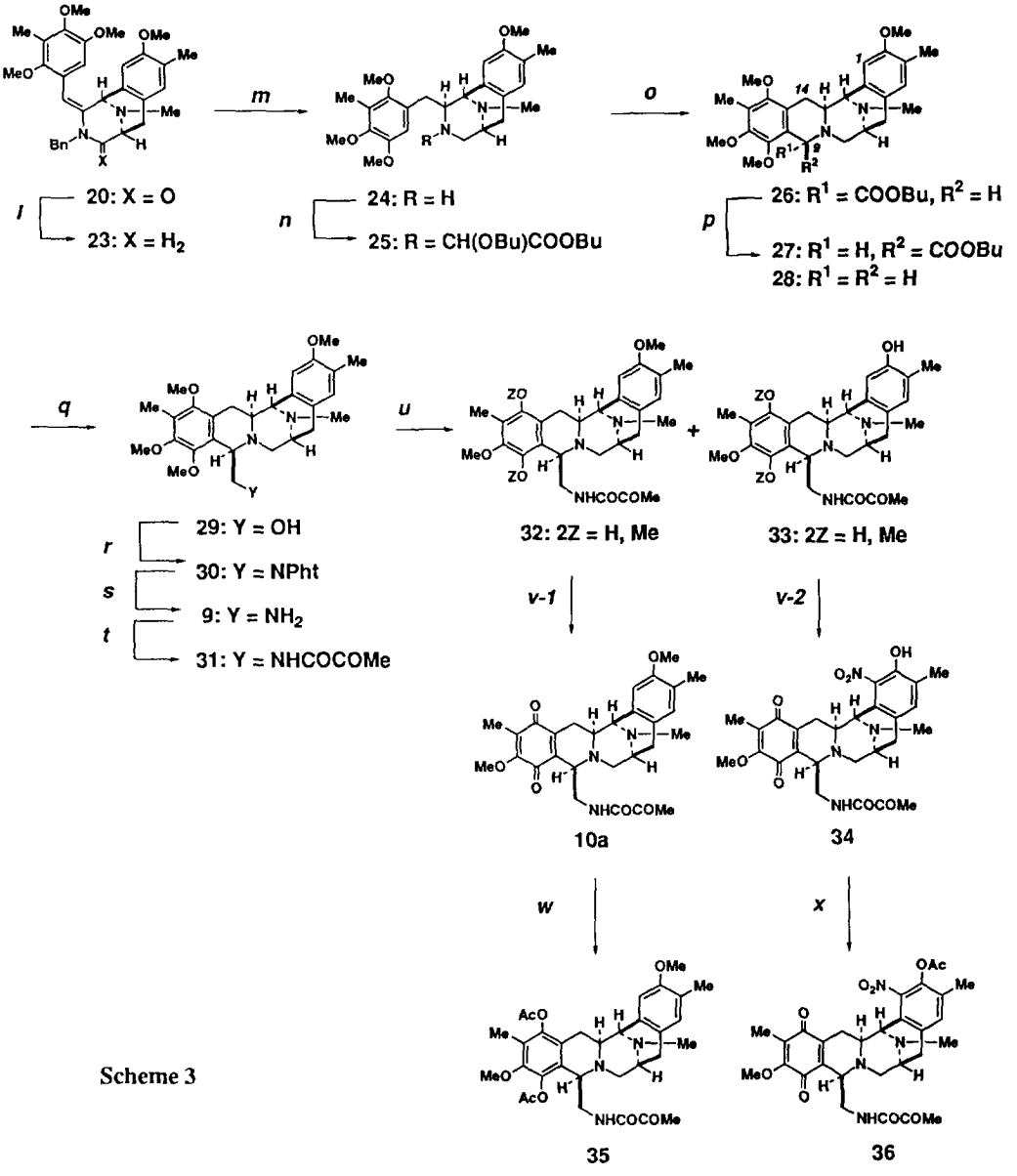
We then investigated the conversion of **20** to the pentacyclic amine **9** (Scheme 3). Reduction of **20** with aluminum hydride at 0 °C for 1 h gave the unstable enamine **23**. Reduction of the double bond of **23** *via* catalytic hydrogenation over 20% Pd/C in ethanol at 80 °C for 40 h occurred cleanly from the α-face accompanied by debenzylation to give the secondary amine **24** in 96% overall yield. The reaction of **24** with a large excess of butyl glyoxylate in the presence of K_2CO_3 in butanol at room temperature for 40 h gave the *O,N*-acetal **25**, which was subsequently treated with trifluoroacetic acid at room temperature for 1 h to provide the pentacyclic product **26** in 69% yield. Epimerization of the C-9 position in **26** by reaction with mercury acetate in 5% aqueous AcOH at 90 °C for 2 h followed by reduction with sodium borohydride afforded the desired ester **27** (68%) along with the decarbobutoxylated compound **28**[13] in 4% yield. The ^1H NMR spectrum of **27** displayed H-9 as a singlet at δ 4.10 and H-14a as a multiplet at δ 2.84, whereas the ^1H NMR spectrum of **26** showed the H-9 peak at δ 4.58 and the H-14a at δ 3.61. The remarkable difference in the chemical shifts of the methine protons must arise from steric interactions between the C-9 side chain and C-14a.[14] Reduction of **27** with lithium aluminum hydride in THF at room temperature for 1 h afforded alcohol **29** in 83% yield.[15] Treatment of **29** with diethyl azodicarboxylate, triphenylphosphine, and phthalimide in THF at room temperature for 3 h to give **30** followed by hydrazine hydrate treatment afforded the amine **9**, which was acylated with pyruvoyl chloride to give the pyruvamide **31** in 92% overall yield.

Conversion of the polymethoxyarene **31** to a mono-*p*-quinone system was achieved using our partial demethylation and oxidative demethylation sequence.[9a] Treatment of **31** with 1.8 equiv of boron tribromide in CH_2Cl_2 at -78 °C for 4 h and then 0 °C for 1 h afforded the phenols **32** and **33**[16] in 45% and 29% yields, respectively (3% yield of **31** recovered).[17] The reaction of **32** with 8M HNO_3 at 0 °C for 1 h gave the *p*-quinone **10a** in 69% yield. In contrast, oxidative demethylation of **33** with 8M HNO_3 at 0 °C for 30 min was accompanied by nitration at the C-1 position to give the *p*-quinone **34** in 61% yield.

Finally, we turned our attention to preparing the phenol **10b** from the quinones **10a** and **34**. Numerous attempts to brominate **10a** at the C-1 position were totally unsuccessful; only starting material was recovered. Accordingly, we evaluated a study the sequence of reactions encompassing demethylation, bromination, and remethylation. Treatment of **10a** with boron tribromide gave only a polar polymeric material. In order to protect the *p*-quinone moiety, reductive acetylation of **10a** with zinc dust in acetic anhydride gave the diacetate **35** in 69% yield. Demethylation of **35** was also fruitless. Furthermore, numerous attempts to methylate **34** under basic conditions were totally unsuccessful, and gave only polar polymeric materials.[18] Acetylation of **34** with acetic anhydride in pyridine gave the acetate **36** in 82% yield. Surprisingly, treatment of **36** with hydrogen in the presence of 20% palladium on carbon in ethanol followed by air oxidation restored **34** in 61% yield.

Conclusion

In summary, we have achieved the total synthesis of safracin type monoquinones **10a** and **34** in 21 steps from 2,5-piperazinedione **11** (3.8% and 2.1% overall yields, respectively). Of course, to reach our final goal, it will be necessary to achieve introduction of a hydroxyl group at the C-1 position and exchange the pyruvoylamide side chain with an alanyl side chain. The following article describes the subsequent transformations of the amine **9** to analogs closely related to saframycin Mx-2 (**4b**).[19]



Scheme 3

reagents and conditions: l) AlH_3, THF, 0°C, 1 h; m) H_2 (4 atm), 20% Pd/C, EtOH, 80 °C, 40 h, 96% (2 steps); n) CHOCOOBu-*n*, *n*-BuOH, K_2CO_3, room temperature, 40 h; o) TFA, room temperature, 1 h, 69% (2 steps); p) $Hg(OAc)_2$, 5% AcOH-H_2O, 90 °C, 2 h and then $NaBH_4$, EtOH-H_2O, room temperature, 1 h (**27**, 68%, **28**, 4%, **26**, 3% recovery); q) $LiAlH_4$, THF, 0 °C, 1 h, 83.1%; r) PhtNH, DEAD, PPh_3, THF, room temperature, 3 h, 100%; s) NH_2NH_2-H_2O, EtOH, reflux, 2 h; t) ClCOCOMe, DMAP, NEt_3, CH_2Cl_2, room temperature, 1 h, 92% (2 steps); u) BBr_3, CH_2Cl_2, -78 °C, 4 h and then 0 °C, 1 h (**32**, 45%; **33**, 29%, **31**, 3% recovery); v-1) 8 M HNO_3, 0 °C, 1 h, 69%; v-2) 8M HNO_3, 0 °C, 30 min, 61 %; w) Zn dust, Ac_2O, room temperature, 30 min, 69%; x) Ac_2O, pyridine, room temperature, 2 h, 82%.

Experimental Section

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. UV spectra were determined in methanol. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 270 and 67.5 MHz, respectively. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained by using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was performed with a rotary evaporator and finally high vacuum. Column chromatography was performed with E. Merck silica gel 60 (70-230 mesh).

1-Acetyl-3-(4-methoxy-3-methylphenylmethyl)-2,5-piperazinedione (11).

The arylidene derivative **5** (11.52 g, 40 mmol) was dissolved in ethanol (100 mL) and DMF (100 mL) and hydrogenated over 10% palladium on carbon (1.5 g), and stirring was continued for 4 h at room temperature. The catalyst was removed by filtration and washed it with ethanol (100 mL). The combined filtrates were evaporated and the residue was diluted with brine (200 mL), and extracted with chloroform (200 ml x 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from acetone gave **11** (8.694 g, 75.0%) as colorless needles: mp 163-165 °C; IR (KBr) 3400-3080, 1690, 1650, 1605 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.06), 275 (3.23), 283 (3.19); ^{1}H NMR δ 2.18 (3H, s, Ar CH_3), 2.59 (3H, s, $COCH_3$), 3.00 (1H, dd, *J* = 14.2, 7.6 Hz, 3-CHAr), 3.18 (1H, dd, *J* = 14.2, 4.0 Hz, 3-CHAr), 3.60 (1H, d, *J* = 18.1 Hz, H-6), 3.81 (3H, s, OCH_3), 4.21 (1H, d, *J* = 18.1 Hz, H-6), 4.30 (1H, ddd, *J* = 7.6, 4.0, 2.6 Hz, H-3), 6.17 (1H, *d*, *J* = 2.6 Hz, NH), 6.76 (1H, d, *J* = 8.2 Hz, H-5'), 6.95 (1H, d, *J* = 2.3 Hz, H-2'), 6.96 (1H, dd, *J* = 8.2, 2.3 Hz, H-6'); EI-MS *m/z* (relative intensity) 290 (M^+, 5), 136 (11), 135 (100). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.86; H, 6.23; N, 9.61.

1,4-Diacetyl-3-(4-methoxy-3-methylphenylmethyl)-2,5-piperazinedione (12).

A solution of the acetate **11** (7.25 g, 25 mmol) in acetic anhydride (100 mL) was heated at 100 °C for 22 h. Removal of the solvent in vacuo afforded the residue, which was partitioned between ethyl acetate (200 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The organic phase was washed with water (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from ethyl acetate-ether gave **12** (8.024 g, 96.7%) as colorless prisms: mp 87-88 °C; IR (KBr) 1715, 1700 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.04), 276 (3.20), 284 (3.12); ^{1}H NMR δ 2.14 (3H, s, Ar CH_3), 2.49 (1H, d, *J* = 19.8 Hz, 6-H), 2.56, 2.59 (each 3H, s, $COCH_3$), 3.11 (1H, dd, *J* = 14.2, 4.3 Hz, 3-CHAr), 3.27 (1H, dd, *J* = 14.2, 4.0 Hz, 3-CHAr), 3.80 (3H, s, OCH_3), 4.48 (1H, d, *J* = 19.8 Hz, H-6), 5.39 (1H, dd, *J* = 4.3, 4.0 Hz, H-3), 6.71 (1H, d, *J* = 7.9 Hz, H-5'), 6.81-6.84 (2H, m, H-2' and H-6'); EI-MS *m/z* (relative intensity) 332 (M^+, 10), 136 (10), 135 (100). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.37; H, 6.05; N, 8.37.

(Z)-1-Acetyl-6-(4-methoxy-3-methylphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (13).

A solution of potassium *tert*-butoxide (2.246 g, 20 mmol) in *tert*-butyl alcohol (40 mL) was added to a stirred solution of 2,4,5-trimethoxy-3-methylbenzaldehyde (4.20 g, 20 mmol) and the diacetyl derivative **12** (6.64 g, 20 mmol) in dry DMF (80 mL) for 20 min at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was poured into water (400 mL), and extracted with benzene (200 mL x 3). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from ether gave **13** (6.974 g, 72.3%) as pale yellow prisms: mp 155-156 °C; IR (KBr) 3220, 1715, 1690, 1620 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.36), 248 (4.06), 336 (4.20); ^{1}H NMR δ 1.81, 2.21 (each 3H, s, Ar CH_3), 2.65 (3H, s, $COCH_3$), 3.09 (1H, dd, *J* = 14.2, 5.0 Hz, 6-CHAr), 3.16 (1H, dd, *J* = 14.2, 3.6 Hz, 6-CHAr), 3.49, 3.72, 3.83, 3.90 (each 3H, s, OCH_3), 5.32 (1H, dd, *J* = 5.0, 3.6 Hz, H-6), 6.32 (1H, s), 6.34 (1H, s), 6.56 (1H, d, *J* = 8.3 Hz, H-5'), 6.72 (1H, d, *J* = 2.3 Hz, H-2'), 6.73 (1H, dd, *J* = 8.3, 2.3 Hz, H-6'), 9.13 (1H, s, NH); ^{13}C NMR δ 9.5 (q), 15.6 (q), 27.1 (q), 37.9 (t), 55.1 (q), 55.6 (q), 58.4 (d), 60.4 (q), 61.2 (q), 109.8 (d), 112.0 (d), 116.2 (d), 121.2 (s), 125.2 (s), 125.6 (s), 126.4 (s), 126.9 (s), 129.4 (d), 132.6 (d), 148.9 (s), 149.1 (s), 149.5 (s), 157.2 (s), 161.4 (s), 165.8 (s), 172.5 (s); EI-MS *m/z* (relative intensity) 482 (M^+, 41), 305 (4), 136 (10), 135 (100). Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.71; H, 6.27; N, 5.81. Found: C, 64.35; H, 6.25; N, 5.72.

(Z)-1-[(Isopropyloxy)carbonyl]-4-benzyl-6-(4-methoxy-3-methylphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (16).

Sodium hydride (60% oil dispersion, washed with dry hexane three times, 312 mg, 13 mmol) was added to a stirred solution of **13** (6.05 g, 12.5 mmol) in dry DMF (70 mL), and stirring was continued for 30 min at 0 °C. Benzyl bromide (1.44 mL, 12.1 mmol) in dry DMF (10 mL) was added during 10 min, 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 water (50 mL) and extracted with benzene (100 mL x 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to furnish **14** (7.15 g, 100%) as a pale yellow oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization from ether to give pure **14** as pale yellow prisms: mp 150-151 °C; IR (KBr) 1710, 1685, 1625 cm^{-1}; UV λ_{max} nm (log ε) 232 (4.31), 250 (4.05), 276 (3.81), 284 (3.83), 342 (4.10); ^{1}H NMR δ 2.11, 2.24 (each 3H, s, Ar CH_3), 2.51 (3H, s, $COCH_3$), 3.07 (1H, dd, *J* = 15.8, 6.9 Hz, 6-CHAr), 3.14 (1H, dd, *J* = 15.8, 7.3 Hz, 6-CHAr), 3.54, 3.67, 3.88, 3.89 (each 3H, s, OCH_3), 4.16, 5.32 (each 1H, d, *J* = 14.9 Hz, N-CHAr), 5.47 (1H, dd, *J* = 7.3, 6.9 Hz, H-6), 6.65 (1H, d, *J* = 8.3 Hz, H-5'), 6.67 (1H, s), 6.72-6.91 (2H, m), 6.91 (1H, d, *J* = 2.0 Hz, H-2'), 6.96 (1H, dd, *J* = 8.3, 2.0 Hz, H-6'), 7.16-7.18 (3H, m), 7.27 (1H, s); ^{13}C NMR δ 9.5 (q), 16.2 (q), 26.8 (q), 37.7 (t), 47.5 (t), 55.1 (q), 56.2 (q), 57.8 (d), 60.5 (q), 61.9 (q), 110.1 (d), 110.2 (d), 120.7 (d), 121.0 (s), 126.1 (s), 126.4 (s), 126.9 (s), 127.6 (d), 127.8 (d), 128.6 (d), 128.7 (s), 131.7 (d),

136.1 (d), 148.9 (s), 150.0 (s), 152.9 (s), 157.0 (s), 164.1 (s), 167.0 (s), 171.5 (s); EI-MS *m/z* (relative intensity) 572 (M^+, 69), 500 (17), 499 (49), 136 (11), 135 (100), 91 (24). Anal. Calcd for $C_{33}H_{36}N_2O_7$: C, 69.21; H, 6.34; N, 4.89. Found: C, 69.12; H, 6.36; N, 4.82.

Hydrazine monohydrate (2.5 mL) was added to a stirred solution of the crude **14** (7.15 g, 12.5 mmol) in dry DMF (80 mL), and the resulting solution was stirred for 1 h at room temperature. After the reaction mixture was concentrated in vacuo, the residue was diluted with 5% $NaHCO_3$ solution (100 mL), and extracted with benzene (100 mL x 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to give **15** (6.62 g, 100%) as pale yellow oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization from ether to give pure **15** as colorless prisms: mp 147-150 °C; IR (KBr) 3230, 1685, 1635 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.30), 244 (3.86), 272 (3.86), 284 (3.96), 316 (4.01); ^1H NMR δ 2.18, 2.22 (each 3H, s, Ar CH_3), 2.87 (1H, dd, *J* = 13.9, 9.9 Hz, 6-CHAr), 3.36 (1H, dd, *J* = 13.9, 4.0 Hz, 6-CHAr), 3.50, 3.77, 3.82, 3.86 (each 3H, s, OCH_3), 4.25 (1H, ddd, *J* = 9.9, 4.0, 3.6 Hz, H-6), 4.64, 4.87 (each 1H, d, *J* = 15.2 Hz, N-CHAr), 6.13 (1H, br s, NH), 6.55 (1H, s), 6.75 (1H, d, *J* = 8.3 Hz, 5'-H), 6.85-6.89 (2H, m), 7.00-7.04 (2H, br d), 7.13-7.18 (4H, m); ^{13}C NMR δ 9.5 (q), 16.2 (q), 38.5 (t), 47.2 (t), 55.3 (q), 56.1 (q), 57.0 (d), 60.4 (q), 61.2 (q), 110.4 (d), 110.6 (d), 118.0 (d), 121.8 (s), 125.9 (s), 126.7 (s), 127.3 (s), 127.4 (d), 127.6 (d), 128.4 (d), 129.0 (s), 131.5 (d), 136.4 (s), 148.9 (s), 149.2 (s), 152.0 (s), 157.2 (s), 164.5 (s), 167.7 (s); EI-MS *m/z* (relative intensity) 530 (M^+, 26), 500 (35), 499 (100), 135 (35), 91 (15). Anal. Calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 70.01; H, 6.48; N, 5.23.

A solution of the crude **15** (6.62 g, 12.5 mmol), triethylamine (3.48 mL, 25 mmol), and 4-(dimethylamino)pyridine (3.05 g, 25 mmol) in dry dichloromethane (100 mL) was cooled with ice-water, and isopropyl chloroformate (5.69 mL, 50 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at room temperature. The organic layer was washed with 1N HCl (100 mL), dried, and concentrated in vacuo to give **16** as a solid, recrystallization of which from ether afforded pure **16** (7.175 g, 92.8%) as colorless needles: mp 112.5-114 °C; IR (KBr) 1775, 1695, 1625 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.38), 276 (3.81), 284 (3.85), 338 (4.08); ^1H NMR δ 1.19, 1.28 (each 3H, d, *J* = 6.3 Hz, $CHCH_3$), 2.14, 2.23 (each 3H, s, Ar CH_3), 3.10 (1H, dd, *J* = 13.9, 7.6 Hz, 6-CHAr), 3.16 (1H, dd, *J* = 13.9, 6.9 Hz, 6-CHAr), 3.52, 3.72, 3.86, 3.88 (each 3H, s, OCH_3), 4.15 (1H, d, *J* = 15.0 Hz, N-CHAr), 4.97 (1H, sept, *J* = 6.3 Hz, OCH), 5.14 (1H, dd, *J* = 7.6, 6.9 Hz, H-6), 5.28 (1H, d, *J* = 15.0 Hz, N-CHAr), 6.63 (1H, s), 6.69 (1H, d, *J* = 8.9 Hz, H-5'), 6.87-6.90 (2H, m), 6.97-6.99 (2H, br d), 7.16-7.18 (3H, m), 7.34 (1H, s); ^{13}C NMR δ 9.5 (q), 16.2 (q), 21.5 (q), 21.6 (q), 38.2 (t), 47.5 (t), 55.2 (q), 56.1 (q), 60.5 (q), 60.7 (d), 60.8 (q), 72.0 (d), 110.2 (d), 110.2 (d), 120.8 (d), 121.2 (s), 126.5 (s), 126.7 (s), 127.0 (s), 127.6 (d), 127.6 (d), 128.5 (d), 128.9 (s), 131.7 (d), 135.9 (s), 148.9 (s), 149.8 (s), 151.3 (s), 152.6 (s), 157.1 (s), 162.0 (s), 166.9 (s); EI-MS *m/z* (relative intensity) 616 (M^+, 75), 586 (40), 585 (100), 543 (12), 541 (10), 500 (19), 499 (57), 363 (12), 135 (94), 91 (36), 43 (11). Anal. Calcd for $C_{35}H_{40}N_2O_8$: C, 68.16; H, 6.54; N, 4.54. Found: C, 68.14; H, 6.53; N, 4.54.

(*E*)-3-Benzyl-2-[(1,2,3,4,5,6-hexahydro-2,4,5-trimethoxy-3-methylphenyl)methylene]-9-methoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylic acid Isopropyl Ester (8a).

Method A: A stirred solution of **16** (6.28 g, 10.195 mmol) in dry THF (200 mL) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminum hydride (10.37 g, 40.45 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (50 mL). The reaction mixture was filtered through a Celite pad, and the filtrates were concentrated in vacuo. The crude diastereomeric mixture of the allylic alcohol **7a** (7.38 g, along with a small amount of **15**) obtained was used for the next step without isolation. A solution of the above mixture in formic acid (100 mL) was heated at 70 °C for 2 h. The reaction mixture was diluted with water (100 mL) and extracted with chloroform (100 mL x 3). The combined organic extracts were washed with 5% $NaHCO_3$ solution, dried, and concentrated in vacuo to give the residue (7.33 g). Chromatography on a silica gel (150 g) column with hexane-ethyl acetate (3:1 - 2:1) as the eluent gave **8a** (3.93 g, 64.2%) as a colorless amorphous powder. Further elution with hexane-ethyl acetate (2:1 - 1:1) as the eluent gave **17** (1.19 g, 19.5%) as a colorless amorphous powder and with ethyl acetate as the eluent gave **13** (426.7 mg, 7.9 %) as a solid. *Method B*: Reduction of **16** (123.3 mg, 0.2 mmol) with lithium tri-*tert*-butoxyaluminum hydride (203.4 mg, 0.8 mmol) as described above afforded **7a** (153.1 mg). A solution of this residue in dry dichloromethane (1 mL) was cooled with ice-water, a dichloromethane solution of titanium(IV) chloride (1.0 M, 0.4 mL, 0.4 mmol) was added dropwise over 5 min. After being kept at room temperature for 1 h, the reaction mixture was poured onto water (15 mL) and the phase separated. The aqueous layer was extracted with dichloromethane (15 mL x 2). The combined extracts were washed with 5% $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give the residue (139.3 mg). Chromatography on a silica gel (12 g) column with hexane-ethyl acetate (3:1 - 2:1) as the eluent gave **8a** (103.1 mg, 85.9%) as a colorless amorphous powder. Further elution with hexane-ethyl acetate (2:1 - 1:1) as the eluent gave **17** (5.3 mg, 4.4%) as a colorless amorphous powder and with ethyl acetate as the eluent gave **13** (4.3 mg, 4.1 %) as a solid. *Method C*: Reduction of **16** (123.3 mg, 0.2 mmol) with lithium tri-*tert*-butoxyaluminum hydride (203.4 mg, 0.8 mmol) as described above afforded **7a** (150.1 mg). A solution of this residue in dry dichloromethane (1 mL) was cooled with ice-water, borron trifluoride diethyl etherate (50 μl, 0.4 mmol) was added dropwise over 5 min. After being kept at room temperature for 14 h, the reaction mixture was poured onto water (15 mL) and the phase separated. The aqueous layer was extracted with dichloromethane (15 mL x 2). The combined extracts were washed with 5% $NaHCO_3$ (10 mL), dried, and concentrated in vacuo to give the residue (137.6 mg). Chromatography on a silica gel (12 g) column with hexane-ethyl acetate (3:1 - 2:1) as the eluent gave **8a** (37.4 mg, 31.2%) as a colorless amorphous powder. Further elution with hexane-ethyl acetate (2:1 - 1:1) as the eluent gave **17** (73.7 mg, 61.0%) as a colorless amorphous powder and with ethyl acetate as the eluent gave **15** (7.0 mg, 6.6%) as a solid.

Compound 8a (not crystallizable): IR ($CHCl_3$) 1685, 1635 cm^{-1}; UV λ_{max} nm (log ε) 276 (4.15), 288 (4.08), 306 (3.84); ^1H NMR (at 50 °C) δ 1.27, 1.31 (each 3H, d, *J* = 6.3 Hz, $CHCH_3$), 2.13, 2.15 (each 3H, s, Ar CH_3), 2.93 (3H, s, OCH_3), 3.13 (1H, d, *J* = 16.2 Hz, H-6β), 3.23 (1H, dd, *J* = 16.2, 5.0 Hz, H-6α), 3.41, 3.81, 3.98 (each 3H, s, OCH_3), 4.58 (1H, d, *J* =

15.0 Hz, N-CHAr), 5.01 (1H, sept, J = 6.3 Hz, OCH), 5.23 (1H, dd, J = 5.0, 0.5 Hz, H-5), 5.56 (1H, d, J = 15.0 Hz, N-CHAr), 5.91 (1H, s, C=CH), 5.97 (1H, s, H-10), 6.63 (3H, br), 6.91 (1H, s, H-7), 7.02-7.14 (3H, m, 3 x ArH), 7.32 (1H, s, ArH); ^{13}C NMR δ (at 50 °C) 9.3 (q, 3'-CH_3), 15.9 (q, 8-CH_3), 22.2 (q, OCHCH_3), 22.2 (q, OCHCH_3), 31.8 (t, ^{6}C), 44.1 (t, NCH_2Ar), 49.1 (d, ^{1}C), 54.2 (d, ^{5}C), 54.9 (q, OCH_3), 56.2 (q, OCH_3), 59.8 (q, OCH_3), 60.3 (q, OCH_3), 69.5 (q, OCH), 106.1 (d, CH=C), 108.2 (d, ^{10}C), 110.9 (d, $^{6'}$C), 123.5 (s), 123.9 (s), 125.2 (s), 126.1 (d), 126.8 (d), 126.9 (s), 128.4 (d), 131.7 (d, ^{7}C), 132.2 (s), 135.9 (s), 137.2 (s), 149.4 (s), 150.9 (s), 153.1 (s, COO), 156.4 (s), 168.8 (s, CO); EI-MS m/z (relative intensity) 600 (M^+, 100), 218 (9), 174 (22), 91 (8); high-resolution EI-MS calcd for $C_{35}H_{40}N_2O_7$ 600.2836, found 600.2856.

Compound 17 (not crystallizable): IR ($CHCl_3$) 1695, 1668, 1603 cm^{-1}; UV λ_{max} nm (log ε) 214 (4.51), 244 (4.05), 288 (3.78), 318 (4.00); ^{1}H NMR δ 1.13 (3H, d, J = 6.3 Hz, $CHCH_3$), 1.20 (3H, d, J = 6.3 Hz, $CHCH_3$), 2.03, 2.17 (each 3H, s, Ar CH_3), 2.93 (2H, d, J = 7.6 Hz), 2.96 (1H, d, J = 21.5 Hz), 3.36 (1H, d, J = 21.5 Hz), 3.64, 3.70, 3.73, 3.80 (each 3H, s, OCH3), 4.79-4.99 (3H, m), 5.28 (1H, br), 6.59 (1H, d, J = 8.3 Hz), 6.96 (1H, br s), 6.99 (1H, br d, J = 8.3 Hz), 7.23-7.47 (5H, m); ^{13}C NMR δ 9.3 (q, Ar CH_3), 15.7 (q, ArCH_3), 21.6 (q, $CHCH_3$), 22.2 (q, $CHCH_3$), 30.4, (t), 35.9 (t), 46.5 (t, NCH_2), 55.2 (q, OCH_3), 59.8 (q, OCH_3), 60.0 (q, OCH_3), 60.8 (q, OCH_3), 70.1 (d, OCH), 109.4 (d), 120.1 (s), 121.2 (s), 124.4 (s), 125.8 (s), 127.0 (d x 2), 127.4 (s), 127.5 (d), 127.6 (d), 127.7 (s), 128.7 (d x 2), 131.8 (d), 136.5 (s), 142.8 (s), 149.6 (s), 151.5 (s, COO), 156.4 (s), 166.8 (s, CO) (three signals not observed); EIMS, m/z (relative intensity) 600 (M^+, 100), 381 (67), 380 (91), 379 (78), 378 (16), 349 (11), 288 (9), 136 (76), 135 (63), 92 (20), 91 (81); high-resolution EI-MS calcd for $C_{35}H_{40}N_2O_7$ 600.2836, found 600.2820.

(*E*)-3-Benzyl-2-[(1,2,3,4,5,6-hexahydro-2,4,5-trimethoxy-3-methylphenyl)methylene]-9-methoxy-8-methyl-1,5-imino-3-benzazocine (18).

From 8a. Concentrated H_2SO_4 (5 mL) was added to a stirred solution of **8a** (3.70 g, 6.167 mmol) in trifluoroacetic acid (100 mL), and the resulting solution was stirred for 19 h at room temperature. The reaction mixture was poured into water (400 mL) and extracted with dichloromethane (150 mL x 3). The combined extracts were washed with diluted NH_4OH, dried, and concentrated in vacuo to give a solid, recrystallization of which from chloroform-ether gave **18** (3.108 g, 98.0 %) as colorless prisms.

From 7a. Concentrated H_2SO_4 (12.5 mL) was added to a stirred solution of **7a** (34.0 g, 55.0 mmol) in trifluoroacetic acid (250 mL), and the resulting solution was stirred for 70 h at room temperature. The usual work-up as described above afforded the residue (32.94 g). Chromatography on a silica gel (100 g) column with ethyl acetate-methanol (20:1) as the eluent gave **18** as a solid, recrystallization of which gave **18** (14.277 g, 50.5 %) as colorless prisms. Further elution with ethyl acetate-methanol (10:1) as the eluent gave **19** (2.518 g, 8.9 %) as colorless needles.

Compound 18. mp 182.5-184 °C; IR (KBr) 3300, 1655, 1620 cm^{-1}; UV λ_{max} nm (log ε) 214 (4.57), 272 (4.10), 280 (4.09), 288 (4.05), 304 (3.77); ^{1}H NMR δ 2.15, 2.16 (each 3H, s, Ar CH_3), 2.30-2.70 (1H, br s, NH), 3.07 (1H, dd, J = 16.2, 0.5 Hz, H-6β), 3.18 (3H, s, OCH_3), 3.21 (1H, dd, J = 16.2, 5.0 Hz, H-6α), 3.45, 3.79, 3.79 (each 3H, s, OCH_3), 4.26 (1H, ddd, J = 5.0, 0.5, 0.5 Hz, H-5), 4.82 (1H, d, J = 15.0 Hz, N-CHAr), 5.17 (1H, d, J = 0.5 Hz, H-1), 5.30 (1H, d, J = 15.0 Hz, N-CHAr), 5.67 (1H, s, C=CH), 5.93 (1H, s, H-10), 6.53 (1H, s, ArH), 6.75 (2H, m), 6.87 (1H, s, 7-H), 7.05-7.15 (3H, m); ^{13}C NMR δ 9.5 (q, 3'-CH_3), 15.9 (q, 8-CH_3), 32.6 (t, C-6), 44.2 (t, NCH_2Ar), 50.5 (d, C-1), 54.3 (d, C-5), 54.9 (q, OCH_3), 56.1 (q, OCH_3), 59.9 (q, OCH_3), 60.3 (q, OCH_3), 103.6 (d, CH=C), 108.5 (d, C-10), 111.2 (d, C-6'), 123.6 (s), 124.6 (s), 126.1 (s), 126.3 (s), 126.3 (d), 126.8 (d), 128.3 (d), 131.0 (d, C-7), 136.4 (s), 147.2 (s), 149.1 (s), 150.4 (s), 156.1 (s), 168.8 (s, CO); EI-MS m/z (relative intensity) 514 (M^+, 100), 499 (13), 484 (43), 334 (11), 333 (14), 313 (10), 175 (16), 174 (80), 91 (21). Anal. Calcd for $C_{31}H_{34}N_2O_5 \cdot 1/2H_2O$: C, 71.11; H, 6.74; N, 5.35. Found: C, 71.39; H, 6.60; N, 5.44.

Compound 19. mp 164-166 °C; IR (KBr) 3330, 1700, 1645, 1625 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.31), 280 (3.65), 286 (3.61), 310sh (2.92); ^{1}H NMR δ 1.90-2.10 (1H, br s, NH), 2.18, 2.23 (each 3H, s, Ar CH_3), 2.97 (1H, dd, J = 14.8, 9.6 Hz, H-2a), 3.09 (1H, d, J = 16.2 Hz, H-6β), 3.31 (1H, dd, J = 14.8, 7.6 Hz, H-2a), 3.34 (1H, dd, J = 16.2, 6.3 Hz, H-6α), 3.48, 3.52 (each 3H, s, OCH_3), 3.67 (1H, dd, J = 9.6, 7.6 Hz, H-2), 3.71, 3.73 (each 3H, s, OCH_3), 4.02 (1H, d, J = 15.5 Hz, NCHAr), 4.07 (1H, d, J = 6.3 Hz, H-5), 5.33 (1H, d, J = 15.5 Hz, NCHAr), 6.19 (1H, s, ArH), 6.66 (2H, d, J = 7.3 Hz), 6.96-7.12 (4H, m); ^{13}C NMR δ 9.5 (q, ArCH_3), 15.9 (q, 8-CH_3), 32.8* (t, C-6), 33.1* (t, C-2a), 47.4 (t, NCH_2Ar), 54.1 (d, C-5), 55.4 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (q, OCH_3), 60.4 (q, OCH_3), 64.7 (s, ^{1}C), 68.8 (d, C-2), 107.1 (d, C-10), 124.4 (s), 125.8 (s), 126.5 (s), 126.9 (d), 128.3 (d), 131.0 (d, C-7), 134.3 (s), 136.2 (s), 137.3 (s), 146.1 (s), 150.5 (s), 151.4 (s), 156.2 (s), 171.4 (s, CO); (* Assignments bearing the same symbols may be interchanged.); EI-MS m/z (relative intensity) 514 (M^+, 4), 364 (7), 135 (9), 91 (100). Anal. Calcd for $C_{31}H_{34}N_2O_5 \cdot 1/4H_2O$: C, 71.72; H, 6.70; N, 5.40. Found: C, 71.50; H, 6.72; N, 5.43.

Treatment of 17 with 5% H_2SO_4 in Trifluoroacetic Acid.

Concentrated H_2SO_4 (0.15 mL) was added to a stirred solution of **17** (73.8 mg, 0.123 mmol) in trifluoroacetic acid (3 mL), and the resulting solution was stirred for 40 h at room temperature. The reaction mixture was poured into water (5 mL) and extracted with dichloromethane (10 mL x 3). The combined extracts were washed with diluted NH_4OH, dried, and concentrated in vacuo. The residue (61.4 mg) was subjected to chromatography (silica gel, 7 g, elution with 200:1 dichloromethane-methanol) to give **20** (42.3 mg, 68.9%) as a solid, which was identical in all respects with **19** prepared above.

(*E*)-3-Benzyl-2-[(1,2,3,4,5,6-hexahydro-2,4,5-trimethoxy-3-methylphenyl)methylene]-9-methoxy-8,11-dimethyl-1,5-imino-3-benzazocine (20).

Formaldehyde (37 wt % solution water 15 mL) was added to a stirred solution of **18** (3.108 g, 6.047 mmol) in formic acid (17.4 mL) at 50 °C for 10 min. After being stirred at 70 °C for 2 h, the reaction mixture was poured into water (50 mL) and extracted with chloroform (100 mL x 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and then water (100 mL), dried and concentrated in vacuo to give a solid, recrystallization of which from ethyl acetate-ether gave **20** (2.69 g, 84.3%) as colorless prisms: mp 165-166 °C; IR (KBr) 1655, 1615, 1580 cm^{-1}; UV λ_{max} nm (log ε) 214 (4.60), 265 (4.11), 279 (4.10), 289 (4.07), 304 (3.76); ^1H NMR δ 2.15, 2.16 (each 3H, s, Ar CH_3), 2.72 (3H, s, NCH_3), 2.99 (1H, d, J = 16.2 Hz, H-6β), 3.13 (3H, s, OCH_3), 3.29 (1H, dd, J = 16.2, 5.9 Hz, H-6α), 3.46, 3.79, 3.80 (each 3H, s, OCH_3), 3.86 (1H, dd, J = 5.9, 0.5 Hz, H-5), 4.89 (1H, d, J = 16.2 Hz, N-CHAr), 4.95 (1H, d, J = 0.5 Hz, H-1), 5.30 (1H, d, J = 16.2 Hz, N-CHAr), 5.85 (1H, s, C=CH), 5.95 (1H, s, H-10), 6.54 (1H, s, ArH), 6.76-6.79 (2H, m), 6.88 (1H, s, 7-H), 7.06-7.16 (3H, m); ^{13}C NMR δ 9.4 (q, 3'-CH_3), 16.0 (q, 8-CH_3), 31.3 (t, C-6), 41.4 (q, NCH_3), 44.2 (t, NCH_2Ar), 54.9 (q, OCH_3), 56.0 (q, OCH_3), 56.7 (d, C-1), 59.7 (q, OCH_3), 60.3 (q, OCH_3), 61.0 (d, C-5), 106.7 (d, *C*H=C), 108.8 (d, C-10), 111.1 (d, C-6'), 123.1 (s), 124.5 (s), 126.1 (s), 126.3 (d), 126.7 (d), 128.4 (d), 130.6 (d, C-7), 132.8 (s), 136.5 (s), 138.5 (s), 147.2 (s), 148.9 (s), 150.4 (s), 156.1 (s), 169.9 (s, CO); EI-MS *m/z* (relative intensity) 528 (M^+, 61), 437 (8), 189 (22), 188 (100). Anal. Calcd for $C_{32}H_{36}N_2O_5$: C, 72.70; H, 6.86; N, 5.30. Found: C, 72.50; H, 6.86; N, 5.25.

Methylation of 19.

Formaldehyde (37 wt % solution water 13.4 mL) was added to a stirred solution of **19** (2.056 g, 4.0 mmol) in formic acid (15.2 mL) at 50 °C for 10 min. After being stirred at 70 °C for 38 h, the reaction mixture was poured into water (50 mL) and extracted with chloroform (100 mL x 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and then water (100 mL), dried and concentrated in vacuo to give a solid, recrystallization of which from ethyl acetate-ether gave **21** (1.836 g, 86.9%) as colorless prisms: mp 209-211 °C; IR (KBr) 1655, 1615, 1580 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.28), 282 (3.57), 286 (3.51); ^1H NMR δ 2.20, 2.23 (each 3H, s, Ar CH_3), 2.32 (3H, s, NCH_3), 2.86 (1H, d, J = 16.8 Hz, H-6β), 3.03 (1H, dd, J = 14.2, 9.6 Hz, H-2a), 3.20 (1H, dd, J = 14.2, 7.3 Hz, H-2a), 3.45 (1H, dd, J = 16.8, 5.6 Hz, H-6α), 3.46 (3H, s, OCH_3), 3.52 (1H, dd, J = 9.6, 7.3 Hz, H-2), 3.56, 3.69, 3.74 (each 3H, s, OCH_3), 3.91 (1H, d, J = 5.6 Hz, H-5), 3.96 (1H, d, J = 15.5 Hz, NCHAr), 5.34 (1H, d, J = 15.5 Hz, NCHAr), 6.17 (1H, s, ArH), 6.58 (2H, d, J = 7.3 Hz), 6.94 (1H, s, ArH), 6.97-7.09 (3H, m); ^{13}C NMR δ 9.5 (q, $ArCH_3$), 15.9 (q, 8-CH_3), 25.5 (t, C-6), 33.2 (t, C-2a), 37.1 (q, NCH_3), 46.9 (t, NCH_2Ar), 55.3 (q, OCH_3), 59.6 (q, OCH_3), 59.8 (q, OCH_3), 60.3 (q, OCH_3), 61.0 (d, C-5), 69.5 (s, C-1), 70.2 (d, C-2), 108.4 (d, C-10), 123.9 (s), 125.6 (s), 126.5 (s), 126.8 (d), 128.2 (d), 129.8 (s), 130.8 (d, ^7C), 131.4 (s), 135.2 (s), 136.2 (s), 147.2 (s), 150.4 (s), 150.4 (s), 156.4 (s), 171.2 (s, CO); EI-MS *m/z* (relative intensity) 528 (M^+, 57), 409 (12), 394 (10), 365 (63), 364 (100), 350 (24), 349 (35), 334 (15), 333 (18), 165 (20), 91 (84). Anal. Calcd for $C_{32}H_{36}N_2O_5$: C, 72.70; H, 6.86; N, 5.30. Found: C, 72.57; H, 6.97; N, 5.29.

X-ray Structure Determination of Compound 21.

Crystals of **21** ($C_{32}H_{36}N_2O_5$) belong to the monoclinic space group $P2_1/n$ with cell constants a = 19.344 (2) Å, b = 11.485 (8) Å, c = 25.266 (3) Å, β = 102.472 (8)°, Z = 8 (two molecules are included in an asymetric unit), d_c = 1.281 g/cm^3. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Cu-Kα radiation. The data were collected at a tempetarure of 23 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 120.2°. A total of 8922 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu-Kα radiation is 7.0 cm^{-1}. An empirical absorption correction using the program DIFABS was applied which resulted in transmission factors ranging from 0.76 to 1.24. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR88)[20] and expanded using Fourier techniques.[21] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 3956 observed reflections ($I > 300\ \delta(I)$) and 991 variable parameters and converged (largest parameter was 5.25 times its esd) with unweighted and weighted agreement factors of R = 0.075 and $R\omega$ = 0.069. The drawing of the molecule was made by ORTEP.

Reduction of 21 with aluminum hydride.

A stirred solution of the lactam **21** (105.4 mg, 0.2 mmol) in dry THF (5 mL) was cooled with ice-water, A THF solution of aluminum hydride (0.5 M, 2.4 mL, 1.2 mmol) was added dropwise over 15 min, and then stirring was continued at 0 °C for 30 min. After being quenched by addition of MeOH (0.5 mL), the reaction mixture was concentrated in vacuo to give a solid (117 mg), which was subjected to chromatography (silica gel, 10 g; elution with 4:1 benzene-ethyl acetate) to give **22** (93.5 mg, 91.1%) as colorless needles: mp 155-156 °C; IR (KBr) 2930, 2905, 2880, 2850, 2820, 2800, 1605, 1595, 1970, 1500, 1490, 1460, 1430, 1400, 1370, 1350, 1310, 1265, 1230, 1200, 1165, 1135, 1110, 1085, 1040, 1025, 1010, 985, 980, 935, 915, 900, 890, 875, 855, 840, 800, 765, 725, 690 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.30), 282 (3.60), 288 (3.51); ^1H NMR δ 2.21, 2.26 (each 3H, s, Ar CH_3), 2.33 (3H, s, NCH_3), 2.49 (1H, d, J = 16.8 Hz, H-6β), 2.63 (1H, dd, J = 11.9, 3.3 Hz, H-4), 2.74 (1H, dd, J = 13.5, 6.3 Hz, H-2a), 3.02 (1H, dd, J = 10.0, 6.3 Hz, H-2), 3.07-3.12 (2H, m, H-4 and H-5), 3.20 (1H, dd, J = 13.5, 10.0 Hz, H-2a), 3.24 (1H, dd, J = 16.8, 7.3 Hz, H-6α), 3.58 (1H, d, J = 13.9 Hz, NCHAr), 3.62 (1H, d, J = 13.9 Hz, NCHAr), 3.63, 3.69, 3.74, 3.78 (each 3H, s, OCH_3), 6.41 (1H, s, ArH), 6.91-6.94 (3H, m), 7.09-7.13 (3H, m); ^{13}C NMR δ 9.4 (q, $ArCH_3$), 16.0 (q, 8-CH_3), 23.8 (t, C-2a), 26.6 (t, C-6), 39.4 (q, NCH_3), 54.1 (t, C-4), 54.7 (d, C-5), 55.4 (q, OCH_3), 58.4 (t, N-CH_2Ar), 59.5 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 70.0 (s, C-1), 71.4 (d, C-2), 109.4 (d, C-10), 124.0 (s), 125.2 (s), 126.6 (d), 127.1 (s), 128.0 (d), 128.0 (d), 129.0 (d, ^7C), 131.4 (s), 132.6 (s), 136.2 (s), 139.2 (s), 147.0 (s), 149.8

(s), 151.1 (s), 155.1 (s); EI-MS *m/z* (relative intensity) 514 (M^+, 20), 424 (79), 423 (100), 394 (10), 161 (29), 91 (51). Anal. Calcd for $C_{32}H_{38}N_2O_4 \cdot 1/10H_2O$: C, 74.42; H, 7.46; N, 5.42. Found: C, 74.22; H, 7.62; N, 5.30.

2-[1,2,3,4,5,6-Hexahydro-2,4,5-trimethoxy-3-methylphenyl)methyl]-9-methoxy-8,11-dimethyl-(1α,2α,5α)-1,5-imino-3-benzazocine (24).

A stirred solution of the lactam **20** (6.336 g, 12 mmol) in dry THF (180 mL) was cooled with ice-water, a THF solution of aluminum hydride (0.5 M, 144 mL, 72 mmol) was added dropwise over 30 min, and then stirring was continued at 0 °C for 1 h. After being quenched by addition of MeOH (10 mL), the reaction mixture was concentrated in vacuo to give **23** (6.34 g) as an amorphous powder, which was used the next step without further purification. An analytical sample was obtained by column chromatography (elution with 100:1 dichloromethane-MeOH): IR ($CHCl_3$) 1660, 1625 cm^{-1}; UV λ_{max} nm (log ε) 206 (4.74), 236sh (4.16), 281 (3.98), 290 (3.96), 308sh (3.77); ^1H NMR δ 2.15 (3H, s, Ar CH_3), 2.19 (3H, s, Ar CH_3), 2.55 (3H, s, NCH_3), 2.63 (1H, d, *J* = 16.2 Hz, H-6β), 2.95 (1H, d, *J* = 10.2 Hz, H-4), 3.06 (3H, s, OCH_3), 3.23 (1H, dd, *J* = 16.2, 7.3 Hz, H-6α), 3.27 (1H, br d, H-5), 3.45 (1H, m, H-4), 3.52, 3.80 (each 3H, s, OCH_3), 3.80 (1H, d, *J* = 15.2 Hz, NCHAr), 3.86 (3H, s, OCH_3), 4.25 (1H, d, *J* = 15.2 Hz, NCHAr), 4.79 (1H, s, H-1), 5.29 (1H, s, C=CH), 5.98 (1H, s, H-10), 6.75 (1H, s, H-7), 6.80-6.84 (2H, m), 6.88 (1H, s, ArH), 7.08-7.12 (3H, m); ^{13}C NMR δ 9.4 (q), 16.0 (q), 28.4 (t), 41.0 (q), 53.5 (d), 55.0 (q), 55.1 (t), 56.0 (q), 57.5 (t), 58.1 (d), 59.5 (q), 60.3 (q), 99.9 (d), 108.9 (d), 111.9 (d), 124.8 (s), 125.2 (s), 126.6 (s), 126.7 (s), 127.1 (d), 128.2 (d), 129.6 (d), 134.5 (s), 138.7 (s), 145.5 (s), 146.0 (s), 148.6 (s), 150.7 (s), 155.4 (s); EI-MS *m/z* (relative intensity) 514 (M^+, 97), 484 (34), 483 (89), 396 (10), 203 (12), 202 (17), 190 (35), 189 (20), 188 (100), 173 (12), 91 (9); high-resolution MS calcd for $C_{32}H_{38}N_2O_4$ 514.2832, found 514.2827. A solution of the crude **23** (6.34 g) in ethanol (40 mL) was shaken for 40 h at 80 °C under 4 atm of hydrogen in the presence of 20% palladium on carbon (2.0 g). The catalyst was removed by filtration and washed it with ethanol (200 mL). The combined filtrates were concentrated in vacuo and the residue was dissolved with benzene (200 mL) and extracted with 1N HCl (100 mL x 3). The combined aqueous layers were made alkaline with 10% NH_4OH and extracted with chloroform (100 mL x 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to give a solid, recrystallization of which from ether gave **24** (4.88 g, 95.5%) as colorless needles: mp 78-80 °C; IR (KBr) 3430, 3350, 1675, 1625, 1600, 1510, 1500, 1475, 1455, 1430, 1415, 1375, 1360, 1345, 1325, 1245, 1220, 1145, 1125, 1110, 1090, 1035, 1015, 990, 945, 920, 880, 860, 850, 790, 770, 750, 730, 710, 695, 660, 640, 625, 610 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.19), 280 (3.63), 288 (3.65); ^1H NMR δ 1.20-2.00 (1H, br s, NH), 2.19 (3H, s, Ar CH_3), 2.21 (3H, s, Ar CH_3), 2.25 (1H,dd, *J* = 14.9, 8.3 Hz, H-2a), 2.32 (3H, s, NCH_3), 2.48 (1H, d, *J* = 17.5 Hz, H-6β), 2.77 (1H, dd, *J* = 14.9, 5.9 Hz, H-2a), 2.99 (1H, d, *J* = 11.2 Hz, H-4), 3.01 (1H, br s, H-5), 3.08 (1H, dd, *J* = 17.5, 7.6 Hz, H-6α), 3.24 (1H, dd, *J* = 11.2, 3.0 Hz, H-4), 3.53 (1H, ddd, *J* = 8.3, 5.9, 2.3 Hz, H-2), 3.56 (1H, d, *J* = 2.3 Hz, H-1), 3.58, 3.78, 3.80, 3.81 (each 3H, s, OCH_3), 6.40 (1H, s, H-10), 6.67 (1H, s, ArH), 6.92 (1H, s, H-7); ^{13}C NMR δ 9.6 (q), 16.0 (q), 26.0 (t, C-2a), 33.2 (t, C-6), 41.8 (q), 52.7 (d, C-5), 54.3 (t, C-4), 55.2 (q), 56.0 (q), 59.6 (d, C-2), 60.2 (q), 60.5 (q), 62.8 (d, ^1C), 110.4 (d, C-6'), 111.1 (d, C-10), 125.3 (s), 125.4 (s), 126.7 (s), 126.9 (s), 129.8 (s), 130.0 (d, C-7), 146.2 (s), 149.2 (s), 150.7 (s), 155.3 (s); EI-MS *m/z* (relative intensity) 426 (M^+, 11), 232 (12), 231 (71), 203 (11), 202 (13), 191 (12), 190 (84), 189 (21), 188 (100). Anal. calcd for $C_{25}H_{34}N_2O_4 \cdot H_2O$: C, 67.54; H, 8.16; N, 6.30. Found, C, 67.14; N, 8.02; N, 6.34.

Butyl 6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9β,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-carboxylate (26).

A solution of **24** (937.2 mg, 2.2 mmol) and anhydrous K_2CO_3 (3.036 g, 22 mmol) in butanol (40 mL) was stirred for 30 min. Butyl glyoxalate (2.86 g, 22 mmol) in butanol (10 mL) was then added dropwise over 30 min, and the mixture was stirred at room temperature for 44 h and then filtered, which was washed with chloroform (200 mL). The combined filtrates were concentrated in vacuo. The *O,N*-acetal **25** (containing butanol) was stirred with trifluoroacetic acid (25 mL) at room temperature for 1 h. The reaction mixture was diluted with water (100 mL), made alkaline with $NaHCO_3$, and extracted with chloroform (40 mL x 3). The combined extracts were washed with water (50 mL), dried, and concentrated in vacuo. The residual oil (3.55 g) was subjected to chromatography (silica gel, 80 g; elution with 1:5 hexane-ethyl acetate) to give **26** (814.1 mg, 68.8%) as colorless amorphous powder: IR ($CHCl_3$) 1720 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.13), 280 (3.55), 287 (3.47); ^1H NMR δ 0.89 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.33 (2H, m, CH_2CH_3), 1.61 (2H, m, OCH_2CH_2), 2.12 (3H, s, Ar CH_3), 2.13 (3H, s, Ar CH_3), 2.32 (3H, s, NCH_3), 2.58 (1H, dd, *J* = 17.5, 10.6 Hz, H-14β), 2.60 (1H, d, *J* = 17.2 Hz, H-5β), 2.88 (1H, dd, *J* = 17.5, 3.0 Hz, H-14α), 2.93 (1H, dd, *J* = 10.5, 3.3 Hz, H-7), 3.04 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.04 (1H, dd, *J* = 10.5, 1.0 Hz, H-7), 3.21 (1H, br d, H-6), 3.59 (3H, s, OCH_3), 3.61 (1H, dd, *J* = 10.6, 3.0 Hz, H-14a), 3.61 (1H, s, H-15), 3.67, 3.71, 3.82 (each 3H, s, OCH_3), 4.11 (2H, m, OCH_2), 4.58 (1H, s, H-9), 6.53 (1H, s, H-1), 6.84 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 13.7 (q, CH_2CH_3), 15.9 (q, 3-CH_3), 19.2 (t, CH_2CH_3), 26.0 (t, C-14), 26.3 (t, C-5), 30.7 (t, OCH_2CH_2), 41.8 (q, NCH_3), 53.2 (d, C-6), 53.5 (d, C-14a), 55.4 (q, OCH_3), 59.2 (t, C-7), 59.5 (q, OCH_3), 59.7 (q, OCH_3), 59.8 (q, OCH_3), 62.1 (d, C-9), 63.8 (d, C-15), 64.2 (t, OCH_2), 112.0 (d, C-1), 123.4 (s), 123.9 (s), 124.0 (s), 125.3 (s), 126.9 (s), 130.3 (d, C-4), 130.6 (s), 145.6 (s), 148.7 (s), 151.6 (s), 154.8 (s), 171.6 (s, CO); EI-MS *m/z* (relative intensity) 538 (M^+, 8), 438 (30), 437 (100), 218 (11), 203 (8), 189 (11), 188 (30); high-resolution EI-MS calcd for $C_{31}H_{42}N_2O_6$ 538.3043, found, 538.3032.

Butyl 6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-carboxylate (27).

A solution of **26** (3.36 g, 6.245 mmol) and mercury(II) acetate (19.90 g, 62.45 mmol) in 5% aqueous acetic acid (200 mL) was heated at 90 °C for 2 h and treated with hydrogen sulfide for 1 h at the same temperature. After filtration of the mixture through cellulose powder and the filter cake was carefully washed with ethanol (300 mL). The combined filtrates were

concentrated in vacuo and the residue was again dissolved in 50% aqueous ethanol (100 mL). The pH was brought to 6-7 with solid $NaHCO_3$, to which was added sodium borohydride (4.74 g, 125 mmol), and the mixture was left at room temperature for 1 h. The solution was acidified with 1N HCl and concentrated to a small volume, the residual solution was extracted with benzene (100 mL x 3). The organic layer was washed with water (100 mL), dried, and concentrated in vacuo to give the neutral fraction (4.39 g), which was subjected to chromatography (silica gel, 120 g; elution with 60:1 dichloromethane-methanol) to give **26** (96.3 mg, 2.9% recovery) as colorless amorphous powder. Further elution with 50:1 dichloromethane-methanol gave **27** (2.28 g, 67.9 %) as colorless amorphous powder. The acidic aqueous layer was made alkaline with diluted NH_4OH and extracted with chloroform (50 mL x 3). The combined extracts were washed with water (50 mL), dried, and concentrated in vacuo to give the residue (230 mg), which was subjected to chromatography (silica gel, 20 g; elution with 100:1 dichloromethane-methanol) to give **28** (120.0 mg, 4.4%) as colorless amorphous powder.

Compound 27 (not crystallizable): IR ($CHCl_3$) 1720 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.22), 280 (3.55), 288 (3.46); ^1H NMR δ 0.81 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.16 (2H, m, CH_2CH_3), 1.40 (2H, m, OCH_2CH_2), 2.16 (3H, s, Ar CH_3), 2.16 (3H, s, Ar CH_3), 2.29 (1H, dd, *J* = 15.2, 11.9 Hz, H-14β), 2.35 (3H, s, NCH_3), 2.51 (1H, d, *J* = 17.2 Hz, H-5β), 2.84 (2H, m, H-14a and H-14α), 2.94 (1H, dd, *J* = 10.5, 2.3 Hz, H-7), 3.02 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.18 (1H, br d, H-6), 3.26 (1H, dd, *J* = 10.5, 2.3 Hz, H-7), 3.60 (1H, d, *J* = 2.4 Hz, H-15), 3.60, 3.71, 3.72, 3.81 (each 3H, s, OCH_3), 3.93 (2H, m, OCH_2), 4.10 (1H, s, H-9), 6.49 (1H, s, H-1), 6.81 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 13.6 (q, CH_2CH_3), 15.9 (q, 3-CH_3), 19.0 (t, CH_2CH_3), 26.5 (t, C-14), 27.1 (t, C-5), 30.4 (t, OCH_2CH_2), 41.4 (q, NCH_3), 53.6 (d, C-6), 55.4 (q, OCH_3), 59.1 (d, C-14a), 59.5 (q, OCH_3), 59.9 (q, OCH_3), 60.1 (q, OCH_3), 61.6 (t, C-7), 64.2 (d, C-9), 64.4 (t, OCH_2), 64.5 (d, C-15), 111.1 (d, C-1), 123.9 (s), 124.0 (s), 124.2 (s), 125.0 (s), 127.3 (s), 129.7 (d, C-4), 130.2 (s), 145.9 (s), 149.0 (s), 150.9 (s), 154.8 (s), 172.1 (s, CO); EI-MS *m/z* (relative intensity) 538 (M^+, 17), 438 (31), 437 (100), 218 (18), 203 (15), 189 (26), 188 (83); high-resolution EI-MS calcd for $C_{31}H_{42}N_2O_6$ 538.3034, found, 538.3054.

Compound 28 (not crystallizable): IR ($CHCl_3$) 2900, 2830, 2750, 1613, 1455, 1445, 1405, 1355, 1345, 1305, 1288, 1140, 1108, 1070, 1008, 963, 905, 888, 855, 845 cm^{-1}; UV λ_{max} nm (log ε) 224 (4.26), 280 (3.51), 288 (3.45); ^1H NMR δ 2.13 (3H, s, Ar CH_3), 2.15 (3H, s, Ar CH_3), 2.38 (3H, s, NCH_3), 2.51 (1H,dd, *J* = 15.8, 11.2 Hz, H-14β), 2.67 (1H, d, *J* = 17.5 Hz, H-5β), 2.70 (1H, ddd, *J* = 11.2, 3.0, 2.6 Hz, H-14a), 2.77 (1H, dd, *J* = 10.5, 3.3 Hz, H-7), 2.84 (1H, dd, *J* = 15.8, 3.0 Hz, H-14α), 3.10 (1H, dd, *J* = 17.5, 7.9 Hz, H-5α), 3.10 (1H, dd, *J* = 10.5, 2.3 Hz, H-7), 3.12 (1H, d, *J* = 16.2 Hz, H-9), 3.27 (1H, br d, H-6), 3.58 (3H, s, OCH_3), 3.63 (1H, d, *J* = 2.6 Hz, H-15), 3.73, 3.76, 3.82 (each 3H, s, OCH_3), 3.99 (1H, d, *J* = 16.2 Hz, H-9), 6.54 (1H, s, H-1), 6.88 (1H, s, H-4); ^{13}C NMR δ 9.0 (q, 12-CH_3), 15.8 (q, 3-CH_3), 26.3 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH_3), 53.2 (d, C-6), 53.3 (t, C-9), 55.3 (q, OCH_3), 59.5 (q, OCH_3), 59.9 (q, OCH_3), 59.9 (d, C-14a), 60.0 (q, OCH_3), 63.3 (d, C-15), 63.4 (t, C-7), 111.6 (d, C-1), 122.4 (s), 122.7 (s), 125.4 (s), 125.5 (s), 126.4 (s), 130.3 (s), 130.6 (d, C-4), 145.1 (s), 149.1 (s), 151.6 (s), 154.8 (s); EI-MS *m/z* (relative intensity) 438 (M^+, 40), 250 (20), 249 (15), 203 (22), 190 (28), 189 (20), 188 (100); high-resolution EI-MS calcd for $C_{26}H_{34}N_2O_4$ 438.2519, found, 438.2530.

6,7,9,14,14a,15-Hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine (28).

A solution of **24** (117.6 mg, 0.276 mmol) and anhydrous K_2CO_3 (305 mg, 2.21 mmol) in ethanol (2 mL) was stirred for 10 min at room temperature. Paraformaldehyde (33.1 mg, 1.103 mmol) was then added in one portion, and the mixture was stirred for 16 h at room temperature and filtered. The residue was washed with chloroform (30 mL). The combined filtrates were concentrated in vacuo. The residue (104 mg) was stirred with trifluoroacetic acid (4 mL) at room temperature for 20 h, then concentrated. The remaining mixture was diluted with water (10 mL), made alkaline with saturated $NaHCO_3$ solution, and extracted with chloroform (20 mL x 3). The combined extracts were washed with water, dried, and concentrated in vacuo to give the residue (84.2 mg), which was subjected to chromatography (silica gel, 10 g, elution with 100:1 dichloromethane-methanol) to give **28** (64.0 mg, 53.0%) as colorless amorphous powder, which was identical in all respects with **28** prepared as above.

6,7,9,14,14a,15-Hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanol (29).

At room temperature. Lithium aluminum hydride (964 mg, 25.4 mmol) was added to a stirred solution of **27** (2.28 g, 4.238 mmol) in dry THF (200 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. After being quenched at 0 °C by addition of water, the mixture was filtered and the filter cake was carefully washed with chloroform (400 mL). The combined filtrates were concentrated in vacuo. The residue was subjected to chromatography (silica gel, 100 g; elution with 40:1 - 20:1 ethyl acetate-methanol) to give a solid, recrystallization of which from ethyl acetate gave **29** (1.648 g, 83.1%) as colorless needles: mp 172-173.5 °C; IR (KBr) 3700-3200, 1615, 1510, 1470, 1435, 1415, 1390, 1365, 1345, 1325, 1300, 1285, 1265, 1245, 1215, 1200, 1155, 1115, 1085, 1050, 1010, 970, 850, 765 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.24), 270 (3.40), 280 (3.60), 289 (3.52); ^1H NMR δ 2.07 (1H, dd, *J* = 14.9, 11.9 Hz, H-14β), 2.15 (3H, s, Ar CH_3), 2.17 (3H, s, Ar CH_3), 2.42 (3H, s, NCH_3), 2.50-2.57 (1H, br, OH), 2.59 (1H, d, *J* = 16.8 Hz, H-5β), 2.88 (1H, dd, *J* = 14.9, 2.6 Hz, H-14α), 2.96 (1H, ddd, *J* = 11.9, 2.6, 2.3 Hz, H-14a), 3.04 (1H, dd, *J* = 10.9, 2.3 Hz, H-7), 3.09 (1H, dd, *J* = 10.9, 1.0 Hz, H-7), 3.13 (1H, dd, *J* = 16.8, 7.3 Hz, H-5α), 3.21 (1H, br d, H-6), 3.28 (1H, dd, *J* = 10.2, 2.0 Hz, *CH*OH), 3.63 (3H, s, OCH_3), 3.66 (1H, br s, H-15), 3.68 (1H, dd, *J* = 10.2, 2.6 Hz, *CH*OH), 3.73 (1H, br s, H-9), 3.74, 3.81, 3.81 (each 3H, s, OCH_3), 6.51 (1H, s, H-1), 6.92 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 16.0 (q, 3-CH_3), 26.7 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH_3), 53.8 (d, C-6), 55.4 (q, OCH_3), 58.8 (d, C-14a), 59.5 (d, C-9), 59.5 (q, OCH_3), 60.1 (q, OCH_3), 60.4 (q, OCH_3), 60.6 (t, C-7), 64.2 (d, C-15), 64.5 (t, 9-CH_2), 111.0 (d, C-1), 123.4 (s), 124.3 (s), 125.7 (s), 126.7 (s), 126.9 (s), 129.7 (d, C-4), 130.2 (s), 145.8 (s), 149.5 (s),

150.7 (s), 155.1 (s); EI-MS *m/z* (relative intensity) 468 (M^+, 1), 438 (32), 437 (100), 204 (10), 189 (8), 188 (45). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74; N, 5.98. Found: C, 69.07; H, 7.72; N, 5.95.

Under reflux. Lithium aluminum hydride (49.5 mg, 1.306 mmol) was added to a stirred solution of **27** (117.0 mg, 0.2174 mmol) in dry THF (8 mL) at 0 °C, and the mixture was heated under reflux for 2 h. After being quenched at 0 °C by addition of water, the mixture was filtered and the filter cake was carefully washed with chloroform (400 mL). The combined filtrates were concentrated in vacuo to give the residue (135 mg). Chromatography on a silica gel (12 g) column with ethyl acetate as the eluent gave **29** (60.8 mg, 59.7%) as a solid. Further elution with ethyl acetate-methanol (50:1) as the eluent gave compound **viii** (18.4 mg, 18.6%) as a solid and with ethyl acetate-methanol (20:1) as the eluent gave the phenol **vii** (5.5 mg, 4.9%) as colorless amorphous powder.

6,7,9,14,14a,15-Hexahydro-10-hydroxy-2,11,13-trimethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanol (vii): IR ($CHCl_3$) 3530, 3500-3300, 1615, 1460, 1405, 1358, 1345, 1320, 1300, 1280, 1145, 1108, 1050, 1008, 908, 885, 855 cm^{-1}; UV λ_{max} nm (log ε) 228 (4.16), 284 (3.76); ^1H NMR δ 2.09 (1H, dd, *J* = 14.5, 11.9 Hz, H-14β), 2.16 (3H, s, Ar CH_3), 2.18 (3H, s, Ar CH_3), 2.45 (3H, s, NCH_3), 2.63 (1H, d, *J* = 17.5 Hz, H-5β), 2.87 (1H, dd, *J* = 14.9, 2.3 Hz, H-14α), 3.04-3.19 (5H, m, 2 x H-7, H-14a, H-5α, and OH), 3.26 (1H, br d, H-6), 3.51 (1H, dd, *J* = 10.6, 2.0 Hz, C*H*OH), 3.61 (3H, s, OCH_3), 3.68 (1H, dd, *J* = 10.6, 4.0 Hz, C*H*OH), 3.73 (3H, s, OCH_3), 3.76 (2H, br s, H-9 and H-15), 3.81 (3H, s, OCH_3), 6.51 (1H, s, H-1), 6.92 (1H, s, H-4); EI-MS *m/z* (relative intensity) 454 (M^+, 1), 424 (32), 423 (100), 204 (12), 189 (12), 188 (66); high-resolution EI-MS calcd for $C_{25}H_{31}N_2O_4$ (base peak) 423.2284, found 423.2269.

6,7,9,14,14a,15-Hexahydro-2,10,11,13-trimethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanol (viii): colorless prisms from ethyl acetate, mp 192-194 °C dec; IR (KBr) 3700-3200, 1615, 1590, 1505, 1490, 1455, 1415, 1370, 1355, 1335, 1325, 1310, 1275, 1230, 1210, 1190, 1150, 1125, 1110, 1075, 1060, 1050, 1045, 1010, 990, 970, 920, 885, 845, 800, 765, 745 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.23), 282 (3.62), 289 (3.48); ^1H NMR δ 2.09 (3H, s, Ar CH_3), 2.14 (1H, dd, *J* = 15.2, 11.6 Hz, H-14β), 2.17 (3H, s, Ar CH_3), 2.33-2.54 (1H, br, OH), 2.42 (3H, s, NCH_3), 2.60 (1H, d, *J* = 17.2 Hz, H-5β), 2.86 (1H, dd, *J* = 15.2, 2.6 Hz, H-14α), 3.03 (1H, ddd, *J* = 11.6, 2.6, 2.4 Hz, H-14a), 3.06 (2H, br s, 2 x H-7), 3.13 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.25 (1H, br d, H-6), 3.35 (1H, dd, *J* = 10.2, 2.0 Hz, C*H*OH), 3.54 (1H, dd, *J* = 4.0, 2.3 Hz, H-9), 3.65 (3H, s, OCH_3), 3.74 (1H, d, *J* = 2.4 Hz, H-15), 3.76 (3H, s, OCH_3), 3.80 (1H, dd, *J* = 10.2, 4.0 Hz, C*H*OH), 3.82 (3H, s, OCH_3), 6.29 (1H, s, H-10), 6.52 (1H, s, H-1), 6.90 (1H, s, H-4); ^{13}C NMR δ 8.8 (q, 12-CH_3), 16.0 (q, 3-CH_3), 26.4 (t, C-14), 26.8 (t, C-5), 41.0 (q, NCH_3), 53.8 (d, C-6), 55.5 (q, OCH_3), 55.6 (q, OCH_3), 58.6 (d, C-14a), 60.0 (t, C-7), 60.3 (q, OCH_3), 64.1 (d, C-9), 64.2 (d, C-15), 65.5 (t, 9-CH_2), 104.1 (d, C-10), 111.0 (d, C-1), 117.7 (s), 120.6 (s), 126.1 (s), 126.1(s), 129.3 (s), 129.8 (d, C-4), 133.6 (s), 155.3 (s), 155.5 (s), 157.0 (s); EI-MS, *m/z* (relative intensity) 438 (M^+, 3), 408 (31), 407 (100), 204 (11), 203 (15), 189 (10), 188 (52). Anal. Calcd for $C_{26}H_{34}N_2O_4 \cdot 3/4H_2O$: C, 69.08; H, 7.92; N, 6.20. Found: C, 68.90; H, 7.65; N, 6.23.

2-[(6,7,9,14,14a,15-Hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (30).

A solution of diethyl azodicarboxylate (1.824 mL, 16.25 mmol) in dry THF (10 mL) was added dropwise to a stirred solution of **29** (1.508 g, 3.25 mmol), phthalimide (2.39 g, 16.24 mmol), and triphenylphosphine (4.26 g, 16.24 mmol) in dry THF (90 mL) at room temperature for 10 min. After the solution was stirred at room temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was diluted with water (200 mL) and extracted with chloroform (100 mL x 3). The combined extracts were washed with water (100 mL), dried, and concentrated in vacuo to furnished **30** (1.924 g, 100%) as a solid, which was used for the next step without further purification. An analytical sample was obtained by recrystallization from ethyl acetate-ether: mp 179-181 °C; IR (KBr) 1775, 1730 cm^{-1}; UV λ_{max} nm (log ε) 212 (4.73), 232sh (4.37), 240sh (4.01), 280 (3.62), 288 (3.59), 300sh (3.06); ^1H NMR δ 1.97 (1H, dd, *J* = 14.5, 11.6 Hz, H-14β), 2.12 (3H, s, Ar CH_3), 2.20 (3H, s, Ar CH_3), 2.35 (3H, s, NCH_3), 2.65 (1H, d, *J* = 17.2 Hz, H-5β), 2.75 (1H, ddd, *J* = 11.6, 2.0, 2.0 Hz, H-14a), 2.86 (1H, dd, *J* = 14.5, 2.0 Hz, H-14α), 3.05 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.09 (1H, dd, *J* = 10.2, 1.0 Hz, H-7), 3.17 (1H, br d, H-6), 3.22 (1H, dd, *J* = 10.9, 2.0 Hz, 7-H), 3.35 (3H, s, OCH_3), 3.37 (1H, dd, *J* = 13.9, 8.6 Hz, C*H*N), 3.54 (3H, s, OCH_3), 3.54 (1H, d, *J* = 2.0 Hz, H-15), 3.55 (1H, dd, *J* = 13.9, 4.0 Hz, C*H*N), 3.62, 3.77 (each 3H, s, OCH_3), 4.04 (1H, dd, *J* = 8.6, 4.0 Hz, H-9), 6.43 (1H, s, H-1), 6.83 (1H, s, H-4), 7.59-7.67 (4H, m); ^{13}C NMR δ 9.3 (q, 12-CH_3), 16.1 (q, 3-CH_3), 26.6 (t, C-5), 27.8 (t, C-14), 41.4 (q, NCH_3), 43.5 (t, 9-CH_2N), 53.8 (d, C-6), 55.4 (q, OCH_3), 56.8 (d, C-9), 59.6 (q, OCH_3), 60.0 (q, OCH_3), 60.1 (d, C-14a), 60.6 (q, OCH_3), 61.4 (t, C-7), 64.2 (d, C-15), 111.6 (d, C-1), 122.6 (d, Pht-C), 123.3 (s), 124.7 (s), 125.4 (s), 126.8 (s), 127.7 (s), 129.7 (d, C-4), 130.5 (s), 133.2 (d, Pht-C), 133.4 (s, Pht-C), 146.2 (s), 149.4 (s), 151.3 (s), 154.7 (s), 168.0 (s, CO); EI-MS *m/z* (relative intensity) 597 (M^+, 1), 438 (31), 437 (100), 188 (22). Anal. Calcd for $C_{27}H_{36}N_2O_5 \cdot 3/4H_2O$: C, 68.78; H, 6.60; N, 6.87. Found: 68.74; H, 6.47; N, 6.78.

6,7,9,14,14a,15-Hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanamine (9).

Hydrazine monohydrate (4 mL) was added to a stirred solution of crude **30** (1.612 g, 2.7 mmol) in ethanol (40 mL), the resulting solution was heated under reflux for 2 h. The reaction mixture was concentrated in vacuo. The residue was diluted with benzene (50 mL) and extracted with 1N HCl (50 mL x 3). The combined acidic aqueous extracts were made alkaline with diluted NH_4OH and extracted with chloroform (50 mL x 3). The combined extracts were washed with water (50 mL), dried, and concentrated in vacuo to give **9** (1.236 g, 98.0%) as colorless amorphous powder, which was used for the next step without further purification: IR ($CHCl_3$) 3400-3100, 1458, 1405, 1358, 1340, 1322, 1302, 1143, 1130, 1108, 1072, 1008, 962, 984,

850 cm^{-1}; UV λ_{max} nm (log ε) 226 (4.15), 280 (3.47), 289 (3.95); ^1H NMR δ 1.50 (2H, br s, NH_2), 2.20 (1H, dd, *J* = 15.6, 12.5 Hz, H-14β), 2.16 (3H, s, Ar CH_3), 2.17 (3H, s, Ar CH_3), 2.36 (3H, s, NCH_3), 2.54 (1H, d, *J* = 17.1 Hz, H-5β), 2.58 (1H, dd, *J* = 13.2, 2.4 Hz, C*H*NH_2), 2.72 (1H, dd, *J* = 13.7, 3.7 Hz, C*H*NH_2), 2.80 (1H, ddd, *J* = 12.5, 2.4, 2.4 Hz, H-14a), 2.83 (1H, dd, *J* = 15.6, 2.4 Hz, H-14α), 2.94 (1H, dd, *J* = 10.7, 2.4 Hz, H-7), 3.00 (1H, dd, *J* = 10.7, 2.4 Hz, H-7), 3.07 (1H, dd, *J* = 17.1, 7.6 Hz, H-5α), 3.14 (1H, br d, H-6), 3.58 (1H, d, *J* = 2.4 Hz, H-15), 3.64 (3H, s, OCH_3), 3.64 (1H, dd, *J* = 3.7, 2.4 Hz, H-9), 3.75, 3.79, 3.82 (each 3H, s, OCH_3), 6.50 (1H, s, H-1), 6.88 (1H, s, H-4); ^{13}C NMR δ 9.3 (q, 12-CH_3), 16.0 (q, 3-CH_3), 26.8 (t, C-5), 27.6 (t, C-14), 41.5 (q, NCH_3), 46.1 (t, 9-CH_2N), 53.8 (d, C-6), 55.4 (q, OCH_3), 59.0 (d, C-14a), 60.0 (q, OCH_3), 60.1 (q, OCH_3), 60.4 (q, OCH_3), 60.7 (d, C-9), 61.1 (t, C-7), 64.4 (d, C-15), 110.9 (d, C-1), 123.2 (s), 125.0 (s), 125.5 (s), 126.9 (s), 127.5 (s), 129.7 (d, C-4), 130.9 (s), 145.8 (s), 149.5 (s), 150.8 (s), 154.7 (s); EI-MS *m/z* (relative intensity) no M^+, 438 (31), 437 (100), 188 (27); high-resolution EI-MS calcd for $C_{26}H_{33}N_2O_4$ 437.2440 (base peak), found 437.2458; positive FAB-MS (magic bullet) *m/z* 468 (M^+ + 1).

***N*-[(6,7,9,14,14a,15-Hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl]-2-oxopropanamide (31).**

A solution of the crude **9** (170.4 mg, 0.3648 mmol), triethylamine (49.5 μL, 0.355 mmol), and 4-(dimethylamino)pyridine (86.8 mg, 0.71 mmol) in dry dichloromethane (8 mL) was cooled with ice-water, and a carbon tetrachloride solution of pyruvoyl chloride (0.8 M, 1.78 mL, 1.424 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at room temperature, and the reaction mixture was diluted with water (10 mL), and extracted with dichloromethane (20 mL x 3). The combined extracts were washed with 5% $NaHCO_3$ solution (20 mL), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 25 g; elution with 100:1 dichloromethane-methanol) to give **31** (179.9 mg, 91.8%) as colorless amorphous powder: IR ($CHCl_3$) 3360, 1730, 1680, 1675 cm^{-1}; UV λ_{max} nm (log ε) 224 (4.29), 270 (3.40), 288 (3.46); ^1H NMR δ 2.04 (1H, dd, *J* = 14.8, 11.9 Hz, H-14β), 2.15 (3H, s, Ar CH_3), 2.19 (3H, s, Ar CH_3), 2.22 (3H, s, $COCH_3$), 2.44 (3H, s, NCH_3), 2.72 (1H, d, *J* = 17.5 Hz, H-5β), 2.83-3.20 (6H, m, H-14a, H-14α, 2 x H-7, 9-CH, and H-5α), 3.24 (1H, br d, H-6), 3.40 (1H, ddd, *J* = 13.2, 6.6, 4.3 Hz, 9-C*H*N), 3.60 (3H, s, OCH_3), 3.68 (1H, br s, H-15), 3.75 (3H, s, OCH_3), 3.85 (1H, m, H-9), 3.85, 3.86 (each 3H, s, OCH_3), 6.48 (1H, br s, NH), 6.50 (1H, s, H-1), 6.91 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 16.0 (q, 3-CH_3), 24.3 (q, CO*C*H_3), 26.5 (t, C-5), 27.2 (t, C-14), 41.3 (q, NCH_3), 43.7 (t, 9-CH_2N), 53.6 (d, C-6), 55.6 (q, OCH_3), 58.3 (d, C-9), 59.1 (d, C-14a), 59.9 (q, OCH_3), 60.3 (q, OCH_3), 60.4 (q, OCH_3), 60.9 (t, C-7), 64.2 (d, C-15), 111.0 (d, C-1), 123.9 (s), 125.0 (s), 125.4 (s), 125.6 (s), 127.1 (s), 129.6 (d, C-4), 129.9 (s), 145.9 (s), 149.6 (s), 151.0 (s), 155.2 (s), 160.1 (s, NHCO), 196.4 (s, *C*OCH_3); EI-MS *m/z* (relative intensity) 537 (M^+, 1>), 438 (34), 437 (100), 218 (12), 188 (24); high-resolution EI-MS calcd for $C_{26}H_{33}N_2O_4$ 437.2440 (base peak), found 437.2440; positive FABMS (magic bullet) *m/z* 538 (M^+ + 1).

Partial Demethylation of 31.

A stirred solution of **31** (92.0 mg, 0.1713 mmol) in dichloromethane (15 mL) was cooled with dry ice-acetone, a dichloromethane solution of boron tribromide (1.0 M, 308 μL, 0.308 mmol) was added dropwise over 5 min. After being kept at -78 °C for 4 h, and then at 0 °C for 1 h, the reaction mixture was poured onto ice-water and the phase separated. The aqueous layer was 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 (80.4 mg). Chromatography of this material on a silica gel (15 g) column with dichloromethane-methanol (100:3) as the eluent gave the starting material **31** (3.1 mg, 3.4% recovery) and with dichloromethane-methanol (20;1) as the eluent gave **32** (40.6 mg, 45.3%) as colorless amorphous powder. Further elution with dichloromethane-methanol (10:1) gave a solid, recrystallization of which from acetone gave **33** (25.0 mg, 28.7%) as colorless needles.

Compound 32: IR ($CHCl_3$) 3380, 1725, 1688, 1680 cm^{-1}; UV λ_{max} nm (log ε) 230 (4.12), 284 (3.66), 288 (3.63); ^1H NMR δ 1.95 (1H, dd, *J* = 15.2, 12.5 Hz, H-14β), 2.11 (3H, s, Ar CH_3), 2.19 (3H, s, Ar CH_3), 2.25 (3H, s, $COCH_3$), 2.47 (3H, s, NCH_3), 2.78 (1H, d, *J* = 17.2 Hz, H-5β), 2.78 (1H, m, H-14a), 2.92 (1H, d, *J* = 15.2 Hz, H-14α), 2.98 (2H, br s, 2 x H-7), 3.05 (1H, ddd, *J* = 13.2, 4.6, 4.6 Hz, 9-C*H*N), 3.13 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.28 (1H, br d, H-6), 3.35 (1H, ddd, *J* = 13.2, 6.6, 3.6 Hz, 9-C*H*N), 3.59 (2H, br s, H-9 and H-15), 3.73, 3.76, 3.85 (each 3H, s, OCH_3), 6.53 (1H, s, H-1), 6.56 (1H, m, NH), 6.93 (1H, s, H-4); ^{13}C NMR δ 9.3 (q, 12-CH_3), 16.1 (q, 3-CH_3), 24.4 (q, CO*C*H_3), 26.5 (t, C-14), 26.8 (t, C-5), 40.8 (q, NCH_3), 44.2 (t, 9-CH_2N), 54.1 (d, C-6), 55.9 (q, OCH_3), 58.0 (d, C-9), 59.3 (d, C-14a), 60.1 (q, OCH_3), 60.4 (q, OCH_3), 60.7 (t, C-7), 64.4 (d, C-15), 111.2 (d, C-1), 118.1 (s), 119.6 (s), 125.4 (s), 126.1 (s), 126.4 (s), 128.8 (s), 129.6 (d, C-4), 143.4 (s), 146.5 (s), 149.4 (s), 155.5 (s), 160.1 (s, NHCO), 196.4 (s, *C*OCH_3); EI-MS *m/z* (relative intensity) 523 (M^+, 1>), 424 (34), 423 (100), 211 (32), 188 (24); high-resolution MS calcd for $C_{25}H_{31}N_2O_4$ 423.2284 (base peak), found 423.2289; positive FABMS (magic bullet) *m/z* 524 (M^+ + 1).

Compound 33: mp 235-238 °C dec; IR (KBr) 3700-3100, 1720, 1665 cm^{-1}; UV λ_{max} nm (log ε) 224 (4.25), 284 (3.71); ^1H NMR δ ($CDCl_3$-CD_3OD) 1.97 (1H, dd, *J* = 14.9, 11.6 Hz, H-14β), 2.12 (3H, s, Ar CH_3), 2.20 (3H, s, Ar CH_3), 2.20 (3H, s, $COCH_3$), 2.39 (3H, s, NCH_3), 2.72 (1H, d, *J* = 17.2 Hz, H-5β), 2.82 (2H, m, H-14a and H-14α), 2.98 (2H, br s, 2 x H-7), 3.09 (1H, dd, *J* = 17.2, 7.6 Hz, H-5α), 3.11 (1H, dd, *J* = 13.2, 3.3 Hz, 9-C*H*N), 3.24 (1H, br d, H-6), 3.38 (1H, dd, *J* = 13.2, 4.6 Hz, 9-C*H*N), 3.61 (2H, br s, H-15), 3.73 (3H, s, OCH_3), 3.77 (1H, dd, *J* = 4.6, 3.3 Hz, H-9), 3.78 (3H, s, OCH_3), 6.49 (1H, s, H-1), 6.87 (1H, s, H-4); ^{13}C NMR δ 9.2 (q, 12-CH_3), 15.9 (q, 3-CH_3), 24.4 (q, CO*C*H_3), 26.8 (t, C-14), 27.0 (t, C-5), 40.8 (q, NCH_3), 43.8 (t, 9-CH_2N), 54.0 (d, C-6), 58.1 (d, C-14a), 59.0 (d, C-9), 60.4 (q, OCH_3), 60.5 (t, C-7), 63.8 (d, C-15), 115.6 (d, C-1), 118.5 (s), 119.6 (s), 123.8 (s), 125.1 (s), 126.1 (s), 129.3 (s), 129.7 (d, C-4), 143.4 (s), 146.6 (s), 149.5 (s), 152.0 (s), 160.1 (s, NHCO), 196.6 (s, *C*OCH_3); EI-MS *m/z* (relative intensity) 509 (M^+, 1>), 410 (30), 409 (100), 204 (11),

174 (26); high-resolution MS calcd for $C_{24}H_{29}N_2O_4$ 409.2127 (base peak), found 409.2129; positive FABMS (magic bullet) *m/z* 510 (M^+ + 1). Anal. Calcd for $C_{28}H_{35}N_3O_6 \cdot H_2O$: C, 63.74; H, 7.07; N, 7.96. Found: C, 63.40; H, 6.72; N, 7.71.

***N*-[(6,7,9,10,13,14,14a,15-Octahydro-2,11-dimethoxy-3,12,16-trimethyl-10,13-dioxo-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (10a).**

A solution of **32** (48.2 mg, 0.092 mmol) in 8 M HNO_3 (3 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (10 mL), and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (37.8 mg) was subjected to chromatography (silica gel, 10 g; elution with 100:1 dichloromethane-methanol) to give **10a** (32.2 mg, 68.9%) as a solid, which was recrystallized from acetone to give pale yellow prisms; mp 193-196 °C dec; IR (KBr) 3420, 3380, 1725, 1690, 1662, 1645, 1625 cm^{-1}; UV λ_{max} nm (log ε) 234sh (3.92), 276 (4.03), 288sh (3.93), 380 (2.77); ^1H NMR δ 1.75 (1H, ddd, *J* = 17.5, 11.9, 3.0 Hz, H-14β), 1.90 (3H, s, 12-CH_3), 2.18 (3H, s, $COCH_3$), 2.22 (3H, s, 3-CH_3), 2.42 (3H, s, NCH_3), 2.58 (1H, d, *J* = 17.5 Hz, H-5β), 2.75 (1H, dd, *J* = 17.5, 1.0 Hz, H-14α), 2.83 (1H, m, H-14a), 3.07 (2H, br s, 2 x H-7), 3.11 (1H, dd, *J* = 17.5, 7.6 Hz, H-5α), 3.20 (1H, ddd, *J* = 13.2, 6.0, 4.3 Hz, 9-C*H*N), 3.24 (1H, br d, H-6), 3.60-3.68 (3H, m, 9-C*H*N, H-9, and H-15), 3.84 (3H, s, 2-OCH_3), 4.01 (3H, s, 11-OCH_3), 6.30 (1H, br, NH), 6.44 (1H, s, H-1), 6.88 (1H, s, H-4); ^{13}C NMR δ 8.6 (q, 12-CH_3), 16.0 (q, 3-CH_3), 24.2 (q, CO*C*H_3), 25.2 (t, C-14), 26.6 (t, C-5), 41.0 (q, NCH_3), 41.2 (t, 9-CH_2N), 53.6 (d, C-6), 55.8 (q, 2-OCH_3), 57.4 (d, C-14a), 57.8 (d, C-9), 59.6 (t, C-7), 61.0 (q, 11-OCH_3), 63.5 (d, C-15), 111.3 (d, C-1), 126.3 (s, C-15a), 126.4 (s, C-3), 127.6 (s, C-12), 129.4 (d, C-4), 129.4 (s, C-4a), 136.8 (s, C-9a), 141.6 (s, C-13a), 155.5 (s, C-2), 160.6 (s, NHCO), 181.3 (s, C-10), 186.1 (s, C-13), 195.5 (s, *C*OCH$_3$); EI-MS *m/z* (relative intensity) 507 (M^+, 14), 409 (16), 408 (23), 407 (75), 204 (15), 203 (13), 202 (13), 190 (13), 189 (23), 188 (100); high-resolution EIMS calcd for $C_{28}H_{33}N_3O_6$ 507.2369, found 507.2376. Anal. Calcd for $C_{28}H_{33}N_3O_6$: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.19; H, 6.54; N, 8.18.

***N*-[(6,7,9,10,13,14,14a,15-Octahydro-2-hydroxy-1-nitro-11-methoxy-3,12,16-trimethyl-10,13-dioxo-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (34).**

A solution of **33** (14.8 mg, 0.029 mmol) in 8 M HNO_3 (2 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (10 mL), and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (15.1 mg) was subjected to chromatography (silica gel, 6 g; elution with 200:3 dichloromethane-methanol) to give **34** (9.5 mg, 60.7%) as a solid, which was recrystallized from acetone to give pale yellow prisms; mp 180-185 °C dec; IR (KBr) 3410, 3380, 1735, 1695, 1665, 1645, 1630 cm^{-1}; UV λ_{max} nm (log ε) 268 (4.03), 362 (3.18); ^1H NMR δ 1.33 (1H, ddd, *J* = 17.5, 11.2, 3.0 Hz, H-14β), 1.88 (3H, s, 12-CH_3), 2.21 (3H, s, $COCH_3$), 2.32 (3H, s, 3-CH_3), 2.44 (3H, s, NCH_3), 2.54 (1H, d, *J* = 16.5 Hz, H-5β), 2.68 (1H, dd, *J* = 17.5, 2.0 Hz, H-14α), 2.76 (1H, ddd, *J* = 11.2, 3.0, 2.0 Hz, H-14a), 2.86 (1H, dd, *J* = 10.9, 1.7 Hz, H-7), 3.05 (1H, dd, *J* = 10.9, 1.0 Hz, H-7), 3.11 (1H, dd, *J* = 16.5, 6.9 Hz, H-5α), 3.15 (1H, br d, H-6), 3.16 (1H, ddd, *J* = 13.5, 4.0, 3.6 Hz, 9-C*H*N), 3.60 (1H, ddd, *J* = 3.1, 3.0, 1.7 Hz, H-9), 3.72 (1H, ddd, J = 13.5, 9.6, 1.7 Hz, 9-C*H*N),4.00 (3H, s, 11-OCH_3), 4.98 (1H, d, *J* = 3.0 Hz, H-15), 6.43 (1H, dd, *J* = 9.6, 4.0 Hz, NH), 7.13 (1H, s, H-4); ^{13}C NMR δ 8.6 (q, 12-CH_3), 16.2 (q, 3-CH_3), 23.6 (t, C-14), 24.3 (q, CO*C*H_3), 27.6 (t, C-5), 40.8 (q, NCH_3), 41.3 (t, 9-CH_2N), 52.2 (d, C-6), 57.1 (d, C-14a), 57.6 (d, C-15), 57.8 (d, C-9), 59.3 (t, C-7), 61.0 (q, 11-OCH_3), 124.6 (s), 127.9 (s), 128.0 (s), 128.9 (s), 135.2 (d, C-4), 136.4 (s), 140.9 (s), 151.4 (s), 156.1 (s), 160.3 (s, NHCO), 181.2 (s, C-10), 185.5 (s, C-13), 195.9 (s, *C*OCH$_3$); EI-MS *m/z* (relative intensity) 538 (M^+, 49), 439 (28), 438 (84), 421 (30), 420 (100), 360 (12), 319 (12), 261 (12), 260 (23), 259 (34), 235 (14), 233 (11), 221 (13), 220 (22), 219 (94), 218 (31), 217 (29), 205 (17), 205 (17), 204 (30), 203 (62), 202 (41), 189 (18), 188 (15), 187 (26), 175 (10), 174 (18), 173 (19), 145 (13); high-resolution EIMS calcd for $C_{27}H_{30}N_4O_8$ 538.2064, found 538.2067. Anal. Calcd for $C_{27}H_{30}N_4O_8 \cdot H_2O$: C, 58.27; H, 5.80; N, 10.07. Found: C, 58.56; H, 5.53; N, 9.96.

Oxidative Demethylation of 31 in Two Steps.

Partial *O*-demethylation of **35** (32.2 mg, 0.06 mmol) with boron tribromide as described above afforded the residue (33.9 mg). A solution of this residue in 8M HNO_3 (1.5 mL) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (5 mL) and extracted with chloroform (10 mL x 3). The combined extracts were washed with water (10 mL), dried, and concentrated in vacuo. The residue (29.6 mg) was subjected to chromatography (silica gel, 8 g; elution with 100:3 dichloromethane-methanol) to give **34** (9.9 mg, 30.7%) as a solid. Further elution with dichloromethane-methanol (50:1-20:1) gave **10a** (11.3 mg, 37.2%) as a solid.

***N*-[(10,13-Diacetoxy-6,7,9,14,14a,15-hexahydro-2,11-dimethoxy-3,12,16-trimethyl-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-yl)methyl]-2-oxopropanamide (35).**

A solution of **10a** (20.3 mg, 0.04 mmol) and zinc dust (10.0 mg) in acetic anhydride (1.0 mL) was stirred at room temperature for 30 min, and then filtered, which was washed with chloroform (50 mL). The combined filtrates were concentrated in vacuo and the residue was dissolved with chloroform (10 mL). This phase was washed with 5% $NaHCO_3$ solution, dried, and concentrated in vacuo. The residue (23.1 mg) was subjected to chromatography (silica gel, 8 g; elution with 40:1 dichloromethane-methanol) to give **35** (16.4 mg, 69%) as a colorless amorphous powder: IR ($CHCl_3$) 3370, 1755, 1715, 1680, 1665 cm^{-1}; UV λ_{max} nm (log ε) 222 (4.24), 280 (3.38), 288 (3.32); ^1H NMR δ 1.98 (1H, dd, *J* = 15.2, 12.2 Hz, H-14β), 2.06 (3H, s, 12-CH_3), 2.20 (3H, s, 3-CH_3), 2.27, 2.33, 2.35 (each 3H, s, $COCH_3$), 2.37 (3H, s, NCH_3), 2.47 (1H, dd, *J* = 15.2, 2.3 Hz, H-14α), 2.61 (1H, d, *J* = 16.8 Hz, H-5β), 2.83 (1H, ddd, *J* = 12.2, 2.3, 2.0 Hz, H-14a), 2.89 (1H, dd, *J* = 10.6, 1.0 Hz, H-7), 2.99 (1H, dd, *J* = 10.6, 1.0 Hz, H-7), 3.01-3.10 (3H, m, 9-CH, H-5α, H-6), 3.36 (1H, ddd, *J* = 13.2, 6.6, 4.2 Hz, 9-C*H*N),

3.52 (1H, d, J = 2.3 Hz, H-15), 3.63 (1H, t like, H-9), 3.70 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.38 (1H, s, H-1), 6.55 (1H, t like, NH), 6.94 (1H, s, H-4); ^{13}C NMR δ 9.9 (q, 12-CH_3), 16.0 (q, 3-CH_3), 20.3 (q, $COCH_3$), 20.7 (q, $COCH_3$), 24.3 (q, $COCOCH_3$), 26.5 (t, C-5), 27.5 (t, C-14), 41.3 (q, NCH_3), 44.1 (t, 9-CH_2), 53.8 (d, C-6), 55.5 (q, 2-OCH_3), 58.0 (d, C-9), 59.1 (d, C-14a), 60.9 (q, 11-OCH_3), 61.6 (t, C-7), 64.1 (d, C-15), 111.1 (d, C-1), 123.9 (s), 125.4 (s), 125.5 (s), 126.0 (s), 127.6 (s), 129.5 (d, C-4), 130.5 (s), 138.8 (s), 144.3 (s), 148.6 (s), 155.1 (s), 160.1 (s, NHCO), 167.9 (s, $OCOCH_3$), 168.6 (s, $OCOCH_3$), 196.2 (s, $COCOCH_3$); EI-MS m/z (relative intensity) 593 (M^+, 1), 494 (34), 493 (100), 451 (15), 188 (45), high-resolution EIMS, calcd for $C_{32}H_{39}N_3O_8$ 593.2737, found, 593.2730.

***N*-[(2-Acetoxy-6,7,9,10,13,14,14a,15-octahydro-1-nitro-11-methoxy-3,12,16-trimethyl-10,13-dioxo-(6α,9α,14aα,15α)-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-ly)methyl]-2-oxopropanamide (36).**

To a stirred solution of **34** (11.5 mg, 0.0214 mmol) in dry pyridine (0.4 mL) was added acetic anhydride (0.2 mL), and the mixture was kept at room temperature for 2 h. After the reaction mixture was diluted with water (10 mL), the mixture was extracted with chloroform (10 mL x 3). The combined extracts were washed with 5% $NaHCO_3$ solution, dried, and concentrated in vacuo. The residue (13.5 mg) was subjected to chromatography (silica gel, 6 g; elution with 100:1 dichloromethane-methanol) to give **36** (10.1 mg, 81.5%) as a solid, this material was recrystallized from ethyl acetate to give pale yellow needles: mp 211-214 °C dec; IR (KBr) 3395, 1785, 1770, 1725, 1685, 1655, 1630, 1615 cm^{-1}; UV λ_{max} nm (log ε) 266 (4.00), 362 (2.83); ^1H NMR δ 1.38 (1H, ddd, J = 17.2, 11.2, 3.0 Hz, H-14β), 1.90 (3H, s, 12-CH_3), 2.23 (3H, s, 3-CH_3), 2.24, 2.28 (each 3H, s, $COCH_3$), 2.38 (3H, s, NCH_3), 2.55 (1H, dd, J = 17.2, 2.3 Hz, H-14α), 2.70 (1H, ddd, J = 11.2, 3.0, 2.3 Hz, H-14a), 2.69 (1H, d, J = 16.8 Hz, H-5β), 2.84 (1H, dd, J = 10.6, 2.3 Hz, H-7), 3.09 (1H, dd, J = 10.6, 1.0 Hz, H-7), 3.11 (1H, dd, J = 16.8, 7.3 Hz, H-5α), 3.19 (1H, br d, H-6), 3.28 (1H, ddd, J = 13.9, 4.3, 4.3 Hz, 9-C*H*N), 3.57 (1H, ddd, J = 4.3, 3.0, 1.7 Hz, H-9), 3.65 (1H, ddd, J = 13.9, 8.9, 1.7 Hz, 9-C*H*N), 3.99 (3H, s, OCH_3), 4.06 (1H, d, J = 2.3 Hz, H-15), 6.49 (1H, dd, J = 8.9, 4.3 Hz, NH), 7.19 (1H, s, H-4); EI-MS m/z (relative intensity) 580 (M^+, 37), 482 (12), 481 (41), 480 (100), 420 (17), 277 (23), 261 (17), 260 (12), 259 (12), 245 (11), 220 (12), 219 (52), 218 (17), 217 (19), 204 (19), 203 (28), 202 (18), 187 (19), 174 (11), 173 (11), 43 (11), high-resolution EIMS calcd for $C_{29}H_{32}N_4O_9$ 580.2169, found 580.2168.

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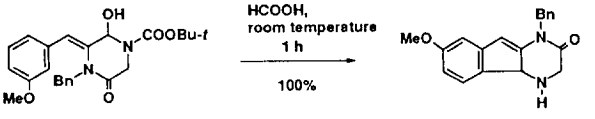
REFERENCES AND NOTES

1. a) Ikeda, Y.; Idemoto, H.; Hirayama, F.; Yamamoto, K.; Iwao, K.; Asao, T.; Munakata, T. *J. Antibiot.* **1983**, *36*, 1279-1283. b) Ikeda, Y.; Matsuki, H.; Ogawa, T.; Munakata, T. *ibid.* **1983**, *36*, 1284-1289. c) Ikeda, Y.; Shimada, Y.; Honjo, K.; Okumoto, T.; Munakata, T. *ibid.* **1983**, *36*, 1290-1294.
2. a) Meyers, E.; Cooper, R.; Trejo, W. H.; Georgopapadaukou, N.; Sykes, R. *J. Antibiot.* **1983**, *36*, 190-193. b) Cooper, R.; Unger, S. *ibid.* **1985**, *38*, 24-30.
3. Okumoto, T.; Kawana, M.; Nakamura, Y.; Isagai, K. *J. Antibiot.* **1985**, *38*, 767-771.
4. Ueda, I.; Kawano, S.; Ikeda, Y.; Matsuki, H.; Ogawa, T. *Acta Crystallogr.* **1984**, *C40*, 1578-1580.
5. Kubo, A.; Saito, N. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, Amsterdam, **1992**, Vol. 10, pp 77-145.
6. Ikeda, Y.; Ogawa, H.; Matsuki, H.; Munakata, T. Jpn. Kokai Tokkyo Koho 84 42382; *Chem. Abstr.* **1984**, *101*, 54802k.
7. a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512-4515; Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J. Jr.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. *J. Nat. Prod.* **1990**, *53*, 771-792. b) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H. -J. *Proc. Natl. Acad. Sci.*

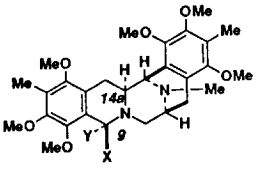
U.S.A. **1992**, *89*, 11456-11460. c) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnel, O. J. *J. Org. Chem.* **1990**, *55*, 4508-4512.

8. a) Irscik, H.; Trowitzch-Kienast, W. Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1988**, *41*, 993-998. b) Trowitzsch-Kienast, W.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1988**, 475-481. c) Reichenbach, H. Jpn. Kokai Tokkyo Koho 88 49092; *Chem. Abstr.* **1989**, *110*, 55972p.
9. a) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295-4310. For an alternative total synthesis of (±)-**2b** see; Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957-4958. b) Saito, N.; Ohira, Y.; Wada, N.; Kubo. A. *Tetrahedron*, **1990**, *46*, 7711-7728.
10. a) Saito, N.; Obara, Y.; Azumaya, M.; Kubo, A. *Chem. Pharm. Bull.* **1992**, *40*, 2620-2626. b) Saito, N.; Obara, Y.; Aihara, T.; Harada, S.; Shida, Y.; Kubo, A. *Tetrahedron*, **1994**, *50*, 3915-3928.
11. Previously, we reported a mild, efficient dehydration/cyclization of an allylic alcohol substrate to give the corresponding (*E*)-1,5-imino-3-benzazocine with methanesulfonyl chloride and triethylamine in dichloromethane; Saito, N.; Yamauchi, R.; Nishioka, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391-5395: However, on treating **7a** under the same conditions at reflux, no cyclization product occurred. Instead, only an unstable polymeric material was obtained.
12. Recently, Joule reported that an allylic alcohol **iii** can be quantitatively converted to the indeno[1.2-*b*]pyrazin-2-one **iv** in formic acid at room temperature for 1 h; Peters, D. A.; Beddoes, R. L.; Joule, J. A. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1217-1224.



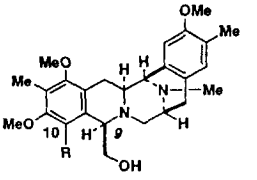
iii iv

13. Treatment of **24** with paraformaldehyde and K_2CO_3 in ethanol at room temperature for 16 h followed by trifluoroacetic acid at room temperature for 20 h gave **28** in 53% overall yield; *see* Experimental section: Kubo, A.; Saito, N.; Kawakami, Matsuyama, Y.; Miwa, T. *Synthesis*, **1987**, 824-827.
14. In the chemistry of our total synthesis of (±)-**1b**, the ^1H NMR spectrum of 9-*epi*-ester **v** showed H-9 (δ 4.56) and H-14a (δ 3.57), whereas the ^1H NMR spectrum of **vi** showed H-9 (δ 4.09) and H-14a (δ 2.84).[9a]



v: X = H, Y = COOBu
vi: X = COOBu, Y = H

15. Reduction of **27** with lithium aluminum hydride in THF under reflux for 2 h gave the alcohol **29** in 60% yield along with the compounds **vii** (5%) and **viii** (19%), *see* Experimental section. Assignment of **viii** was made by ^{1}H NMR analysis. When H-10 (δ 6.29) was irradiated, nuclear Overhauser enchancement of the methylene protons at δ 3.35 and 3.80 was observed.



vii: R = OH
viii: R = H

16. A preliminary experiment for the partial demethylation of compound **31** was carried out under a variety of conditions; boron tribromide (1.5 equiv) gave **32** (55%), **33** (11%), and **31** (27% recovery); boron tribromide (2.5 equiv) gave **32** (37%) and **33** (31%); boron tribromide (5 equiv) gave only **33** (8%).
17. The orientation of the methyl ether substituents on the aromatic E ring of the phenols **32** and **33** is still undetermined.
18. Methylation of **34** using Meerwein's trimethyloxonium tetrefluoroborate salts or diazomethane catalyzed by silica gel failed; only starting material was recovered.
19. Saito, N.; Harada, S.; Inouye, I.; Yamaguchi, K.; Kubo, A. *Tetrahedron* accompanying paper.
20. Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D.; *J. Appl. Crystallogr.* **1989**, *22*, 389-403.
21. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smith, J. M. M.; Smykalla, C., the DIRDIF program system, *Technical Report of the Crystallography Laboratory*, University of Nijmegen, the Netherlands.

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