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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-benzarocine 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.<sup>1</sup> The Squibb Laboratories group independently isolated 1b from Pseudomonas fluorescens SC 12695 in the same year.<sup>2</sup> 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.<sup>3</sup> The absolute configuration of the safracins was elucidated by X-ray crystallography of the 4-brominated derivative of safracin A (1c).<sup>4</sup> 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 le 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)<sup>8</sup> 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  $(\pm)$ -saframycin B  $(2b)^{9a}$  and the transformation of  $(\pm)$ -2b into  $(\pm)$ -saframycins C (2c) and D (2d).<sup>9b</sup> 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.<sup>10</sup> 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%).<sup>11</sup> This dehydration/cyclization reaction when run at room temperature with TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave 8a (86%) and 17 (4%). On the other hand, treatment of 7a with BF<sub>3</sub>-OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature afforded 8a (32%) and 17 (61%). Deprotection of 17 with trifluoroacetic acid and H<sub>2</sub>SO<sub>4</sub> 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 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).<sup>12</sup> Reduction of 21 with aluminum hydride at 0 °C for 30 min gave the amine 22 in 91% yield.





reagents and conditions: a) H<sub>2</sub>, 10% Pd/C, DMF-EtOH = 1:1, 75%; b) Ac<sub>2</sub>O, 100 °C, 22 h, 97%; c) 2,4,5trimethoxy-3-methylbenzaldehyde, *tert*-BuOK, *tert*-BuOH, DMF, room temperature, 3 h, 72%; d) NaH, BnBr, DMF, room temperature, 1 h; e) NH<sub>2</sub>NH<sub>2</sub>-H<sub>2</sub>O, DMF, room temperature, 1 h; f) ClCOOPr-*i*, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 1 h, 93% (3 steps); g) Li(*tert*-BuO)3AlH, THF, 0 °C, 1 h, 100%; h) Method A: HCOOH, 70 °C, 2 h (8a, 64%; 17, 20%; 15, 8%); Method B: TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 1 h (8a: 86%; 17, 4%; 15, 4%); Method C: BF<sub>3</sub>OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 14 h (8a, 31%; 17, 61%, 15, 6.6%); i-1) TFA-H<sub>2</sub>SO<sub>4</sub>, room temperature, 19 h, 98%; i-2) TFA-H<sub>2</sub>SO<sub>4</sub>, room temperature, 40 h, 69%, i-3) TFA-H<sub>2</sub>SO<sub>4</sub>, 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<sub>3</sub>, THF, 0 °C, 30 min, 91%.

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

Fig. 3







Molecular Structure I

Molecular Structure 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  $\alpha$ -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 <sup>1</sup>H NMR spectrum of 27 displayed H-9 as a singlet at  $\delta$  4.10 and H-14a as a multiplet at  $\delta$  2.84, whereas the <sup>1</sup>H NMR spectrum of 26 showed the H-9 peak at  $\delta$  4.58 and the H-14a at  $\delta$  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.<sup>14</sup> Reduction of 27 with lithium aluminum hydride in THF at room temperature for 1 h afforded alcohol 29 in 83% yield.<sup>15</sup> 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.<sup>9a</sup> Treatment of 31 with 1.8 equiv of boron tribromide in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 4 h and then 0 °C for 1 h afforded the phenols 32 and 33<sup>16</sup> in 45% and 29% yields, respectively (3% yield of 31 recovered).<sup>17</sup> The reaction of 32 with 8M HNO<sub>3</sub> at 0 °C for 1 h gave the *p*-quinone 10a in 69% yield. In contrast, oxidative demethylation of 33 with 8M HNO<sub>3</sub> 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.<sup>18</sup> 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).<sup>19</sup>



reagents and conditions: 1) AlH3, THF, 0°C, 1 h; m) H2 (4 atm), 20% Pd/C, EtOH, 80 °C, 40 h, 96% (2 steps); n) CHOCOOBU-n, n-BuOH, K2CO3, room temperature, 40 h; o) TFA, room temperature, 1 h, 69% (2 steps); p) Hg(OAc)2, 5% AcOH-H2O, 90 °C, 2 h and then NaBH4, EtOH-H2O, room temperature, 1 h (27, 68%, 28, 4%, 26, 3% recovery); q) LiAlH4, THF, 0 °C, 1 h, 83.1%; r) PhiNH, DEAD, PPh3, THF, room temperature, 3 h, 100%; s) NH2NH2-H2O, EtOH, reflux, 2 h; t) CICOCOMe, DMAP, NEt3, CH2Cl2, room temperature, 1 h, 92% (2 steps); u) BBr3, CH2Cl2, -78 °C, 4 h and then 0 °C, 1 h (32, 45%; 33, 29%, 31, 3% recovery); v-1) 8 M HNO3, 0 °C, 1 h, 69%; v-2) 8M HNO3, 0 °C, 30 min, 61 %; w) Zn dust, Ac2O, room temperature, 30 min, 69%; x) Ac2O, 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. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured in CDCl<sub>3</sub> 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 acctone gave 11 (8.694 g, 75.0%) as colorless needles: mp 163-165 °C; IR (KBr) 3400-3080, 1690, 1650, 1605 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 226 (4.06), 275 (3.23), 283 (3.19); <sup>1</sup>H NMR  $\delta$  2.18 (3H, s, Ar CH3), 2.59 (3H, s, COCH3), 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, dd, J = 18.1 Hz, H-6), 3.81 (3H, s, OCH3), 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<sup>+</sup>, 5), 136 (11), 135 (100). Anal. Calcd for C15H18N2O4: 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 NaHCO3 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.04), 276 (3.20), 284 (3.12); <sup>1</sup>H NMR  $\delta$  2.14 (3H, s, Ar CH3), 2.49 (1H, d, *J* = 19.8 Hz, 6-H), 2.56, 2.59 (each 3H, s, COCH3), 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, OCH3), 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<sup>+</sup>, 10), 136 (10), 135 (100). Anal. Calcd for C17H20N2O5: 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.36), 248 (4.06), 336 (4.20); <sup>1</sup>H NMR  $\delta$  1.81, 2.21 (each 3H, s, Ar CH<sub>3</sub>), 2.65 (3H, s, COCH<sub>3</sub>), 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<sub>3</sub>), 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); <sup>13</sup>C NMR  $\delta$  9.5 (q), 15.6 (q), 27.1 (q), 37.9 (t), 55.1 (q), 55.4 (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), (s), 125.9 (s), 125.4 (d), 136 (10), 135 (100). Anal. Calcd for C<sub>26H30</sub>N<sub>2</sub>O<sub>7</sub>: 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 232 (4.31), 250 (4.05), 276 (3.81), 284 (3.83), 342 (4.10); <sup>1</sup>H NMR  $\delta$  2.11, 2.24 (each 3H, s, Ar CH<sub>3</sub>), 2.51 (3H, s, COCH<sub>3</sub>), 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<sub>3</sub>), 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); <sup>13</sup>C NMR  $\delta$  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), 128.7 (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<sup>+</sup>, 69), 500 (17), 499 (49), 136 (11), 135 (100), 91 (24). Anal. Calcd for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>7</sub>: 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<sub>3</sub> 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.30), 244 (3.86), 272 (3.86), 284 (3.96), 316 (4.01); <sup>1</sup>H NMR  $\delta$  2.18, 2.22 (each 3H, s, Ar CH<sub>3</sub>), 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<sub>3</sub>), 4.25 (1H, dd, *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, dJ, *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); <sup>13</sup>C NMR  $\delta$  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), 155.2 (s), 157.2 (s), 167.7 (s), 52.8 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 IN 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 230 (4.38), 276 (3.81), 284 (3.85), 338 (4.08); <sup>1</sup>H NMR  $\delta$  1.19, 1.28 (each 3H, d, J = 6.3 Hz, CHCH3), 2.14, 2.23 (each 3H, s, Ar CH3), 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, OCH3), 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), 6.69 (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); <sup>13</sup>C NMR  $\delta$  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), 120.8 (d), 121.2 (s), 126.5 (s), 126.7 (s), 127.0 (s), 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<sup>+</sup>, 75), 586 (40), 585 (100), 543 (12), 541 (10), 500 (19), 499 (57), 363 (12), 135 (94), 91 (36), 43 (11). Anal. Calcd for C35H40N208: C, 68.16; H, 6.54; 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% NaHCO3 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 clution with hexane-ethyl acetate (2:1 - 1:1) as the cluent 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% NaHCO3 (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 cluent 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  $\mu$ J, 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% NaHCO3 (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<sub>3</sub>) 1685, 1635 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 276 (4.15), 288 (4.08), 306 (3.84); <sup>1</sup>H NMR (at 50 °C)  $\delta$  1.27, 1.31 (each 3H, d, J = 6.3 Hz, CHCH<sub>3</sub>), 2.13, 2.15 (each 3H, s, Ar CH<sub>3</sub>), 2.93 (3H, s, OCH<sub>3</sub>), 3.13 (1H, d, J = 16.2 Hz, H-6 $\beta$ ), 3.23 (1H, dd, J = 16.2, 5.0 Hz, H-6 $\alpha$ ), 3.41, 3.81, 3.98 (each 3H, s, OCH<sub>3</sub>), 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  $\delta$  (at 50 °C) 9.3 (q, 3'-CH3), 15.9 (q, 8-CH3), 22.2 (q, OCHCH3), 22.2 (q, OCHCH3), 31.8 (t, <sup>6</sup>C), 44.1 (t, NCH2Ar), 49.1 (d, <sup>1</sup>C), 54.2 (d, <sup>5</sup>C), 54.9 (q, OCH3), 56.2 (q, OCH3), 59.8 (q, OCH3), 60.3 (q, OCH3), 69.5 (q, OCH), 106.1 (d, CH=C), 108.2 (d, <sup>10</sup>C), 110.9 (d, <sup>6</sup>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, <sup>7</sup>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<sup>+</sup>, 100), 218 (9), 174 (22), 91 (8); high-resolution EI-MS calcd for C35H40N2O7 600.2836, found 600.2856.

**Compound 17** (not crystallizable): IR (CHCl<sub>3</sub>) 1695, 1668, 1603 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 214 (4.51), 244 (4.05), 288 (3.78), 318 (4.00); <sup>1</sup>H NMR  $\delta$  1.13 (3H, d, J = 6.3 Hz, CHCH<sub>3</sub>), 1.20 (3H, d, J = 6.3 Hz, CHCH<sub>3</sub>), 2.03, 2.17 (each 3H, s, Ar CH<sub>3</sub>), 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, OCH<sub>3</sub>), 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); <sup>13</sup>C NMR  $\delta$  9.3 (q, Ar CH<sub>3</sub>), 15.7 (q, ArCH<sub>3</sub>), 21.6 (q, CHCH<sub>3</sub>), 22.2 (q, CHCH<sub>3</sub>), 30.4, (t), 35.9 (t), 46.5 (t, NCH<sub>2</sub>), 55.2 (q, OCH<sub>3</sub>), 59.8 (q, OCH<sub>3</sub>), 60.0 (q, OCH<sub>3</sub>), 60.8 (q, OCH<sub>3</sub>), 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<sup>+</sup>, 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<sub>35</sub>H<sub>40</sub>N<sub>2</sub>O7 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 NH4OH, 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<sub>2</sub>SO4 (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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 214 (4.57), 272 (4.10), 280 (4.09), 288 (4.05), 304 (3.77); <sup>1</sup>H NMR  $\delta$  2.15, 2.16 (each 3H, s, Ar CH<sub>3</sub>), 2.30-2.70 (1H, br s, NH), 3.07 (1H, dd, J = 16.2, 0.5 Hz, H-6 $\beta$ ), 3.18 (3H, s, OCH<sub>3</sub>), 3.21 (1H, dd, J = 16.2, 5.0 Hz, H-6 $\alpha$ ), 3.45, 3.79, 3.79 (each 3H, s, OCH<sub>3</sub>), 4.26 (1H, dd, 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); <sup>13</sup>C NMR  $\delta$  9.5 (q, 3'-CH<sub>3</sub>), 15.9 (q, 8-CH<sub>3</sub>), 32.6 (t, C-6), 44.2 (t, NCH<sub>2</sub>Ar), 50.5 (d, C-1), 54.3 (d, C-5), 54.9 (q, OCH<sub>3</sub>), 56.1 (q, OCH<sub>3</sub>), 59.9 (q, OCH<sub>3</sub>), 60.3 (q, OCH<sub>3</sub>), 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 (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<sup>+</sup>, 100), 499 (13), 484 (43), 334 (11), 333 (14), 313 (10), 175 (16), 174 (80), 91 (21). Anal. Calcd for C<sub>31H34N2O5</sub>·1/2H<sub>2O</sub>: 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.31), 280 (3.65), 286 (3.61), 310sh (2.92); <sup>1</sup>H NMR  $\delta$  1.90-2.10 (1H, br s, NH), 2.18, 2.23 (each 3H, s, Ar CH3), 2.97 (1H, dd, J = 14.8, 9.6 Hz, H-2a), 3.09 (1H, d, J = 16.2 Hz, H-6 $\beta$ ), 3.31 (1H, dd, J = 14.8, 7.6 Hz, H-2a), 3.34 (1H, dd, J = 16.2, 6.3 Hz, H-6 $\beta$ ), 3.43 (1H, dd, J = 14.8, 7.6 Hz, H-2a), 3.34 (1H, dd, J = 16.2, 6.3 Hz, H-6 $\beta$ ), 3.43 (1H, dd, J = 15.5 Hz, NCHAr), 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); <sup>13</sup>C NMR  $\delta$  9.5 (q, ArCH3), 15.9 (q, 8-CH3), 32.8\* (t, C-6), 33.1\* (t, C-2a), 47.4 (t, NCH2Ar), 54.1 (d, C-5), 55.4 (q, OCH3), 60.0 (q, OCH3), 60.1 (q, OCH3), 60.4 (q, OCH3), 64.7 (s, <sup>1</sup>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<sup>+</sup>, 4), 364 (7), 135 (9), 91 (100). Anal. Calcd for C31H34N2O5<sup>-1</sup>/4H2O: C, 71.72; H, 6.70; N, 5.40. Found: C, 71.50; H, 6.72; N, 5.43.

#### Treatment of 17 with 5% H2SO4 in Trifluoroacetic Acid.

Concentrated H<sub>2</sub>SO<sub>4</sub> ( $\overline{0.15}$  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<sub>4</sub>OH, 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 NaHCO3 (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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 214 (4.60), 265 (4.11), 279 (4.10), 289 (4.07), 304 (3.76); <sup>1</sup>H NMR  $\delta$  2.15, 2.16 (each 3H, s, Ar CH<sub>3</sub>), 2.72 (3H, s, NCH<sub>3</sub>), 2.99 (1H, d, *J* = 16.2 Hz, H-6 $\beta$ ), 3.13 (3H, s, OCH<sub>3</sub>), 3.29 (1H, dd, *J* = 16.2, 5.9 Hz, H-6 $\alpha$ ), 3.46, 3.79, 3.80 (each 3H, s, OCH<sub>3</sub>), 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); <sup>13</sup>C NMR  $\delta$  9.4 (q, 3'-CH<sub>3</sub>), 16.0 (q, 8-CH<sub>3</sub>), 31.3 (t, C-6), 41.4 (q, NCH<sub>3</sub>), 44.2 (t, NCH<sub>2</sub>Ar), 54.9 (q, OCH<sub>3</sub>), 56.0 (q, OCH<sub>3</sub>), 56.7 (d, C-1), 59.7 (q, OCH<sub>3</sub>), 60.3 (q, OCH<sub>3</sub>), 61.0 (d, C-5), 106.7 (d, CH=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), 16.99 (s, CO); EI-MS *m/z* (relative intensity) 528 (M<sup>+</sup>, 61), 437 (8), 189 (22), 188 (100). Anal. Calcd for C32H36N2O5: 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<sub>3</sub> (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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 226 (4.28), 282 (3.57), 286 (3.51); <sup>1</sup>H NMR  $\delta$  2.20, 2.23 (each 3H, s, Ar CH<sub>3</sub>), 2.32 (3H, s, NCH<sub>3</sub>), 2.86 (1H, d, *J* = 16.8 Hz, H-6 $\beta$ ), 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-63), 3.46 (3H, s, OCH<sub>3</sub>), 3.52 (1H, dd, *J* = 9,6, 7.3 Hz, H-2), 3.56, 3.69, 3.74 (each 3H, s, OCH<sub>3</sub>), 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); <sup>13</sup>C NMR  $\delta$  9.5 (q, ArCH<sub>3</sub>), 15.9 (q, 8-CH<sub>3</sub>), 25.5 (t, C-6), 33.2 (t, C-2a), 37.1 (q, NCH<sub>3</sub>), 46.9 (t, NCH<sub>2</sub>Ar), 55.3 (q, OCH<sub>3</sub>), 59.6 (q, OCH<sub>3</sub>), 59.8 (q, OCH<sub>3</sub>), 60.3 (q, OCH<sub>3</sub>), 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), 126.5 (d), 128.2 (d), 129.8 (s), 130.8 (d, <sup>7</sup>C), 131.4 (s), 135.2 (s), 136.2 (s), 147.2 (s), 150.4 (s), 150.4 (s), 155.4 (s), 157.1 (z), CO); EI-MS *m*/z (relative intensity) 528 (M<sup>+</sup>, 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<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>: 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<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>) belong to the monoclinic space group P2<sub>1</sub>/n with cell constants a = 19.344 (2) Å, b = 11.485 (8) Å, c = 25.266 (3) Å,  $\beta = 102.472$  (8)°, Z = 8 (two molecules are included in an asymetric unit),  $d_c = 1.281$  g/cm<sup>3</sup>. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Cu-K $\alpha$  radiation. The data were collected at a tempetarure of 23 ± 1 °C using the  $\omega$ -2 $\theta$  scan technique to a maximum 2 $\theta$  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,  $\mu$ , for Cu-K $\alpha$  radiation is 7.0 cm<sup>-1</sup>. 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)<sup>20</sup> and expanded using Fourier techniques.<sup>21</sup> 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 &(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; eluion 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, 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.30), 282 (3.60), 288 (3.51); <sup>1</sup>H NMR & 2.21, 2.26 (each 3H, s, Ar CH<sub>3</sub>), 2.33 (3H, s, NCH<sub>3</sub>), 2.49 (1H, d, *J* = 16.8 Hz, H-6\beta), 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-6 $\infty$ ), 3.58 (1H, d, *J* = 13.9 Hz, NCHAr), 3.62 (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<sub>3</sub>), 6.41 (1H, s, ArH), 6.91-6.94 (3H, m), 7.09-7.13 (3H, m); <sup>13</sup>C NMR  $\delta$  9.4 (q, ArCH<sub>3</sub>), 16.0 (q, 8-CH<sub>3</sub>), 23.8 (t, C-2a), 26.6 (t, C-6), 39.4 (q, NCH<sub>3</sub>), 54.1 (t, C-4), 54.7 (d, C-5), 55.4 (q, OCH<sub>3</sub>), 58.4 (t, N-CH<sub>2</sub>Ar), 59.5 (q, OCH<sub>3</sub>), 60.0 (q, OCH<sub>3</sub>), 60.2 (q, OCH<sub>3</sub>), 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, <sup>7</sup>C), 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<sup>+</sup>, 20), 424 (79), 423 (100), 394 (10), 161 (29), 91 (51). Anal. Calcd for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>·1/10H<sub>2</sub>O: C, 74.42; H, 7.46; N, 5.42. Found: C, 74.22; H, 7.62; N, 5.30.

# $2-[1,2,3,4,5,6-Hexahydro-2,4,5-trimethoxy-3-methylphenyl)methyl]-9-methoxy-8,11-dimethyl-(1\alpha,2\alpha,5\alpha)-1,5-imino-3-benzazocine$ (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 guenched 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-McOH): IR (CHCl<sub>3</sub>) 1660, 1625 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 206 (4.74), 236sh (4.16), 281 (3.98), 290 (3.96), 308sh (3.77); <sup>1</sup>H NMR & 2.15 (3H, s, Ar CH<sub>3</sub>), 2.19 (3H, s, Ar CH<sub>3</sub>), 2.55 (3H, s, NCH<sub>3</sub>), 2.63 (1H, d, J = 16.2 Hz, H-6 $\beta$ ), 2.95 (1H, d, J = 10.2 Hz, H-4), 3.06 (3H, s, OCH<sub>3</sub>), 3.23 (1H, dd, J = 16.2, 7.3 Hz, H-6a), 3.27 (1H, br d, H-5), 3.45 (1H, m, H-4), 3.52, 3.80 (each 3H, s, OCH3), 3.80 (1H, d, J = 15.2 Hz, NCHAr), 3.86 (3H, s, OCH3), 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-10) 7), 6.80-6.84 (2H, m), 6.88 (1H, s, ArH), 7.08-7.12 (3H, m); <sup>13</sup>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<sup>+</sup>, 97), 484 (34), 483 (89), 396 (10), 203 (12), 202 (17), 190 (35), 189 (20), 188 (100), 173 (12), 91 (9); highresolution MS calcd for C32H38N2O4 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% NH4OH 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.19), 280 (3.63), 288 (3.65); <sup>1</sup>H NMR  $\delta$  1.20-2.00 (1H, br s, NH), 2.19 (3H, s, Ar CH<sub>3</sub>), 2.21 (3H, s, Ar CH3), 2.25 (1H,dd, J = 14.9, 8.3 Hz, H-2a), 2.32 (3H, s, NCH3), 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-6 $\alpha$ ), 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, OCH3), 6.40 (IH, s, H-10), 6.67 (IH, s, ArH), 6.92 (IH, s, H-7); <sup>13</sup>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, <sup>1</sup>C), 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<sup>+</sup>, 11), 232 (12), 231 (71), 203 (11), 202 (13), 191 (12), 190 (84), 189 (21), 188 (100). Anal. calcd for C25H34N2O4 H2O: 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- $(6\alpha,9\beta,14a\alpha,15\alpha)$ -6,15-imino-5H-isoquino[3,2-b][3]benzazocine-9-carboxylate (26).

A solution of 24 (937.2 mg, 2.2 mmol) and anhydrous K2CO3 (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 NaHCO3, 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<sub>3</sub>) 1720 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 230 (4.13), 280 (3.55), 287 (3.47); <sup>1</sup>H NMR  $\delta$  0.89 (3H, t, J = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.33 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.61 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>), 2.12 (3H, s, Ar CH<sub>3</sub>), 2.13 (3H, s, Ar CH<sub>3</sub>), 2.32  $(3H, s, NCH_3), 2.58$  (1H, dd, J = 17.5, 10.6 Hz, H-14 $\beta$ ), 2.60 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.60 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.60 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.60 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.80 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.80 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.80 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.80 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.88 (1H, dd, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 2.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H-14 $\beta$ ), 3.80 (1H, d, J = 17.5, 3.0 Hz, H=17.5, 3.0 (1H, d, J = 17.5, 3 14a), 2.93 (1H, dd, J = 10.5, 3.3 Hz, H-7), 3.04 (1H, dd, J = 17.2, 7.6 Hz, H-5a), 3.04 (1H, dd, J = 10.5, 1.0 Hz, H-7), 3.21 (1H, br d, H-6), 3.59 (3H, s, OCH3), 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, OCH3), 4.11 (2H, m, OCH2), 4.58 (1H, s, H-9), 6.53 (1H, s, H-1), 6.84 (1H, s, H-4); <sup>13</sup>C NMR δ 9.2 (q, 12-CH3), 13.7 (q, CH2CH3), 15.9 (q, 3-CH3), 19.2 (t, CH2CH3), 26.0 (t, C-14), 26.3 (t, C-5), 30.7 (t, OCH2CH2), 41.8 (q, NCH3), 53.2 (d, C-6), 53.5 (d, C-14a), 55.4 (q, OCH3), 59.2 (t, C-7), 59.5 (q, OCH3), 59.7 (q, OCH3), 59.8 (q, OCH3), 62.1 (d, C-9), 63.8 (d, C-15), 64.2 (t, OCH2), 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<sup>+</sup>, 8), 438 (30), 437 (100), 218 (11), 203 (8), 189 (11), 188 (30); high-resolution EI-MS calcd for C31H42N2O6 538.3043, found, 538.3032.

# Butyl 6,7,9,14,14a,15-hexahydro-2,10,11,13-tetramethoxy-3,12,16-trimethyl- $(6\alpha,9\alpha,14a\alpha,15\alpha)$ -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<sub>3</sub>, 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 NH4OH and extracted with the residue (230 mg), which was subjected to chromatography (silica gel, 20 g; elution with 100:1 dichloromethane-methanol) 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<sub>3</sub>) 1720 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 226 (4.22), 280 (3.55), 288 (3.46); <sup>1</sup>H NMR  $\delta$  0.81 (3H, t, J = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.16 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.40 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>), 2.16 (3H, s, Ar CH<sub>3</sub>), 2.16 (3H, s, Ar CH<sub>3</sub>), 2.29 (1H, dd, J = 15.2, 11.9 Hz, H-14 $\beta$ ), 2.35 (3H, s, NCH<sub>3</sub>), 2.51 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.84 (2H, m, H-14a and H-14 $\alpha$ ), 2.94 (1H, dd, J = 10.5, 2.3 Hz, H-7), 3.02 (1H, dd, J = 17.2, 7.6 Hz, H-5 $\alpha$ ), 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<sub>3</sub>), 3.93 (2H, m, OCH<sub>2</sub>), 4.10 (1H, s, H-9), 6.49 (1H, s, H-1), 6.81 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.2 (q, 12-CH<sub>3</sub>), 13.6 (q, CH<sub>2</sub>CH<sub>3</sub>), 15.9 (q, 3-CH<sub>3</sub>), 19.0 (t, CH<sub>2</sub>CH<sub>3</sub>), 26.5 (t, C-14), 27.1 (t, C-5), 30.4 (t, OCH<sub>2</sub>CH<sub>2</sub>), 41.4 (n, NCH<sub>3</sub>), 53.6 (d, C-6), 55.4 (q, OCH<sub>3</sub>), 59.1 (d, C-1), 123.9 (s), 124.0 (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); E1-MS *m/z* (relative intensity) 538 (M<sup>+</sup>, 17), 438 (31), 437 (100), 218 (18), 203 (15), 189 (26), 188 (83); high-resolution EI-MS calcd for C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub> 538.3034, found, 538.3054.

**Compound 28** (not crystallizable): IR (CHCl<sub>3</sub>) 2900, 2830, 2750, 1613, 1455, 1445, 1405, 1355, 1345, 1305, 1288, 1140, 1108, 1070, 1008, 963, 905, 888, 855, 845 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 224 (4.26), 280 (3.51), 288 (3.45); <sup>1</sup>H NMR  $\delta$  2.13 (3H, s, Ar CH<sub>3</sub>), 2.15 (3H, s, Ar CH<sub>3</sub>), 2.38 (3H, s, NCH<sub>3</sub>), 2.51 (1H,dd, *J* = 15.8, 11.2 Hz, H-14 $\beta$ ), 2.67 (1H, d, *J* = 17.5 Hz, H-5 $\beta$ ), 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-14 $\alpha$ ), 3.10 (1H, dd, *J* = 17.5, 7.9 Hz, H-5 $\alpha$ ), 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<sub>3</sub>), 3.63 (1H, d, *J* = 2.6 Hz, H-15), 3.73, 3.76, 3.82 (each 3H, s, OCH<sub>3</sub>), 3.99 (1H, d, *J* = 16.2 Hz, H-9), 6.54 (1H, s, H-1), 6.88 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.0 (q, 12-CH<sub>3</sub>), 15.8 (q, 3-CH<sub>3</sub>), 26.3 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH<sub>3</sub>), 53.2 (d, C-6), 53.3 (t, C-9), 55.3 (q, OCH<sub>3</sub>), 59.5 (q, OCH<sub>3</sub>), 59.9 (d, C-14a), 60.0 (q, OCH<sub>3</sub>), 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); E1-MS *m*/z (relative intensity) 438 (M<sup>+</sup>, 40), 250 (20), 249 (15), 203 (22), 190 (28), 189 (20), 188 (100); high-resolution EI-MS calcd for C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O4 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-5Hisoquino[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<sub>3</sub> 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- $(6\alpha,9\alpha,14a\alpha,15\alpha)$ -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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 226 (4.24), 270 (3.40), 280 (3.60), 289 (3.52); <sup>1</sup>H NMR  $\delta$  2.07 (1H, dd, J = 14.9, 11.9 Hz, H-14 $\beta$ ), 2.15 (3H, s, Ar CH3), 2.17 (3H, s, Ar CH3), 2.42 (3H, s, NCH3), 2.50-2.57 (1H, br, OH), 2.59 (1H, d,  $J = 10.8, 12, H-5\beta$ ), 2.88 (1H, dd, J = 14.9, 2.6 Hz, H-14 $\alpha$ ), 2.96 (1H, dd, J = 10.9, 2.3 Hz, H-5 $\alpha$ ), 3.21 (1H, br d, H-6), 3.28 (1H, dd, J = 10.2, 2.0 Hz, CHOH), 3.63 (3H, s, OCH3), 6.51 (1H, s, H-15), 3.68 (1H, dd, J = 10.2, 2.0 Hz, CHOH), 3.73 (1H, br s, H-9), 3.74, 3.81, 3.81 (each 3H, s, OCH3), 6.51 (1H, s, H-15), 6.92 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.2 (q, 12-CH3), 16.0 (q, 3-CH3), 26.7 (t, C-5), 27.1 (t, C-14), 41.4 (q, NCH3), 53.8 (d, C-6), 55.4 (q, OCH3), 58.8 (d, C-14a), 59.5 (d, C-9), 59.5 (q, OCH3), 60.1 (q, OCH3), 60.6 (t, C-7), 64.2 (d, C-15), 64.5 (t, 9-CH2), 111.0 (d, C-1), 123.4 (s), 124.5 (25.7 (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<sup>+</sup>, 1), 438 (32), 437 (100), 204 (10), 189 (8), 188 (45). Anal. Calcd for C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>: 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.

**67,9,14,14a,15**-Hexahydro-10-hydroxy-2,11,13-trimethoxy-3,12,16-trimethyl-( $6\alpha$ ,9 $\alpha$ ,14 $a\alpha$ ,15 $\alpha$ )-6,15imino-5*H*-isoquino[3,2-*b*][3]benzazocine-9-methanol (vii): IR (CHCl<sub>3</sub>) 3530, 3500-3300, 1615, 1460, 1405, 1358, 1345, 1320, 1300, 1280, 1145, 1108, 1050, 1008, 908, 885, 855 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 228 (4.16), 284 (3.76); <sup>1</sup>H NMR  $\delta$  2.09 (1H, dd, *J* = 14.5, 11.9 Hz, H-14 $\beta$ ), 2.16 (3H, s, Ar CH<sub>3</sub>), 2.18 (3H, s, Ar CH<sub>3</sub>), 2.45 (3H, s, NCH<sub>3</sub>), 2.63 (1H, d, *J* = 17.5 Hz, H-5 $\beta$ ), 2.87 (1H, dd, *J* = 14.9, 2.3 Hz, H-14 $\alpha$ ), 3.04-3.19 (5H, m, 2 x H-7, H-14 $\alpha$ , H-5 $\alpha$ , and OH), 3.26 (1H, br d, H-6), 3.51 (1H, dd, *J* = 10.6, 2.0 Hz, CHOH), 3.61 (3H, s, OCH<sub>3</sub>), 3.68 (1H, dd, *J* = 10.6, 4.0 Hz, CHOH), 3.73 (3H, s, OCH<sub>3</sub>), 3.76 (2H, br s, H-9 and H-15), 3.81 (3H, s, OCH<sub>3</sub>), 6.51 (1H, s, H-1), 6.92 (1H, s, H-4); EI-MS *m*/z (relative intensity) 454 (M<sup>+</sup>, 1), 424 (32), 423 (100), 204 (12), 189 (12), 188 (66); high-resolution EI-MS calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O4 (base peak) 423.2284, found 423.2269.

**6**,7,9,14,14**a**,15-Hexahydro-2,10,11,13-trimethoxy-3,12,16-trimethyl-( $6\alpha$ ,9 $\alpha$ ,14 $\alpha$ ,15 $\alpha$ )-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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 226 (4.23), 282 (3.62), 289 (3.48); <sup>1</sup>H NMR  $\delta$  2.09 (3H, s, Ar CH<sub>3</sub>), 2.14 (1H, dd, *J* = 15.2, 11.6 Hz, H-14 $\beta$ ), 2.17 (3H, s, Ar CH<sub>3</sub>), 2.33-2.54 (1H, br, OH), 2.42 (3H, s, NCH<sub>3</sub>), 2.60 (1H, d, *J* = 17.2 Hz, H-5 $\beta$ ), 2.86 (1H, dd, *J* = 15.2, 2.6 Hz, H-14 $\alpha$ ), 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-5 $\alpha$ ), 3.25 (1H, br d, H-6), 3.35 (1H, dd, *J* = 10.2, 2.0 Hz, CHOH), 3.54 (1H, dd, *J* = 4.0, 2.3 Hz, H-9), 3.65 (3H, s, OCH<sub>3</sub>), 3.74 (1H, d, *J* = 2.4 Hz, H-15), 3.76 (3H, s, OCH<sub>3</sub>), 3.80 (1H, dd, *J* = 10.2, 4.0 Hz, CHOH), 3.82 (3H, s, OCH<sub>3</sub>), 6.29 (1H, s, H-10), 6.52 (1H, s, H-1), 6.90 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  8.8 (q, 12-CH<sub>3</sub>), 16.0 (q, 3-CH<sub>3</sub>), 26.4 (t, C-14), 26.8 (t, C-5), 41.0 (q, NCH<sub>3</sub>), 53.8 (d, C-6), 55.5 (q, OCH<sub>3</sub>), 55.6 (q, OCH<sub>3</sub>), 58.6 (d, C-14a), 60.0 (t, C-7), 60.3 (q, OCH<sub>3</sub>), 64.1 (d, C-9), 64.2 (d, C-15), 65.5 (t, 9-CH<sub>2</sub>), 104.1 (d, C-10), 11.0 (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), 155.5 (s), 157.0 (s); EI-MS, *miz* (relative intensity) 438 (M<sup>+</sup>, 3), 408 (31), 407 (100), 204 (11), 203 (15), 189 (10), 188 (52). Anal. Calcd for C<sub>2</sub>6H<sub>3</sub>4N<sub>2</sub>O<sub>4</sub>·3/4H<sub>2</sub>O: 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)-6,15imino-5H-isoquino[3,2-b][3]benzazocin-9-yl)methyl]-1H-isoindole-1,3(2H)-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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 212 (4.73), 232sh (4.37), 240sh (4.01), 280 (3.62), 288 (3.59), 300sh (3.06); <sup>1</sup>H NMR  $\delta$  1.97 (1H, dd, J = 14.5, 11.6 Hz, H-14 $\beta$ ), 2.12 (3H, s, Ar CH<sub>3</sub>), 2.20 (3H, s, Ar CH3), 2.35 (3H, s, NCH3), 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-14a), 3.05 (1H, dd, J = 17.2, 7.6 Hz, H-5a), 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, OCH3), 3.37 (1H, dd, J = 13.9, 8.6 Hz, CHN), 3.54 (3H, s, OCH3), 3.54 (1H, d, J = 2.0 Hz, H-15), 3.55 (1H, dd, J = 13.9, 4.0 Hz, CHN), 3.62, 3.77 (each 3H, s, OCH3), 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); <sup>13</sup>C NMR δ 9.3 (q, 12-CH3), 16.1 (q, 3-CH3), 26.6 (t, C-5), 27.8 (t, C-14), 41.4 (q, NCH3), 43.5 (t, 9-CH2N), 53.8 (d, C-6), 55.4 (q, OCH3), 56.8 (d, C-9), 59.6 (q, OCH3), 60.0 (q, OCH3), 60.1 (d, C-14a), 60.6 (q, OCH3), 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<sup>+</sup>, 1), 438 (31), 437 (100), 188 (22). Anal. Calcd for C27H36N2O5-3/4H2O: 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- $(6\alpha,9\alpha,14a\alpha,15\alpha)$ -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 NH4OH 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<sub>3</sub>) 3400-3100, 1458, 1405, 1358, 1340, 1322, 1302, 1143, 1130, 1108, 1072, 1008, 962, 984,

850 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log ε) 226 (4.15), 280 (3.47), 289 (3.95); <sup>1</sup>H NMR δ 1.50 (2H, br s, NH<sub>2</sub>), 2.20 (1H, dd, *J* = 15.6, 12.5 Hz, H-14β), 2.16 (3H, s, Ar CH<sub>3</sub>), 2.17 (3H, s, Ar CH<sub>3</sub>), 2.36 (3H, s, NCH<sub>3</sub>), 2.54 (1H, d, *J* = 17.1 Hz, H-5β), 2.58 (1H, dd, *J* = 13.2, 2.4 Hz, CH/NH<sub>2</sub>), 2.72 (1H, dd, *J* = 13.7, 3.7 Hz, CH/NH<sub>2</sub>), 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, ddd, *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<sub>3</sub>), 3.64 (1H, dd, J = 3.7, 2.4 Hz, H-9), 3.75, 3.79, 3.82 (each 3H, s, OCH<sub>3</sub>), 6.50 (1H, s, H-1), 6.88 (1H, s, H-4); <sup>13</sup>C NMR δ 9.3 (q, 12-CH<sub>3</sub>), 16.0 (q, 3-CH<sub>3</sub>), 26.8 (t, C-5), 27.6 (t, C-14), 41.5 (q, NCH<sub>3</sub>), 46.1 (t, 9-CH<sub>2</sub>N), 53.8 (d, C-6), 55.4 (q, OCH<sub>3</sub>), 59.0 (d, C-14a), 60.0 (q, OCH<sub>3</sub>), 60.1 (q, OCH<sub>3</sub>), 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<sup>+</sup>, 438 (31), 437 (100), 188 (27); high-resolution EI-MS calcd for C<sub>26</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub> 437.2440 (base peak), found 437.2458; positive FAB-MS (magic bullet) *m/z* 468 (M<sup>+</sup> + 1).

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

A solution of the crude 9 (170.4 mg, 0.3648 mmol), triethylamine (49.5  $\mu$ L, 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% NaHCO3 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 (CHCl3) 3360, 1730, 1680, 1675 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\epsilon$ ) 224 (4.29), 270 (3.40), 288 (3.46); <sup>1</sup>H NMR  $\delta$  2.04  $(1H, dd, J = 14.8, 11.9 Hz, H-14\beta)$ , 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-5B), 2.83-3.20 (6H, m, H-14a, H-14a, 2 x H-7, 9-CH, and H-14a, H-14aH-5a), 3.24 (1H, br d, H-6), 3.40 (1H, ddd, J = 13.2, 6.6, 4.3 Hz, 9-CHN), 3.60 (3H, s, OCH3), 3.68 (1H, br s, H-15), 3.75 (3H, s, OCH3), 3.85 (1H, m, H-9), 3.85, 3.86 (cach 3H, s, OCH3), 6.48 (1H, br s, NH), 6.50 (1H, s, H-1), 6.91 (1H, s, H-4); <sup>13</sup>C NMR δ 9.2 (q, 12-CH<sub>3</sub>), 16.0 (q, 3-CH<sub>3</sub>), 24.3 (q, COCH<sub>3</sub>), 26.5 (t, C-5), 27.2 (t, C-14), 41.3 (q, NCH<sub>3</sub>), 43.7 (t, 9-CH2N), 53.6 (d, C-6), 55.6 (q, OCH3), 58.3 (d, C-9), 59.1 (d, C-14a), 59.9 (q, OCH3), 60.3 (q, OCH3), 60.4 (q, OCH3), 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, COCH3); EI-MS m/z (relative intensity) 537 (M<sup>+</sup>, 1>), 438 (34), 437 (100), 218 (12), 188 (24); high-resolution EI-MS calcd for C26H33N2O4 437.2440 (base peak), found 437.2440; positive FABMS (magic bullet) m/z 538 (M<sup>+</sup> + 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  $\mu$ L, 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 (20;1) 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<sub>3</sub>) 3380, 1725, 1688, 1680 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 230 (4.12), 284 (3.66), 288 (3.63); <sup>1</sup>H NMR  $\delta$  1.95 (1H, dd, J = 15.2, 12.5 Hz, H-14 $\beta$ ), 2.11 (3H, s, Ar CH<sub>3</sub>), 2.19 (3H, s, Ar CH<sub>3</sub>), 2.25 (3H, s, COCH<sub>3</sub>), 2.47 (3H, s, NCH<sub>3</sub>), 2.78 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.78 (1H, m, H-14a), 2.92 (1H, d, J = 15.2 Hz, H-14 $\alpha$ ), 2.98 (2H, br s, 2 x H-7), 3.05 (1H, ddd, J = 13.2, 4.6, 4.6 Hz, 9-CI/N), 3.13 (1H, dd, J = 17.2, 7.6 Hz, H-5 $\alpha$ ), 3.28 (1H, br d, H-6), 3.35 (1H, ddd, J = 13.2, 6.6, 3.6 Hz, 9-CHN), 3.59 (2H, br s, H-9 and H-15), 3.73, 3.76, 3.85 (each 3H, s, OCH<sub>3</sub>), 6.53 (1H, s, H-1), 6.56 (1H, m, NH), 6.93 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.3 (q, 12-CH<sub>3</sub>), 16.1 (q, 3-CH<sub>3</sub>), 24.4 (q, COCH<sub>3</sub>), 26.5 (t, C-14), 26.8 (t, C-5), 40.8 (q, NCH<sub>3</sub>), 44.2 (t, 9-CH<sub>2</sub>N), 54.1 (d, C-6), 55.9 (q, OCH<sub>3</sub>), 58.0 (d, C-9), 59.3 (d, C-14a), 60.1 (q, OCH<sub>3</sub>), 60.4 (q, OCH<sub>3</sub>), 60.7 (t, C-7), 64.4 (d, C-15), 111.2 (d, C-1), 118.1 (s), 119.6 (s), 125.4 (s), 126.4 (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, COCH<sub>3</sub>); EI-MS *m/z* (relative intensity) 523 (M<sup>+</sup>, 1>), 424 (34), 423 (100), 211 (32), 188 (24); high-resolution MS calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2O4</sub> 423.2284 (base peak), found 423.2289; positive FABMS (magic bullet) *m/z* 524 (M<sup>+</sup> + 1).

Compound 33: mp 235-238 °C dec; IR (KBr) 3700-3100, 1720, 1665 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log  $\varepsilon$ ) 224 (4.25), 284 (3.71); <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>-CD<sub>3</sub>OD) 1.97 (1H, dd, J = 14.9, 11.6 Hz, H-14 $\beta$ ), 2.12 (3H, s, Ar CH<sub>3</sub>), 2.20 (3H, s, Ar CH<sub>3</sub>), 2.20 (3H, s, COCH<sub>3</sub>), 2.39 (3H, s, NCH<sub>3</sub>), 2.72 (1H, d, J = 17.2 Hz, H-5 $\beta$ ), 2.82 (2H, m, H-14a and H-14 $\alpha$ ), 2.98 (2H, br s, 2 x H-7), 3.09 (1H, dd, J = 17.2, 7.6 Hz, H-5 $\alpha$ ), 3.11 (1H, dd, J = 13.2, 3.3 Hz, 9-CHN), 3.24 (1H, br d, H-6), 3.38 (1H, dd, J = 13.2, 4.6 Hz, 9-CHN), 3.61 (2H, br s, H-15), 3.73 (3H, s, OCH<sub>3</sub>), 3.77 (1H, dd, J = 4.6, 3.3 Hz, H-9), 3.78 (3H, s, OCH<sub>3</sub>), 6.49 (1H, s, H-1), 6.87 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.2 (q, 12-CH<sub>3</sub>), 15.9 (q, 3-CH<sub>3</sub>), 24.4 (q, COCH<sub>3</sub>), 26.8 (t, C-14), 27.0 (t, C-5), 40.8 (q, NCH<sub>3</sub>), 43.8 (t, 9-CH<sub>2</sub>N), 54.0 (d, C-6), 58.1 (d, C-14a), 59.0 (d, C-9), 60.4 (q, OCH<sub>3</sub>), 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, COCH<sub>3</sub>); EI-MS *m*/z (relative intensity) 509 (M<sup>+</sup>, 1>), 410 (30), 409 (100), 204 (11),

174 (26); high-resolution MS calcd for C24H29N2O4 409.2127 (base peak), found 409.2129; positive FABMS (magic bullet) m/z 510 (M<sup>+</sup> + 1). Anal. Calcd for C28H35N3O6 H2O: 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-(6a,9a,14aa,15a)-6,15-imino-5H-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 HNO3 (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<sup>-1</sup>; UV λ<sub>max</sub> nm (log ε) 234sh (3.92), 276 (4.03), 288sh (3.93), 380 (2.77); <sup>1</sup>H NMR  $\delta$  1.75 (1H, ddd, J = 17.5, 11.9, 3.0 Hz, H-14 $\beta$ ), 1.90 (3H, s, 12-CH<sub>3</sub>), 2.18 (3H, s, COCH3), 2.22 (3H, s, 3-CH3), 2.42 (3H, s, NCH3), 2.58 (1H, d, J = 17.5 Hz, H-5β), 2.75 (1H, dd, J = 17.5, 1.0 Hz, H-14 $\alpha$ ), 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-5 $\alpha$ ), 3.20 (1H, ddd, J = 13.2, 6.0, 4.3 Hz, 9-CHN), 3.24 (1H, br d, H-6), 3.60-3.68 (3H, m, 9-CHN, H-9, and H-15), 3.84 (3H, s, 2-OCH3), 4.01 (3H, s, 11-OCH3), 6.30 (1H, br, NH), 6.44 (1H, s, H-1), 6.88 (1H, s, H-4); <sup>13</sup>C NMR δ 8.6 (q, 12-CH3), 16.0 (q, 3-CH3), 24.2 (q, COCH3), 25.2 (t, C-14), 26.6 (t, C-5), 41.0 (q, NCH3), 41.2 (t, 9-CH2N), 53.6 (d, C-6), 55.8 (q, 2-OCH3), 57.4 (d, C-14a), 57.8 (d, C-9), 59.6 (t, C-7), 61.0 (q, 11-OCH3), 63.5 (d, C-15), 111.3 (d, C-1), 126.3 (s, C-15a), 126.4 (s, C-3), 127.6 (s, C-15a), 127.6 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, COCH3); EI-MS m/z (relative intensity) 507 (M<sup>+</sup>, 14), 409 (16), 408 (23), 407 (75), 204 (15), 203 (13), 202 (13), 190 (13), 189 (23), 188 (100); high-resolution EIMS caled for C28H33N3O6 507.2369, found 507.2376. Anal. Caled for C28H33N3O6: 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- $(6\alpha,9\alpha,14a\alpha,15\alpha)$ -6,15-imino-5H-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 HNO3 (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<sup>-1</sup>; UV λ<sub>max</sub> nm (log ε) 268 (4.03), 362 (3.18); <sup>1</sup>H NMR  $\delta$  1.33 (1H, ddd, J = 17.5, 11.2, 3.0 Hz, H-14 $\beta$ ), 1.88 (3H, s, 12-CH<sub>3</sub>), 2.21 (3H, s, COCH<sub>3</sub>), 2.32 (3H, s, 3-CH<sub>3</sub>), 2.44 (3H, s, NCH<sub>3</sub>), 2.54 (1H, d, J = 16.5 Hz, H-5 $\beta$ ), 2.68 (1H, dd, J = 17.5, 2.0 Hz, H-14 $\alpha$ ), 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-5 $\alpha$ ), 3.15 (1H, br d, H-6), 3.16 (1H, ddd, J = 13.5, 4.0, 3.6 Hz, 9-CHN), 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-CI/N),4.00 (3H, s, 11-OCH<sub>3</sub>), 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); <sup>13</sup>C NMR δ 8.6 (q, 12-CH<sub>3</sub>), 16.2 (q, 3-CH<sub>3</sub>), 23.6 (t, C-14), 24.3 (q, COCH<sub>3</sub>), 27.6 (t, C-5), 40.8 (q, NCH3), 41.3 (t, 9-CH2N), 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-OCH3), 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, COCH3); EI-MS m/z (relative intensity) 538 (M<sup>+</sup>, 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 C27H30N4O8 538.2064, found 538.2067. Anal. Calcd for C27H30N4O8:H2O: 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 HNO3 (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-5H-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% NaHCO3 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 (CHCl3) 3370, 1755, 1715, 1680, 1665 cm<sup>-1</sup>; UV  $\lambda_{max}$  nm (log ε) 222 (4.24), 280 (3.38), 288 (3.32); <sup>1</sup>H NMR δ 1.98 (1H, dd, J = 15.2, 12.2 Hz, H-14β), 2.06 (3H, s, 12-CH3), 2.20 (3H, s, 3-CH3), 2.27, 2.33, 2.35 (each 3H, s, COCH3), 2.37 (3H, s, NCH3), 2.47 (1H, dd, J = 15.2, 2.3 Hz, H-14 $\alpha$ ), 2.61 (1H, d, J = 16.8 Hz, H-5 $\beta$ ), 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-14 $\alpha$ ), 2.89 (1H, dd, J = 10.6, 1.0 Hz, Hz, H-14 $\alpha$ ), 2.89 (1H, dd, J = 10.6, 1.0 Hz, Hz, Hz, Hz, Hz, Hz, Hz 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-CHN),

3.52 (1H, d, J = 2.3 Hz, H-15), 3.63 (1H, t like, H-9), 3.70 (3H, s, OCH3), 3.82 (3H, s, OCH3), 6.38 (1H, s, H-1), 6.55 (1H, t like, NH), 6.94 (1H, s, H-4); <sup>13</sup>C NMR  $\delta$  9.9 (q, 12-CH3), 16.0 (q, 3-CH3), 20.3 (q, COCH3), 20.7 (q, COCH3), 24.3 (q, COCOCH3), 26.5 (t, C-5), 27.5 (t, C-14), 41.3 (q, NCH3), 44.1 (t, 9-CH2), 53.8 (d, C-6), 55.5 (q, 2-OCH3), 58.0 (d, C-9), 59.1 (d, C-14a), 60.9 (q, 11-OCH3), 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, OCOCH3), 168.6 (s, OCOCH3), 196.2 (s, COCOCH3); E1-MS *m*/z (relative intensity) 593 (M<sup>+</sup>, 1), 494 (34), 493 (100), 451 (15), 188 (45), high-resolution EIMS, calcd for C32H39N308 593.2737, found, 593.2730.

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

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% NaHCO3 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<sup>-1</sup>; UV  $\lambda_{max}$  nm (log e) 266 (4.00), 362 (2.83); <sup>1</sup>H NMR  $\delta$  1.38 (1H, ddd, J = 17.2, 11.2, 3.0 Hz, H-14 $\beta$ ), 1.90 (3H, s, 12-CH3), 2.23 (3H, s, 3-CH3), 2.24, 2.28 (each 3H, s, COCH3), 2.38 (3H, s, NCH3), 2.55 (1H, dd, J = 17.2, 2.3 Hz, H-14 $\alpha$ ), 2.70 (1H, ddd, J = 11.2, 3.0, 2.3 Hz, H-14 $\alpha$ ), 2.69 (1H, d, J = 16.8 Hz, H-5 $\beta$ ), 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-5 $\alpha$ ), 3.19 (1H, br d, H-6), 3.28 (1H, ddd, J = 13.9, 4.3, 4.3 Hz, 9-C/IN), 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/IN), 3.99 (3H, s, OCH3), 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<sup>+</sup>, 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 C29H32N409 580.2169, found 580.2168.

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- 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.
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- Treatment of 24 with paraformaldehyde and K2CO3 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 <sup>1</sup>H NMR spectrum of 9-epi-ester v showed H-9 (δ 4.56) and H-14a (δ 3.57), whereas the <sup>1</sup>H NMR spectrum of vi showed H-9 (δ 4.09) and H-14a (δ 2.84).<sup>9a</sup>



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 <sup>1</sup>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.



- 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.
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