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SAFRAMYCIN SYNTHETIC STUDIES

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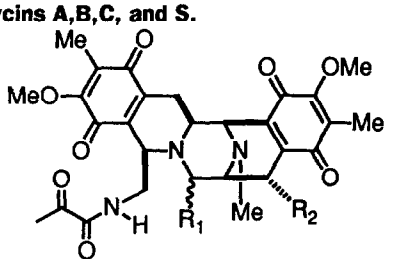
Abstract A conceptually simple and direct synthetic route to racemic saframycin B, a bis-isoquinoline quinone antitumor antibiotic, was studied relying on transformations of a key C-2 symmetric intermediate.

The saframycins are a family of *bis*-isoquinoline quinone alkaloids isolated from *Streptomyces lavendulae* and first reported by Arai in 1977 (Figure 1).[1] The simplest member of the family is saframycin B (**2**), the structure of which was determined by comparison with saframycin C (**3**) by proton and ^{13}C NMR spectroscopy [2] The structure of saframycin C was elucidated by an X-ray crystallographic study, ultimately, the structure of saframycin B was confirmed by total synthesis [3-5] Other important congeners of saframycin B are saframycins A[1] (**1**) and S[6] (**4**), which are two orders of magnitude more active than saframycins B or C in antitumor bioassays Saframycin A has recently succumbed to total synthesis [7]

Figure 1. Saframycins A,B,C, and S.



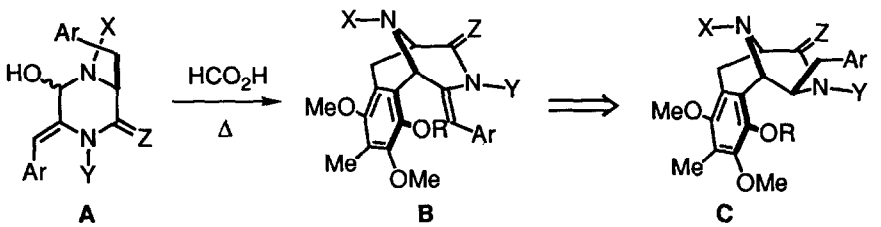
Saframycin	R_1	R_2
A (**1**)	CN	H
B (**2**)	H	H
C (**3**)	H	OMe
S (**4**)	OH	H

A key structural feature of saframycin B is the all-*cis* relative stereochemistry of the substituent groups about the central piperazine ring - this relative stereochemistry is shared by the pyruvamide side chain In the biosynthesis of saframycin C, incorporation of [^{14}C]tyrosine implies that the absolute stereochemistry of the saframycins retains the stereogenic sense of the S-amino acid [8] There has been reasonable effort directed toward the synthesis of the saframycins[3-5,7,9-12] and three syntheses have been completed to date [3-5,7] Common to these efforts was the generation of an N-acyl hemiaminal derived by partial reduction of an unsymmetrically substituted 2,5-piperazinedione (**A**, Eqn 1), which was heated in formic acid to effect iminium ion generation and arene cyclization to give the key 1,5-imino-3-benzazocine skeleton **B** (as shown on page 4) Hydrogenation established

the necessary all *cis* stereochemistry around the piperazine ring Construction of the key intermediate A required differential functionalization of the nitrogen atoms of the piperazinedione with attendant increases in synthetic complexity

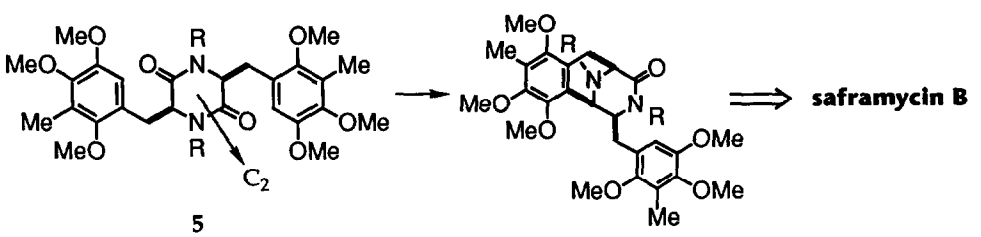
Conceptually, a simpler and more direct route to the requisite benzazocine originates with the C-2 symmetric piperazinedione **5** (Eqn 2) Useful synthetic opportunities accrue from the presence of the symmetry element First, if **5** were prepared enantiomerically pure, reduction and bridging ring closure of the derived iminium ion would result in retention of absolute stereochemistry in the product benzazocine, *regardless of which carbonyl group was reduced* Second, no differentiation of the nitrogen atoms is required *prior* to cyclization, since one nitrogen is transformed into a tertiary amine, while the other remains a tertiary lactam As a consequence of these issues, the preparation of the piperazinedione is simplified because of the degeneracy of the synthetic operations leading to it (see below)

Eqn. 1



A **B** **C**

Eqn. 2



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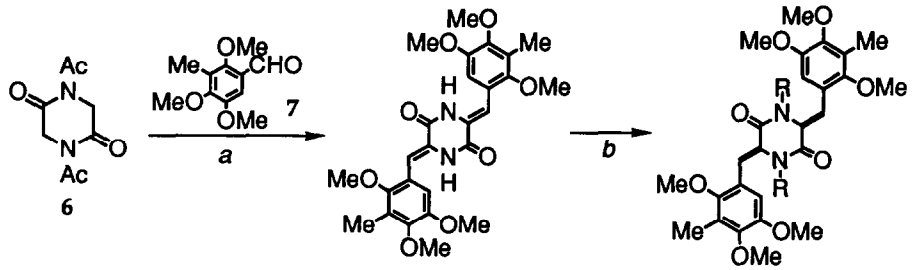
Results and Discussion

Following the Gallina procedure[13] for the synthesis of *bis*-arylidenepiperazinediones, reaction of diacetylpiperazinedione (**6**) with 2,4,5-trimethoxy-3-methylbenzaldehyde (**7**) led to none of the desired material, **8** (Eqn 3) However, heating the components with potassium carbonate in DMF (120 °C, 24 h) afforded the desired *bis*-arylidene products (58%) along with unreacted aldehyde (23%) A survey of other bases led to the discovery that Cs_2CO_3 in DMF effected the condensation under

milder conditions (80 °C, 3h) and provided product reproducibly in better yield (64%) along with recovered aldehyde (27%) Catalytic reduction[14] of **8** gave the crystalline *bis*-(aryl)methyl compound **9** in 94 % yield as a 15 to 1 mixture of *cis* and *trans* isomers Benzylation to **10** was effected with benzyl bromide and sodium hydride in DMF, in 92 % yield (Equation 3)

Eqn. 3

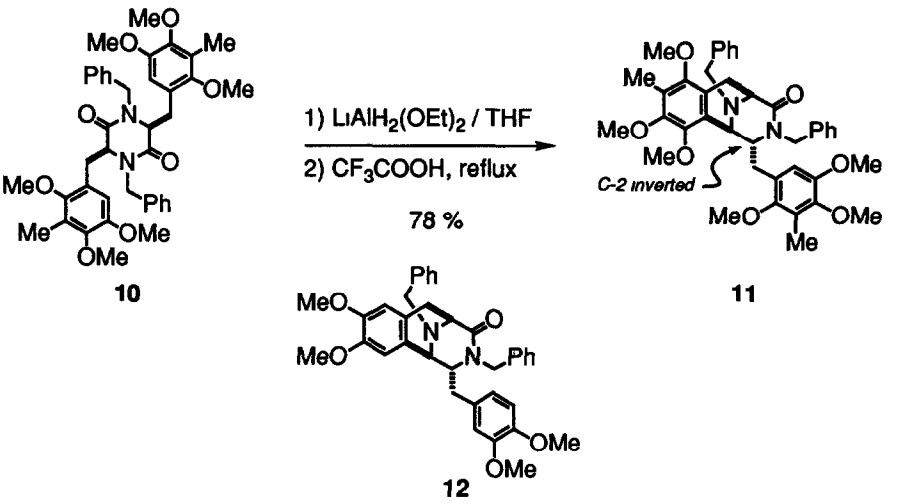


[a] K_2CO_3 in DMF at 120 °C, 58%, Cs_2CO_3 in DMF at 80 °C, 64% [b] H_2, Pd/C in HOAc then NaH, $PhCH_2Br$ in DMF, 86% overall from **8**

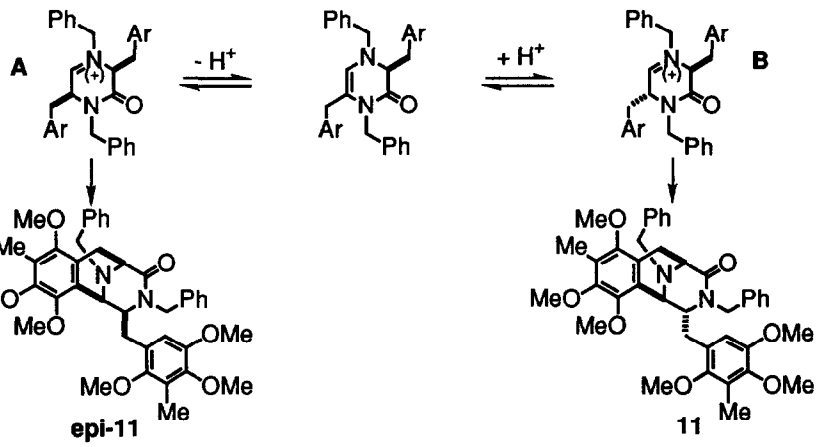
The selective mono-reduction of **10** with lithium diethoxyaluminohydride in THF[15] proceeded smoothly, and the reaction mixture was quenched with damp ether and filtered through sodium sulfate to remove suspended aluminum salts Solvolysis of the crude hemiaminal in CF_3CO_2H at reflux resulted in efficient generation of the benzazocine skeleton, however the product obtained (**11**) had inverted stereochemistry at the C-2 substituent (Eqn 4) The assignment of stereochemistry to **11** was made on the basis of an X-ray crystallographic study of an analogous benzazocine **12** derived from 3,4-dimethoxybenzaldehyde during an early model study using the same chemistry shown in equations 3 and 4 [16] Also, **11** was converted into **17a**, a compound epimeric with an intermediate in the Kubo synthesis of saframycin B (see below)

The formation of epimer **11** can be rationalized by the iminium ion – enamine equilibration shown in Scheme 1 Cyclization of iminium ion **A** would produce the desired isomer, epi-**11**, however, cyclization apparently is difficult because of unfavorable non-bonded interactions between the bridging aryl group and the *cis* benzylic substituent Equilibration to iminium ion **B** allows formation of the observed product **11** through a less hindered transition state [17]

Eqn. 4



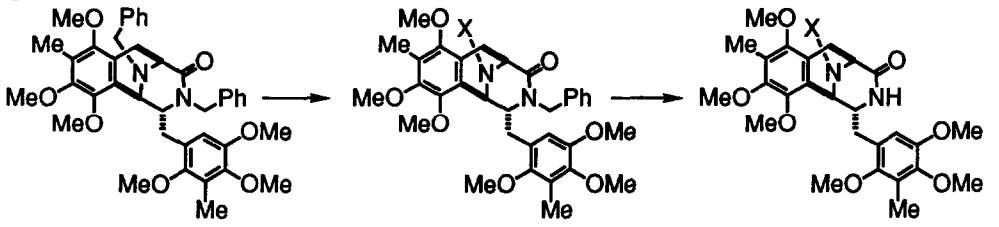
Scheme 1



Because of the overall efficiency of the preparation of benzazocine **11**, N-deprotection and reinversion of the stereochemistry at C-2 was explored as a practical entry to saframycin B synthesis The application of catalytic hydrogen transfer conditions (Pd/C, HCOOH/MeOH)[18] for the selective hydrogenolysis of **11** produced the monodebenzylated compound **13** in 80 % yield in 45 min (Eqn 5) This was methylated to **14a** in 90 % yield using iodomethane, alternatively, when the hydrogenolysis was allowed to proceed for 6 h, the secondary amine produced in situ was formylated, presumably by methyl formate generated in the reaction mixture The N-formyl derivative **14b** so produced was isolated in 67 % yield Debenzylation of the N-benzyl lactam of **14a** and **14b** proceeded smoothly, in

each case, using a dissolving metal reduction[19] with sodium in ammonia - THF at -78 °C, 96 % of the N-methyl derivative **15a** and 77 % of the N-formyl lactam **15b** were obtained As described below, these secondary lactams were subjected to several sets of conditions designed to introduce unsaturation at C-2, hydrogenation of which would set the proper stereochemistry of the natural product

Eqn. 5

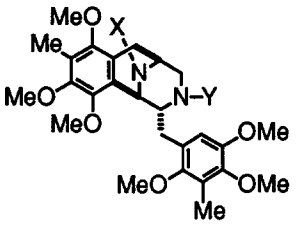


11 **13: X = H** **14a: X = Me** **14b: X = CHO** **15a: X = Me** **15b: X = CHO**

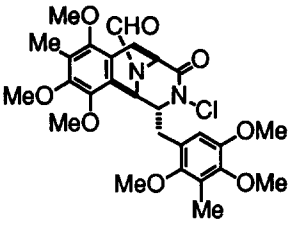
Other benzazocine derivatives of potential use for C-2 inversion were prepared as well The initial hydrogenolysis product **13** was reduced with dichloroalane[20] and formylated with ethyl formate[21] in 87 % overall yield to give the N-formyl benzylamine **16b** which was debenzylated in 83 % yield under hydrogenolysis conditions to the secondary amine **17b** The analogous N-methyl derivatives were prepared in similar fashion; for example, the secondary lactam **15a** was reduced with alane in 97 % yield to the benzazocine **17a** This material is an epimer of an intermediate in the Kubo synthesis of saframycin B, and comparison of the proton NMR of this material and Kubo's intermediate support the structural assignment made on the basis of the X-ray structure mentioned above In addition to these substrates, the N-methylated hydrogenolysis product **14a** was reduced with dichloroalane in 84 % yield to afford the N-benzyl derivative **16a**

The first attempts in a survey of reactions to introduce unsaturation at C-2 of the benzazocine substrates centered on the N-halogenation of the secondary lactams **15a** and **15b** Reactions of the N-methyl benzazocine **15a** with *tert*-butyl hypochlorite under various conditions[22,23] were unsuccessful, as were attempted reactions with tBuOBr,[24] tBuOI,[25] N-iodosuccinimide, PhSeCl,[26] and PhSe(O)Cl [27] Attempts to cleanly functionalize the benzylic positions using CrO_3/tBuOOH,[28] NBS/benzoyl peroxide,[29] or DDQ[30,31] were also unsuccessful The reaction of **15a** with $Mn(acac)_3$ in the presence of peracetic acid[32] gave only the N-oxide of the tertiary amine, verified by the regeneration of starting material by deoxygenation with Et_3P On the assumption that the difficulties in oxidizing the amide

N–H were associated with the nucleophilic nucleophilic tertiary amine of **15a**, chlorination of the N-formyl substituted **15b** was attempted and led to the isolation of the N-chloro derivative **18** However, all attempts to dehydrochlorinate this material were fruitless



16a: X = Me, Y = Bn
16b: X = CHO, Y = Bn
17a: X = Me, Y = H
17b: X = CHO, Y = H

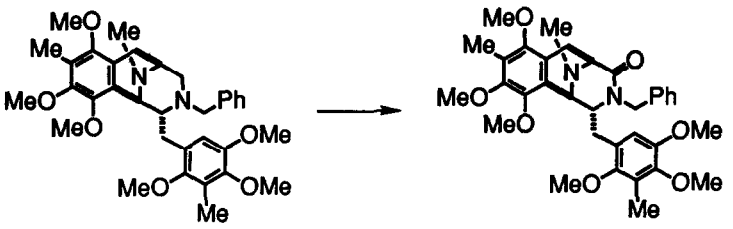


18

An interesting note regarding the N-formyl substrates is the presence of relatively stable rotomers about the formamide carbon – nitrogen bond These were observed in the proton and ^{13}C NMR spectra and on thin layer chromatography During flash chromatography the rotomers eluted coincidentally; however, reference has been made[33] to the isolation of such rotomers in structurally related Pavinan alkaloid derivatives and others

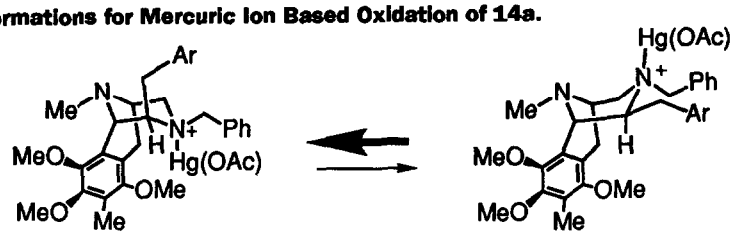
The oxidation of tertiary and secondary amines by various means has been found to proceed at the more substituted carbon atom adjacent to nitrogen in unsymmetrical cases One such reaction is the mercuric ion dehydrogenation of benzylamines [34,35] Application of this reaction to benzazocine **16a** or **16b** would likely give the (desired) more substituted enamine, by deprotonation of the iminium ion formed by the oxidation reaction In practice (Eqn 6), the N-methyl derivative was oxidized at the *less* substituted carbon atom to give benzazocine **14a** in 43 % yield along with 36 % of recovered starting material, the corresponding N-formyl lactam **16b** was inert to these oxidation conditions Oxidation at the less substituted position of **16a** is likely due to a conformation of the amine-mercuric ion complex in which the methine proton cannot easily achieve an orientation antiperiplanar to the nitrogen-mercuric ion bond (ie **19a**, Figure 2) In this case, the iminium ion formed by dehydrogenation is probably hydrated and then oxidized by mercuric ion to the observed lactam

Eqn. 6



16a 14a

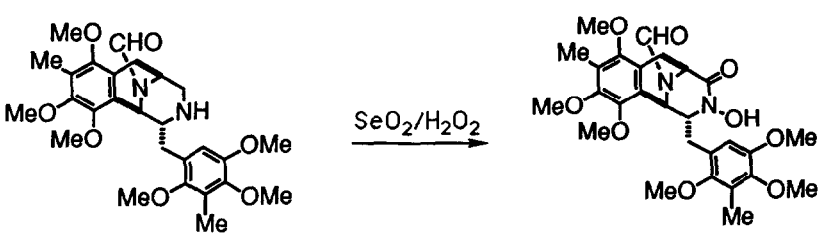
Figure 2. Conformations for Mercuric Ion Based Oxidation of 14a.



19a 19b

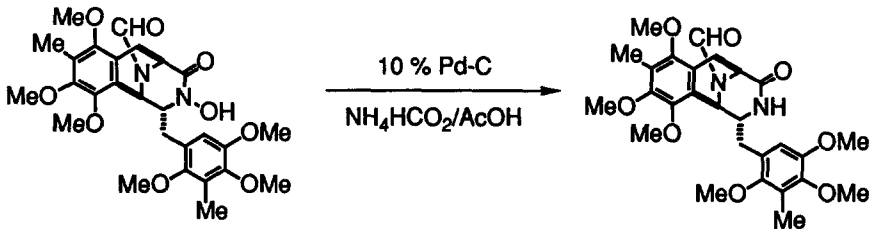
The final set of conditions investigated were those of Murahashi[36] for the oxidation of secondary amines to the corresponding nitrone, a functionality that on reduction (catalytic hydrogenation[37], LAH-$TiCl_3$[38]) would serve to invert stereochemistry at C-2 Again, oxidation of the more substituted carbon atom adjacent to nitrogen was seen in simple systems However, reaction of benzazocine **17b** with selenium dioxide and hydrogen peroxide did not produce a nitrone, rather a product assigned the hydroxamic acid structure **20** was obtained(Eqn 7) The generation of hydroxamic acids from secondary amines has been reported by Murahashi[39] to proceed under the same conditions as for the generation of nitrones from certain substrates, and is stated to proceed *via* the nitrone In the case of benzazocine **17b**, the oxidation of the undesired less substituted carbon atom is again indicated On reduction (Pd-C/NH_4HCO_2/AcOH, reflux), **20** gave a good recovery of the secondary lactam **15b** (Eqn 8)

Eqn. 7



17b 20

Eqn. 8



20 **15b**

The work described here demonstrates the feasibility of rapidly synthesizing the 1,5-imino-3-benzazocine skeleton from symmetrically substituted 2,5-piperazinediones This method of preparation is highly efficient both in terms of yield and manipulative ease, accomplishing in a few steps what had required several operations in previously described routes. The applicability of this method to the saframycin B problem relies on the successful deprotection of the initial cyclization product and its elaboration to the all-*cis* benzazocine, necessitating isomerization at the C-2 carbon While the selective deprotection methods described here are versatile and efficient, a means of isomerizing the C-2 carbon stereochemistry remains undiscovered

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EXPERIMENTAL PROCEDURES

Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (60F-254) obtained from EM Reagents which were visualized by UV light (254 nm), phosphomolybdic acid stain (5% w/v in MeOH) and/or vanillin stain (5% w/v vanillin, in 5% v/v H_2SO_4 in 50% aqueous ethanol) Column chromatography was performed using 60-200 mesh silica gel for gravity columns or 230-400 mesh for pressurized columns Concentration refers to rotary evaporation, and was routinely followed by exposure to vacuum at 0 2 to 1 0 mm Hg Solvents were dried *per* the following. diethyl ether, tetrahydrofuran (THF), and benzene from sodium-benzophenone ketyl, methylene chloride, dimethylformamide, and triethylamine from calcium hydride ^{13}C NMR DEPT experiments were performed according to techniques described by Derome [40]

2,4,5-Trimethoxy-3-methylbenzaldehyde (7) was prepared by a modification of the Sachleben procedure for the preparation of the related 5-benzyloxyaldehyde: [41] *1,4-Diacetylpiperazine-2,5-dione (6)* In a dry 250 mL round-bottomed flask were taken 20 g of glycine anhydride (Aldrich) and 200 mL of acetic anhydride The resulting solution was heated with an oil bath at 150 °C overnight with slow distillation. The reaction mixture, which was dark brown at this time, was concentrated and placed on a vacuum pump, whereupon crystallization occurred. The solid was collected on a glass frit (M) and triturated with absolute ethanol, followed by recrystallization from 50 mL of absolute ethanol The product was collected and dried *in vacuo* to yield 23 g (66%) of the desired material as colorless crystals mp. 101-101.5 °C (lit [42] mp = 104 5-105 °C); ^{1}H NMR (360 MHz, $CDCl_3$). 4 603 (s, 2 H, CH_2), 2 595 (s, 3 H, $COCH_3$); IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3420, 3055, 3020, 2840, 2805, 1728, 1710, 1433, 1413, 1367, 1304, 1275-1245, 1188, 1130, 1070, 1039, 978, 950, 812. *2,4-Dimethoxy-3-methylbenzaldehyde.* According to the method of Lewin,[43] 81 0 g (0 449 mol, 1 0 equiv , Aldrich) of 2,6-dimethoxytoluene was taken in 120 mL of dry methylene chloride in an addition funnel and added slowly to a cold (ice-acetone bath) solution of 50 mL (0 56 mol, 1 3 equiv , Aldrich 97%) of dichloromethyl methyl ether and 200 g (1 05 mol, 2 0 equiv , Aldrich) of titanium tetrachloride in 160 mL of dry methylene chloride in a dry 1 L 3-neck flask equipped with a large magnetic stirring bar HCl gas generated in the reaction was swept out through a syringe needle with a slight positive pressure of dry nitrogen The rate of addition was maintained such that the temperature of the reaction mixture registered on an immersion thermometer did not exceed 4 °C The addition was completed during a period of one hour, whereupon TLC analysis (SiO_2) showed the absence of starting material and the presence of a single new UV-active component The reaction mixture was poured onto ice (contained in a 1 L vessel) and rinsed with a little CH_2Cl_2 The phases were separated, and the aqueous phase washed with two 50 mL portions of CH_2Cl_2 The combined organic phases were back-washed with one 100 mL and two 50 mL portions of water, dried with anhydrous $MgSO_4$, filtered, and concentrated The crude product which crystallized while concentrating under vacuum was purified by Kugelrohr distillation to give 91 8 g (95 8%) of the desired material as colorless needles b p (Kugelrohr) 105-110 °C at 0 65 mm Hg, mp 51-53 °C (lit [41] mp = 52-53 °C), ^{1}H NMR (360 MHz, $CDCl_3$) δ 10 231 (s, 1 H, C*H*O), 7 747 (d, J = 8 6 Hz, 1 H, Ar*H*-5), 6 749 (d, J = 8 6 Hz, 1 H, Ar*H*-6), 3 909, 3 863 (s, s, 3 H each, OCH_3 x2), 2 165 (s, 3 H, $ArCH_3$) *1-Acetoxymethyl-2,4,5-trimethoxy-3-methylbenzene* Into a dry 100 mL round-bottomed flask was weighed 20 24 g (84 35 mmol, 1 0 equiv) of 2,4-dimethoxy-3-methyl-5-acetoxymethylphenol prepared from 2,4-dimethoxy-3-methylbenzaldehyde according to the method of Sachleben [41] Potassium carbonate (23 g, 17 x 10^1 mmol, 2 0 equiv) was added and the reactants were suspended in 26 mL of reagent grade acetone while 26 mL (0 42 mol, 5 0 equiv) of iodomethane was introduced The mixture was heated to reflux and stirred vigorously for 36 h, whereupon TLC analysis showed the diminution of starting material R_f = 0 18 and the presence of a major new UV-active component with an R_f of 0 40 (SiO_2, eluting with 33% ether in hexanes) The reaction was cooled and the reactants partitioned between 200 mL of water and 200 mL of methylene chloride The aqueous phase was extracted with two 50 mL portions of methylene chloride and the combined organic phases were dried (Na_2SO_4) and concentrated to give 21 35 g of crude material Chromatography on silica gel (400 g, 230-400 mesh)

eluting with 25% ether in hexanes followed by 33% ether in hexanes provided 20 0 g (93 4%) of the desired material as a colorless oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.768 (s, 1 H, Ar*H*), 5.120 (s, 2 H, ArCH_2), 3 844, 3 803, 3 727 (singlets, 3 H each, OCH_3 x2), 2 225 (s, 3 H, ArCH_3), 2 103 (s, 3 H, COCH_3), IR (NaCl plates, film, cm^{-1}): 3000, 2942, 2840, 1735, 1598, 1485, 1463, 1418, 1380, 1362, 1336, 1230, 1125, 1088, 1012, 957, 920, 838, 770, 735, 693, 668; Anal Calculated for $C_{13}H_{18}O_5$, MW = 254 283: C = 61 41%, H = 7 13% Found C = 61 31%, H = 7 19% *1-Hydroxymethyl-2,4,5-trimethoxy-3-methylbenzene* According to the procedure of Sachleben,[41] 20 0 g (78 7 mmol, 1 0 equiv.) of 2,4-dimethoxy-3-methyl-5-acetoxymethylbenzene was taken in 55 mL of dry methylene chloride and 34 3 mL (94 4 mmol, 1 2 equiv) of a 2 75 M solution of NaOH in methanol was added The mixture was swirled and heated to boiling with a heat gun and set aside TLC analysis after 10 min showed the absence of starting material (R_f = 0 55) and the presence of a new UV-active component with an R_f of 0 35 (SiO_2, eluting with 50% ether in hexanes) The reaction was neutralized by the addition of small pieces of dry ice, and the reaction mixture concentrated and partitioned between ether and brine The brine was extracted with two portions of ether and the ethereal phases washed with two small portions of brine, dried ($MgSO_4$), and concentrated Removal of solvent on a vacuum pump resulted in crystallization to yield 16 3 g (98 1%) of the desired material as colorless crystals mp 62 5 - 63 5 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 6 768 (s, 1 H, Ar*H*), 4 681 (d, J = 6 0 Hz, 2 H, ArCH_2), 3 848, 3 795, 3 738 (singlets, 3 H each, OCH_3 x3), 2 221 (s, 3 H, ArCH_3), 2 043 (t, J = 6 0 Hz, 1 H, CH_2OH), IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3610, 3050, 3003, 2945, 2890, 2845, 1598, 1491, 1477, 1421, 1396, 1340, 1246, 1233, 1196, 1125, 1093, 1015, 980, 853, 828, Anal · Calculated for $C_{11}H_{16}O_4$, MW = 212 246 C = 62 25%, H = 7 60% Found C = 62 29%, H = 7.62% *2,4,5-Trimethoxy-3-methylbenzaldehyde (7)* According to the method of Sachleben,[41] 19 12 g (88 69 mmol, 1 15 molar equiv , Aldrich) of pyridinium chlorochromate and 16 3 g of anhydrous magnesium sulfate were weighed into a dry 500 mL round bottom flask and 64 mL of dry methylene chloride was added The flask was fitted with a reflux condenser and 16 29 g (77 12 mmol, 1 0 equiv) of the benzyl alcohol described above in 64 mL of dry methylene chloride was added with a cannula The reaction mixture warmed to reflux and was heated with an oil bath after the addition of alcohol was complete TLC analysis after 15 min showed the absence of starting material (R_f = 0 35 and the presence of a new UV-active component at R_f = 0 63 (SiO_2, eluting with 50% ether in hexanes) The reaction was cooled and diluted with 150 mL of 50% ether in hexanes and filtered through Celite The filtrate was concentrated and subjected to chromatography on silica gel (300 g, 230-400 mesh) eluting with 25% ether in hexanes to give 15 4 g (94 9%) of the desired material as a colorless oil that crystallized on standing mp 52-53 °C, lit [44] mp = 51-53 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10 293 (s, 1 H, C*H*O), 7 229 (s, 1 H, Ar*H*), 3 891, 3 877, 3 840 (singlets, 3 H each, OCH_3 x3), 2 232 (s, 3 H, ArCH_3), IR (NaCl cells, CH_2Cl_2, cm^{-1}): 3344, 3060, 3010, 2950, 2875, 1734, 1682, 1595, 1486, 1470, 1422, 1398, 1340, 1291, 1253, 1218, 1204, 1187, 1135, 1093, 1010, 960, 871, 636, Anal Calculated for $C_{11}H_{14}O_4$, MW = 210 230 C = 62 85%, H = 6 71% Found C = 62 75%, H = 6 72%

(3Z,6Z)-3,6-Bis-(2,4,5-trimethoxy-3-methylphenyl) methylenepiperazinedione (8): Into a dry 250 mL round-bottomed flask was taken 2 64 g (13 3 mmol, 1 0 equiv) of 1,4-diacetylpiperazinedione, 6 16 g (29 3 mmol, 2 2 molar equiv) of 2,4,5-trimethoxy-3-methylbenzaldehyde, and 9 55 g (29 3 mmol, 2 4 molar equiv , Aldrich) of cesium carbonate To these was added 100 mL of dry

dimethylformamide (Aldrich, anhydrous) and the resulting slurry heated with an oil bath at 80 °C for 3 h During this time, a lemon-yellow precipitate had appeared on the walls of the flask The reaction was cooled, diluted with dry methylene chloride, and filtered through silica gel (100 g, 60-200 mesh) with dry methylene chloride until the filtrate was colorless The filtrate was concentrated, whereupon crystallization occurred, and the concentrate was dried on a vacuum pump Dry diethyl ether was added to the oily (DMF) residue and removed into a trap with a filter stick, leaving 4.27 g (64 3%) of the desired material as lemon yellow crystals. The triturant was concentrated, placed on a vacuum pump, and passed through a plug of silica gel as an ethereal solution to give 1 69 g (27 4%) of recovered 2,4,5-trimethoxy-3-methylbenzaldehyde mp· 231-232 °C (dimethylformamide); ^{1}H NMR (300 MHz, $CDCl_3$). δ 9 576 (br s, 2 H, N*H*), 6 890 (s, 2 H), 6 691 (s, 2 H), 3 847, 3 837, 3 669 (singlets, 6 H each, OCH_3 x3), 2.268 (s, 6 H, ArCH_3), ^{13}C NMR (75 1 MHz, $CDCl_3$) δ 157.20, 149.58, 149 08, 148 94, 126 50, 125 34, 113 61, 112 13, 60 99, 60.29, 55 81, 9 46; IR (NaCl cells, CH_2Cl_2, cm^{-1}). 3250, 3050, 3000, 2960, 2935, 2840, 2678, 1645, 1590, 1487, 1462, 1452, 1433, 1422, 1381, 1353, 1333, 1245, 1230, 1125, 1087, 1000, 995, 960, 935; Anal Calculated for $C_{26}H_{30}N_2O_8$, MW = 498 534 C = 62 64%, H = 6 07% Found C = 62 69%, H = 6 10%

3,6-Bis-(2,4,5-trimethoxy-3-methylphenyl)methyl-(3α,6α)-piperazinedione (9): According to the method of Izumiya,[14] 8 92 g (17 89 mmol) of bis-arylidenepiperazinedione 8 was taken in a round-bottomed flask and reduced with 2 g of 10% palladium on activated carbon (Aldrich) in 150 mL of glacial acetic acid Hydrogen was delivered as a stream under oil bubbler pressure and the reaction vessel heated with an oil bath at 50 °C After 3 h, the supernatant liquid was clear and colorless, and the reaction was filtered through Celite and concentrated The residue was azeotroped three times to remove acetic acid by concentration from cyclohexane on a rotary evaporator Dry diethyl ether was added to the gummy residue, resulting in crystallization The product was collected on a glass frit (M) to yield 8 415 g (93 5%) of the desired material as a colorless, crystalline solid, which contained 6% of the (3α,6β) isomer as determined by proton NMR. The filtrate was concentrated, azeotroped with cyclohexane and placed on a vacuum pump to give 201 3 mg of material that was 50% in the (3α,6β) isomer mp 179-180 °C (diethyl ether), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6 585 (s, 2 H, Ar*H*), 6 522 (br s, 2 H, N*H*), 4 181 (br dd, J = 3 2, 9 0 Hz, 2 H, C*H*), 3 824, 3 791, 3 690 (singlets, 6 H each, OCH_3 x2x3), 3 328 (dd, J = 3 3, 14 0 Hz, 2 H, CH'*H*), 2 754 (dd, J = 9 0, 14 0 Hz, 2 H, CH*H*'), 2 220 (s, 6 H, ArCH_3 x2), ^{13}C NMR (75 1 MHz, $CDCl_3$) δ 167 92, 150 73, 149 37, 147 21, 125 79, 123 74, 111 70, 60 46, 60 08, 55 88, 55 59, 32 79, 9 57, IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3370, 3320, 3050, 2995, 2940, 2840, 1685, 1595, 1487, 1465, 1453, 1416, 1350, 1332, 1235, 1120, 1087, 1010, 990, 835, Anal Calculated for $C_{26}H_{34}N_2O_8$, MW = 502 566 C = 62 14%, H = 6 82% Found C = 62 19%, H = 6 83% *Trans* (minor) isomer ^{1}H NMR (360 MHz, $CDCl_3$) δ 6 530 (s, 2 H, Ar*H*), 6 173 (br s, 2 H, N*H*), 3 947 (ddd, J = 1 5, 4 0, 8 5 Hz, 2 H, CH_2C*H*), 3 789, 3 777, 3 662 (singlets, 6 H each, OCH_3 x2x3), 3 244 (dd, J = 3 9, 13 9 Hz, 2 H, CH'*H*), 2 894 (dd, J = 8 5, 13 9 Hz, 2 H, CH*H*'), 2 206 (s, 6 H, ArCH_3 x2)

1,4-Bis-(phenyl)methyl-3,6-bis-(2,4,5-trimethoxy-3-methylphenyl) methyl-(3α,6α)-piperazinedione (10): Into a dry 250 mL round-bottomed flask containing 4 65 g (9 25 mmol, 1 0 equiv) of piperazinedione 9 were added 65 mL of dry dimethylformamide (Aldrich, anhydrous) and 687 mg (27 8 mmol, 3 0 molar equiv , Aldrich 97%) of sodium hydride, followed immediately by 6 6

mL (56 mmol, 6 0 molar equiv.) of benzyl bromide The reaction was heated with an oil bath at 40 °C for 3 h, whereupon TLC analysis showed the presence of a major new UV-active component with an R_f of 0 32 (SiO_2, eluting with 33% hexanes in ether) The reaction was cooled, diluted with reagent grade chloroform to a volume of 500 mL and filtered through anhydrous Na_2SO_4 The concentrated filtrate was distilled at vacuum pressure to remove DMF and the residue chromatographed on silica gel (200 g, 230-400 mesh) eluting with 33% ether in hexanes followed by 50% ether in hexanes. By this method, 5 83 g (92 3%) of the desired material was obtained which gave colorless crystals on standing in dry diethyl ether. mp. 133-134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7 23-7.25 (m, 6 H, C_6H_5), 6 90-6.93 (m, 4 H, C_6H_5), 6 603 (s, 2 H, Ar*H*), 5 350 (d, J = 14 7 Hz, 2 H, PhCH'*H*), 4 156 (dd, J = 4 2, 8 1 Hz, 2 H, C*H*), 3.848, 3 805, 3 744 (singlets, 6 H each, OCH_3), 3 277 (d, J = 15 0 Hz, 2 H, PhCH*H'*), 3 158 (dd, J = 4 5, 13 8 Hz, 2 H, ArCH'*H*), 2 919 (dd, J = 8 1, 13 8 Hz, 2 H, PhCH*H'*), 2 254 (s, 6 H, ArCH_3), IR (NaCl cells, $CDCl_3$, cm^{-1}) 2935, 1655, 1647, 1485, 1465, 1453, 1340, 1240, 1230, 1125, 1085, 1020, Anal Calculated for $C_{40}H_{46}N_2O_8$, MW = 682 815 C = 70 36%, H = 6 79% Found. C = 70.10%, H = 6.83%

2-(2,4,5-Trimethoxyphenyl)methyl-3-(phenyl)methyl-4-oxo-7,9,10-trimethoxy-8-methyl-11-(phenyl)methyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (11): A *Generation of $LiAlH_2(OEt)_2$* A solution of $LiAlH_2(OEt)_2$ was generated by the action of 0 36 mL of dry ethanol on 6 mL of a 1M solution of $LiAlH_4$ in tetrahydrofuran (THF) (Aldrich) at -78 °C This was warmed to room temperature and stirred 10 min prior to use This reagent is assumed to be 0 94 M in $LiAlH_2(OEt)_2$

B *Reduction of piperazinedione **10*** A solution of 5 827 g (8 533 mmol, 1 0 equiv) of piperazinedione **10** in 85 mL of dry tetrahydrofuran was treated with 13 6 mL (12 8 mmol, 1.5 molar equiv) of a 0 94 M solution of $LiAlH_2(OEt)_2$ in THF at -10 °C TLC analysis after 90 min indicated the absence of starting material (R_f = 0 32) and the presence of a new yellow, UV-active component at R_f = 0 42 (SiO_2, eluting with 33% hexanes in ether) The reaction was quenched with reagent grade ether, diluted with dry ether, and stirred with anhydrous Na_2SO_4 before filtering through a column of anhydrous Na_2SO_4 The filtrate was concentrated and the crude material was used immediately in the next step

C *Ring closure via iminium ion generation* The crude material described above was dissolved in 100 mL of trifluoroacetic acid and heated at reflux for 36 h, whereupon TLC analysis showed the presence of a major new UV-active component with an R_f of 0 35 (SiO_2, eluting with 33% hexanes in ether) The reaction was cooled, diluted on addition to a separatory funnel with 200 mL of dry methylene chloride, and quenched by the addition of small portions of saturated potassium carbonate solution The funnel was swirled often and shaken only when effervescence had ceased, the pH was determined by drawing an aliquot of the lower, aqueous phase and testing with litmus Addition of base was stopped when the aqueous layer was at a pH of about 9 The organic phase was washed with brine, dried with anhydrous sodium sulfate, and concentrated The residue (5.05 g) was chromatographed on silica gel (250 g, 230-400 mesh) eluting with 33% ether in hexanes followed by 60% ether in hexanes to give 4 46 g (78 3%) of the desired material as a colorless gum which crystallized in dry diethyl ether mp 136-137 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 7 465 (d, J = 7 1 Hz, 2 H, C_6H_5), 7 364 (t, J = 7 6 Hz, 2 H, C_6H_5), 7 292 (t, J = 7 4 Hz, 1 H, C_6H_5), 7 007 (t, J = 7 3 Hz, 1 H,

C_6H_5), 6 913 (t, J = 7 2 Hz, 2 H, C_6H_5), 6 634 (d, J = 7 3 Hz, 2 H, C_6H_5), 6 248 (s, 1 H, ArH), 5 504 (d, J = 15 0 Hz, 1 H, CONCH'H), 3 890 (br s, 1 H, CH), 3 842 (d, J = 5.2 Hz, 1 H), 3.774 (d, J = 15 0 Hz, 1 H, CONHH'), 3 764, 3 696, 3.675, 3 588, 3 527, 2 976 (singlets, 3 H each, OCH_3 x6), 3 65-3 70 (m, 2 H by integration of methoxy region), 3 260 (dd, J = 9.5, 11 8 Hz, 1 H), 3 213 (dd, J = 1 4, 9 9 Hz, 1 H), 3 091 (dd, J = 1 5, 11 6 Hz, 1 H), 3.045 (dd, J = 5 9, 17 6 Hz, 1 H), 2.871 (dd, J = 1 0, 17 7 Hz, 1 H), 2 204, 2 192 (s, s, 3 H each, OCH_3); ^{13}C NMR (75.1 MHz, $CDCl_3$)· Determined by the DEPT experiment CH_3 δ 9 16, 9 59, 56.06, 59 06, 59.69, 60 16, 60 41 CH_2 δ 20 67, 33 29, 46 40, 55 63 CH δ 52 21, 56 47, 66 28, 111 91, 126 58, 127 14, 127 44, 127 80, 128 44, 128 89 C· δ 122 10, 123 82, 125 23, 125 27, 137 01, 138 02, 146 64, 146 71, 148 83, 149 70, 151 08, 151 77, 170.69 , IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3042, 3000, 2948, 2845, 1648, 1604, 1493, 1472, 1460, 1415, 1385, 1363, 1344, 1305, 1241, 1201, 1149, 1124, 1087, 1018, 972, 842, 814, 664, Anal Calculated for $C_{40}H_{46}N_2O_7$, M W = 666 816 C = 72 05%, H = 6 95% Found C = 72 08%, H = 7 00%

2-(2,4,5-Trimethoxyphenyl)methyl-3-(phenyl)methyl-4-oxo-7,9,10-trimethoxy-8-methyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (13): Into a dry nitrogen-charged 250 mL round-bottomed flask were weighed 2 72 g (4 08 mmol, 1 0 equiv) of benzazocine **11** and 2 7 g of 10% palladium on carbon (Aldrich) The reaction vessel was carefully evacuated and dry nitrogen admitted, and 70 mL of 10% formic acid (Aldrich 97%) in methanol was added The reaction was stirred at room temperature for 45 min, whereupon TLC analysis (aliquot sat'd K_2CO_3 / CH_2Cl_2) showed the absence of starting material (R_f = 0 77) and the presence of a major new UV-active component with an R_f of 0 29 (SiO_2, eluting with ammonia-saturated ether) Powdered potassium carbonate was added to neutralize formic acid, and the reaction mixture was filtered through a plug of celite and the filtrate concentrated. The residue was suspended in dry methylene chloride, filtered through anhydrous sodium sulfate, and concentrated to give 2 34 g of crude material that was chromatographed on silica gel (50 g, 230-400 mesh Elution with ethyl acetate and then 4% methanol in ethyl acetate gave 1 88 g (80 2%) of the desired material as a white foam ^1H NMR (360 MHz, $CDCl_3$) δ 7 033 (t, J = 8 9 Hz, 1 H, C_6H_5), 6 942 (t, J = 7 4 Hz, 2 H, C_6H_5), 6 625 (d, J = 7 3 Hz, 2 H, C_6H_5), 6 550 (s, 1 H, ArH), 5 557 (d, J = 14 8 Hz, 1 H, NCH'H), 4 027 (d, J = 5 8 Hz, 1 H), 3 988 (s, 1 H), 3 797, 3 781, 3 703, 3 660, 3 512, 3 056 (singlets, 3 H each, OCH_3 x6), 3 742 (d, J = 15 1 Hz, 1 H, NCHH'), 3 35-3 39 (m, 2 H), 3 199 (dd, J = 1 4, 17 0 Hz, 1 H, CH'H), 3 150 (d, J = 2 5 Hz, 1), 3 129 (s, 1 H), 2 907 (dd, J = 6 0, 17 0 Hz, 1 H, CHH'), 2 225, 2 171 (s, s, 3 H each, $ArCH_3$); ^{13}C NMR (75 1 MHz, $CDCl_3$) Determined by the DEPT experiment CH_3 δ 9 12, 9 63, 55 92, 59 04, 59 71, 59 92, 60 19, 60 70 CH_2 δ 29 37, 32 43, 46 62 CH δ 46 97, 61 69, 111 48, 126 69, 127 12, 127 93 CH· δ 122 68, 123 76, 125 36, 125 58, 136 86, 145 38, 146 76, 149 00, 149 55, 151 08, 152 18, 170 61 , IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3338, 3050, 3000, 2945, 2880, 2842, 1640, 1598, 1490, 1468, 1415, 1342, 1302, 1240, 1197, 1120, 1080, 1014, 998, 969, 839, 809, 795, Anal Calculated for $C_{33}H_{40}N_2O_7$, MW = 576 691 C = 68 73%, H = 6 99% Found C = 68 49%, H = 7 12%

2-(2,4,5-Trimethoxyphenyl)methyl-3-(phenyl)methyl-4-oxo-7,9,10-trimethoxy-8,11-dimethyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (14a): Into a flame-dried, nitrogen-charged 25 mL round-bottomed flask was transferred 570.mg (0 998 mmol, 1 0 equiv) of benzazocine **13** with dry tetrahydrofuran (THF) The vessel was flushed with dry nitrogen and 50 mg (2 02 mmol, 2 0

equiv , Aldrich 97%) of sodium hydride was weighed in and to the reactants were added 7 mL of dry THF followed immediately by 0 62 mL (9.9 mmol, 10 equiv) of iodomethane The reaction was stirred at room temperature and monitored for the disappearance of starting material by TLC After 2 h, the starting material (R_f = 0 13) had diminished and a new UV-active component at R_f = 0 50 (SiO_2, eluting with ethyl acetate) predominated. The reaction mixture was diluted with water and extracted with methylene chloride (3x) and the organic phases dried (Na_2SO_4) and concentrated to give 547 mg of crude material Chromatography on silica gel (14 g, 23-400 mesh) eluting with 50% hexanes in ether followed by 33% hexanes in ether gave 526 0 mg (90 1%) of the desired material as a colorless gum ^{1}H NMR (360 MHz, $CDCl_3$). δ 7 020 (t, J = 7.3 Hz, 1 H, C_6H_5), 6 925 (t, J = 7 5 Hz, 2 H, C_6H_5), 6 622 (d, J = 7.4 Hz, 2 H, C_6H_5), 6 578 (s, 1 H, Ar*H*), 5.519 (d, J = 14 8 Hz, 1 H, NCH'*H*0, 3.811, 3 794, 3 686, 3 678, 3 517, 3 009 (singlets, 3 H each, OCH_3 x6), 3 831 (d, J = 5.5 Hz, 1 H), 3 731 (d, J = 14 8 Hz, 1 H), 3 718 (s, 1 H), 3 273 (d x m, J = 12 3 Hz, 1 H), 3 220 (dd, J = 9 7, 12 4 Hz, 1 H, CH'*H*), 3 087 (dd, J = 2 8, 12 1 Hz, 1 H, CH*H'*), 3 019 (dd, J = 6.2, 17 4 Hz, 1 H, CH'*H*), 2 815 (d, J = 17 6 Hz, 1 H, CH*H'*), 2 396 (s, 3 H, NCH_3), 2 228, 2 171 (s, s, 3 H each, $ArCH_3$), ^{13}C NMR (75 1 MHz, $CDCl_3$) Determined using the DEPT experiment CH_3 δ 9 08, 9 56, 39 19, 55 81, 59 03, 59 60, 59 91, 60 15, 60 44 CH_2: δ 20 11, 33 07, 46 41 CH δ 52 92, 58 93, 61 96, 111 96, 126 59, 127 13, 127 82 C· δ 121 86, 123 59, 124 98, 125 23, 126 31, 126 97, 146 59, 146 66, 148 82, 146 55, 151 04, 151 58, 170 61, IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3050, 3000, 2945, 2842, 1643, 1608, 1492, 1472, 1417, 1342, 1300, 1240, 1198, 1120, 1080, 1014, 998, 969, 840, 813, Anal · Calculated for $C_{34}H_{42}N_2O_7$, MW = 590 718 C = 69 13%, H = 7 17% Found. C = 68 90%, H = 7 12%

2-(2,4,5-Trimethoxyphenyl)methyl-4-oxo-7,9,10-trimethoxy-8,11-dimethyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (15a): In a flame-dried, nitrogen-charged 25 mL round-bottomed flask were taken 448 mg (0 759 mmol, 1 0 equiv) of N-methylbenzazocine **14a** in 5 mL of dry tetrahydrofuran and 0 09 mL (1 5 mmol, 2 0 equiv) of dry (3Å sieves) ethanol. The solution was cooled to -78 °C and approximately 5 mL of ammonia was introduced, distilled from sodium metal and delivered through tygon tubing and a glass pipet The reaction was stirred vigorously at -78 °C and 35 mg (1 5 mmol, 2 0 equiv) of sodium metal was added in a single portion Over the next hour, another 6 equivalents of sodium were added along with an additional 0 09 mL of ethanol, until a dirty rust colored heterogeneous mixture resulted in which a blue color was detectable The sodium metal appeared as a molten, metallic red mass in the reaction mixture TLC analysis of an aliquot indicated the presence of a single component with an R_f of 0 29 (SiO_2, eluting with ethyl acetate) The reaction was quenched by the addition of solid ammonium chloride and dry ethanol, stirring at -78 °C until the sodium was consumed The reaction was allowed to warm and vent through a syringe needle until the ammonia was discharged The remaining material was diluted with methylene chloride, dried with anhydrous K_2CO_3, and filtered through anhydrous Na_2SO_4 on a glass frit (M) Concentration gave 476 1 mg of crude material and chromatography on silica gel (10 g, 230-400 mesh) eluting with 33% hexanes in ethyl acetate followed by ethyl acetate gave 365 mg (96 0%) of material that crystallized spontaneously as colorless needles mp 204-205 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 6 606 (s, 1 H, Ar*H*)), 5 64 (br s, 1 H, N*H*), 3 828, 3 788, 3 743, 3 709, 3 655, 3 631 (singlets, 3 H each, OCH_3 x2x3), 3.54-3 60 (m, 1 H, C*H*), 3 182 (dd, J = 6 8, 13 1 Hz, 1 H), 3 654 (dd J =

0 9, 18 0 Hz, 1 H CH'*H*), 3 848 (s, 1 H, C*H*), 2 94-3 04 (m, 2 H), 2 754 (dd, J = 0 9, 18 0 Hz, 1 H, CH*H'*), 2 406 (s, 3 H, NCH_3), 2 216, 2 155 (s, s, 3 H each, ArCH_3), ^{13}C NMR (75 1 MHz, $CDCl_3$): Determined using the DEPT experiment CH_3 δ 9 05, 9 47, 39 24, 55 80, 59 52, 59.68, 59 72, 60 01, 60.43. CH_2 δ 19 12, 36 40. CH: δ 52 96, 58 32, 58 88, 111 75 C. δ 121 34, 123 86, 125 28, 125 36, 125 74, 146.47, 146 65, 148 81, 149 58, 151 02, 151.70, 172 31, IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3390, 3045, 2995, 2938, 2837, 1667, 1598, 1488, 1463, 1410, 1375, 1340, 1317, 1300, 1280, 1237, 1195, 1178, 1111, 1088, 1072, 1009, 990, 963, 835, 645, Anal . Calculated for $C_{27}H_{36}N_2O_7$, MW = 500 593. C = 64 78%, H = 7 25% Found C = 64 79%, H = 7 29%

2-(2,4,5-Trimethoxyphenyl)methyl-7,9,10-trimethoxy-8,11-dimethyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (17a): The general procedure is that of Sachleben [41] A *Preparation of alane (AlH$_3$).* In a flame-dried, nitrogen-charged 100 mL round-bottomed flask, 15 mL of dry tetrahydrofuran (THF) was added to 450 mg (3 37 mmol, 1 0 equiv) of aluminum chloride with ice-bath cooling After stirring at room temperature, the solution of $AlCl_3$ was cooled to 0 °C and 10 5 mL (10 5 mmol, 3 1 molar equiv , Aldrich) of a 1 M solution of $LiAlH_4$ in THF was slowly added and the solution stirred at room temperature for 30 min The resulting solution contained 13 50 mmol of alane

B *Reduction of benzazocine lactam 15a* The solution of alane prepared above was cooled with an ice-water bath and 523 mg (1 045 mmol) of benzazocine **15a** was added in one portion Some effervescence was noted as the solution was warmed to room temperature The solution was stirred at room temperature for 90 min, whereupon TLC analysis showed the diminution of starting material (R_f = 0 58) and the presence of a major new UV-active component having an R_f of 0 19 (SiO_2, eluting with 7 5% *i*-PrOH in chloroform) The reaction was quenched at 0 °C until the evolution of hydrogen ceased, warmed to room temperature, and 10 mL of 3 N HCl were added, resulting in solution of the aluminum salts The reaction mixture was transferred to an Erlenmeyer flask and diluted with methylene chloride, whereupon concentrated ammonium chloride was added until the solution was basic A large amount of precipitated material was present at this time, and the mixture was filtered through Celite The filtrate was concentrated to give 521 mg of crude material that was purified by chromatography on silica gel (20 g, 230-400 mesh) eluting with ammonia-saturated ether to give 495 mg (97 4%) of the desired material as a colorless gum ^{1}H NMR (360 MHz, $CDCl_3$) δ 6 719 (s, 1 H, Ar*H*), 3 828, 3 784, 3 747, 3 720, 3 706, 3 608 (singlets, 3 H each, OCH_3 x2x3), 3 543 (dd, J = 8 0, 13 1 Hz, 1 H, CH'*H*), 3 143 (dd, J = 6 7, 13 2 Hz, 1 H, CH*H'*), 2 92-3 05 (3 H, m), 2,716 (d, J = 13 8 Hz, 1 H), 2 436 (d, J = 17 3 Hz, 1 H), 2 249 (s, 3 H, NCH_3), 2 223, 2 170 (s, s, 3 H each, ArCH_3 x2), ^{13}C NMR (75 1 MHz, $CDCl_3$) δ 151 06, 150 98, 149 28, 148 72, 146 46, 146 04, 128 23, 127 97, 125 10, 124 00, 122 83, 111 53, 60 56, 60 12, 59 94, 59 83, 59 50, 57 59, 55 79, 54 84, 52 01, 48 15, 42 08, 31 59, 20 37, 9 54, 9 15, IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3330, 3040, 2995, 2938, 2840, 1595, 1485, 1460, 1407, 1340, 1308, 1232, 1195, 1112, 1085, 1062, 1038, 1011, 993, 965, 912, 860, 835, MS High resolution electron impact Measured for $C_{27}H_{38}N_2O_6$, exact mass = 486 2730, intensity = 0 59%, deviation = -3 7 ppm

2-(2,4,5-Trimethoxyphenyl)methyl-3-(phenyl)methyl-7,9,10-trimethoxy-8,11-dimethyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (16a): A *Preparation of dichloroalane (AlHCl$_2$) solution* A solution of dichloroalane was prepared by the addition of 0 61 mL (0 61 mmol,

1 0 molar equiv. relative to $AlCl_3$, Aldrich) of a 1 M solution of $LiAlH_4$ in tetrahydrofuran (THF) to 245 mg (1 84 mmol, 3 0 molar equiv relative to $LiAlH_4$) of $AlCl_3$ in 2 mL of dry THF at 0 °C The solution was warmed to room temperature and stirred for 15 min

B *Reduction of benzazocine* **14a** The solution of $AlHCl_2$ prepared above (2 44 mmol, 6 22 molar equiv relative to benzazocine **14a**) was cooled with an ice-water bath and added to a solution of 231 6 mg (0 3921 mmol, 1 0 equiv) in 3 mL of dry THF at 0 °C The reaction was stirred 2 h at 0 °C, whereupon TLC analysis showed the absence of starting material (R_f = 0 59) and the presence of a major new UV-active component with an R_f of 0 91 (SiO_2, eluting with ammonia-saturated ether). The reaction was quenched by the addition of water and warmed to room temperature, when 6 N HCl was added to produce a homogeneous solution Saturated ammonium hydroxide was added until wet litmus paper held above the solution indicated a basic solution The mixture was stirred with and filtered through anhydrous Na_2SO_4 and concentrated to give 0 22 g of crude material Chromatography on silica gel (5 5 g, 230-400 mesh) eluting with 50% hexanes in ethyl acetate and then 33% hexanes in ethyl acetate gave 189 4 mg (83 8%) of the desired material as a colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 7 04 - 7 12 (m, 3 H, C_6H_5), 6 86 - 6 92 (m, 2 H, C_6H_5), 6 599 (s, 1 H, Ar*H*), 3 790, 3 777, 3 739, 3 702, 3 622, 3 278 (singlets, 3 H each, OCH_3 x2x3), 3 572 (d, 1 H, 14 1 Hz), 3 17-3 25 (m, 2 H), 3 05-3 08 (m, 1 H), 2 86-2 97 (m, 4 H), 2 506 (dd, J = 1 8, 10 8 Hz, 1 H), 2 383 (d, J = 18 0 Hz, 1 H), 2 283 (s, 3 H, NCH_3), 2 223, 2 212 (s, s, 3 H each, $ArCH_3$ x2), ^{13}C NMR (75 1 MHz, $CDCl_3$) Determined using the DEPT experiment. CH_3 δ 9 14, 9 53, 41 43, 55 69, 59 49, 59 64, 59 79, 60 12, 60 48 CH_2 δ 21 43, 23 45, 53 78, 57 82 CH δ 52 70, 53 89, 62 17, 111 76, 111 81, 126.36, 127 70, 127 97 C δ 121 79, 124 89, 125 09, 128 37, 128 71, 139 93, 145 81, 146 22, 148 63, 148 77, 150 53, 150.93, IR (NaCl cells, Et_2O, cm^{-1}). 1605, 1490, 1470-1450, 1417, 1405-1375, 1345, 1330, 1250, 1243, 1020, 985, 930, 870, 840, 765, 745, 710, 650, Anal Calculated for $C_{34}H_{44}N_2O_6$, MW = 576 734 C = 70 81%, H = 7 69% Found C = 71 00%, H = 7 76%

2-(2,4,5-Trimethoxyphenyl)methyl-3-(phenyl)methyl-4-oxo-7,9,10-trimethoxy-8,11-dimethyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (14a): Mercuric Acetate Oxidation of N-Methyl-N-benzylbenzazocine **16a** In a 10 mL round-bottomed flask were taken 72 5 mg (0.126 mmol, 1 0 equiv) of benzazocine **16a**, 117 mg (0 315 mmol, 2 5 molar equiv) of mercuric acetate and 117 mg (0 315 mmol, 2 5 equiv) of $Na_2EDTA\ 2H_2O$ The reactants were dissolved in 1 mL of 1% acetic acid in water and heated with an oil bath at 85 °C for 6 h During this time, the reaction became turbid with darkening and the formation of elemental mercury TLC analysis indicated the presence of starting material (R_f = 0 40) and a new UV-active component having an R_f of 0 21 (SiO_2, eluting with 33% hexanes in ethyl acetate) The reaction was cooled, diluted with methylene chloride, and neutralized with sat'd sodium bicarbonate solution The aqueous phase was extracted with methylene chloride and the combined organic phases were dried (Na_2SO_4), concentrated and chromatographed on silica gel (3 5 g, 230-400 mesh) eluting with 50% hexanes in ethyl acetate In this way, 25 8 mg (35 6%) of starting benzazocine were recovered along with 32 1 mg (43 2%) of a compound with proton NMR spectrum and TLC behavior identical to that of N-methylbenzazocine **14a**

2-(2,4,5-Trimethoxyphenyl)methyl-3-chloro-4-oxo-7,9,10-trimethoxy-8-methyl-11-formyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (18): According to the method of Poisel,[23] 71 2 mg (0 1384 mmol, 1 0 equiv) of benzazocine **15b** was taken in a flame-dried, nitrogen-charged 10 mL round-bottomed flask along with approximately 1 mg of potassium *tert*-butoxide To these was added 1 mL of dry toluene and the reaction vessel was wrapped in aluminum foil, whereupon 16 μL (0 1453 mmol, 1 05 equiv, Baker) of *tert*-butyl hypochlorite was added with a syringe The reaction was stirred at room temperature for 3 h, when TLC analysis showed the absence of starting material (R_f = 0 27 and 0 39) and the presence of two new UV-active components with R_f values of 0 70 and 0 83 (SiO_2, EtOAc). The new components streaked on the TLC plate The reaction mixture was concentrated without removal of the foil and subjected to vacuum pressure prior to dilution with carbon tetrachloride and filtration through anhydrous Na_2SO_4. The filtrate was concentrated and solvent removed on a vacuum pump to give 88 9 mg (>100%) of the desired material as a light gold foam ^{1}H NMR (300 MHz, $CDCl_3$)· δ 8 310, 8 302 (1H, s, s, C*H*O), 7 162, 6 618 (1 H, s, s, Ar*H*), 5 655 (br s), 5 419 (d, 6 0 Hz), 3 913, 3 848, 3 805 (6 H), 3 760, 3 702, 3 660, 3 637, 3 600, 3 589, 3 330, 3 263 (3H each, singlets, OCH_3 x6x2), 2 441 (dd, 11 4, 12 9 Hz), 2 253, 2 242, 2 106, 2 096 (3 H each, singlets, ArCH_3 x2x2), unassigned· 3 188, 3 131, 3 067,3 044, 3 021, 2 999, 2 985, 2 963, 2 955, 2 940, 2 918 (sum 4 H), ^{13}C NMR (75 1 MHz, $CDCl_3$) Determined by the DEPT experiment CH_3· δ 9 24, 9 51, 9 56, 55 84, 56 06, 59 33, 59 44, 59 85, 60 11, 60 17, 60 52, 60 85 CH_2 26 98, 29 26, 31 02, 32 71 CH 44 34, 49 46, 50 65, 55 62, 72 49, 73 16, 111 33, 113 15, 159 28, 160 30 C 120 34, 121 34, 123 49, 123 60, 124 08, 124 42, 125 09, 125 68, 125.87, 126 04 IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3065, 2960, 2880, 2850, 1685, 1600,1494, 1472, 1245, 1123, 1095, 1082, 1015, 970, 960, 795, MS· High resolution electron impact Measured for $C_{27}H_{33}N_2O_8Cl$, exact mass = 548 1925241 amu, intensity = 2 58%, deviation = 1 4 ppm

2-(2,4,5-Trimethoxyphenyl)methyl-3-hydroxy-4-oxo-7,9,10-trimethoxy-8-methyl-11-formyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (20): Selenium Dioxide - Hydrogen Peroxide Oxidation of Benzazocine 17b: In a 10 mL round-bottomed flask were taken 154 mg (0 398 mmol, 1 0 equiv) of formylbenzazocine **17b** and 5 8 mg (5 7 x 10^{-2} mmol, 19 mol%) of selenium dioxide in 2 mL of acetone The reactants were cooled with an ice bath and 105 mg (0 927 mmol, 3 0 equiv.) of 30% hydrogen peroxide in 1 mL of acetone at 0 °C was added The reaction was stirred at 0 °C for 3 h, at which time TLC analysis indicated the disappearance of starting material and the presence of two new UV-active components having R_f values of 0 33 and 0 45 (SiO_2, eluting with 4% *i*-PrOH in chloroform The reaction mixture was concentrated, diluted with methylene chloride, and dried with anhydrous Na_2SO_3 and Na_2SO_4 Chromatography on silica gel (6 g, 230-400 mesh) eluting with chloroform and then 4% *i*-PrOH in chloroform gave 101 mg (67 0%) of N-hydroxybenzazocine **20** as a yellow foam No separation of the two components noted on TLC occurred during chromatography A white solid was obtained by adding heptane to a methylene chloride solution of this material and collecting on a frit mp 107-110 °C (methylene chloride - heptane), ^{1}H NMR (360 MHz, $CDCl_3$) Ratio of rotomers = 2 1 A *Major rotomer* δ 9 4 (1 H, br s), 8 346 (1 H, s, NC*H*O), 6 690 (1 H, s, Ar*H*), 5 336 (1 H, d, 6 4 Hz), 4 817 (1 H, s), 3 683, 3 834, 3 718, 3 673, 3 605, 3 326 (3 H each, singlets, OCH_3 x6), 3 897 (1 H, dd, 2 5, 10 4 Hz), 3 293 (1 H, d, 2 9 Hz), 3 276 (1 H, dd, 1 8, 15 8 Hz), 3 183 (1 H, dd, 1 1, 16 7 Hz), 2 93-3 05 (1 H, m), 2 267, 2 125 (3 H each, s, s, ArCH_3), B *Minor rotomer* δ

9 0 (1 H, br s), 8 337 (1 H, s, NC*H*O), 7.156 (1 H, s, Ar*H*), 5 712 (1 H, s, C*H*), 4 631 (1 H, d, 6 6 Hz), 3 943, 3 830, 3 760, 3 661, 3 617, 3 324, (3 H each, singlets, OCH_3), 4 055 (1H, dd, 2 5, 9 6 Hz), 3.575 (1 H, d, 2 9 Hz), 2 93-3 05 (1 H, m), 2 460 (1H, dd, 1 1, 16 7 Hz), 2 166, 2.121 (3H each, s, s, ArCH_3), ^{13}C NMR (75 1 MHz, $CDCl_3$) Methine resonances were determined using the DEPT experiment CH: δ 43 74, 48 25, 48 88, 53.35, 66 85, 68 06, 111 42, 113 06, 159 56, 160 60. Other· 9 10, 9 46, 9 48, 13 91, 22 43, 26.04, 30 11, 31 36, 32 09, 55 76, 55 84, 55 91, 59 29, 59 72, 59 75, 60 03, 60 07, 60 43, 60 82, 120.20, 121 05, 124 05, 124 14, 124 53, 124 88, 124 96, 125 22, 125 47, 125 58, 144 93, 145 41, 146 57, 146 83, 148 73, 149 38, 149.76, 150 13, 150 80, 151 03, 151 91, 152.19, 162 70, 163 23, IR (NaCl cells, CH_2Cl_2, cm^{-1}): 3300, 3060, 3000, 2940, 2870, 2840, 1678, 1650, 1490, 1475, 1430, 1411, 1345, 1331, 1291, 1238, 1193, 1155, 1118, 1080, 1010, 949, 912, 887, 835, 812, 651, 620, Anal · Calculated for $C_{27}H_{34}N_2O_9$ (hydroxamic acid structure **20**), MW = 530 576 C = 61 12%, H = 6 46% Found C = 61 52% (error = 0 65%), H = 6 86% (error = 6 2%), MS High resolution electron impact· Measured for $C_{27}H_{34}N_2O_9$ - [O], exact mass = 514 2314 amu, intensity = 26 18%, deviation = 0 8 ppm. Deviation from $C_{27}H_{34}N_2O_9$ - [NH_2] (exact mass = 514 2077) = 47 ppm, deviation from $C_{27}H_{34}N_2O_9$ - [CH_4] (exact mass = 514 1951) = 71 ppm

2-(2,4,5-Trimethoxyphenyl)methyl-4-oxo-7,9,10-trimethoxy-8-methyl-11-formyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (15b): Hydrogen Transfer Hydrogenation of Benzazocine 20: Into a round-bottomed flask were taken 64 4 mg (0 121 mmol, 1 0 equiv) of the hydroxamic acid described above, 80 mg (1 3 mmol, 11 equiv) of ammonium formate (Aldrich) and 65 mg of 10% palladium on carbon (Aldrich) The reactants were suspended in 0 5 mL of glacial acetic acid and heated with an oil bath at 110 °C for 6 h TLC analysis showed the absence of starting material and the presence of two new UV-active components with R_f values of 0 40 and 0 54 The reaction was cooled and filtered through Celite with acetic acid, concentrated and azeotroped with heptane, dissolved in methylene chloride and basified with ammonium hydroxide, dried with anhydrous Na_2SO_4, and concentrated to give 67 2 mg of crude material This was chromatographed on silica gel (3g, 230-400 mesh) eluting with ethyl acetate and then with 1% ammonium hydroxide in ethyl acetate to give 50 5 mg (80 6%) of a white foam This material was identical in all respects to benzazocine **15b** (see above)

MODEL STUDIES. SYNTHESIS OF BENZAZOCINE 12.

(3Z,6Z)-Bis-3,6-(3,4-dimethoxyphenyl)methylenepiperazinedione: According to the procedure of Richardson,[45] 1 1436 g (10 023 mmol, 1 0 equiv) of glycine anhydride (Aldrich) was weighed into a 25 mL round-bottomed flask along with 3 997 g (24 79 mmol, 2 4 equiv) of 3,4-dimethoxybenzaldehyde and 3 29 g (40 1 mmol, 4 0 equiv) of anhydrous sodium acetate Acetic anhydride (6 1 mL, 65 mmol, 6 4 equiv) was added and the reaction vessel was fitted with a reflux condenser and flushed with nitrogen The reaction was heated with an oil bath at 125 °C for 4 h, by which time the reaction had become heterogeneous with a yellow precipitate deposited on the walls of the flask The reaction was left to stir overnight at room temperature Water was added to reaction mixture and the yellow crystals collected on a glass frit (M), these were washed with water and triturated with three portions of ethanol The product was recrystallized by stirring in 100 mL of boiling glacial acetic acid (solution not complete) and cooling the slurry momentarily in an ice bath The bright yellow crystalline solid was collected and dried *in vacuo* to give 2 21 g (53 7%) of the

desired material. mp 302-303 °C (HOAc), ^{1}H NMR (360 MHz, hot d_6-DMSO): δ 10 357 (s, 2 H, N*H*), 7 31-7 29 (m, 4 H, ArH_2), 7 18-7 14 (m, 2 H, Ar*H*), 6 894 (s, 2 H, CC*H*), 3.963 (s, 6 H, OCH_3), 3 950 (s, 6 H, OCH_3), IR (NaCl plates, mineral oil mull, cm^{-1}). 3296, 2030, 1870, 1678, 1634, 1603, 1585, 1520, 1464, 1440, 1414, 1380, 1355, 1343, 1298, 1263, 1248, 1203, 1171, 1166, 1143, 1025, 972, 938, 880, 847, 806, 782, 776, 628, Anal · Calculated for $C_{22}H_2N_2O_6$, MW = 410.427: C = 64 38%, H = 5 40% Found C = 64 49%, H = 5 44%

3,6-Bis-(3,4-dimethoxyphenyl)methyl-(3α,6α)-piperazinedione: According to the method of Izumiya,[14] 15.00 g (36 55 mmol) of the bisarylidene diketopiperazine above was taken in a round-bottomed flask and reduced with 600 mg of palladium black (Aldrich) in 300 mL of glacial acetic acid Hydrogen was delivered as a stream under oil bubbler pressure and the reaction vessel heated with an oil bath at 60 °C. After 12 h, the supernatant liquid was clear and colorless, with Pd present as a flocculent mass. The reaction mixture was filtered through Celite with acetic acid, concentrated, and residual acetic acid removed as the azeotrope with cyclohexane on a rotary evaporator The white residue was recrystallized from 125 mL of boiling, freshly dried chloroform (passed through silica) to give 8 97 g of the desired material as crystalline colorless powder as a single isomer, the concentrated filtrate was crystallized to give an additional 4 66 g of the desired material, containing a trace of the *trans* isomer Obtained in this way was 13 6 g (90 0%) mp: 185-187 °C, ^{1}H NMR (360 MHz, $CDCl_3$) δ 6 842 (d, *J* = 8 6 Hz, 2 H, Ar*H*), 6 67-6 65 (m, 4 H, Ar*H*), 5 858 (2 H, s, N*H*), 4 151 (ddd, *J* = 3 3, 7 5, 8 4 Hz, 2 H, C*H*), 3 877, 3 856 (s, s, 6 H each, OCH_3), 3 091 (dd, *J* = 3 4, 13 8 Hz, 2 H, CH'*H*), 2 319 (dd, *J* = 8 7, 13 8 Hz, 2 H, CH*H'*), IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3360, 3035, 2997, 2950, 2920, 2813, 1671, 1600, 1582, 1508, 1458, 1432, 1410, 1311, 1232, 1148, 1132, 1020, 803, 690, Anal Calculated for $C_{22}H_{26}N_2O_6$, MW = 414 459 C = 63 76%, H = 6 32% Found C = 63 86%, H = 6 34%

3,6-Bis-(3,4-dimethoxyphenyl)methyl-(3α,6β)-piperazinedione: By the method described above, 1 165 g (2 838 mmol) of bisarylidenepiperazinedione was reduced to give 1 2865 g of crude material in which two components were seen by TLC analysis The major (3α,6α) compound had an R_f of 0 22 and a minor component was present at R_f = 0 31 The two components were separated by chromatography on silica gel (65 g, 230-400 mesh) eluting with chloroform and then with 4% *i*-PrOH in chloroform to give 1 0599 g (90 1%) of the (3α,6α) isomer and 145 mg (12 3%) of the minor (3α,6β) isomer as a white crystalline powder mp: 230-231 °C (chloroform), ^{1}H NMR (360 MHz, $CDCl_3$) δ 6 811 (d, *J* = 7 9 Hz, 2 H, Ar*H*), 6 687 (dd, *J* = 1 8, 8 1 Hz, 2 H, Ar*H*), 6 637 (d, *J* = 1 8 Hz, 2 H, Ar*H*), 5 701 (s, 2 H, N*H*), 3 875, 3 834 (s, s, 3 H each, OCH_3), 3 68-3 74 (d x m, 2 H, C*H*), 3 166 (dd, *J* = 3 6, 13 9 Hz, 2 H, CH'*H*), 2 840 (dd, *J* = 8 4, 13 9 Hz, 2 H, CH*H'*), IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3380, 3020, 2970, 2960, 2940, 2845, 1685, 1522, 1469, 1461, 1445, 1433, 1322, 1268, 1244, 1030, MS: High resolution electron impact Measured for $C_{22}H_{26}N_2O_6$, exact mass = 414 1791, intensity = 4 43%, deviation = 0 2 ppm

1,4-Bis-(phenyl)methyl-3,6-bis-(3,4-dimethoxyphenyl)methyl-(3α,6α)-piperazinedione (11b): Into a flame-dried, nitrogen-charged 250 mL round-bottomed flask was taken 5 16 g (12 5 mmol, 1 0 equiv) of the cis disubstituted piperazinedione above This was dissolved in 125 mL of dry dimethylformamide (Aldrich, anhydrous) and 5 9 mL (50 mmol, 4 0 molar equiv , Aldrich) of benzyl bromide were added, followed immediately by 1 2 g (49 mmol, 3 9 molar equiv , Aldrich, 97%) of

sodium hydride. Effervescence was observed and the reaction darkened somewhat The reaction was heated with an oil bath at 60 °C for 30 min to effect solution of the reactants, and stirred at room temperature for 4 h TLC analysis at this time showed the presence of a major new UV-active component with an R_f of 0 35 (SiO_2, eluting with 20% hexanes in ether) The reaction was quenched by the addition of water, diluted with water (300 mL), and extracted with three 150 mL portions of ether The combined organics were washed with water (3 x 150 mL), brine, and dried over sodium sulfate Concentration gave 8 47 g of crude material which was chromatographed on silica gel (425 g, 230-400 mesh) eluting with 50% hexanes in ether followed by 25% hexanes in ether to give 6 05 g (68 2%) of the desired compound as a white foam ^{1}H NMR (360 MHz, $CDCl_3$)· δ 7 25-7 30 (m, 3 H, C_6H_5), 6 94-6 97 (m, 2 H, C_6H_5), 6 844 (d, J = 7 8 Hz, 1 H, Ar*H*), 6 60-6 62 (m, 2 H, Ar*H*), 5 383 (d, J = 14 9 Hz, 1 H, PhCH'*H*), 4 157 (dd, J = 3 7, 7 2 Hz, 1 H, C*H*), 3 867, 3 856 (s, s, 3 H each, OCH_3x2), 3 430 (d, J = 14 9 Hz, 1 H, PhC*H*H'), 3 009 (dd, J = 3.7, 14.2 Hz, 1 H, ArCH'*H*), 2 328 (dd, J = 7 3, 14 2 Hz, 1 H, ArC*H*H'), IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3022, 2955, 2940, 2910, 2815, 1645, 1595, 1580, 1503, 1450, 1438, 1405, 1310, 1227, 1143, 1128, 1013, 795, Anal Calculated for $C_{36}H_{38}N_2O_6$, MW = 594 714 C = 72 71%, H = 6 44%. Found C = 72 71%; H = 6 68%

2-(3,4-Dimethoxyphenyl)methyl-3-(phenyl)methyl-4-oxo-8,9-dimethoxy-11-(phenyl)methyl-(1α,2β,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (12).

A· Generation of $LiAlH_2(OEt)_2$ A solution of $LiAlH_2(OEt)_2$ was generated by the action of 0 36 mL of dry ethanol on 6 mL of a 1M solution of $LiAlH_4$ in tetrahydrofuran (THF) (Aldrich) at -78 °C This was warmed to room temperature and stirred 10 min prior to use This reagent is assumed to be 0 94 M in $LiAlH_2(OEt)_2$

B *Reduction of dibenzylpiperazinedione* A solution of 1 165 g (1 959 mmol, 1 1 equiv) of the dibenzylpiperazinedione above was taken in 35 mL of dry THF and cooled to -10 °C with an ice-acetone bath 2 9 mL (2 7 mmol, 1 4 molar equiv) of the forementioned solution of $LiAlH_2(OEt)_2$ were added slowly with a syringe, and the reaction monitored for disappearance of starting material TLC analysis of the reaction mixture after 15 min showed the disappearance of starting material (R_f = 0 35, SiO_2, eluting with 20% hexanes in ether) and the presence of a major new UV-active component with an R_f of 0 39 (yellow spot, staining blue in cold vanillin) The reaction was quenched with reagent grade ether, warmed to room temperature, and stirred for 15 minutes The faintly yellow turbid mixture was stirred with anhydrous sodium sulfate and filtered through a column of anhydrous sodium sulfate, concentrated, and placed on a vacuum pump to give 1 19 g of the crude reduction product as a pale yellow foam which was used immediately in the next step

C *Ring closure via immonium ion generation* The crude material described above was dissolved in 50 mL of trifluoroacetic acid and heated at reflux overnight, during this time, the reaction mixture had paled considerably from an initial bright gold color TLC analysis indicated the diminution of the yellow reduction product and the presence of a major new UV-active component having an R_f of 0 37 (SiO_2, eluting with 20% hexanes in ether) The reaction was cooled, diluted on addition to a separatory funnel with 200 mL of dry methylene chloride, and quenched by the addition of small portions of saturated potassium carbonate solution The funnel is swirled often and shaken only when effervescence has ceased, the pH is determined by drawing an aliquot of the lower, aqueous

phase and testing with litmus Addition of base was stopped when the aqueous layer was at a pH of about 9 The organic phase was washed with brine, dried with anhydrous sodium sulfate, and concentrated The residue (1.11 g) was chromatographed on silica gel (60 g, 230-400 mesh) eluting with 33% hexanes in ether to give 969 0 mg (85 5%) of the desired material This colorless foam crystallized as colorless needles after dissolving in dry ether mp: 113-114 °C (diethyl ether); ^{1}H NMR (360 MHz, $CDCl_3$)· δ 7.40-7 47 (m, 5 H, C_6H_5), 7.080 (t, J = 7 2 Hz, 1 H, C_6H_5), 6.987 (t, J = 7 0 Hz, 2 H, C_6H_5), 6 636 (s, 1 H, Ar*H*), 6 600 (d, J = 8 2 Hz, 1 H, Ar*H*), 6 519 (d, J = 7 4 Hz, 2 H, Ar*H*), 6.319 (d, J = 1 8 Hz, 1 H, Ar*H*), 6.078 (dd, J = 1 6, 8 4 Hz, 1 H, Ar*H*), 5 790 (s, 1 H, Ar*H*), 5 549 (d, J = 15 0 Hz, 1 H, PhCH'*H*), 3 965 (d, J = 5.0 Hz, 1 H, C*H*), 3 929 (s, 3 H, OCH_3), 3 791 (d, J = 13 0 Hz, 1 H, CH'*H*), 3 745 (d, J = 15 1 Hz, 1 H, PHCH*H'*), 3 853, 3 695 (s, s, 3 H each, OCH_3x2), 3 605 (d, J = 13 0 Hz, 1 H, CH*H'*), 3 541 (s, 3 H, OCH_3), 3.469 (s, 1 H, C*H*), 3 297 (dd, J = 5 7, 16 6 Hz, 1 H, CH'*H*), 2 95-3 05 (m, 3 H), 2 850 (d, J = 16 6 Hz, 1 H, CH*H'*); IR (NaCl cells, CH_2Cl_2, cm^{-1}) 3040, 2950, 2927, 2830, 1638, 1605, 1511, 1462, 1449, 1413, 1352, 1318, 1230, 1210, 1150, 1135, 1105, 1022, 993, 960, 857, 805, Anal Calculated for $C_{36}H_{38}N_2O_5$, MW = 578 709: C = 74 72%, H = 6 62% Found C = 74 57%, H = 6 64%

X-Ray Crystal Structure Data for 12.[16]

Centering of a single crystal of **12** and data collection were carried out at ambient temperature on a Syntex $P2_1$ diffractometer with a Molybdenum radiation source (K_α λ = 0 71069 Å) and a graphite monochromator The structure was solved using a Data Eclipse S-140 computer with Nicolet SHELXTL software by direct methods The cell dimensions were determined on the basis of 10 reflections, and the final R values for the solved structure were R = 0 0539 and R_w = 0 0545 and a Goodness of fit (GOOF) = 1.490

Figure 1. Chem 3D Plus Representation of $C_{36}H_{38}N_2O_5$, 12.

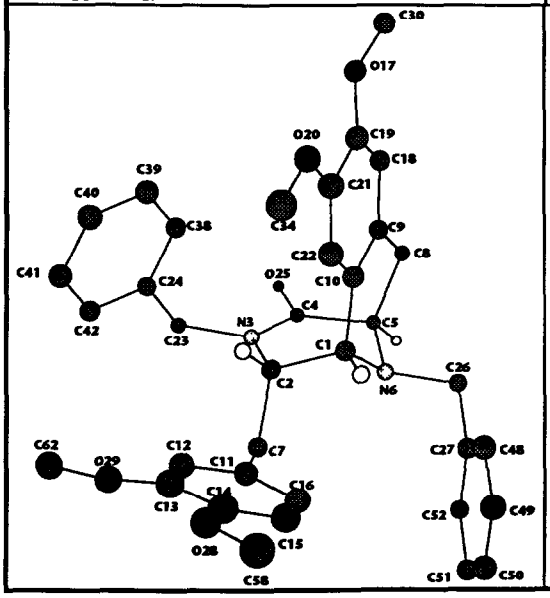

Table 1. Bond Lengths (Å) for $C_{36}H_{38}N_2O_5$.

Crystal Data	
Formula	$C_{36}H_{38}N_2O_5$
Formula Weight	578 71
Space Group	Monoclinic $P2_1C$
a (Å)	15 6889 (60)
b (Å)	11 4889 (57)
c (Å)	18 4890 (77)
V (Å^3)	3164
Z	4
density (g cm^{-3})	1 22
crystal dimensions (mm)	0 3, 0 4, 0 7
m (calc, cm^{-1})	0 75
Data Collection	
R(merge), R(sigma)	0 0279, 0 0399
Total reflections measured	4589
Unique reflections	3097
Scan type	Wykoff ω
2θ Range	3-45°
Scan speed (deg cm^{-1})	4 0-15 0
Reflections measured	+h +k ±l

Table 2. Bond Lengths (A) for $C_{36}H_{38}N_2O_5$.

Bond	Length	Bond	Length
C(1)-C(2)	1.509	C(15)-C(16)	1 386
C(1)-N(6)	1 460	O(17)-C(19)	1 365
C(1)-C(10)	1 517	O(17)-C(30)	1 417
C(2)-N(3)	1 468	C(18)-C(19)	1 369
C(2)-C(7)	1 533	C(19)-C(21)	1 389
N(3)-C(4)	1.344	O(20)-C(21)	1 369
N(3)-C(23)	1 462	O(20)-C(34)	1 413
C(4)-C(5)	1 513	C(21)-C(22)	1 368
C(4)-O(25)	1.229	C(23)-C(24)	1 505
C(5)-N(6)	1 463	C(24)-C(38)	1 369
C(5)-C(8)	1.514	C(24)-C(42)	1 370
N(6)-C(26)	1 468	C(26)-C(27)	1 507
C(7)-C(11)	1 504	C(27)-C(48)	1 377
C(8)-C(9)	1.514	C(27)-C(52)	1 370
C(9)-C(10)	1.381	O(28)-C(58)	1 408
C(9)-C(18)	1.387	O(29)-C(62)	1 417
C(10)-C(22)	1 400	C(38)-C(39)	1 386
C(11)-C(12)	1 385	C(39)-C(40)	1 362
C(11)-C(16)	1 372	C(40)-C(41)	1 358
C(12)-C(13)	1.373	C(41)-C(42)	1 392
C(13)-C(14)	1 391	C(48)-C(49)	1 383
C(13)-O(29)	1 364	C(49)-C(50)	1 344
C(14)-C(15)	1.364	C(50)-C(51)	1 375
C(14)-O(28)	1.368	C(51)-C(52)	1 382

Table 3. Bond Angles (°) for $C_{36}H_{38}N_2O_5$.

Bond	Angle	Bond	Angle
C(2)-C(1)-N(6)	105 950	C(13)-C(14)-O(28)	114 959
C(2)-C(1)-C(10)	111.825	C(15)-C(14)-O(28)	125.845
N(6)-C(1)-C(10)	114 453	C(14)-C(15)-C(16)	120.652
C(1)-C(2)-N(3)	109.267	C(11)-C(16)-C(15)	120.689
C(1)-C(2)-C(7)	113 158	C(19)-O(17)-C(30)	117.354
N(3)-C(2)-C(7)	111 979	C(9)-C(18)-C(19)	121 234
C(2)-N(3)-C(4)	123 843	O(17)-C(19)-C(18)	124.303
C(2)-N(3)-C(23)	116 448	O(17)-C(19)-C(21)	116 160
C(4)-N(3)-C(23)	119.615	C(18)-C(19)-C(21)	119.522
N(3)-C(4)-C(5)	118 641	C(21)-O(20)-C(34)	117 358
N(3)-C(4)-O(25)	122 404	C(19)-C(21)-O(20)	115.585
C(5)-C(4)-O(25)	118 900	C(19)-C(21)-C(22)	119 666
C(4)-C(5)-N(6)	111 523	O(20)-C(21)-C(22)	124 752
C(4)-C(5)-C(8)	108 014	C(10)-C(22)-C(21)	121 094
N(6)-C(5)-C(8)	112 817	N(3)-C(23)-C(24)	112 018
C(1)-N(6)-C(5)	107.314	C(23)-C(24)-C(38)	120.542
C(1)-N(6)-C(26)	113.654	C(23)-C(24)-C(42)	120 591
C(5)-N(6)-C(26)	114 175	C(38)-C(24)-C(42)	118 856
C(2)-C(7)-C(11)	110 670	N(6)-C(26)-C(27)	110.537
C(5)-C(8)-C(9)	110.327	C(26)-C(27)-C(48)	121.390
C(8)-C(9)-C(10)	119 953	C(26)-C(27)-C(52)	120 489
C(8)-C(9)-C(18)	120 465	C(48)-C(27)-C(52)	118 122
C(10)-C(9)-C(18)	119.570	C(14)-O(28)-C(58)	117.547
C(1)-C(10)-C(9)	121.300	C(13)-O(29)-C(62)	117 921
C(1)-C(10)-C(22)	119 704	C(24)-C(38)-C(39)	120.314
C(9)-C(10)-C(22)	118 870	C(38)-C(39)-C(40)	119 970
C(7)-C(11)-C(12)	119 171	C(39)-C(40)-C(41)	120 780
C(7)-C(11)-C(16)	122.341	C(40)-C(41)-C(42)	118 982
C(12)-C(11)-C(16)	118.372	C(24)-C(42)-C(41)	121 098
C(11)-C(12)-C(13)	121 248	C(27)-C(48)-C(49)	120.530
C(12)-C(13)-C(14)	119 758	C(48)-C(49)-C(50)	120 797
C(12)-C(13)-O(29)	125 116	C(49)-C(50)-C(51)	119 771
C(14)-C(13)-O(29)	115 125	C(50)-C(51)-C(52)	119 600
C(13)-C(14)-C(15)	119 183	C(27)-C(52)-C(51)	121 178

References and Footnotes

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