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SYNTHETIC STUDIES ON SAFRAMYCIN ANIBIOTICS: AN IMPROVED SYNTHESIS OF TRICYCLIC LACTAM INTERMEDIATE AND CONSTRUCTION OF THE CORE RING SYSTEM OF SAFRAMYCIN A

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This paper is dedicated to Professor Dr. Isao Kuwajima (Professor Emeritus, Tokyo Institute of Technology) on the occasion of his 77th birthday.

Abstract – An improved synthesis of the tricyclic lactam intermediate of saframycin antibiotics and the construction of the core ring system having a cyano group at C-21 position were presented.[1] The stereochemistry of several key intermediates was determined by X-ray crystallographic analysis.

INTRODUCTION

Natural products belonging to the bistetrahydroisoquinolinequinone family and their reduced forms, including saframycins,[2] renieramycins,[3] and the most notable example, ecteinascidin 743,[4] have received considerable attention due to their potent biological activities and structural diversity, as well as their meager availability in nature (Figure 1).[5] Among them, saframycin A is the most representative compound because of its remarkable antitumor activity.[6] To date, one racemic and three asymmetric total syntheses of saframycin A have been accomplished by the groups of Fukuyama,[7] Corey,[8] Myers,[9] and Liu.[10]

In the course of our research on new metabolites, which involves the isolation and characterization of biologically active compounds and the synthesis of their respective analogues, we have developed the total syntheses of (±)-saframycins B[11] and C,[12] and (-)-*N*-acetylsaframycin Mx 2.[13] Furthermore, we have reported the total syntheses of (±)-renieramycin G[14] and (±)-cribrostatin 4.[15] However, none of

those compounds exhibited biological activities, the reason being that a cyano or a hydroxyl group at C-21 position is essential to producing the desired biological activities, and the elimination of those functional groups under physiological conditions results in the formation of a reactive iminium species that is responsible for covalent bond formation with its target compound.[16]

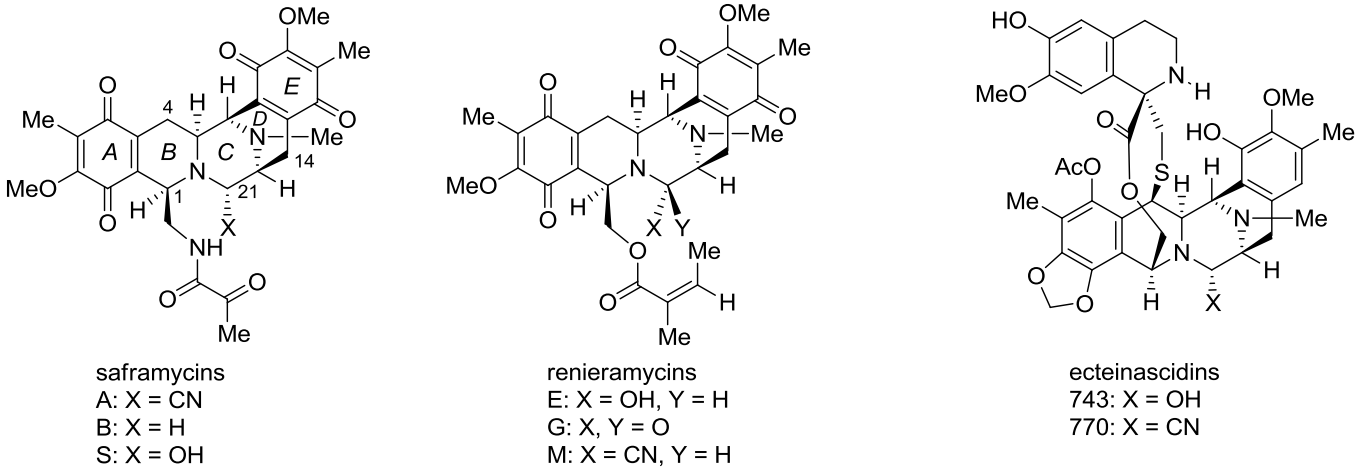
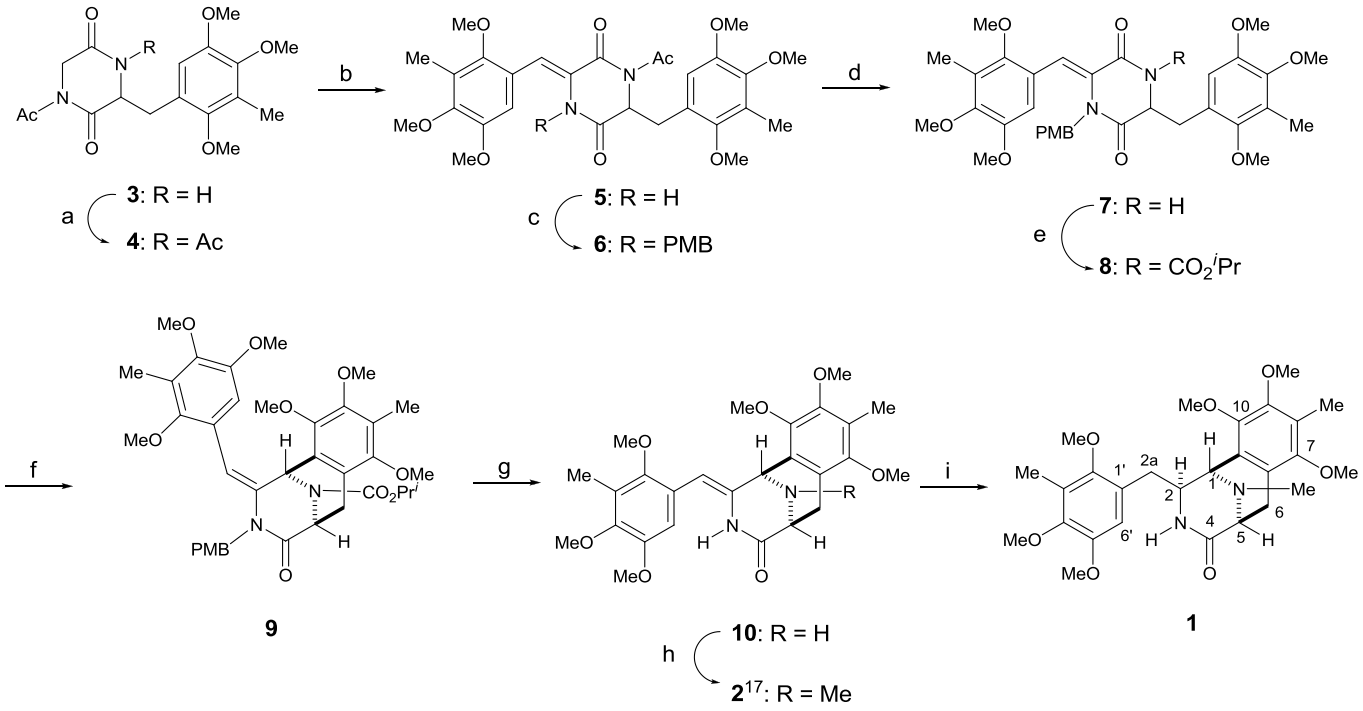


Figure 1. Structures of bistetrahydroisoquinoline natural products

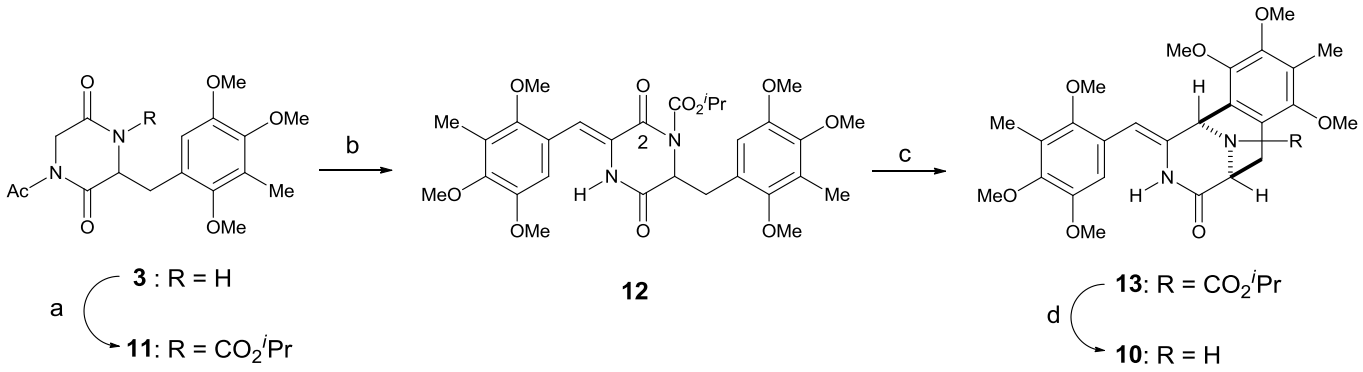
We have already reported the preparation of the key tricyclic lactam intermediate of saframycin A.[17] In this paper, we describe new developments in the total synthesis of saframycin A, including an improved synthesis of the tricyclic lactam intermediate of saframycin A and the construction of the core ring system having a cyano group at C-21 position.

RESULTS AND DISCUSSION

Our strategy for the synthesis of saframycin A was based on retrosynthetic analysis using tricyclic lactam (**1**) as the key intermediate. Reduction of the double bond of **2**[17] by catalytic hydrogenation (2.7 MPa) in the presence of 20% $Pd(OH)_2/C$ in ethanol at 80 °C for 22 h occurred cleanly from the α-face to give **1** in 94% yield (Scheme 1). With key intermediate **1** in hand, we looked into ways to establish a practical conversion of **3**[18] into **10** with reduction of the number of steps from seven (26.5% overall yield) to four (Scheme 2). Treatment of **3** with isopropyl chloroformate gave imide **11** in 96% yield. Condensation of **11** with 2,4,5-trimethoxy-3-methylbenzaldehyde in the presence of a base afforded **12** in 78% yield. Chemoselective reduction of the carbonyl group at C-2 of **12** with lithium tri-*tert*-butoxyaluminum hydride, followed by treatment with formic acid at 60 °C for 1 h gave **13** in 64% yield. Deprotection of **13** with TFA and H_2SO_4 at 25 °C for 5 h gave (*Z*)-lactam **10** in 91% yield. Thus, we were able to devise a four-step transformation of **3** into **10** in 43.6% overall yield.



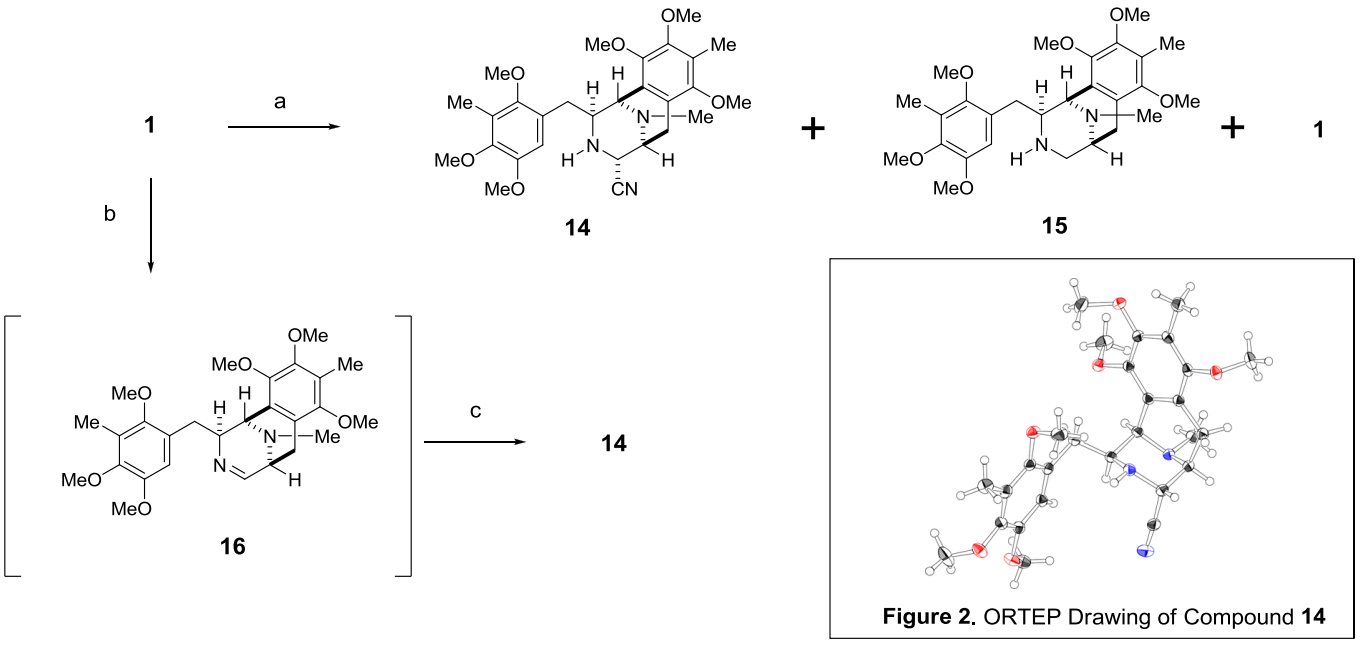
Scheme 1. a) Ac_2O, 110 °C, 4 h, 83%; b) 2,4,5-trimethoxy-3-methylbenzaldehyde, KO^{t}Bu, ^{t}BuOH, DMF, 25 °C, 24 h, 81%; c) NaH, DMF, PMBCl, 25 °C, 2 h,100%; d) NH_2NH_2•H_2O, DMF, 25 °C, 1 h, 86%; e) $ClCO_2{}^i$Pr, CH_2Cl_2, Et_3N, DMAP, 25 °C, 1 h, 91%; f) LiAl(OBu^t)$_3$H, THF, 0 °C, 1 h, and then MsCl, CH_2Cl_2, TEA, reflux, 20 h, 70%; g) H_2SO_4, TFA = 1 : 20, 25 °C, 72%; h) 37% HCHO-HCO_2H, 70 °C, 1 h, 80%; i) H_2 (2.7 MPa), 20% $Pd(OH)_2$/C, EtOH, 80 °C, 22 h, 94%.



Scheme 2. a) $ClCO_2{}^i$Pr, CH_2Cl_2, Et_3N, DMAP, 25 °C, 2 h, 96%; b) 2,4,5-trimethoxy-3-methylbenzaldehyde, KOBu^t, ^{t}BuOH, DMF, 25 °C, 1.5 h, 78%; c) LiAl(O^{t}Bu)$_3$H, THF, 0 °C, 4.5 h, and then HCO_2H, 60 °C, 1 h, 64%; d) H_2SO_4, TFA (1 : 20), 25 °C, 5 h, 91%.

Then, we investigated the conversion of lactam **1** into α-aminonitrile **14** (Scheme 3). $LiAlH_4$ reduction of **1** followed by KCN and acetic acid gave desired product **14** in only 18% yield together with secondary amine **15** (50%) and recovered **1** (18%). After numerous attempts under a variety of conditions, a sequence of reactions via cyclic imine **16** was achieved. Reaction of **1** with Cp_2ZrHCl (Schwartz's reagent)[19] gave **16**, and the subsequent treatment of **16** with trimethylsilyl cyanide (TMSCN) produced **14**

in a one-pot operation, stereoselectively (95% yield). X-Ray crystallographic analysis revealed that the cyano group had α-axial orientation (Figure 2).



Scheme 3. a) $LiAlH_4$ (8 equiv.), THF, 0 °C 2 h and 25 °C, 3 h, and then KCN, AcOH-H_2O, 25 °C, 17 h, **14** (18%), **15** (50%), **1** (18%); b) Cp_2ZrHCl (3 equiv.), THF, -17 °C, 1 h and 25 °C, 1 h; c) TMSCN (1.4 equiv.), THF, 25 °C, 1 h, 95% (2 steps).

We next investigated the construction of the core ring system having a cyano group at C-21 position from **14**. We anticipated obtaining thermodynamically stable compound **17a** in order to avoid the steric repulsion between the side chain and the cyano group (**Chart 1**).

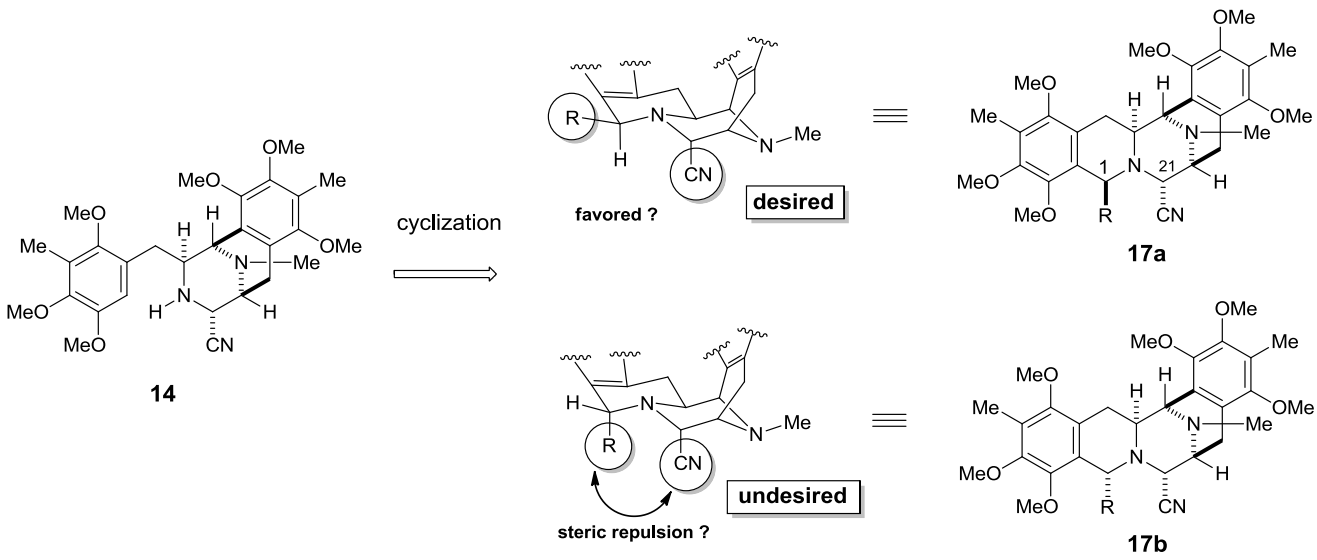
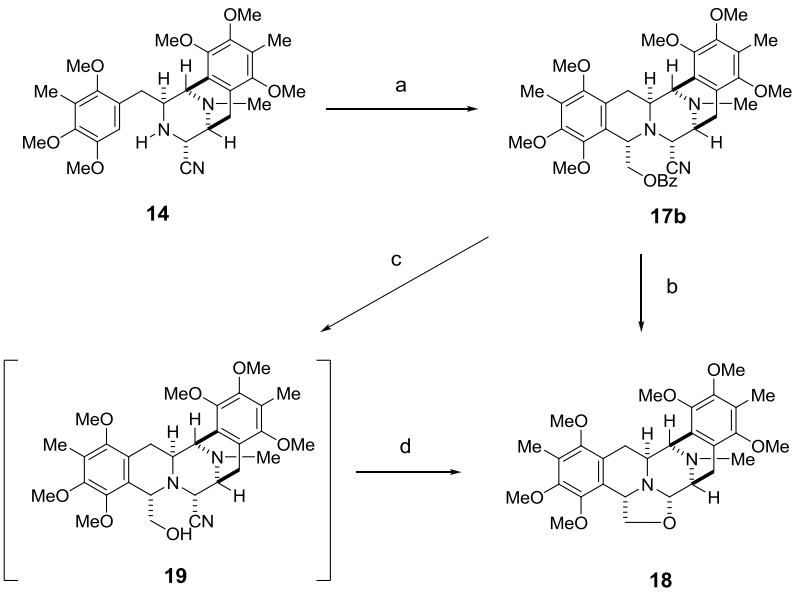


Chart 1. Working hypothesis

According to the results of our recent model conversion,[20] treatment of **14** with 2,2-diethoxyethyl benzoate[21] (8 equiv.) and TMSOTf (2 equiv.) in $(CH_2Cl)_2$ at 25 °C for 100 h gave **17b** in 46% yield, and 27% of starting material **14** was recovered (Scheme 4). After performing several experiments to verify the optimum reaction conditions, the following procedure was found to be best in terms of product yield and reproducibility of the reaction. Treatment of **14** with a large excess of benzoyloxyacetaldehyde[21] in TFA-AcOH (4:1) at 25 °C for 4 h afforded **17b** in 97% yield according to the procedure of Ong et al.[22] However, the stereochemistry of **17b** could not be determined at this stage. Numerous efforts to hydrolyze the benzoyl ester at C-1 position of **17b** under basic or acidic condition failed to bear fruit. However, treatment of **17b** with hydrazine hydrate in methanol at 60 °C for 6 h gave oxazolidine **18** in high yield. The formation of the oxazolidine ring was proven by the emergence of the characteristic *N,O*-acetal carbon signal at δ 95.8 ppm and the analysis of the heteronuclear multiple-bond correlation (HMBC) NMR spectrum. The stereochemical structure of **18** was finally confirmed by X-ray crystallographic analysis (Figure 3). Another approach involved the hydride reduction of **17b** with diisobutylaluminum hydride (DIBAL-H) in THF at -78 °C for 15 h to generate alcohol **19** in 61% yield. However, this compound was easily transformed into **18** during purification by silica gel column chromatograpy.[23]



Scheme 4. a) $CHOCH_2OBz$, TFA-AcOH (4 : 1), 25 °C, 4 h, 97%; b) $NH_2NH_2{\cdot}H_2O$, MeOH, 60 °C, 6 h, 94%; c) DIBAL-H, THF, -78 °C, 15 h, 61%; d) SiO_2, 25 °C.

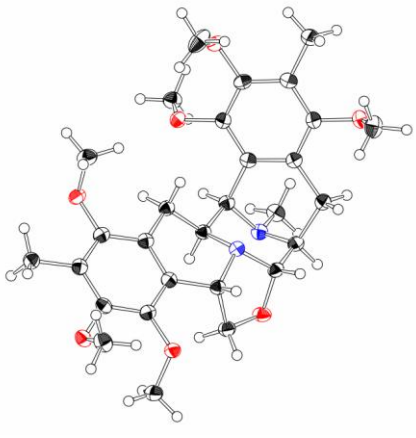


Figure 3. ORTEP Drawing of Compound **18**

In summary, we succeeded in reducing the number of steps for the synthesis of intermediate **10** from **3**, i.e., from the original seven steps (26.5% overall yield) to four, in 43.6% overall yield. Stereoselective cyclization of α-aminonitrile **14** generated **17b** in high yield, but its C-1 configuration was the opposite of

that of saframycin A. Investigations of the isomerization at C-1 position of the core ring system and its application to the total synthesis of saframycin A and renieramycin M are under way.[24]

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a Shimadzu Prestige-21/IR Affinity-1 Fourier Transform Infrared (FT-IR) spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL ECA-500 NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, on a JEOL ECS-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, on a JEOL AL-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, and on a JEOL AL-300 spectrometer at 300 MHz for ^{1}H. NMR spectra were measured in $CDCl_3$, DMSO-d_6, or MeOD and the chemical shifts were recorded in δ_H values relative to $(CH_3)_4Si$ (TMS) as the internal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.

(1*R**,2*S**,5*S**)-7,9,10-Trimethoxy-8,11-dimethyl-4-oxo-2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (**1**)

A suspension of **2** (996 mg, 2.00 mmol) in EtOH (40 mL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (280 mg, 0.40 mmol) at 80 °C for 22 h under 2.7 MPa hydrogen. The catalyst was removed by filtration and the residue trapped by the filter paper was washed with $CHCl_3$ and MeOH. The combined filtrates were concentrated in vacuo to give a residue, the recrystallization of which from hexane-EtOAc afforded **1** (857 mg, 85.7%) as colorless prisms. The mother liquid (148 mg) was subjected to column chromatography on SiO_2 (15 g) with $CHCl_3$-MeOH (90:1-80:1) to afford a solid, the recrystallization of which from hexane-EtOAc gave an additional amount of **1** (79 mg, 7.9%; total amount: 936 mg, 93.6%), mp 165-167 °C.

ν_{max} (KBr) 3433, 3385, 2940, 2905, 1676, 1489, 1464, 1408, 1339, 1242, 1113, 1009, 999 cm^{-1}. δ_H (400 MHz) 2.02 (1H, dd, *J* = 14.0, 11.3 Hz, 2a-Hβ), 2.18 (3H, s, 3'-OCH_3), 2.23 (3H, s, 8-OCH_3), 2.53 (3H, s, *N*CH_3), 2.97 (1H, d, *J* = 17.9 Hz, 6H-β), 3.10 (1H, dd, *J* = 17.9, 7.3 Hz, 6H-α), 3.29 (1H, dd, *J* = 14.0, 2.4 Hz, 2a-Hα), 3.56 (3H, s, 2'-OCH_3), 3.59 (1H, d, *J* = 7.3 Hz, 5-H), 3.72 (3H, s, 7-OCH_3), 3.77 (3H, s, 4'-OCH_3 or 10-OCH_3), 3.80 (3H, s, 5'-OCH_3), 3.82 (3H, s, 9-OCH_3), 3.85 (3H, s, 4'-OCH_3 or 10-OCH_3), 4.25-4.31 (2H, overlapped, 1-H and 2-H), 5.55 (1H, s, *N*H), 6.45 (1H, s, 6'-H). δ_C (100 MHz) 9.4 (8-CH_3), 9.6 (3'-CH_3), 23.8 (C-6), 32.2 (C-2a), 40.4 (*N*CH_3), 54.6 (C-1), 55.5 (C-2), 55.9 (C-5'), 58.2 (C-5), 59.8 (7-OCH_3), 60.0 (C-9), 60.2 (C-4' and C-10), 110.8 (C-6'), 122.3 (C-6a), 122.6 (C-10a), 124.7 (C-1' and C-8), 126.2 (C-3'), 146.9 (C-4'), 147.2 (C-10), 149.3 (C-5'), 149.8 (C-9), 151.1 (C-2'), 152.4 (C-7),

171.9 (CO). EIMS *m/z* (%): 500 (M^+, 15), 250 (9), 249 (29), 248 (100), 218 (11). Anal. Calcd for $C_{27}H_{36}N_2O_3$: C 64.78, H 7.25, N 5.60. Found: C 64.51, H 7.15, N 5.24.

1-Acetyl-3-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-4-isopropoxycarbonylpiperazine-2,5-dione (**11**)

Isopropyl chloroformate (10.9 mL, 96.0 mmol) was added to a mixture of **3** (8.38 g, 23.9 mmol), Et_3N (7.0 mL, 48.0 mmol), and DMAP (5.86 g, 48.0 mmol) in CH_2Cl_2 (400 mL) over 10 min at 0 °C, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (600 mL) and extracted with $CHCl_3$ (3 x 600 mL). The combined extracts were washed with 1 M aqueous HCl solution (600 mL) and then with 5% aqueous $NaHCO_3$ solution (600 mL), dried, and concentrated in vacuo. The residue (12.01 g) was subjected to column chromatography on SiO_2 (200 g) with hexane-EtOAc (4:1) to give **11** (9.99 g, 95.7%) as a colorless syrup.

ν_{max} ($CHCl_3$) 3021, 1782, 1721, 1487, 1369, 1304, 1261, 1233, 1202, 1103, 1088 cm^{-1}. δ_H (400 MHz) 1.31 (3H, d, *J* = 6.3 Hz, CH(CH_3)$_2$), 1.34 (3H, d, *J* = 6.3 Hz, CH(CH_3)$_2$), 2.15 (3H, s, 3'-CH_3), 2.55 (3H, s, COCH_3), 3.10 (1H, d, *J* = 18.8 Hz, 6-H), 3.21 (1H, dd, *J* = 13.7, 5.4 Hz, 3a-H), 3.31 (1H, dd, *J* = 13.7, 6.3 Hz, 3a-H), 3.63 (3H, s, 2'-OCH_3), 3.76 (3H, s, 5'-OCH_3), 3.78 (3H, s, 4'-OCH_3), 4.64 (1H, d, *J* = 18.8 Hz, 6-H), 5.06 (1H, sept, *J* = 6.3 Hz, C*H*(CH$_3$)$_2$), 5.13 (1H, dd, *J* = 6.3, 5.4 Hz, 3-H), 6.45 (1H, s, 6'-H). δ_C (100 MHz) 9.7 (3-CH_3), 21.6 (CH(*C*H$_3$)$_2$), 21.7 (CH(*C*H$_3$)$_2$), 26.9 (CO*C*H$_3$), 33.4 (C-3a), 46.6 (C-6), 56.0 (5'-OCH_3), 60.4 (4'-OCH_3), 60.6 (1'-OCH_3), 61.2 (C-3), 72.3 (*C*H(CH$_3$)$_2$), 111.6 (C-6'), 121.6 (C-1'), 125.9 (C-3'), 147.9 (C-4'), 149.2 (C-5'), 150.9 (*C*O$_2$^{i}Pr), 151.2 (C-2'), 163.1 (C-5), 167.3 (C-2), 171.0 (s, *C*OCH$_3$). EIMS *m/z* (%): 436 (M^+, 16), 196 (11), 195 (100), 165 (6). HREIMS *m/z* 436.1845 (M^+, calcd for $C_{21}H_{28}N_2O_8$, 436.1846).

(*Z*)-1-Isopropoxycarbonyl-6-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-3-[(2,4,5-trimethoxy-3-methyl-phenyl)methylene]-piperazine-2,5-dione (**12**).

A solution of *tert*-BuOK in *tert*-BuOH (1 M, 3.4 mL, 3.38 mmol) was added to a solution of **11** (1.23 g, 2.81 mmol) and 2,4,5-trimethoxy-3-methylbenzaldehyde (591 mg, 2.81 mmol) in CH_2Cl_2 (10 mL) over 30 min at 0 °C, and the mixture was stirred at 0 °C for 40 min, and then at 25 °C for 1.5 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo. The residue (1.48 g) was subjected to column chromatography on SiO_2 (50 g) with hexane-EtOAc (2:1) to give **12** (1.28 g, 77.7 %) as a pale yellow amorphous powder.

ν_{max} (KBr) 1701, 1489, 1466, 1456, 1422, 1377, 1341, 1281, 1238, 1180, 1123, 1105, 1088, 1009 cm^{-1}. δ_H (400 MHz) 1.37 (3H, d, *J* = 6.3 Hz, CH(CH_3)$_2$), 1.40 (3H, d, *J* = 6.3 Hz, CH(CH_3)$_2$), 2.01 (3H, s, 3"-CH_3),

2.20 (3H, s, 3'-CH_3), 3.07 (1H, dd, *J*= 13.7, 3.6 Hz, 6a-H), 3.39 (3H, s, 5"-OCH_3), 3.42 (1H, dd, *J* = 13.7, 5.7 Hz, 6a-H), 3.50 (3H, s, 4'-OCH_3), 3.58 (3H, s, 2"-OCH_3), 3.72 (3H, s, 4"-OCH_3), 3.83 (3H, s, 2'-OCH_3), 3.95 (3H, s, 5'-OCH_3), 5.10 (1H, dd, *J* = 5.7, 3.6 Hz, 6-H), 5.16 (1H, sep, *J* = 6.3 Hz, C*H*(CH_3)$_2$), 6.26 (1H, s, 6"-H), 6.42 (1H, s, 3a-H), 6.50 (1H, s, 6'-H), 9.05 (1H, br-s, *N*H). δ_C (100 MHz) 9.5 (3'-CH_3 or 3"-CH_3), 9.6 (3'-CH_3 or 3"-CH_3), 21.8 and 21.8 (CH(*C*H_3)$_2$), 33.3 (C-6a), 55.1 (5"-OCH_3), 55.6 (5'-OCH_3), 59.9 (4"-OCH_3), 60.2 (C-6), 60.3 (2'-OCH_3), 60.3 (2"-OCH_3), 61.2 (4'-OCH_3), 71.7 (*C*H(CH_3)$_2$), 111.8 (C-6"), 112.0 (C-6'), 115.8 (C-3a), 121.0 (C-1'), 121.8 (C-1"), 125.2 (C-3), 125.5 (C-3'), 125.7 (C-3'), 147.6 (C-4"), 148.4 (C-4'), 148.5 (C-2'), 148.9 (C-5"), 149.2 (C-5'), 151.7 (C-2"), 152.0 (*C*O_2^{i}Pr), 158.6 (C-2), 165.5 (C-5). EIMS *m/z* (%): 586 (M^+, 45), 570 (8), 196 (12), 195 (100), 165 (5). HREIMS *m/z* 586.2528 (M^+, calcd for $C_{30}H_{38}N_2O_{10}$, 586.2526).

Isopropyl (*Z*)-(1*R**,5*S**)-7,9,10-Trimethoxy-8-methyl-4-oxo-2-[(2,4,5-trimethoxy-3-methylphenyl-methylene)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylate (**13**)

Li(*tert*-BuO)$_3$AlH (1.27 g, 5.00 mmol) was added to a solution of **12** (586 mg, 1.00 mmol) in THF (33 mL) at 0 °C over 20 min, and the reaction mixture was stirred at the same temperature for 4.5 h. Anhydrous Na_2SO_4 (4.2 g) was added and the reaction was quenched by the addition of water (2.8 mL). The reaction mixture was filtered through Celite pad, and the residue was washed with $CHCl_3$ (150 mL). The combined filtrates were diluted with brine (150 mL) and extracted with $CHCl_3$ (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo to give a residue in the form of a pale yellow amorphous powder, and this was used in the next step without further purification. A solution of the above product (684 mg) in formic acid (16.5 mL) was heated at 60 °C for 1 h. After the reaction mixture was concentrated in vacuo, the residue was diluted with 5% aqueous $NaHCO_3$ solution (100 mL) and extracted with $CHCl_3$ (100 mL x 3). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo to give a residue (600 mg), which was subjected to column chromatography on SiO_2 (25 g) with hexane-EtOAc (7:3) to afford **13** (367 mg, 63.8%) as a colorless amorphous powder. Further elution with hexane-EtOAc (3:1) gave **12** (61 mg, 10.4% recovery). ν_{max} (KBr) 1694, 1489, 1466, 1423, 1408, 1342, 1298, 1265, 1244, 1111, 1088, 1069, 1000 cm^{-1}. δ_H (DMSO-d_6, 140 °C, 400 MHz) 1.15 (3H, d, *J* = 6.2 Hz, CH(CH_3)$_2$), 1.17 (3H, d, *J* = 6.2 Hz, CH(CH_3)$_2$), 2.02 (3H, s, 3'-CH_3), 2.14 (3H, s, 8-CH_3), 2.95-2.96 (2H, overlapped, 6-H_2), 3.34 (3H, s, 2'-OCH_3), 3.56 (3H, s, 7-OCH_3), 3.641 (3H, s, 4'-OCH_3 or 9-OCH_3), 3.74 (3H, s, 4'-OCH_3 or 9-OCH_3), 3.78 (3H, s, 5'-OCH_3), 3.93 (3H, s, 10-OCH_3), 4.77-4.88 (1H, overlapped, 5-H), 4.80 (1H, sep, *J* = 6.2 Hz, C*H*(CH_3)$_2$), 5.82 (1H, s, 1-H), 5.84 (1H, s, 2a-H), 6.62 (1H, s, 6'-H), 8.50 (1H, br s, *N*H). δ_C (DMSO-d_6, 140 °C, 100 MHz) 8.4 (3'-CH_3 or 8-CH_3) 8.5 (3'-CH_3 or 8-CH_3), 21.0 (CH(*C*H_3)$_2$), 25.8 (C-6), 49.3 (C-1), 51.4 (C-5),

55.8 (5'-OCH_3), 58.8, 58.9, and 59.0 (4'-OCH_3, 7-OCH_3, and 9-OCH_3), 59.2 (2'-OCH_3), 59.3 (10-OCH_3), 68.6 ($CH(CH_3)_2$), 102.0 (C-2a), 111.9 (C-6'), 119.8 (C-6a or C-10a), 121.2 (C-1'), 123.6 (C-8), 123.9 (C-3'), 124.3 (C-6a or C-10a), 132.4 (C-2), 144.9 (C-10), 146.7 (C-4'), 148.0 (C-5'), 148.7 (C-2'), 149.1 (C-9), 151.4 (C-7), 152.2 ($CO_2{}^i$Pr), 166.8 (C-4). EIMS *m/z* (%): 570 (M^+, 100), 469 (5), 279 (5), 278 (10), 234 (20), 206 (6), 204 (7). HREIMS *m/z* 570.2572 (M^+, calcd $C_{30}H_{38}N_2O_9$, 570.2577).

(*Z*)-(1*R**,5*S**)-7,9,10-Trimethoxy-8-methyl-4-oxo-2-[(2,4,5-trimethoxy-3-methylphenyl)methylene]-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (**10**)

Concentrated H_2SO_4 (2.0 mL) was added to a stirred solution of **13** (1.14 g, 2.00 mmol) in TFA (40 mL) over 5 min at 0 °C, and the mixture was stirred at 25 °C for 5 h. The reaction mixture was diluted with water (130 mL) at 0 °C, made alkaline with concentrated NH_4OH (90 mL), and extracted with $CHCl_3$ (3 x 130 mL). The combined extracts were washed with brine (130 mL), dried, and concentrated in vacuo to give a residue. The residue (1.17 g) was subjected to column chromatography on SiO_2 (36 g) with $CHCl_3$-MeOH (200:1) to give a fraction (1.07 g) containing **10**, the recrystallization of which from hexane-EtOAc afforded **10** (861 mg, 88.9%) as colorless prisms. The mother liquid (91 mg) was subjected to column chromatography on SiO_2 (8.4 g) with $CHCl_3$-MeOH (350:1) to give a solid, the recrystallization of which from hexane-EtOAc afforded an additional amount of **10** (19 mg, 2.0%; total amount: 880 mg, 90.9%), mp 126-127 °C (lit.,[17] mp 125.5-127 °C).

δ_H (300 MHz) 2.17 (3H, s, Ar-CH_3), 2.19 (3H, s, Ar-CH_3), 3.09 (1H, dd, *J* = 17.3, 6.5 Hz, 6-Hα), 3.18 (1H, dd, *J* = 17.3, 1.5 Hz, 6-Hβ), 3.40 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.03 (1H, dd, *J* = 6.5, 1.5 Hz, 5-H), 4.98 (1H, s, 1-H), 5.87 (1H, s, 2a-H), 6.57 (1H, s, ArH), 8.40 (1H,br s, *N*H).

Compound **10** was identical with an authentic sample on direct comparison of spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, MS) and TLC behavior.

Preparation of compound **14**.

Method A: A solution of $LiAlH_4$ in THF (1.0 M, 400 μL, 400 μmol) was added to a stirred solution of **1** (25.0 mg, 50.0 μmol) in THF (2 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 2 h and then at 25 °C for 3 h. Aqueous KCN solution (4.5 M, 67 μL, 300 μmol) and AcOH (400 μL) were added, and stirring was continued at 25 °C for 17 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue (33.4 mg), which was subjected to column chromatography on SiO_2 (10 g) with $CHCl_3$-MeOH (200:1) to furnish **14** (4.7 mg,

18.4%). Further elution with $CHCl_3$-MeOH (99:1) gave **1** (4.5 mg, 18.0% recovery), and elution with $CHCl_3$-MeOH (20:1) afforded **15** (12.1 mg, 49.8%) as a pale yellow amorphous powder.

(1*R**,2*S**,4*R**,5*S**)-7,9,10-Trimethoxy-8,11-dimethyl-2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-4-carbonitrile (**14**)

An analytical sample was obtained by recrystallization from hexane-EtOAc as colorless prisms, mp 168-169 °C. ν_{max} ($CHCl_3$) 3021, 2938, 2359, 1487, 1464, 1408, 1194, 1136, 1111, 1076, 1043, 1013, 995, 976, 962 cm^{-1}. δ_H (500 MHz) 2.15 (3H, s, 3'-CH_3), 2.19 (1H, dd, *J* = 14.9, 11.4 Hz, 2a-Hβ), 2.22 (3H, s, 8-CH_3), 2.36 (3H, s, *N*CH_3), 2.45 (1H, d, *J* = 18.2 Hz, 6-Hβ), 2.997 (1H, dd, *J* = 14.9, 2.7 Hz, 2a-Hα), 3.004 (1H, dd, *J* = 18.2, 7.5 Hz, 6-Hα), 3.29 (1H, br d, *J* = 7.5 Hz, 5-H), 3.49 (3H, s, 2'-OCH_3), 3.70 (3H, s, 7-OCH_3), 3.77 (3H, s, 4'-OCH_3), 3.81 (3H, s, 10-OCH_3), 3.82 (3H, s, 5'-OCH_3 or 9-OCH_3), 3.81-3.84 (1H, overlapped with OCH_3 signals, 2-H), 3.84 (3H, s, 5'-OCH_3 or 9-OCH_3), 3.91 (1H, d, *J* = 2.4 Hz, 4-H), 4.08 (1H, d, *J* = 2.1 Hz, 1-H), 6.61 (1H, s, 6'-H). δ_C (125 MHz) 9.4 (8-CH_3), 9.6 (3'-CH_3), 21.4 (C-6), 31.2 (C-2a), 42.1 (*N*CH_3), 53.9 (C-4), 54.4 (d, C-5), 56.0 (5'-OCH_3 or 9-OCH_3), 56.3 (C-2), 57.3 (C-1), 59.6 (7-OCH_3), 60.0 (5'-OCH_3 or 9-OCH_3), 60.2 (4'-OCH_3), 60.3 (10-OCH_3), 60.4 (2'-OCH_3), 109.5 (C-6'), 120.0 (s, CN), 123.1 (C-10a), 123.5 (C-8), 123.7 (C-6a), 125.6 (C-3'), 125.8 (C-1'), 146.3 (C-4'), 147.6 (C-10), 149.4 (C-5' or C-9), 149.5 (C-5' or C-9), 151.2 (C-2'), 151.2 (C-7). FABMS *m/z* 512 $[M + H]^+$. HRFABMS *m/z* 512.2764 ($[M + H]^+$, calcd for $C_{28}H_{38}N_3O_6$, 512.2761). Anal. Calcd for $C_{28}H_{38}N_3O_6$: C 65.73, H 7.29, N 8.21. Found: C 65.80, H 7.20, N 8.20.

(1*R**,2*S**,5*S**)-7,9,10-Trimethoxy-8,11-dimethyl-2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (**15**).

This sample was identical with an authentic sample[11b] on direct comparison of spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, MS) and TLC behavior. δ_H (300 MHz) 2.02 (1H, dd, *J* = 14.4, 11.2 Hz, 2a-Hβ), 2.15 (3H, s, ArCH_3), 2.23 (3H, s, ArCH_3), 2.33 (3H, s, *N*CH_3), 2.51 (1H, d, *J* = 17.2 Hz, 6-Hβ), 2.89 (1H, dd, *J* = 12.2, 1.4 Hz, 4-H), 2.97 (1H, dd, *J* = 14.4, 2.7 Hz, 2a-Hα), 2.99 (1H, dd, *J* = 17.2, 7.7 Hz, 6-Hα), 3.04 (1H, m, 5-H), 3.14 (1H, dd, *J* = 12.2, 2.4 Hz, 4-H), 3.48 (1H, ddd, *J* = 11.2, 2.7, 2.7 Hz, 2-H), 3.51 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.06 (1H, d, *J* = 2.7 Hz, 1-H), 6.62 (1H, s, ArH).

Method B: A suspension of Cp_2ZrHCl (2.01 g, 7.80 mmol) in dry THF (45 mL) was added to a stirred solution of **1** (1.30 g, 2.60 mmol) in THF (20 mL) at -20 °C, and this mixture was stirred at the same temperature for 1 h and then at 25 °C for 2 h to generate imine intermediate **16**. TMSCN (458 μL, 3.64 mmol) was added to the reaction mixture over 5 min, and the stirring was continued for 1 h at 25 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (1 L) and extracted with $CHCl_3$ (3 x 1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo to give a

residue (1.62 g), which was subjected to column chromatography on SiO_2 (80 g) with $CHCl_3$ to furnish **14** (1.26 g, 94.7%) as a colorless amorphous powder.

(1*R**,2*S**,5*S**)-7,9,10-Trimethoxy-8,11-dimethyl-2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-1,2,5,6-tetrahydro-1,5-imino-3-benzazocine (**16**).

An analytical sample of **16** was obtained as a pale yellow amorphous powder by filtration (hexane) of the reaction mixture treated with Cp_2ZrHCl, concentration in vacuo, and column chromatography (elution with $CHCl_3$-MeOH).

ν_{max} ($CHCl_3$) 3015, 2938, 2832, 1663, 1487, 1463, 1408, 1337, 1227, 1111, 1086, 1013, 1001 cm^{-1}. δ_H (400 MHz) 7.80 (1H, t, *J* = 2.9 Hz, 4-H), 6.70 (1H, s, 6'-H), 4.32 (1H, br d, *J* = 11.9 Hz, 2-H), 4.19 (1H, d, *J* = 4.9 Hz, 1-H), 3.78 (6H, s, 9-OCH_3 and 10-OCH_3), 3.77 (3H, s, 5'-OCH_3), 3.72 (3H, s, 4'-OCH_3), 3.68 (3H, s, 8-OCH_3), 3.58 (3H, s, 2'-OCH_3), 3.58 (1H, br d, *J* = 6.2 Hz, 5-H), 3.35 (1H, dd, *J* = 14.6, 2.9 Hz, 2a-Hα), 2.85 (1H, dd, *J* = 17.7, 6.2 Hz, 6-Hα), 2.67 (1H, d, *J* = 17.7 Hz, 6-Hβ), 2.40 (3H, s, *N*CH_3), 2.18 (3H, s, 8-CH_3), 2.16 (3H, s, 3'-CH_3), 1.98 (1H, dd, *J* = 14.6, 11.9 Hz, 2a-Hβ). δ_C (100 MHz) 9.4 (8-CH_3), 9.6 (3'-CH_3), 20.8 (C-6), 31.8 (C-2a), 40.2 (*N*CH_3), 54.4 (C-5), 55.8 (C-1), 55.8 (5'-OCH_3), 59.7 (7-OCH_3), 60.0 (9-OCH_3 or 10-OCH_3), 60.1 (9-OCH_3 or 10-OCH_3), 60.1 (4'-OCH_3), 60.3 (2'-OCH_3), 61.0 (C-2), 111.1 (C-6'), 121.3 (C-6a or C-10a), 123.8 (C-8), 124.7 (C-6a or C-10a), 125.0 (C-3'), 128.5 (C-1'), 145.8 (C-4'), 147.6 (C-10), 148.9 (C-4'), 150.0 (C-9), 150.8 (C-2'), 152.6 (C-7), 162.5 (C-4). EIMS *m/z* (%): 484 (M^+, 100), 453 (27), 289 (15), 262 (12), 261 (28), 250 (14), 249 (33), 248 (81), 246 (12), 218 (17). HREIMS *m/z* calcd for $C_{27}H_{36}N_2O_6$, 484.2573. Found: 484.2574.

X-Ray Structure Determination of Compound **14**.

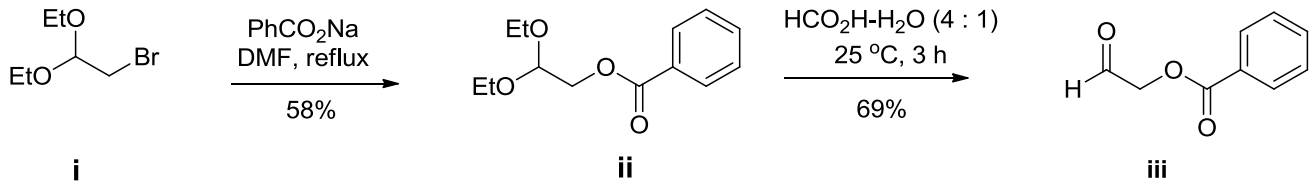
Crystals of **14** ($C_{28}H_{38}N_3O_6$) belong to triclinic space group P-1 (#2) with a = 9.0438(2) Å, b = 11.1268(2) Å, c = 13.8750(2) Å, V = 1353.13(5) $Å^3$, Z = 2, and D_{calcd} = 1.256 g/cm^3. X-Ray intensities were measured with a Rigaku R-AXIS RAPID diffractometer in the graphite-monochromatic CuKα radiation mode (λ = 1.54187 Å). The final cycle of the full-matrix least-squares refinement was based on 4883 unique reflections ($2\theta < 136.5^o$) and 348 variable parameters, and converged with unweighted and weighted agreement factors of R = 0.0441, R_w = 0.1102, and R_1 = 0.0394 for $I > 2.0\sigma$ (*I*) data. The drawing of the molecule was made by ORTEP as shown here. CCDC-No. (999806) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of C2 unit.

According to the published protocol,[21] we prepared 2,2-diethoxyethyl benzoate (**ii**) and

benzoyloxyacetaldehyde (**iii**). Both compounds were much easier to handle after purification by vacuum distillation. Compound **ii** (68% yield, pale yellow oil, bp 125-130 °C (2 mmHg)) δ_H (300 MHz) 1.17 (6H, t, *J* = 7.0 Hz, 2 x CH_2CH_3), 3.55 (2H, dq, *J* = 9.4, 7.1 Hz, CH_2CH_3), 3.69 (2H, dq, *J* = 9.4, 7.0 Hz, CH_2CH_3), 4.27 (2H, d, *J* = 5.4 Hz, 2-H), 4.76 (1H, t, *J* = 5.4 Hz, CH), 7.37 (2H, t, *J* = 7.3 Hz, 3'-H), 7.50 (1 H, t, *J* = 7.3 Hz, 4'-H), 7.99 (2H, d, *J* = 7.1 Hz, 2'-H).

Compound **iii** (69% yield, pale yellow oil, bp 100 °C (3-4 mmHg)) δ_H (300 MHz) 4.90 (2H, s, 2-H), 7.48 (2H, t, *J* = 7.6 Hz, 3'-H), 7.62 (1H, dt, *J* = 7.6, 7.3 Hz, 4'-H), 8.11 (2H, d, *J* = 7.3 Hz, 2'-H), 9.73 (1H, s, CHO).



i **ii** **iii**

((6*S**,7*R**,9*S**,14a*S**,15*R**)-7-Cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinolin-9-yl)methylbenzoate (**17b**)

Method A: TMSOTf (18.1 mL, 0.10 mmol) was added to a stirred solution of **14** (25.5 mg, 0.05 mmol) and 2,2-diethoxyethyl benzoate[21] (95.2 mg, 0.40 mmol) in $(CH_2Cl)_2$ (0.2 mL), and the mixture was stirred at 25 °C for 100 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue (65.9 mg), which was subjected to column chromatography on SiO_2 (12 g) with hexane-EtOAc (3:1) to furnish **17b** (10.7 mg, 46.0%) as a pale yellow amorphous powder. Further elution with the same solvent system afforded **14** (6.9 mg, 27% recovery).

Method B: TFA (3.2 mL) was added to a stirred solution of **14** (67.0 mg, 0.131 mmol) and benzoyloxyacetaldehyde[21] (219.0 mg, 1.31 mmol) in acetic acid (0.8 mL), and the mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (120 mL) and extracted with $CHCl_3$ (3 x 120 mL). The combined extracts were washed with brine (120 mL), dried, and concentrated in vacuo to give a residue (277.0 mg), which was subjected to column chromatography on SiO_2 (11 g) with hexane-EtOAc (3:1) to afford **17b** (83.5 mg, 96.9%) as a pale yellow amorphous powder.

ν_{max} ($CHCl_3$) 2938, 2228, 1719, 1464, 1452, 1410, 1273, 1252, 1113, 1096, 1072, 1026 cm^{-1}. δ_H (400 MHz) 1.98 (3H, s, 3-CH_3), 2.00 (3H, s, 12-CH_3), 2.23 (3H, s, *N*CH_3), 2.40 (1H, d, *J* = 17.8 Hz, 5-Hβ), 2.88 (1H, dd, *J* = 17.2, 9.0 Hz, 14-Hβ), 2.93 (1H, dd, *J* = 17.8, 7.6 Hz, 5-Hα), 3.27 (1H, dd, *J* = 7.6, 2.4

Hz, 6-H), 3.30 (1H, dd, *J* = 17.2, 3.4 Hz, 14-Hα), 3.50 (3H, s, 13-OCH_3), 3.55 (3H, s, 4-OCH_3), 3.61 (3H, s, 2-OCH_3), 3.64 (3H, s, 11-OCH_3), 3.69 (3H, s, 10-OCH_3), 3.75 (3H, s, 1-OCH_3), 3.99 (1H, d, *J* = 2.4 Hz, 15-H), 4.19-4.22 (1H, overlapped, 14a-H), 4.21 (1H, d, *J* = 2.4 Hz, 7-H), 4.39 (1H, t, *J* = 4.7 Hz, 9-H), 4.48 (1H, dd, *J* = 11.6, 4.7 Hz, 17-H), 4.53 (1H, dd, *J* = 11.6, 4.7 Hz, 17-H), 7.42 (2H, t, *J* = 7.5 Hz, 3'-H), 7.53 (1H, t, *J* = 7.5 Hz, 4'-H), 8.04 (2H, d, *J* = 7.5 Hz, 2'-H). δ_C (100 MHz) 9.1 (3-CH_3), 9.2 (12-CH_3), 21.6 (C-5), 22.8 (C-14), 42.0 (*N*CH_3), 53.4 (C-14a), 55.5 (C-6), 56.6 (C-9), 57.5 (C-15), 59.5 (13-OCH_3), 59.5 (4-OCH_3), 59.7 (2-OCH_3), 59.8 (11-OCH_3), 60.2 (10-OCH_3), 60.3 (1-OCH_3), 60.7 (C-7), 66.3 (C-17), 119.8 (CN), 122.2 (C-13a), 122.5 (C-4a), 123.1 (C-12), 123.4 (C-15a), 126.0 (C-9a), 128.3 (C-3'), 129.7 (C-2'), 130.2 (C-1'), 132.8 (C-4'), 144.1 (C-10), 147.7 (C-1), 148.5 (C-2), 148.9 (C-11), 151.2 (C-4), 151.5 (C-13), 166.3 (PhCO). EIMS *m/z* (%): 657 (M^+, 7), 523 (8), 522 (22), 495 (22), 289 (10), 288 (59), 249 (37), 248 (100), 234 (10), 218 (14), 105 (11). HREIMS *m/z* calcd for $C_{37}H_{43}N_3O_8$, 657.3050. Found: 657.3043.

(4b*S**,6a*S**,7*S**,13*R**,13a*S**)-1,3,4,9,11,12-Hexamethoxy-2,10,15-trimethyl-4b,5,6a,7,8,13,13a,14-octahydro-6-oxa-14a[1],15-diaza-7,13-methanobenzo[g]benzo[5,6]cycloocta[1,2,3-*cd*]indene (**18**)

Hydrazine monohydrate (2.0 mL, 40 mmol) was added to a solution of **17b** (262.8 mg, 0.40 mmol) in EtOH (10 mL) at 25 °C, and the reaction mixture was stirred at 60 °C for 3 h. As the starting material still remained at this stage, additional hydrazine monohydrate (0.5 mL, 10 mmol) was introduced to the reaction mixture and the whole was heated at 60 °C for 3 h. The reaction mixture was diluted with 1 M HCl (50 mL) and extracted with $CHCl_3$ (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated in vacuo to give a residue (246.9 mg), which was subjected to column chromatography on SiO_2 (10 g) with $CHCl_3$-MeOH (98:2) to furnish **18** (198.1 mg, 94.2%) as a colorless amorphous powder. An analytical sample was obtained by recrystallization from hexane-EtOAc as colorless prisms, mp 105-107 °C.

ν_{max} ($CHCl_3$) 3019, 2995, 2938, 2833, 1464, 1410, 1207, 1113, 1072, 1009 cm^{-1}. δ_H (400 MHz) 2.15 (3H, s, 2-CH_3), 2.18 (1H, dd, *J* = 16.3, 12.1 Hz, 14-Hβ), 2.19 (3H, s, 10-CH_3), 2.46 (3H, s, *N*CH_3), 2.58 (1H, d, *J* = 18.2 Hz, 8-Hβ), 3.08 (1H, dd, *J* = 16.3, 2.6 Hz, 14-Hα), 3.11 (1H, dd, *J* = 18.2, 8.4 Hz, 8-Hα), 3.22 (1H, ddd, *J* = 12.1, 2.6, 2.6 Hz, 13a-H), 3.59 (1H, dd, *J* = 8.4, 1.5 Hz, 7-H), 3.62 (3H, s, 1-OCH_3), 3.71 (1H, dd, *J* = 8.7, 7.2 Hz, 5-H), 3.713 (3H, s, 9-OCH_3), 3.75 (3H, s, 3-OCH_3), 3.77 (3H, s, 4-OCH_3), 3.78 (3H, s, 11-OCH_3), 3.86 (3H, s, 12-OCH_3), 4.03 (1H, d, *J* = 2.6 Hz, 13-H), 4.23 (1H, dd, *J* = 8.7, 7.2 Hz, 5-H), 4.37 (1H, t, *J* = 8.7 Hz, 4a-H), 4.56 (1H, d, *J* = 1.5 Hz, 6a-H). δ_C (100 MHz) 9.2 (3-CH_3), 9.4 (10-CH_3), 21.0 (C-8), 27.2 (C-14), 41.1 (*N*CH_3), 52.7 (C-13a), 53.3 (C-7), 55.9 (C-13), 59.5 (9-OCH_3), 59.6 (1-OCH_3), 59.8, 59.9, and 60.0 (3-OCH_3, 4-OCH_3 and 11-OCH_3), 59.9 (C-4a), 60.2 (12-OCH_3), 67.8

(C-5), 95.4 (C-6a), 123.1 (C-8a), 123.1 (C-12a), 123.6 (C-2 or C-10), 123.9 (C-10 or C-2), 124.4 (C-14a), 125.8 (C-4a), 146.3 (C-4), 147.5 (C-12), 149.3 (C-3), 149.5 (C-11), 151.8 (C-9), 152.1 (C-1). EIMS *m/z* (%): 526 (M^+, 28), 496 (15), 278 (47), 262 (21), 249 (21), 248 (100). HREIMS *m/z* calcd for $C_{29}H_{38}N_2O_7$, 526.2679. Found: 526.2674. Anal. Calcd for $C_{29}H_{38}N_2O_7$: C 66.14, H 7.27, N 5.32. Found: C 66.15, H 7.19, N 5.17.

X-Ray Structure Determination of Compound **18**.

Crystals of **18** ($C_{29}H_{38}N_2O_7$) belong to triclinic space group P-1 (#2) with a = 11.0963(2) Å, b = 11.2124(2) Å, c = 11.4822(2) Å, V = 1313.71(5) $Å^3$, Z = 2, and D_{calcd} = 1.331 g/cm^3. X-Ray intensities were measured with a Rigaku R-AXIS RAPID diffractometer in the graphite-monochromatic CuKα radiation mode (λ = 1.54187 Å). The final cycle of the full-matrix least-squares refinement was based on 4739 unique reflections (2θ < 136.5°) and 352 variable parameters, and converged with unweighted and weighted agreement factors of R = 0.0455, R_w = 0.1100, and R_1 = 0.0399 for I > 2.0σ (*I*) data. The drawing of the molecule was made by ORTEP as shown in Figure 2. CCDC-No.999807 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(6*S**,7*R**,9*S**,14a*S**,15*R**)-9-(Hydroxymethyl)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile (**19**)

A solution of DIBAL-H in toluene (1.0 M, 400 μL, 400 μmol) was added to a stirred solution of **17b** (32.9 mg, 0.05 mmol) in THF (2 mL) at - 78 °C over 15 min, and the reaction mixture was stirred at the same temperature for 11 h. Anhydrous Na_2SO_4 (4.2 g) was added and the reaction was quenched by the addition of water (2.0 mL). The reaction mixture was filtered through Celite pad and the residue was washed with $CHCl_3$ (150 mL). The combined filtrates were diluted with brine (20 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (33.4 mg), which was subjected to column chromatography on SiO_2 (4 g) with hexane-AcOEt (1:2) to furnish **19** (16.9 mg, 61.0%). Further elution with AcOEt gave **18** (5.1 mg, 19.0%).

ν_{max} (KBr) 3502, 2935, 2892, 2831, 2223, 1463, 1409, 1340, 1215, 1112, 1072, 1004, 962 cm^{-1}. δ_H (400 MHz) 2.00 (6H, s, 12-CH_3 and 3-CH_3), 2.24 (3H, s, *N*CH_3), 2.58 (1H, d, *J* = 18.5 Hz, 5-Hβ), 2.87 (1H, dd, *J* = 17.5, 8.6 Hz, 14-Hβ), 2.94 (1H, dd, *J* = 18.5, 8.1 Hz, 5-Hα), 3.26 (1H, dd, *J* = 17.5, 3.3 Hz, 14-Hα), 3.26 (1H, br d, *J* = 6.6 Hz, 6-H), 3.56 (3H, s, 13-OCH_3), 3.59 (3H, s, 4-OCH_3), 3.61 (3H, s, 11-OCH_3), 3.65 (3H, s, 10-OCH_3), 3.66 (3H, s, 2-OCH_3), 3.73 (3H, s, 1-OCH_3), 3.79 (2H, d, *J* = 4.3 Hz, 17-H), 3.96

(1H, br d, J = 2.3 Hz, 15-H), 4.09 (1H, t, J = 4.3 Hz, 9-H), 4.16 (1H, dt, J = 8.6, 3.3 Hz, 14a-H), 4.24 (1H, d, J = 2.5 Hz, 7-H). δ_C (100 MHz) 9.1 (12-CH_3), 9.2 (3-CH_3), 21.6 (C-5), 23.3 (C-14), 42.0 (NCH_3), 53.6 (C-14a), 55.2 (C-6), 57.3 (C-15), 59.3 (C-9), 59.5 (4-OCH_3 and 13-OCH_3), 59.8, 60.2, and 60.2 (2-OCH_3, 10-OCH_3 and 11-OCH_3), 60.2 (1-OCH_3), 60.4 (C-7), 64.8 (C-17), 120.6 (CN), 122.3 (C-4a), 122.3 (C-15a), 123.1 (C-3 or C-12), 123.2 (C-3 or C-12), 123.7 (C-13a), 126.7 (C-9a), 144.0 (C-10), 147.8 (C-1), 148.6 (C-11), 148.9 (C-2), 151.2 (C-4), 151.5 (C-13). FABMS *m/z* (%): 554 $[M + H]^+$. HRFABMS *m/z* calcd for $C_{30}H_{40}N_3O_7$, 554,2866. Found: 554.2858.

Transformation of **19** into **18**.

A mixture of **19** (8.5 mg) with silica gel (10.0 mg) in $CHCl_3$ (2.9 mL) was stirred at 25 °C for several hours. The reaction mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried, and concentrated in vacuo. The residue was subjected to silica gel column chromatography with $CHCl_3$-MeOH (50:1) to give **18** (7.6 mg, 92% yield).

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23. Treatment of **18** with boron trifluoride and TMSCN in $(CH_2Cl)_2$ at -30 ^oC for 20 min generated **19**, but **18** was recovered during purification.
24. Four synthetic compounds (**14**, **16**, **17b**, **18**) were tested for in vitro antitumor activity against

HCT116 human colon carcinoma, QG56 human lung carcinoma, and DU145 human prostate carcinoma cell lines. None of the compounds showed antitumor activity. Benzoyl ester **17b** showed very low cytotoxic activity against HCT116 (IC_{50} = 0.86 μM).