Tetrahedron 68 (2012) 4166–4181

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chemistry of renieramycins. Part 12: An improved total synthesis of (±)-renieramycin G

Masashi Yokoya, Kimiko Shinada-Fujino, Saiko Yoshida, Masahiro Mimura, Hiroki Takada, Naoki Saito *

Graduate School of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

ARTICLE INFO

Article history:
Received 6 March 2012
Received in revised form 24 March 2012
Accepted 26 March 2012
Available online 30 March 2012

Keywords:
Total synthesis
Marine natural product
Isoquinoline
Renieramycin G
Cytotoxicity

ABSTRACT

An improved total synthesis of (±)-renieramycin G (**1g**) from readily available 2-hydroxy-3-methyl-4,5-dimethoxybenzaldehyde (**7**) in 21 steps (6.3% overall yield) is described. The synthesis features the concise construction of a pentacyclic framework using the stereoselective Pictet–Spengler type cyclization reaction of lactam (**25**) with ethyl diethoxyacetate, followed by the base-catalyzed epimerization of the C-1 stereo center of aldehyde (**30a**). The results of cytotoxicity studies are also presented.

1. Introduction

Natural products belonging to the tetrahydroisoquinolinequinone family and their reduced forms, such as renieramycin marine natural products (**1**), together with saframycin (**2**) and safracin (**3**) antibiotics, have attracted considerable interest over the past 30 years due to their unique structures and meager availability in nature, and for their potent antitumor activity (Fig. 1).[1,2] The most bioactive member of this family, ecteinascidin 743 (**4a**: Yondelis™, trabectedin), has a unique mechanism of action, that is, based on its binding to the minor groove of DNA to interfere with cell division, activated transcription, and DNA repair.[3,4] Following the first discovery of renieramycins by Frincke and Faulkner from the Mexican blue sponge *Reniera* sp. in 1982,[5] more than 10 marine natural renieramycins,[6–9] along with jorumycin[10] and jorunnamycins,[11] were isolated from several kinds of marine organisms. Renieramycins are expected to be one of the candidates for new anticancer drugs. However, the structure–activity relationships (SARs) of renieramycins are little explored[12,13] because these marine natural products are available in very minute quantities.

As part of our search for new metabolites via the isolation and characterization of biologically active compounds from Thai marine animals, we successfully isolated renieramycin M (**1m**) in gram scale from the Thai blue sponge *Xestospongia* sp. by pretreatment with potassium cyanide.[14,15] We have prepared a variety of renieramycin derivatives from **1m** for the investigation of SARs.[16,17] Furthermore, we were able to find three new minor renieramycins T, U,[18] and V.[19] We focused on renieramycins C, D, and G along with cribrostatin 4 (=renieramycin H: **1h**) having a lactam carbonyl at C-21 position (see **1e**, **1m**, **2a**, **2s**, **3a**, **3c**, **4a**, and **4c**), because these compounds retained their cytotoxicity despite the lack of such essential functional groups as hemiaminal or aminonitrile at that position. To date, four total syntheses of **1g**[20–23] and four total syntheses of **1h**[24–27] have been reported. Recently, we completed a 25-step stereocontrolled total synthesis of (±)-**1g** in 1.0% overall yield.[28] In this paper, we present a full account of our total synthesis of (±)-**1g** along with our improved 21-step version. The results of cytotoxicity studies are also presented.

Our retrosynthetic analysis of **1g** was based on the pathway that we had established for saframycin B,[29] *N*-acetylsaframycin Mx 2,[30] and renieramycin derivatives,[31] which involved the key transformations outlined in Scheme 1: (1) regioselective synthesis of the highly substituted piperazine-2,5-dione (**III**) having a masked *para* quinone equivalent at both benzene rings; (2) the Pictet–Spengler type cyclization reaction of the non-basic nitrogen of the secondary amide (**II**) with ethyl diethoxyacetate to construct the pentacyclic framework, with reference to the encouraging results of our model study;[32] (3) and epimerization of the pentacyclic compound (**I**) at C-1 position[33] and subsequent transformation to generate **1g**.

Our strategy was expected to yield a 1-*epi*-pentacyclic compound. A serendipitous discovery afforded an unnatural analog as

* Corresponding author. Tel./fax: +81 42 495 8794; e-mail address: naoki@my-pharm.ac.jp (N. Saito).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.03.105

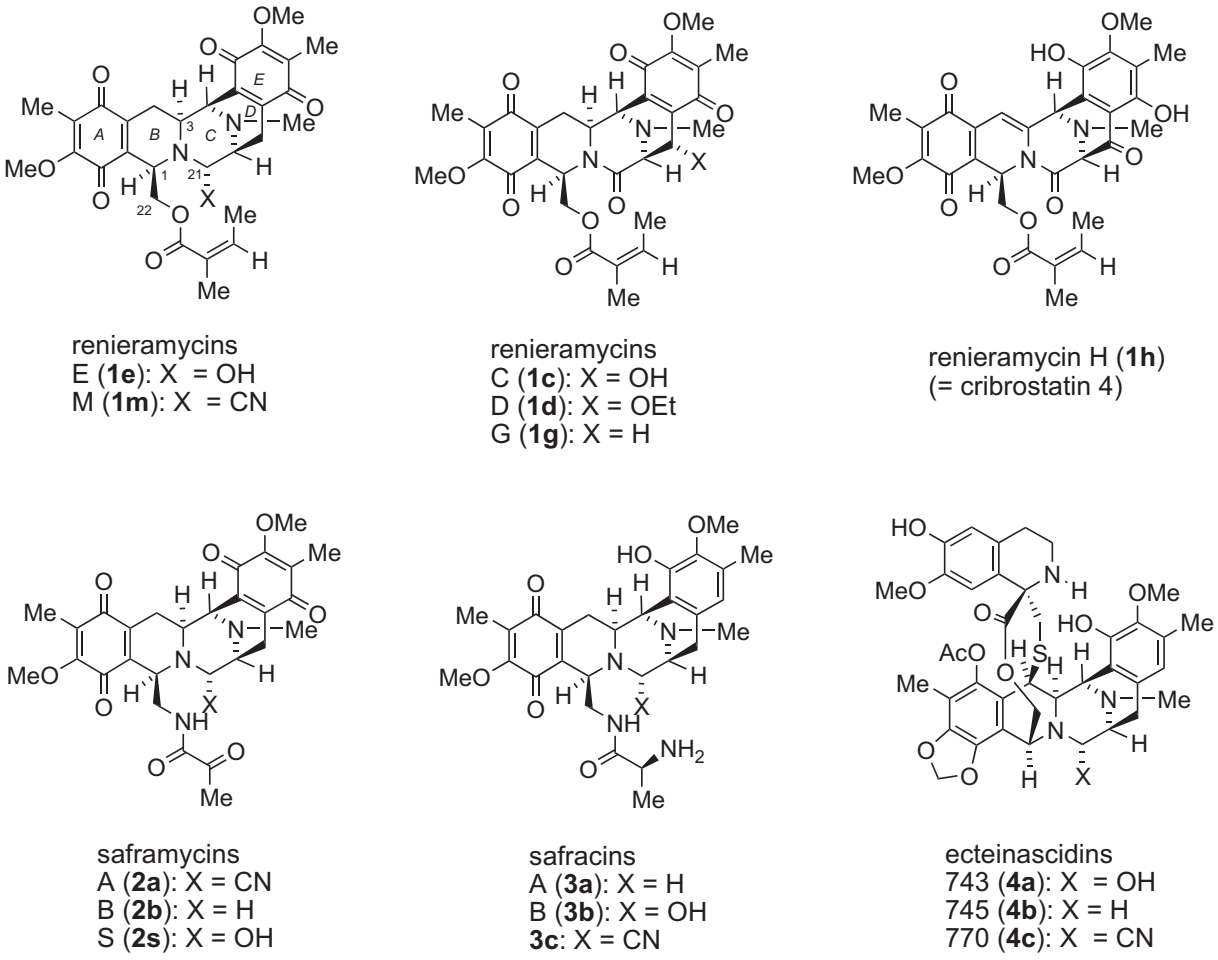
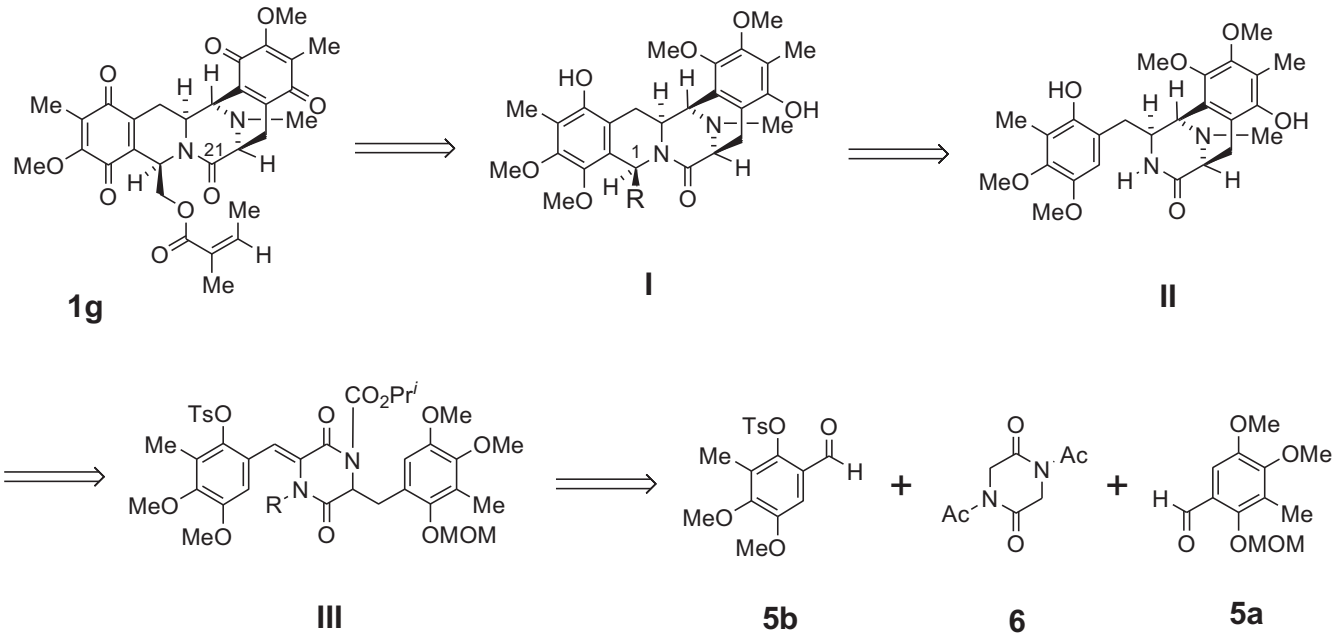


Fig. 1. Structures of bis-1,2,3,4-tetrahydroisoquinolinequinones and their related natural products.

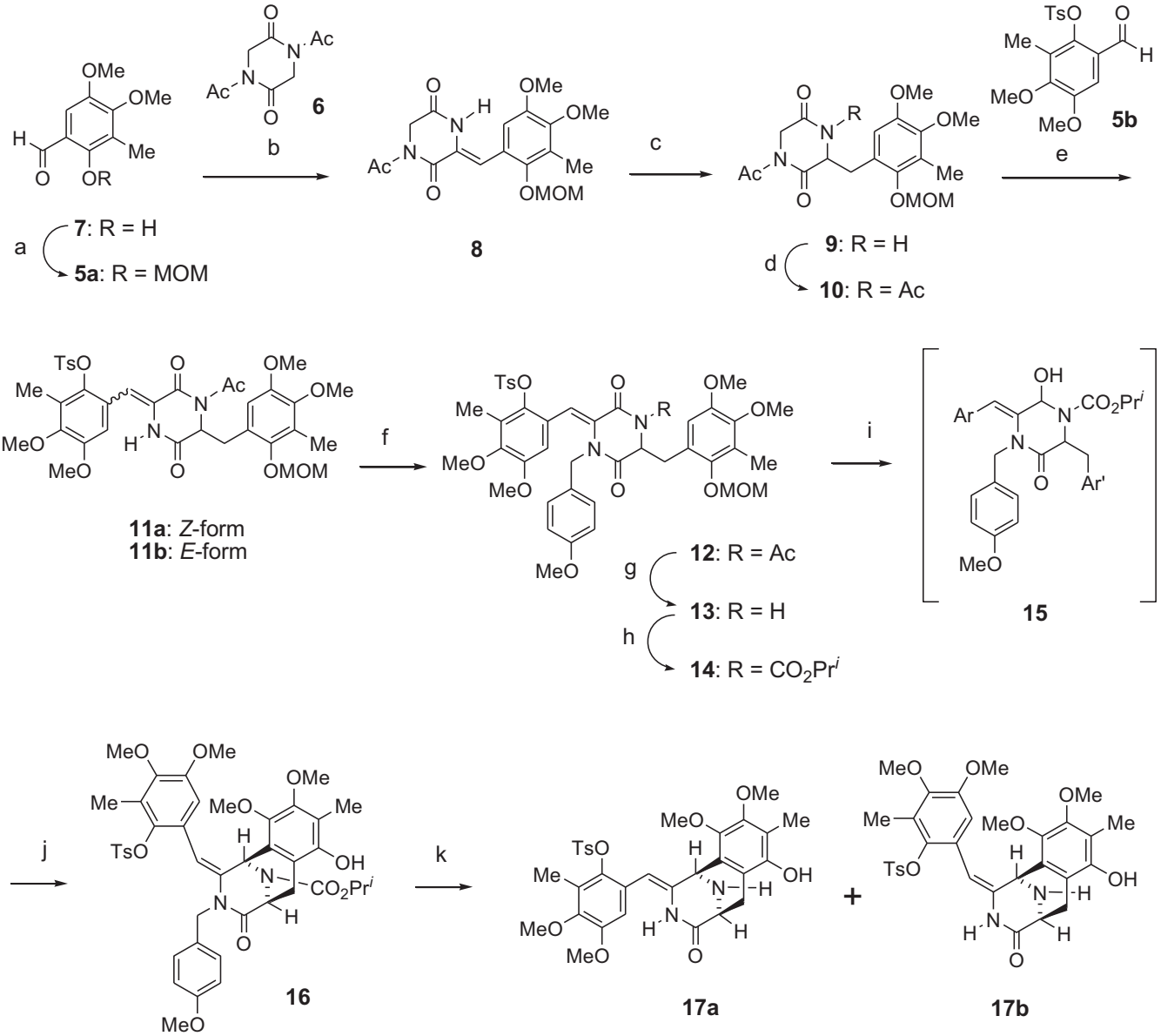


Scheme 1. Retrosynthesis of renieramycin G base on our total synthesis of **2b**.

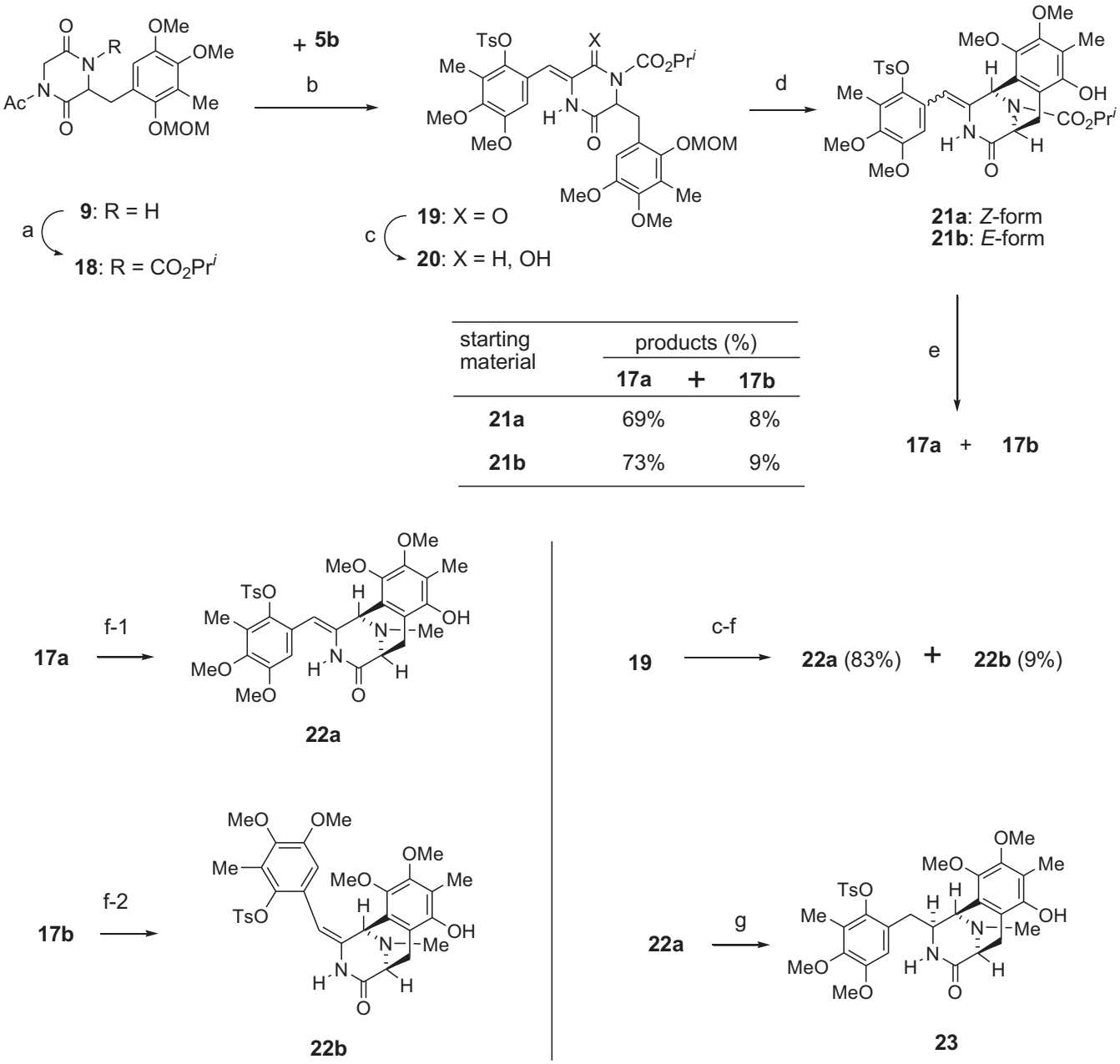
part of a comprehensive study of this family of biologically active compounds.

Phenol **7**[34] was protected with a methoxymethyl (MOM) group to afford **5a** (Scheme 2), the condensation of which with diacetate **6**[35,36] in the presence of a base gave (*Z*)-arylidenepiperazinedione **8** in 73% yield. Catalytic hydrogenation of **8** over 5% Rh–C in 2-propanol at 25 °C for 14 h gave **9**, which was subsequently treated with acetic anhydride to provide diacetate **10** in 88% overall yield. Condensation of **10** with **5b**[37] and a base gave (*Z*)-isomer **11a** and (*E*)-isomer **11b** in 89% and 3% yields, respectively. The transformation of **11a** into carbamate **14** in three steps was achieved with the method disclosed in our synthetic approach to saframycin A[38] (**2a**) in 87% overall yield. Regioselective hydride reduction at C-2 carbonyl to generate unstable alcohol **15** and sequential dehydration/cyclization of **15** afforded (*E*)-1,5-imino-3-benzazocine **16** in 89% yield. Deprotection of **16** with trifluoroacetic acid (TFA) and H_2SO_4 (20/1) at 25 °C for 20 h gave (*Z*)-lactam **17a** and (*E*)-lactam **17b** in 64% and 1.5% yields, respectively.

With key intermediate **17a** in hand, we looked into ways to establish a practical conversion of **9** into **17a** with a reduction of the number of steps from nine to six (Scheme 3). The piperazinedione ring of **9** was activated by the introduction of a 2-propyloxycarbonyl group to give imide **18** in 96% yield. Condensation of **18** with **5b** and a base gave **19** in 70% yield. Chemoselective reduction of **19** in the usual manner afforded a diastereomeric mixture of alcohol **20**, which on treatment with formic acid at 60 °C for 2.5 h afforded **21a** (73%) along with **21b** (17%). Deprotection of **21a** with TFA and H_2SO_4 at 25 °C for 6 h gave (*Z*)-lactam **17a** and (*E*)-lactam **17b** in 69% and 8% yields, respectively. Deprotection of **21b** in the same manner afforded **17a** and **17b** in 73% and 9% yields, respectively. Reductive N-methylation of **17a** and **17b** gave **22a** and **22b** in 93% and 91% yields, respectively. Detailed 2-D NMR studies were performed to confirm



Scheme 2. (a) NaH, DMF, then MOMCl, 25 °C, 2 h, 100%; (b) ^{t}BuOK, ^{t}BuOH, CH_2Cl_2, 25 °C, 1 h, 73%; (c) H_2, 5% Rh–C, 25 °C, 2-propanol, 14 h; (d) Ac_2O, pyridine, DMAP, 25 °C, 2.5 h, 88% (two steps); (e) ^{t}BuOK, ^{t}BuOH, THF, 5.5 h, **11a** (89%) and **11b** (3%) (two steps); (f) NaH, DMF, 25 °C, 0.5 h, then 4-$MeOC_6H_4CH_2Cl$, 25 °C, 14 h; (g) 5% $NaHCO_3$–H_2O, EtOH, reflux, 2.5 h, 87% (two steps); (h) $ClCO_2^iPr$, TEA, DMAP, CH_2Cl_2, 25 °C, 23 h, 100%; (i) Li(^{t}BuO)$_3$AlH, THF, 0 °C, 4.5 h; (j) HCO_2H, 60 °C,1 h, 89% (two steps); (k) H_2SO_4–TFA (1/20), 25 °C, 20 h, **17a** (64%) and **17b** (1.5%).



starting material	products (%)		
	17a	+	**17b**
21a	69%		8%
21b	73%		9%

Scheme 3. (a) $ClCO_2^iPr$, TEA, DMAP, CH_2Cl_2, 25 °C, 2 h, 96%; (b) ^{t}BuOK, ^{t}BuOH, CH_2Cl_2, 25 °C, 40 min, 70%; (c) Li(^{t}BuO)$_3$AlH, THF, 0 °C, 4.5 h; (d) HCO_2H, 60 °C, 2.5 h, **21a** (73%) and **21b** (17%) (two steps); (e) H_2SO_4, TFA, 25 °C, 6 h (for yields, see table); (f-1) 37% HCHO–H_2O, HCO_2H, 70 °C, 1 h, 93%; (f-2) 37% HCHO–H_2O, HCO_2H, 70 °C, 2 h, 91%; (g) H_2 (2.8 MPa), 20% $Pd(OH)_2$–C, EtOH, 80 °C, 41 h, 93%.

the structures of **22a** and **22b**. The NMR spectrum of **22a** displayed H-14 and H-15 proton signals at δ 5.93 and δ 4.60, respectively, whereas the NMR spectrum of **22b** had H-14 and H-15 proton signals appearing at δ 5.48 and δ 4.97, respectively. An observable NOE revealed the relative stereochemistries of the *exo*-double bonds of both **22a** and **22b** (Fig. 2).

Accordingly, the sequence of transformations of **19** into **22** without any purification of the intermediates was found to be the best choice in terms of overall yield (**22a** in 83% yield and **22b** in 9% yield). We were also able to devise a six-step transformation of **9** into **22a** in 56% overall yield. Reduction of the double bond of **22a** through the action of hydrogen (28 atm) on 20% $Pd(OH)_2$–C in ethanol at 80 °C for 41 h occurred from the less hindered α-face to afford **22a** in 93% yield.

Treatment of **23** with a large excess of paraformaldehyde in acetic acid–TFA (4/1) at 80 °C for 15 h provided **24** in 66% yield, according to the procedure of Ong et al.[39–41] The stereochemistry of **24** was readily identified on the basis of the chemical shifts of H-4β (δ 2.20) and H-3 (δ 3.89), along with the coupling between H-4β

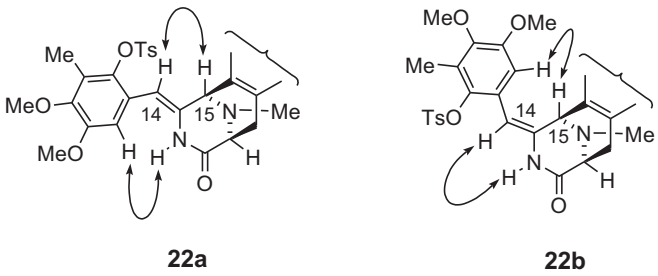
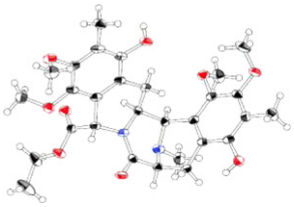


Fig. 2. Key NOE correlations of **22a** and **22b**.

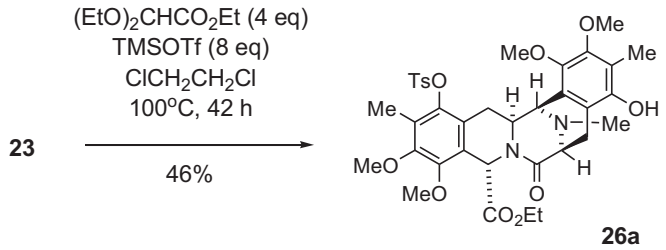
and H-3 (J=12.2 Hz), as noted previously for related systems (Scheme 4).[42]

Then, we examined several routes for the construction of a pentacyclic framework having a hydroxymethyl substituent at C-1 using the modified Pictet–Spengler reaction via the *O*-trimethylsilyllactim intermediate with ethyl diethoxyacetate. Attempts made under a variety of conditions that were based on the results of our recent model conversion[32] were fruitless (Scheme 5).[43] We



ORTEP drawing of the ester **26**.

Scheme 4. (a) $(HCHO)_n$, AcOH–TFA (4/1), 80 °C, 15 h, 66%; (b) NH_2NH_2–H_2O, MeOH, reflux, 73 h, 80%; (c) $(EtO)_2CHCO_2Et$ (4 equiv), TMSOTf (1.04 equiv), $(CH_2Cl)_2$, 120 °C, 13 h, 77%; (d) BnBr, K_2CO_3, acetone, reflux, 12 h, 88%; (e) 0.1 M LiOH–H_2O, THF–MeOH (3/1), 25 °C, 8 days; (f) $ClCO_2Et$, TEA, THF, −7 °C, 3 h; and then $NaBH_4$, H_2O, 0 °C, 2 h, 81% (three steps); (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then TEA at −40 °C, 92%; (h) DBU (1 equiv), THF, 24 h, **30a** (85%) and **30b** (4%) (three times); (i) $NaBH_3CN$, THF, AcOH, 25 °C, 3.5 h, 65%; (j) H_2, 20% $Pd(OH)_2$–C, MeOH, 25 °C, 2 h, 100%; (k) CAN, MeCN–H_2O, 0 °C, 15 min; (l) (*Z*)-MeCH=C(Me)COCl, CH_2Cl_2, 25 °C, 25 h, 36% (two steps); (m) (*Z*)-MeCH=C(Me)COCl, CH_2Cl_2, 25 °C, 2 h, 93%; (n) CAN, MeCN–H_2O, 0 °C, 15 min, 80%.



Scheme 5. Preparation of **26a** from **23**.

then tried to increase the reactivity of the A-ring, such as phenol **25**, which was easily prepared from **23** in 80% yield. The reaction of **23** with ethyl diethoxyacetate in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloroethane at 120 °C for 13 h gave cyclized ester **26** in 77% yield. X-ray crystallographic analysis of **26** revealed that the stereochemistry at C-1 was epimeric to that of natural renieramycins.

The remaining problem was the isomerization at C-1 of **26**. As **26** was not sufficiently soluble in any solvent, we thought it would be better to convert **26** into **27** before starting our study of the isomerization at C-1. Thus, benzylation of **26** with benzyl bromide and a base gave **27** in 88% yield. Another problem was that obtained ester **27** should be oriented in the α-axial direction because the β-equatorial space was hindered by both the methoxyl group at the *peri* position and the lactam carbonyl at C-21. Indeed, voluminous effort to epimerize **27** under basic conditions was unsuccessful. Nevertheless, this problem was solved by selecting the smallest carbonyl functional group at C-1. Treatment of ester **27** with aqueous LiOH in THF–MeOH (3/1) at 25 °C for 8 days gave corresponding carboxylic acid **28**, which was subsequently subjected to hydride reduction via the mixed anhydride to afford alcohol **29a** in 81% overall yield. The Swern oxidation of **29a** afforded aldehyde **30a** in 92% yield. Treatment of **30a** with 1.0 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[44–46] in THF at 25 °C for 24 h afforded **30b** in 62% yield, and 33% of starting material **30a** was recovered.[47] Isomerization of recovered **30a** by repeating twice gave finally **30b** and **30a** in 85% and 4%, respectively. The ^{1}H NMR spectrum of **30b** displayed an H-1 signal that appeared as a singlet at δ 6.06 and an H-3 signal at δ 3.92, whereas the ^{1}H NMR spectrum of **30a** showed an H-1 signal at δ 6.27 and an H-3 signal at δ 4.18. The remarkable difference in the chemical shifts of the methine protons must be due to the steric interactions between the side chains at C-1 and C-3.[48] Reduction of **30b** with sodium cyanoborohydride ($NaBH_3CN$) in THF in the presence of a catalytic amount of AcOH gave **29b** in 65% yield.[49,50]

Debenzylation of **29b** gave **31** in a quantitative yield. Oxidative demethylation of **31** with ceric ammonium nitrate (CAN) in aqueous acetonitrile afforded **32**, which was a Magnus **1g** intermediate.[20] The final step of our total synthesis involved the treatment of **32** with angeloyl chloride in CH_2Cl_2 to give (±)-renieramycin G (**1g**) in 36% overall yield according to the procedure of Magnus.[20] The yield of the two-step process from **31** to **1g** via **32** was disappointingly low. This low yield plus the exceedingly troublesome procedure prompted us to examine another approach that involved the conversion **31** into **1g** via **33**. Treatment of **31** with angeloyl chloride in CH_2Cl_2 at 25 °C for 2 h afforded **33** in 93% yield. Oxidative demethylation of **33** with CAN in aqueous acetonitrile at 0 °C for 15 min gave **1g** in 80% yield. Synthetic **1g** was identical with the natural one on comparison of their spectroscopic data along with data of the racemic compound by Magnus.

Despite having a lactam carbonyl group at C-21, Davidson reported that natural (−)-renieramycin G (**1g**) showed moderate cytotoxicity to two human cancer cell lines, KB and LoVo, with MIC values of 0.5 and 1.0 μg/mL, respectively.[7] Williams and coworkers also reported that synthetic (−)-**1g** and the corresponding epimer, 3-*epi*-renieramycin G had minimal inhibitory effects on both human colon (HCT116) and human lung (A549) cancer cell lines.[12] Thus, the compounds synthesized above, including natural (−)-renieramycin M (**1m**), were tested in vitro for cytotoxicity using three representative human solid tumor cell lines (HCT116 human colon carcinoma, QG56 human lung carcinoma, and DU145 prostate carcinoma) following the standard 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method (Table 1). Synthetic (±)-**1g** displayed very weak micromolar inhibitory effects and all of the pentacyclic analogs did not show any cytotoxicity.

Table 1
Cytotoxicities of racemic renieramycin G (**1g**) and related compounds to various human cancer cell lines (IC_{50} μM)

Compound	HCT116	QG56	DU145
26	>2	>2	>2
27	>2	>2	>2
29a	>2	>2	>2
29b	>2	>2	>2
30a	>2	>2	>2
30b	>2	>2	>2
31	>2	>2	>2
32	>2	1.7	>2
33	>2	>2	>2
(±)-**1g** (renieramycin G)	1.1	1.3	1.3
(−)-**1m** (renieramycin M)	5.2×10^{-3}	17.0×10^{-3}	1.7×10^{-3}

In summary, we have succeeded in reducing the number of steps of our total synthesis of (±)-renieramycin G from 25 steps in 1.0% overall yield to 21 steps in 6.3% overall yield. We have embarked on a more general SAR study to gain a more detailed understanding of this family of compounds. Ways to utilize this approach for the synthesis of other members of the renieramycin family, including renieramycins E (**1e**) and M (**1m**), together with the corresponding C-1 epimers, are under study in our laboratories.

2. Experimental section

2.1. General

IR spectra were obtained with a Shimadzu Prestige 21/IRA Affinity-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 500 FT NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C; a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C (parts per million, *J* in hertz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL 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.

*2.1.1. 2-Hydroxy-4,5-dimethoxy-3-methylbenzaldehyde (**7**).*[36,51]
2.1.1.1. 3,4-Dimethoxy-2-methylphenol.[52,53] Sodium hydride (60% oil dispersion, washed with dry hexane three times, 9.36 g, 390 mmol) was added to a stirred solution of 2,3-dimethoxyphenol (30.0 g, 195 mmol) in DMF (170 mL), and the resulting mixture was stirred at 0 °C for 30 min. Then, MOMCl (29.6 mL, 390 mmol) was added over 30 min and the reaction mixture was stirred at 0 °C for 2 h. Thereafter, the reaction mixture was diluted with water (750 mL) and extracted with ether (3×750 mL). The combined extracts were washed with water (300 mL), dried, and concentrated in vacuo to give (3,4-dimethoxy-2-methylphenoxy)methyl methyl

ether as a dark oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.49 (3H, s, CH_2OCH_3), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.12 (2H, s, OCH_2O), 6.59 (1H, dd, J=8.6, 2.8 Hz, 6-H), 6.63 (1H, d, J=2.8 Hz, 2-H), 6.76 (1H, d, J=8.6 Hz, 5-H).

A solution of *n*-BuLi (1.65 mmol hexane solution, 296 mL, 488 mmol) was added to a solution of the above residue in THF (280 mL) at −17 °C for 2 h, and the reaction mixture was stirred at the same temperature for 1 h. A solution of iodomethane (36.4 mL, 585 mmol) in THF (115 mL) was added over 1 h and the resulting mixture was stirred for 2 h at 0 °C. Thereafter, the reaction mixture was diluted with water (500 mL) and extracted with ether (3×500 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give a residue, which was also used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (3H, s, 2-CH_3), 3.49 (3H, s, CH_2OCH_3), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.12 (2H, s, OCH_2O), 6.67 (1H, d, J=9.0 Hz, 6-H), 6.77 (1H, d, J=9.0 Hz, 5-H).

Concentrated hydrochloric acid (0.9 mL) was added to a stirred solution of the above residue in ethanol (900 mL) and this mixture was heated under reflux for 1.5 h. The reaction mixture was concentrated in vacuo and the residue was diluted with 5% aqueous $NaHCO_3$ solution (600 mL) and then extracted with chloroform (3×600 mL). The combined extracts were washed with water (600 mL), dried, and concentrated in vacuo to produce a solid, the recrystallization of which from ether gave 3,4-dimethoxy-2-methylphenol (10.0 g, 85.0%) as pale yellow needles, mp 99.5–101.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (3H, s, 2-CH_3), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.51 (1H, d, J=8.8 Hz, 6-H), 6.64 (1H, d, J=8.8 Hz, 5-H). The OH signal could not be detected.

*2.1.1.2. 2-Hydroxy-4,5-dimethoxy-3-methylbenzaldehyde (**7**).* A solution of the above phenol (10.0 g, 59.5 mmol) and hexamethylenetetramine (25.0 g, 178 mmol) in acetic acid (500 mL) was heated at 125 °C for 1 h. The reaction mixture was diluted with water (500 mL) and extracted with chloroform (3×600 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (600 mL), dried, and concentrated in vacuo to give a solid, the recrystallization of which from ether gave **7** (9.35 g, 80.0%) as colorless needles, mp 76.0–76.5 °C. IR (KBr) 3015, 2924, 1854, 1649, 1624, 1485, 1328, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (3H, s, 3-CH_3), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.86 (1H, s, 6-H), 9.75 (1H, s, CHO), 11.29 (1H, s, OH); EIMS m/z (%) 196 (M^+, 100), 181 (51), 153 (13). HREIMS m/z 196.0739 (M^+, calcd for $C_{10}H_{12}O_4$, 196.0736). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.46; H, 6.17.

*2.1.2. 4,5-Dimethoxy-2-(methoxymethoxy)-3-methylbenzaldehyde (**5a**).* Sodium hydride (60% oil dispersion, washed with dry hexane three times, 7.20 g, 300 mmol) was added to a stirred solution of **7** (19.6 g, 100 mmol) in DMF (500 mL), and the reaction mixture was stirred at 0 °C for 30 min. Then, MOMCl (22.8 mL, 300 mmol) was added over 10 min and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (800 mL) and extracted with ether (3×800 mL). The combined extracts were washed with water (800 mL), dried, and concentrated in vacuo to give **5a** (24.0 g, 100%), the recrystallization of which from ether gave colorless needles, mp 43.5–44 °C. IR (KBr) 2940, 1686, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (3H, s, 3-CH_3), 3.59 (3H, s, CH_2OCH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.02 (2H, s, OCH_2O), 7.24 (1H, s, 6-H), 10.25 (1H, s, CHO); EIMS m/z (%) 240 (M^+, 82), 195 (54), 194 (100), 45 (63). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.02; H, 6.70.

*2.1.3. 4,5-Dimethoxy-3-methyl-2-[(4-methylphenylsulfonyl)oxy]-benzaldehyde (**5b**).* 4-Toluenesulfonyl chloride (28.6 g, 150 mmol) was added to a stirred solution of **7** (19.6 g, 100 mmol) and triethylamine (20.9 mL, 150 mmol) in CH_2Cl_2 (200 mL) at 0 °C over 10 min, and stirring was continued at 25 °C for 3 h. The reaction mixture was diluted with brine (500 mL) and extracted with CH_2Cl_2 (3×1000 mL). The combined extracts were washed with water (800 mL), dried, and concentrated in vacuo to give a solid, the recrystallization of which from benzene gave **7b** (33.3 g, 95%) as pale red prisms, mp 147–148 °C. IR (KBr) 2940, 1686, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (3H, s, 3-CH_3), 2.49 (3H, s, 4′-CH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.29 (1H, s, 6-H), 7.37 (2H, d, J=8.3 Hz, 2×ArH), 7.76 (2H, d, J=8.3 Hz, 2×ArH), 9.78 (1H, s, CHO); EIMS m/z (%) 350 (M^+, 27), 195 (100). HREIMS m/z 350.0825 (M^+, calcd for $C_{17}H_{18}O_6S$, 350.0824). Anal. Calcd for $C_{17}H_{18}O_6S$: C, 58.27; H, 5.18. Found: C, 58.44; H, 5.17.

*2.1.4. (3Z)-1-Acetyl-3-[[4,5-dimethoxy-2-(methoxymethoxy)-3-methylphenyl]methylene]piperazine-2,5-dione (**8**).* A solution of potassium *tert*-butoxide (13.5 g, 120 mmol) in *tert*-butyl alcohol (120 mL) was added to a stirred solution of **5a** (24.0 g, 100 mmol) and 1,4-diacetylpiperazine-2,5-dione **6**[35,36] (19.8 g, 100 mmol) in CH_2Cl_2 (400 mL) at 0 °C over 1 h, and stirring was continued at 25 °C for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (2.0 L) and extracted with CH_2Cl_2 (3×800 mL). The combined extracts were washed with brine (1.0 L), dried, and concentrated in vacuo to give a solid, the recrystallization of which from hexane–ethyl acetate gave **8** (27.6 g, 73.0%) as pale yellow prisms, mp 133–134 °C. IR (KBr) 3279, 1678, 1642, 1386, 1332, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (3H, s, 3′-CH_3), 2.65 (3H, s, $COCH_3$), 3.54 (3H, s, CH_2OCH_3), 3.84 (6H, s, 2×OCH_3), 4.47 (2H, s, 6-H_2), 4.85 (2H, s, OCH_2O), 6.66 (1H, s, 6′-H), 7.09 (1H, s, 3a-H), 8.84 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 10.3 (3′-CH_3), 27.1 ($COCH_3$), 46.2 (C-6), 56.0 (OCH_3), 58.2 (OCH_3), 60.4 (OCH_3), 100.4 (OCH_2O), 111.1 (C6′), 117.7 (C3a), 121.7, 125.4, 127.2, 146.9, 149.4, 149.9, 160.4 (CO), 162.5 (CO), 172.5 (CO); EIMS m/z (%) 378 (M^+, 76), 346 (100), 304 (77), 291 (61), 206 (30). Anal. Calcd for $C_{18}H_{22}N_2O_7$: C, 57.09; H, 5.86; N, 7.40. Found: C, 57.09; H, 5.95; N, 7.33.

*2.1.5. 1,4-Diacetyl-3-[(4,5-dimethoxy-2-methoxymethoxy-3-methylphenyl)methyl]piperazine-2,5-dione (**10**).*

*2.1.5.1. 1-Acetyl-3-[(4,5-dimethoxy-2-methoxymethoxy-3-methylphenyl)methyl]piperazine-2,5-dione (**9**).* A solution of **8** (5.0 g, 6.16 mmol) in 2-propanol (200 mL) was hydrogenated over 5% Rh–C (2.6 g, 1.28 mmol) at 25 °C for 14 h. The catalyst was removed by filtration and washed with 2-propanol (200 mL) and then $CHCl_3$ (200 mL). The combined filtrate was concentrated in vacuo. Crude solid **9** (5.33 g) was used in the following step without further purification. An analytical sample of **9** was obtained by recrystallization from hexane–ethyl acetate as colorless prisms, mp 116–117 °C. IR (KBr) 3100, 1720, 1700, 1455, 1270, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (3H, s, 3′-CH_3), 2.60 (3H, s, $COCH_3$), 3.08 (1H, dd, J=14.1, 8.3 Hz, 3a-H), 3.44 (1H, dd, J=14.1, 4.1 Hz, 3a-H), 3.59 (3H, s, CH_2OCH_3), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.10 (1H, d, J=17.8 Hz, 6-H), 4.30 (1H, d, J=17.8 Hz, 6-H), 4.37 (1H, ddd, J=8.3, 4.1, 1.7 Hz, 3-H), 4.94 (2H, s, OCH_2O), 6.50 (1H, br s, NH) 6.57 (1H, s, 6′-H); EIMS m/z (%) 380 (M^+, 34), 348 (41), 225 (30), 220 (13), 195 (13), 193 (11), 182 (16), 181 (100), 180 (29), 165 (14), 45 (32). Anal. Calcd for $C_{18}H_{24}N_2O_7 \cdot 1/10H_2O$: C, 56.57; H, 6.38; N, 7.33. Found: C, 57.07; H, 6.40; N, 6.86.

*2.1.5.2. Diacetate (**10**).* A solution of the above residue (**9**: 5.33 g) and DMAP (323 mg, 2.6 mmol) in pyridine (80 mL) was cooled with ice water and acetic anhydride (1.5 mL, 16 mmol) was added dropwise over 10 min. The reaction mixture was stirred at 25 °C for 1 h. The solvent was removed in vacuo and then, the residue was taken up in water (500 mL) and extracted with ethyl acetate (3×500 mL). The combined extracts were washed with

brine (500 mL), dried, and concentrated in vacuo to give a solid, the recrystallization of which from hexane–ethyl acetate afforded **10** (4.90 g, 88%, two steps) as colorless prisms, mp 105 °C. IR (KBr) 1708, 1238, 1219, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (3H, s, 3′-CH_3), 2.55 (3H, s, $COCH_3$), 2.56 (3H, s, $COCH_3$), 2.93 (1H, d, J=19.0 Hz, 6-H), 3.22 (1H, dd, J=13.9, 4.6 Hz, 3a-H), 3.37 (1H, dd, J=13.9, 6.4 Hz, 3a-H), 3.53 (3H, s, CH_2OCH_3), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.56 (1H, d, J=19.0 Hz, 6-H), 4.81 (2H, s, OCH_2O), 5.39 (1H, dd, J=6.4, 4.6 Hz, 3-H), 6.43 (1H, s, 6′-H); EIMS m/z (%) 422 (M^+, 62), 225 (100), 195 (30), 181 (47), 45 (31). Anal. Calcd for $C_{20}H_{26}N_2O_8$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.01; H, 6.35; N, 6.56.

*2.1.6. (3Z)-1-Acetyl-6-[4,5-dimethoxy-2-(methoxymethoxy)-3-methylphenylmethyl]-3-[4,5-dimethoxy-3-methyl-2-[(4-methylphenylsulfoxy) phenyl]methylene]piperazine-2,5-dione (**11a**).* A solution of potassium *tert*-butoxide (4.48 g, 40.0 mmol) in *tert*-butyl alcohol (80 mL) was added to a stirred solution of **10** (16.9 g, 40.0 mmol) and **5b** (14.0 g, 140.0 mmol) in THF (80 mL) at 0 °C over 20 min, and stirring was continued at 25 °C for 5.5 h. The reaction mixture was poured into brine (2.0 L) and extracted with ethyl acetate (3×2.0 L). The combined extracts were washed with brine (2.0 L), dried, and concentrated in vacuo to give a solid, the recrystallization of which from ether–ethyl acetate gave **11a** (25.1 g, 88.0%) as pale yellow prisms, mp 169–170 °C. IR (KBr) 1701, 1489, 1375, 1228, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (3H, s, $ArCH_3$), 2.18 (3H, s, $ArCH_3$), 2.39 (3H, s, $ArCH_3$), 2.60 (3H, s, $COCH_3$), 3.06 (1H, dd, J=13.8, 2.8 Hz, 6a-H), 3.35 (1H, dd, J=13.8, 5.5 Hz, 6a-H), 3.44 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.75 (1H, d, J=6.0 Hz, OCHO), 4.77 (1H, d, J=6.0 Hz, OCHO), 5.31 (1H, dd, J=5.5, 2.8 Hz, 6-H), 6.16 (1H, s, 3a-H), 6.21 (1H, s, ArH), 6.53 (1H, s, ArH), 7.24 (2H, d, J=8.1 Hz, 2×ArH), 7.39 (1H, s, NH), 7.65 (2H, d, J=8.1 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 67.5 Hz) δ 10.3 ($ArCH_3$), 11.2 ($ArCH_3$), 21.7 ($ArCH_3$), 27.2 ($COCH_3$), 33.0 (C6a), 55.5 (OCH_3), 56.0 (OCH_3), 57.3 (C6), 57.7 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 99.9 (OCH_2O), 110.4 (CH), 112.3 (CH), 114.1 (C3a), 122.3, 122.7, 125.3, 126.1, 128.3 (2×CH), 128.5, 129.7 (2×CH), 133.2, 139.4, 145.5, 148.1, 148.7, 149.5, 149.6, 151.6, 159.0 (CO), 165.5 (CO), 172.4 (CO); EIMS m/z (%) 712 (M^+, 100), 558 (20), 557 (42), 377 (58), 335 (36), 317 (20), 246 (25), 235 (45), 225 (45), 192 (23), 181 (88); HREIMS m/z 712.2299 (M^+, calcd for $C_{35}H_{40}N_2O_{12}S$, 712.2302). Anal. Calcd for $C_{35}H_{40}N_2O_{12}S$: C, 58.98; H, 5.66; N, 3.99. Found: C, 58.98; H, 5.72; N, 3.89.

After collecting the crystals of **11a** described above, the filtrate was concentrated in vacuo to give a residue, which showed two major spots on TLC. Chromatography on a silica gel column with hexane–ethyl acetate (3/2) as the eluent gave an additional amount of **11a** (330.4 mg, 1.0%) as colorless prisms. Further elution with hexane–ethyl acetate (1/1) afforded **11b** (940.0 mg, 3.0%) as a pale yellow amorphous powder.

*2.1.7. (3E)-1-Acetyl-6-[4,5-dimethoxy-2-(methoxymethoxy)-3-methylphenylmethyl]-3-[4,5-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]piperazine-2,5-dione (**11b**).* IR (KBr) 1697, 1489, 1384, 1238, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (3H, s, $ArCH_3$), 2.07 (3H, s, $ArCH_3$), 2.42 (3H, s, $COCH_3$), 2.46 (3H, s, $ArCH_3$), 3.15 (1H, dd, J=14.0, 4.9 Hz, 6a-H), 3.42 (1H, dd, J=14.0, 5.9 Hz, 6a-H), 3.56 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.84 (1H, d, J=6.3 Hz, OCHO), 4.85 (1H, d, J=6.3 Hz, OCHO), 5.39 (1H, dd, J=5.9, 4.9 Hz, 6-H), 6.02 (1H, s, 3a-H), 6.50 (1H, s, ArH), 6.72 (1H, s, ArH), 7.30 (2H, d, J=8.3 Hz, 2×ArH), 7.72 (2H, d, J=8.3 Hz, 2×ArH), 8.29 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 67.5 Hz) δ 10.5 ($ArCH_3$), 10.8 ($ArCH_3$), 21.7 ($ArCH_3$), 27.3 ($COCH_3$), 33.6 (C6a), 56.0 (OCH_3), 56.3 (OCH_3), 57.0 (C6), 57.7 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 100.0 (OCH_2O), 112.0 (CH), 112.4 (CH), 119.3 (C3a), 123.0, 123.4, 125.4, 125.7, 126.5, 128.3 (2×CH), 129.9 (2×CH), 133.8, 140.6, 145.6, 147.7, 148.4, 149.4, 149.8, 150.5, 158.9 (CO), 166.8 (CO), 172.1 (CO); EIMS m/z (%) 712 (M^+, 86), 557 (49), 377 (64), 181 (100); HREIMS m/z 712.2305 (M^+, calcd for $C_{35}H_{40}N_2O_{12}S$, 712.2302).

*2.1.8. (3Z)-6-[4,5-Dimethoxy-2-(methoxymethoxy)-3-methylphenylmethyl]-3-[4,5-dimethoxy-3-methyl-2-[(4-methylphenyl) sulfoxyphenyl]methylene]-4-(4-methoxyphenylmethyl)-piperazine-2,5-dione (**13**).* Sodium hydride (60% oil dispersion, washed with dry hexane three times, 360 mg, 15.0 mmol) was added to a stirred solution of **11a** (10.7 g, 15.0 mmol) in DMF (300 mL) at 0 °C, and the reaction mixture was stirred at 25 °C for 30 min. Then, 4-methoxybenzyl chloride (2.35 g, 16.5 mmol) was added over 20 min and the resulting mixture was stirred at 25 °C for 14 h. The reaction mixture was diluted with water (1 L) and extracted with ethyl acetate (3×1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo. Obtained crude solid **12** (14.5 g) was used in the following step without further purification. An analytical sample was obtained by recrystallization from ether–ethyl acetate as colorless prisms, mp 159–160 °C. IR (KBr) 1672, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.91 (3H, s, $ArCH_3$), 2.04 (3H, s, $ArCH_3$), 2.46 (3H, s, $ArCH_3$), 2.51 (3H, s, $COCH_3$), 3.20 (1H, dd, J=14.0, 7.0 Hz, 6a-H), 3.28 (1H, dd, J=14.0, 5.6 Hz, 6a-H), 3.50 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.15 (1H, d, J=14.1 Hz, *N*CH), 4.77 (1H, d, J=5.7 Hz, OCHO), 4.81 (1H, d, J=5.7 Hz, OCHO), 5.01 (1H, d, J=14.1 Hz, *N*CH), 5.44 (1H, dd, J=7.0, 5.6 Hz, 6-H), 6.41 (1H, s, 3a-H), 6.72 (2H, d, J=8.8 Hz, 2×ArH), 6.90 (1H, s, ArH), 7.07 (1H, s, ArH), 7.09 (2H, d, J=8.8 Hz, 2×Ar), 7.32 (2H, d, J=8.2 Hz, 2×ArH), 7.85 (2H, d, J=8.2 Hz, 2×ArH); EIMS m/z (%) 832 (M^+, 4), 661 (17), 660 (17), 616 (16), 394 (12), 393 (47), 121 (100). Anal. Calcd for $C_{43}H_{48}N_2O_{13}S$: C, 62.01; H, 5.81; N, 3.36. Found: C, 61.78; H, 5.82; N, 2.96.

A solution of the above residue (**12**: 14.5 g) in ethanol (500 mL) and aqueous 5% $NaHCO_3$ solution (100 mL) was heated under reflux for 2.5 h. The reaction mixture was concentrated in vacuo and then, the residue was diluted with water (1 L) and extracted with ethyl acetate (3×1 L). The combined extracts were washed with brine (1 L) and concentrated in vacuo to give a solid, the recrystallization of which from ether gave **13** (10.3 g, 87.0%, two steps) as colorless prisms, mp 152–153 °C. IR (KBr) 3250, 1688, 1636, 1487, 1375, 1244, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.99 (3H, s, $ArCH_3$), 2.21 (3H, s, $ArCH_3$), 2.40 (3H, s, $ArCH_3$), 3.05 (1H, dd, J=14.0, 4.9 Hz, 6a-H), 3.51 (1H, dd, J=14.0, 4.2 Hz, 6a-H), 3.59 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.13 (1H, d, J=15.0 Hz, *N*CH), 4.43 (1H, dd, J=9.3, 4.2 Hz, 6-H), 4.88 (1H, d, J=15.0 Hz, *N*CH), 4.95 (1H, d, J=6.0 Hz, OCHO), 4.97 (1H, d, J=6.0 Hz, OCHO), 6.25 (1H, br s, NH), 6.59 (1H, s, ArH), 6.65 (1H, s, ArH), 6.76 (2H, d, J=8.8 Hz, 2×ArH), 6.82 (2H, d, J=8.8 Hz, 2×ArH), 6.89 (1H, s, 3a-H), 7.28 (2H, d, J=8.5 Hz, 2×ArH), 7.76 (2H, d, J=8.5 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 10.5 ($ArCH_3$), 10.8 ($ArCH_3$), 21.6 ($ArCH_3$), 32.3 (C6a), 47.8 (NCH_2), 55.1 (OCH_3), 55.4 (OCH_3), 55.9 (C6), 55.9 (OCH_3), 57.5 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 99.8 (OCH_2O), 110.2 (CH), 111.7 (CH), 113.5 (2×CH), 117.0 (C3a), 124.2, 124.4, 125.8, 127.4, 128.2 (2×CH), 128.5, 128.5 (2×CH), 129.7 (2×CH), 131.1, 133.3, 140.1, 145.3, 147.2, 148.3, 148.7, 149.6, 150.9, 158.6, 163.9 (CO), 167.3 (CO); EIMS m/z (%) 790 (M^+, 5), 619 (17), 618 (24), 394 (18), 393 (63), 272 (11), 181 (10); HREIMS m/z 790.2772 (M^+, calcd for $C_{41}H_{46}N_2O_{12}S$, 790.2781). Anal. Calcd for $C_{41}H_{46}N_2O_{12}S\cdot 1/2(CH_3CH_2)_2O$: C, 62.38; H, 6.21; N, 3.38. Found: C, 62.44; H, 6.22; N, 3.36.

*2.1.9. (3Z)-1-Isopropyloxycarbonyl-6-[4,5-dimethoxy-2-(methoxymethoxy)-3-methylphenylmethyl]-3-[4,5-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-4-(4-methoxyphenylmethyl) piperazine-2,5-dione (**14**).* A solution of **13** (12.7 g, 16.1 mmol), TEA

(8.9 mL, 64.2 mmol), and DMAP (7.84 g, 64.2 mmol) in dichloromethane (1 L) was cooled with ice water and isopropyl chloroformate (3.22 mL, 28.0 mmol) was added dropwise over 10 min. The reaction mixture was stirred at 25 °C for 23 h. The organic layer was washed with 1 M aqueous HCl (50 mL) and then water (50 mL), dried, and concentrated in vacuo to give a residue (15.7 g). Chromatography on a silica gel (110 g) column with hexane–ethyl acetate (1/1) as the eluent gave **14** (14.1 g, 100%) as a pale yellow amorphous powder. IR (KBr) 1772, 1722, 1693, 1487, 1244, 1176, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (3H, d, J=6.3 Hz, OCHCH_3), 1.26 (3H, d, J=6.3 Hz, OCHCH_3), 2.01 (3H, s, $ArCH_3$), 2.13 (3H, s, $ArCH_3$), 2.46 (3H, s, $ArCH_3$), 3.19 (1H, dd, J=13.8, 7.3 Hz, 6a-H), 3.35 (1H, dd, J=13.8, 6.3 Hz, 6a-H), 3.52 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.15 (1H, d, J=15.0 Hz, *N*CH), 4.83 (1H, d, J=6.0 Hz, OCHO), 4.87 (1H, d, J=6.0 Hz, OCHO), 4.94 (1H, sept, J=6.3 Hz, OCH), 4.96 (1H, d, J=15.0 Hz, *N*CH), 5.19 (1H, dd, J=7.3, 6.3 Hz, 6-H), 6.45 (1H, s, ArH), 6.73 (2H, d, J=8.7 Hz, 2×ArH), 6.85 (1H, s, ArH), 7.09 (2H, d, J=8.7 Hz, 2×ArH), 7.16 (1H, s, 3a-H), 7.34 (2H, d, J=8.2 Hz, 2×ArH), 7.90 (2H, d, J=8.2 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 10.5 ($ArCH_3$), 11.0 ($ArCH_3$), 21.6 ($OCHCH_3$), 21.8 ($OCHCH_3$), 21.9 ($ArCH_3$), 33.1 (C6a), 49.7 (NCH_2), 55.2 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 57.6 (OCH_3), 59.9 (C6), 60.0 (OCH_3), 60.6 (OCH_3), 71.7 (OCH), 100.0 (OCH_2O), 110.0 (CH), 111.8 (CH), 113.7 (2×CH), 119.7 (C3a), 123.1, 123.4, 125.5, 127.8, 128.4 (2×CH), 128.4, 129.4 (2×CH), 129.9 (2×CH), 130.0, 132.8, 140.5, 145.4, 147.2, 148.7, 149.0, 149.2, 151.0, 151.0, 158.8, 161.5 (CO), 166.7 (CO); FABMS m/z 877 $[M+H]^+$; HRFABMS m/z 877.3210 (M^++1, calcd for $C_{45}H_{53}N_2O_{14}S$, 877.3218).

2.1.10. Isopropyl (E)-(1R,5S*)-1,2,3,4,5,6-hexahydro-7-hydroxy-3-(4-methoxyphenylmethyl)-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate (**16**).* A stirred solution of **14** (13.6 g, 15.5 mmol) in THF (480 mL) was cooled with ice water and lithium tri-*tert*-butoxyaluminohydride (15.8 g, 62.1 mmol) was added over 10 min. After continued stirring at 0 °C for 4.5 h, anhydrous Na_2SO_4 (10.0 g) was added and the reaction mixture was quenched with water (20 mL). The reaction mixture was filtered through Celite pad and then, the filtrate was diluted with brine (1 L) and extracted with chloroform (3×1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo to give **15**, which was used in the next step without further purification. A solution of crude **15** in formic acid (240 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 (500 mL) and extracted with chloroform (3×1 L). The combined extracts were washed with water (500 mL), dried, and concentrated in vacuo to give a residue, the recrystallization of which from ether gave **16** (11.1 g, 89.0%) as colorless prisms, mp 128–130 °C. IR (KBr) 3412, 2978, 2933, 1701, 1631, 1514, 1458, 1410, 1348, 1296, 1247, 1174, 1117, 1074 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 140 °C) δ 1.20 (3H, d, J=6.1 Hz, OCHCH_3), 1.25 (3H, d, J=6.1 Hz, OCHCH_3), 2.06 (3H, s, $ArCH_3$), 2.16 (3H, s, $ArCH_3$), 2.42 (3H, s, $ArCH_3$), 2.87 (1H, dd, J=17.0, 6.1 Hz, 6-Hα), 2.92 (3H, s, OCH_3), 3.05 (1H, dd, J=17.0, 1.7 Hz, 6-Hβ), 3.54 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.43 (1H, d, J=16.1 Hz, 3-CH), 4.75 (1H, d, J=16.1 Hz, 3-CH), 4.85 (1H, dd, J=6.1, 1.7 Hz, 5-H), 4.87 (1H, sept, J=6.1 Hz, OCH), 5.93 (1H, br s, 1-H), 6.13 (1H, s, 2a-H), 6.60 (2H, d, J=8.8 Hz, 2×ArH), 6.69 (2H, d, J=8.8 Hz, 2×ArH), 7.07 (1H, s, 6′-H), 7.35 (2H, d, J=8.5 Hz, 2×ArH), 7.69 (2H, d, J=8.5 Hz, 2×ArH), 7.76 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 100 Hz, 140 °C) δ 8.4 ($ArCH_3$), 10.1 ($ArCH_3$), 20.2 ($ArCH_3$), 20.9 ($OCHCH_3$), 21.0 ($OCHCH_3$), 26.6 (C6), 43.2 (NCH_2), 45.5 (C1), 52.5 (C5), 54.4 (OCH_3), 55.7 (OCH_3), 58.1 (OCH_3), 58.6 (OCH_3), 59.1 (OCH_3), 68.6 (OCH), 105.1 (C2a), 112.6 (CH), 113.0 (2×CH), 115.2, 118.3, 122.9, 124.9, 125.3, 126.6 (2×CH), 126.9 (2×CH), 127.7, 128.9 (2×CH), 133.4, 136.6, 139.7, 142.4, 144.3, 146.3, 148.0, 148.6, 149.8, 152.0, 157.6, 166.5 (C4); FABMS m/z 817 $[M+H]^+$; HRFABMS m/z 817.2999 (M^++1, calcd for $C_{43}H_{48}N_2O_{12}S$, 817.3006). Anal. Calcd for $C_{43}H_{48}N_2O_{12}S$: C, 63.22; H, 5.92; N, 3.38. Found: C, 63.21; H, 6.15; N, 3.30.

2.1.11. (Z)-(1R,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine (**17a**).* Concentrated H_2SO_4 (7.2 mL) was added to a stirred solution of **16** (6.0 g, 7.35 mmol) in TFA (144.0 mL) at 0 °C over 5 min, and the reaction mixture was stirred at 25 °C for 20 h. The reaction mixture was poured into water (800 mL) at 0 °C, basified with concentrated NH_4OH (200 mL), and then extracted with chloroform (3×1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo to give a residue (5.86 g). Chromatography of this residue on a silica gel (30 g) column with chloroform–methanol (50/1) gave **17a** (2.88 g, 64.0%) as a solid, the recrystallization of which from methanol–dichloromethane afforded **17a** as colorless needles, mp 230–232 °C. IR (KBr) 3310, 3194, 2945, 1668, 1361, 1332, 1283, 1250, 1221, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.91 (3H, s, 3′-CH_3), 2.17 (3H, s, 8-CH_3), 2.48 (3H, s, $TsCH_3$), 3.02 (1H, dd, J=17.4, 1.3 Hz, 6-Hβ), 3.08 (1H, dd, J=17.4, 7.0 Hz, 6-Hα), 3.77 (3H, s, OCH_3), 3.79 (3H, s, 9-OCH_3), 3.82 (3H, s, OCH_3), 3.90 (3H, s, 10-OCH_3), 3.96 (3H, br s, OH, 2×NH), 4.08 (1H, dd, J=7.0, 1.3 Hz, 5-H), 4.95 (1H, br s, 1-H), 5.93 (1H, s, 2a-H), 6.59 (1H, s, 6′-H), 7.36 (2H, d, J=8.1 Hz, 2×ArH), 7.73 (2H, d, J=8.1 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.6 (3′-CH_3), 10.4 (8-CH_3), 21.2 ($TsCH_3$), 26.6 (C6), 48.0 (C1), 51.5 (C5), 55.7 (5′-OCH_3), 59.8 (9-OCH_3), 60.0 (4′-OCH_3), 60.0 (10-OCH_3), 102.4 (C2a), 110.1 (C6′), 114.6 (C6a), 118.9 (C8), 124.0 (C1′), 124.2 (C10a), 127.4 (C3′), 127.9 (2×CH), 129.6 (2×CH), 133.6 (C1″), 135.6 (C2), 139.5 (C2′), 143.3 (C10), 145.4 (C4″), 146.9 (C4′), 148.4 (C7), 149.6 (C9), 151.2 (C5′), 171.0 (C4); EIMS m/z 610 (M^+, 14), 456 (32), 455 (100), 221 (12), 220 (50); HREIMS m/z 610.1985 (M^+, calcd for $C_{31}H_{34}N_2O_9S$, 610.1982). Anal. Calcd for $C_{31}H_{34}N_2O_9S$: C, 60.97; H, 5.61; N, 4.59. Found: C, 60.95; H, 5.74; N, 4.36.

Further elution with chloroform–methanol (10/1) gave **17b** (65.2 mg, 1.5%) as a colorless amorphous powder.

2.1.12. (E)-(1R,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine (**17b**).* IR (KBr) 3539, 3442, 1674, 1460, 1354, 1192, 1172, 1072, 866 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (3H, s, 3′-CH_3), 2.08 (3H, s, 8-CH_3), 2.42 (3H, s, $TsCH_3$), 2.89 (1H, d, J=15.3 Hz, 6-Hβ), 2.98 (3H, s, 10-OCH_3), 3.11 (1H, dd, J=15.3, 7.3 Hz, 6-Hα), 3.59 (3H, s, 9-OCH_3), 3.78 (1H, d, J=7.3 Hz, 5-H), 3.82 (3H, s, 4′-OCH_3), 3.85 (3H, s, 5′-OCH_3), 4.82 (1H, br s, 1-H), 5.15 (1H, br s, OH), 5.39 (1H, s, 2a-H), 6.69 (1H, s, 6′-H), 7.30 (2H, d, J=8.5 Hz, 2×ArH), 7.76 (2H, d, J=8.5 Hz, 2×ArH), 8.30 (1H, br d, NH); ^{13}C NMR ($CDCl_3$, 125.7 Hz) δ 8.9 (3′-CH_3), 11.0 (8-CH_3), 21.8 ($TsCH_3$), 27.7 (C6), 45.4 (C1), 52.5 (C5), 56.0 (10-OCH_3), 59.0 (9-OCH_3), 59.9 (4′-OCH_3), 60.5 (5′-OCH_3), 102.7 (C2a), 112.0 (C6′), 115.1 (C6a), 117.4 (C8), 125.1 (C1′), 126.5 (C10a), 126.5 (C3′), 128.0 (2×CH), 129.7 (2×CH), 134.1 (C1″), 138.5 (C2), 139.6 (C2′), 143.4 (C10), 145.3 (C4″), 146.4 (C4′), 147.6 (C7), 149.1 (C9), 150.8 (C5′), 171.9 (C4); EIMS m/z 610 (M^+, 13), 456 (35), 455 (100), 221 (16), 220 (60), 205 (11); HREIMS m/z 610.1985 (M^+, calcd for $C_{31}H_{34}N_2O_9S$, 610.1992).

2.2. Improved synthesis of 17a

*2.2.1. 1-Acetyl-4-isopropyloxycarbonyl-3-(4,5-dimethoxy-2-methoxymethoxy-3-methylphenyl)methyl]piperazine-2,5-dione (**18**).* A solution of **9** (380.0 mg, 1.0 mmol), TEA (0.28 mL, 2.0 mmol), and DMAP (244.0 mg, 2.0 mmol) in dichloromethane

(30 mL) was cooled with ice water, and isopropyl chloroformate (0.46 mL, 4.0 mmol) was added dropwise over 20 min. The reaction mixture was stirred at 25 °C for 2 h. The organic layer was washed with 1 M aqueous HCl (50 mL) and then water (50 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel (20 g) column with hexane–ethyl acetate (3/1) as the eluent gave **18** (447 mg, 96.0%) as a pale yellow amorphous powder. IR ($CHCl_3$) 3022, 2940, 1780, 1717, 1261, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (3H, d, J=6.2 Hz, OCHCH_3), 1.32 (3H, d, J=6.2 Hz, OCHCH_3), 2.14 (3H, s, 3′-CH_3), 2.56 (3H, s, $COCH_3$), 3.24 (1H, dd, J=13.8, 6.2 Hz, 3a-H), 3.25 (1H, d, J=18.8 Hz, 6-H), 3.38 (1H, dd, J=13.8, 6.2 Hz, 3a-H), 3.55 (3H, s, CH_2OCH_3), 3.78 (6H, s, 2×OCH_3), 4.70 (1H, d, J=18.8 Hz, 6-H), 4.84 (1H, d, J=5.6 Hz, OCHO), 4.86 (1H, d, J=5.6 Hz, OCHO), 5.03 (1H, sept, J=6.2 Hz, OCH), 5.15 (1H, t, J=6.2 Hz, 3-H), 6.47 (1H, s, 6′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.4 (3′-CH_3), 21.7 (CHCH_3), 21.8 (CHCH_3), 27.0 ($COCH_3$), 33.7 (C3a), 46.7 (C6), 56.0 (OCH_3), 57.7 (OCH_3), 60.5 (OCH_3), 61.2 (C3), 72.4 (OCHCH$_3$), 99.9 (OCH_2O), 111.7 (C6′), 122.4 (C3a), 126.0, 147.8, 149.1, 149.5, 151.0 (NCO_2), 163.5 (C2), 167.3 (C5), 171.1 ($COCH_3$); EIMS m/z (%) 466 (M^+, 50), 348 (31), 225 (100), 195 (26), 181 (65), 180 (26), 45 (30). HREIMS m/z 466.1951 (M^+, calcd for $C_{22}H_{30}N_2O_9$, 466.1953).

*2.2.2. (Z)-1-Isopropyloxycarbonyl-6-[4,5-dimethoxy-2-(methoxymethoxy)-3-methylphenylmethyl]-3-[4,5-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-4-(4-methoxyphenylmethyl) piperazine-2,5-dione (**19**).* A solution of potassium *tert*-butoxide (1.65 g, 14.7 mmol) in *tert*-butyl alcohol (14.7 mL) was added to a stirred solution of **5b** (4.3 g, 12.3 mmol) and **18** (5.7 g, 12.3 mmol) in dichloromethane (50 mL) at 0 °C over 60 min, and stirring was continued at 25 °C for 40 min. The reaction mixture was poured into brine (500 mL) and extracted with ethyl acetate (3×500 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel (60 g) column with hexane–ethyl acetate (2/1) as the eluent gave **19** (6.5 g, 70.0%) as a colorless amorphous powder. IR (KBr) 2940, 2982, 1772, 1692, 1489, 1375, 1279, 1244, 1224, 1177, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (3H, d, J=6.3 Hz, OCHCH_3), 1.41 (3H, d, J=6.3 Hz, OCHCH_3), 1.96 (3H, s, $ArCH_3$), 2.26 (3H, s, $ArCH_3$), 2.38 (3H, s, $ArCH_3$), 3.18 (1H, dd, J=13.9, 3.9 Hz, 6a-H), 3.36 (1H, dd, J=13.9, 6.0 Hz, 6a-H), 3.55 (3H, s, CH_2OCH_3), 3.59 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.77 (1H, d, J=6.0 Hz, OCHO), 4.84 (1H, d, J=6.0 Hz, OCHO), 5.03 (1H, dd, J=16.0, 3.9 Hz, 6-H), 5.15 (1H, sept, J=6.3 Hz, OCH), 6.18 (1H, s, C3a), 6.28 (1H, s, ArH), 6.47 (1H, s, 6′-H), 6.55 (1H, s, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.5 ($ArCH_3$), 11.6 ($ArCH_3$), 21.8 ($ArCH_3$), 21.9 (CHCH_3), 22.0 (CHCH_3), 33.7 (C6a), 55.8 (OCH_3), 56.1 (OCH_3), 57.7 (CH_2OCH_3), 59.8 (C6), 60.2 (OCH_3), 60.5 (OCH_3), 72.0 (OCHCH$_3$), 99.8 (OCH_2O), 109.9 (CH), 112.7 (CH), 114.0 (C3a), 122.1, 122.3, 125.1, 125.8, 128.2 (2×CH), 128.8, 129.8 (2×CH), 132.5, 139.6, 145.4, 147.8, 148.6, 149.2, 149.2, 151.3, 151.9 (NCO_2), 157.1 (C2), 165.0 (C5); EIMS m/z (%) 756 (M^+, 100), 584 (25), 483 (35), 303 (43), 235 (39), 225 (32), 220 (34), 181 (65). HREIMS m/z 756.2564 (M^+, calcd for $C_{37}H_{44}N_2O_{13}S$, 756.2562).

*2.2.3. Isopropyl (Z)-(1R*5S*)-1,2,3,4,5,6-hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate (**21a**).* A stirred solution of **19** (611.0 mg, 0.81 mmol) in THF (30 mL) was cooled with ice water and lithium tri-*tert*-butoxyaluminohydride (1.0 g, 4.0 mmol) was added over 5 min. After continued stirring at 0 °C for 4.5 h, anhydrous Na_2SO_4 (1.0 g) was added and the reaction mixture was quenched with water (2.0 mL). The reaction mixture was filtered through Celite pad and then, the filtrate was diluted with brine (100 mL) and extracted with chloroform (3×50 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated in vacuo to give **20**, which was used in the next step without further purification. A solution of crude **20** in formic acid (13 mL) was heated at 60 °C for 2.5 h. After the reaction mixture was concentrated in vacuo, the residue was diluted with 5% aqueous $NaHCO_3$ solution (70 mL) and extracted with chloroform (3×70 mL). The combined extracts were washed with water (70 mL), dried, and concentrated in vacuo to give a residue. Chromatography on a silica gel (20 g) column with hexane–ethyl acetate (2/1) as the eluent gave **21a** (413.3 mg, 73.0%) as a pale yellow amorphous powder. IR (KBr) 3429, 3389, 2980, 2938, 1682, 1460, 1422, 1375, 1348, 1300, 1273, 1246, 1219, 1192, 1177, 1113, 1069 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 100 °C) δ 1.24 (3H, d, J=6.2 Hz, OCHCH_3), 1.26 (3H, d, J=6.2 Hz, OCHCH_3), 1.97 (3H, s, $ArCH_3$), 2.08 (3H, s, $ArCH_3$), 2.44 (3H, s, $ArCH_3$), 2.92 (2H, d, J=5.6 Hz, 6-H_2), 3.71 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.81 (1H, d, J=5.6 Hz, 5-H), 4.89 (1H, sept, J=6.1 Hz, OCH), 5.76 (1H, br s, 1-H or 2a-H), 5.77 (1H, s, 1-H or 2a-H), 6.67 (1H, s, 6′-H), 7.44 (2H, d, J=8.5 Hz, 2×ArH), 7.72 (2H, d, J=8.5 Hz, 2×ArH), 8.01 (1H, s, OH); ^{13}C NMR (DMSO-d_6, 100 Hz, 100 °C) δ 8.8 ($ArCH_3$), 10.3 ($ArCH_3$), 20.6 ($ArCH_3$), 21.3 (OCHCH_3), 21.3 (OCHCH_3), 26.0 (C6), 48.9 (C1), 51.6 (C5), 55.6 (OCH_3), 59.2 (OCH_3), 59.2 (OCH_3), 59.5 (OCH_3), 68.7 (OCH), 101.1 (C2a), 111.6 (CH), 114.6, 118.3, 123.7, 123.8, 125.8, 127.1 (2×CH), 129.2 (2×CH), 132.4, 133.8, 138.3, 142.4, 144.7, 146.1, 148.0, 148.8, 150.1, 152.2 (NCO_2), 167.3 (C4); EIMS m/z 696 (M^+, 24), 542 (50), 541 (100), 456 (22), 455 (83), 220 (53). HREIMS m/z 696.2353 (M^+, calcd for $C_{35}H_{40}N_2O_{11}S$, 696.2350).

Further elution with chloroform gave **21b** (94.1 mg, 17.0%) as a pale yellow amorphous powder.

2.2.4. Isopropyl (E)-(1R,5S*)-1,2,3,4,5,6-hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)-sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate (**21b**).* IR (KBr) 3447, 1674, 1458, 1423, 1346, 1300, 1248, 1173, 1113, 1070 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 100 °C) δ 1.18 (3H, d, J=6.2 Hz, OCHCH_3), 1.24 (3H, d, J=6.2 Hz, OCHCH_3), 2.02 (3H, s, $ArCH_3$), 2.18 (3H, s, $ArCH_3$), 2.38 (3H, s, $ArCH_3$), 2.81 (1H, dd, J=17.2, 5.6 Hz, 6-Hα), 2.91 (1H, d, J=17.2 Hz, 6-Hβ), 3.04 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.66 (1H, br d, J=5.6 Hz, 5-H), 4.83 (1H, sept, J=6.1 Hz, OCH), 5.68 (1H, br s, 1-H), 7.14 (1H, s), 7.26 (2H, d, J=8.1 Hz, 2×ArH), 7.72 (2H, d, J=8.1 Hz, 2×ArH), 7.94 (1H, s), 8.20 (1H, s, OH), 9.50 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 100 Hz, 100 °C) δ 8.7 ($ArCH_3$), 10.3 ($ArCH_3$), 20.6 ($ArCH_3$), 21.2 (OCHCH_3), 21.3 (OCHCH_3), 25.9 (C6), 43.9 (C1), 51.6 (C5), 55.8 (OCH_3), 58.5 (OCH_3), 58.9 (OCH_3), 59.3 (OCH_3), 68.6 (OCH), 102.4 (C2a), 111.6 (CH), 114.9, 118.1, 123.5, 125.3, 125.5, 126.9 (2×CH), 128.8 (2×CH), 133.0, 135.6, 139.4, 142.1, 144.2, 145.8, 148.0, 148.4, 149.9, 152.1 (NCO_2), 166.9 (C4); EIMS m/z 696 (M^+, 25), 542 (44), 541 (100), 456 (21), 455 (79), 221 (11), 220 (47). HREIMS m/z 696.2353 (M^+, calcd for $C_{35}H_{40}N_2O_{11}S$, 696.2352).

2.2.5. (Z)-(1R,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine (**17a**).* Concentrated H_2SO_4 (0.4 mL) was added to a stirred solution of **21a** (298.0 mg, 0.43 mmol) in TFA (8 mL) at 0 °C over 5 min, and the reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was poured into water (800 mL) at 0 °C, basified with concentrated NH_4OH (10 mL), and then extracted with chloroform (3×50 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (30 g) column with chloroform–methanol (50/1) gave **17a** (179.0 g, 69.0%) as a solid, the recrystallization of which from methanol–dichloromethane afforded **17a** as colorless needles, mp 230–232 °C. Its spectra were identical with those of an authentic sample described above. Further elution with chloroform–methanol (20/1) gave **17b** (21.0 mg,

8.0%) as a pale yellow amorphous powder, the spectra of which were also identical with those of an authentic sample described above.

Almost the same results were obtained when the reaction was initiated from **21b** (30.0 mg, 43.1 mmol) to give **17a** (19.3 mg, 73.0%) and **17b** (2.4 mg, 9.0%).

2.2.6. (Z)-(1R,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,5-imino-3-benzazocine (**22a**).* A 37% aqueous solution of formaldehyde (86 mL) was added to a stirred solution of **17a** (5.26 g, 8.6 mmol) in formic acid (103 mL) at 50 °C, and the reaction mixture was heated at 70 °C for 1 h. After being concentrated in vacuo, the reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (1 L) and extracted with chloroform (3×1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (80 g) column with chloroform–methanol (50/1) gave a solid, the recrystallization of which from ethyl acetate–ether afforded **22a** (5.01 g, 93.0%) as colorless prisms, mp 218–220 °C. IR (KBr) 3385, 3267, 2937, 1674, 1483, 1460, 1418, 1404, 1368, 1348, 1281, 1244, 1219, 1175, 1111, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.89 (3H, s, 3′-CH_3), 2.15 (3H, s, 8-CH_3), 2.45 (3H, s, TsCH_3), 2.57 (3H, s, *N*CH_3), 2.92 (1H, dd, *J*=17.1, 1.0 Hz, 6-Hβ), 3.06 (1H, dd, *J*=17.1, 7.3 Hz, 6-Hα), 3.64 (1H, dd, *J*=7.3, 1.0 Hz, 5-H), 3.76 (3H, s, 4′-OCH_3), 3.77 (3H, s, 5′-OCH_3), 3.78 (3H, s, 9-OCH_3), 3.88 (3H, s, 10-OCH_3), 4.60 (1H, s, 1-H), 5.30 (1H, br s, OH), 5.93 (1H, s, 2a-H), 6.49 (1H, s, 6′-H), 7.30 (2H, d, *J*=8.2 Hz, 2×ArH), 7.71 (2H, d, *J*=8.2 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.8 (3′-CH_3), 10.8 (8-CH_3), 21.7 (TsCH_3), 26.7 (C6), 41.5 (*N*CH_3), 55.6 (C1), 56.1 (9-OCH_3), 59.1 (C5), 60.1 (4′-OCH_3), 60.3 (5′-OCH_3), 60.3 (10-OCH_3), 104.2 (C2a), 110.1 (C6′), 114.2 (C6a), 117.6 (C8), 124.8 (C1′), 125.9 (C10a), 128.0 (C3′), 128.3 (2×CH), 129.8 (2×CH), 133.9 (C1″), 134.7 (C2), 139.6 (C2′), 143.9 (C10), 145.3 (C4″), 147.2 (C4′), 147.8 (C7), 149.8 (C9), 151.4 (C5′), 170.2 (C4); EIMS *m*/*z* 624 (M^+, 13), 470 (30), 469 (100), 235 (12), 234 (39); HREIMS *m*/*z* 624.2142 (M^+, calcd for $C_{32}H_{36}N_2O_9S$, 624.2137). Anal. Calcd for $C_{32}H_{36}N_2O_9S$: C, 61.52; H, 5.81; N, 4.48. Found: C, 61.25; H, 5.90; N, 4.40.

2.2.7. (E)-(1R,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxyphenyl]methylene]-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,5-imino-3-benzazocine (**22b**).* A 37% aqueous solution of formaldehyde (1.0 mL) was added to a stirred solution of **17b** (61.0 mg, 0.1 mmol) in formic acid (1.2 mL) at 50 °C, and the reaction mixture was heated at 70 °C for 2 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (20 mL) and extracted with chloroform (3×20 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (15 g) column with chloroform–methanol (60/1) gave a solid, the recrystallization of which from chloroform–hexane afforded **22b** (57.0 mg, 91.3%) as colorless prisms, mp 224–225 °C. IR (KBr) 3370, 2938, 1670, 1460, 1418, 1346, 1173, 1115, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.11 (3H, s, 8-CH_3), 2.23 (3H, s, 3′-CH_3), 2.36 (3H, s, TsCH_3), 2.60 (3H, s, *N*CH_3), 2.95 (1H, dd, *J*=17.1, 2.0 Hz, 6-Hβ), 3.01 (1H, dd, *J*=17.1, 6.3 Hz, 6-Hα), 3.11 (3H, s, 10-OCH_3), 3.63 (1H, dd, *J*=6.3, 2.0 Hz, 5-H), 3.65 (3H, s, 9-OCH_3), 3.84 (3H, s, 4′-OCH_3), 3.87 (3H, s, 5′-OCH_3), 4.97 (1H, s, 1-H), 5.48 (1H, s, 2a-H), 6.83 (1H, s, 6′-H), 7.02 (2H, d, *J*=8.5 Hz, 2×ArH), 7.73 (2H, d, *J*=8.5 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.9 (3-CH_3), 11.2 (12-CH_3), 21.6 (TsCH_3), 26.4 (C6), 41.3 (*N*CH_3), 51.1 (C1), 55.9 (5′-OCH_3), 59.2 (C5), 59.3 (10-OCH_3), 59.9 (9-OCH_3), 60.5 (4′-OCH_3), 106.6 (C2a), 110.4 (C6′), 114.26 (C6a), 117.7 (C8), 124.7 (C10a), 126.0 (C1′), 127.7 (C3′), 128.3 (2×CH), 129.4 (2×CH), 134.3 (C1″), 135.4 (C2), 141.2 (C2′), 144.1 (C10), 145.3 (C4″), 146.8 (C4′), 147.8 (C7), 149.4 (C9), 150.8 (C5′), 170.4 (C4); EIMS *m*/*z* 624 (M^+, 13), 470 (30), 469 (100), 235 (12), 234 (39); HREIMS *m*/*z* 624.2142 (M^+, calcd for $C_{32}H_{36}N_2O_9S$, 624.2137).

2.3. Practical synthesis of 22a from 19

A stirred solution of **19** (3.01 g, 3.98 mmol) in THF (130 mL) was cooled with ice water and lithium tri-*tert*-butoxyaluminohydride (5.04 g, 19.8 mmol) was added over 10 min. After continued stirring at 25 °C for 24 h, anhydrous Na_2SO_4 (10.0 g) was added and the reaction mixture was quenched with water (20 mL). The reaction mixture was filtered through Celite pad and then, the filtrate was diluted with brine (200 mL) and extracted with chloroform (3×200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated in vacuo to give **20**, which was used in the next step without further purification. A solution of crude **20** in formic acid (40 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 (200 mL) and extracted with chloroform (3×200 mL). The combined extracts were washed with water (200 mL), dried, and concentrated in vacuo to give **21a** along with **21b**, which was used in the next step without further purification.

Concentrated H_2SO_4 (4.0 mL) was added to a stirred solution of the above products in TFA (80 mL) at 0 °C over 5 min, and the reaction mixture was stirred at 25 °C for 7.5 h. The reaction mixture was poured into water (600 mL) at 0 °C, basified with concentrated NH_4OH (100 mL), and then extracted with chloroform (3×500 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give **17a** along with **17b**, which was used in the next step without further purification.

A 37% aqueous solution of formaldehyde (40.5 mL) was added to a stirred solution of the above mixture of products **17a** and **17b** in formic acid (46.5 mL) at 50 °C, and the reaction mixture was heated at 70 °C for 2 h. After being concentrated in vacuo, the reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (300 L) and extracted with chloroform (3×300 L). The combined extracts were washed with brine (300 L), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (80 g) column with chloroform–methanol (100/1) gave a solid, the recrystallization of which from ethyl acetate–ether afforded **22a** (2.06 g, 82.9%, four steps) as colorless prisms. Further elution with chloroform–methanol (50/1) gave **22b** (230.0 mg, 9.3%) as colorless prisms.

2.3.1. (1R,2S*,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[3,4-dimethoxy-3-methyl-2-[(4-methylphenyl)sulfoxy]-phenyl]methyl]-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,5-imino-3-benzazocine (**23**).* A solution of **22a** (998.4 mg, 1.60 mmol) in ethanol (40 mL) was hydrogenated over 20% $Pd(OH)_2$ (448.0 mg) at 80 °C for 41 h under 2.8 MPa hydrogen. The catalyst was removed by filtration and washed with ethanol (200 mL) and then $CHCl_3$ (200 mL). The combined filtrate was concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (80 g) column with chloroform–methanol (50/1) gave a solid, the recrystallization of which from ethyl acetate–ether afforded **23** (928.0 mg, 93.0%) as colorless prisms, mp 200.5–202 °C. IR (KBr) 3375, 3267, 2940, 1665, 1459, 1418, 1368, 1346, 1244, 1219, 1175, 1111, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.92 (3H, s, 3′-CH_3), 2.19 (3H, s, 8-CH_3), 2.20 (1H, dd, *J*=14.7, 11.6 Hz, 2a-Hβ), 2.45 (3H, s, TsCH_3), 2.46 (3H, s, *N*CH_3), 2.85 (1H, d, *J*=17.4 Hz, 6-Hβ), 2.98 (1H, dd, *J*=17.4, 7.3 Hz, 6-Hα), 3.62 (1H, d, *J*=7.3 Hz, 5-H), 3.66 (1H, dd, *J*=14.7, 2.1 Hz, 2a-Hα), 3.75 (3H, s, 4′-OCH_3), 3.81 (3H, s, 5′-OCH_3 or 9-OCH_3), 3.82 (3H, s, 5′-OCH_3 or 9-OCH_3), 3.84 (3H, s, 10-OCH_3), 4.21 (1H, d, *J*=1.8 Hz, 1-H), 4.31 (1H, ddd, *J*=11.6, 2.1, 1.8 Hz, 2-H), 5.36 (1H, s, NH), 6.25 (1H, s, OH), 6.54 (1H, s, 6′-H), 7.33 (2H, d, *J*=8.2 Hz, 2×ArH), 7.70 (2H, d, *J*=8.2 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.0 (3′-CH_3), 10.9 (8-CH_3), 21.7 (TsCH_3), 23.1 (C6), 33.6 (C2a), 40.0 (*N*CH_3), 54.5 (C1),

55.7 (C2), 55.9 (OCH_3), 58.0 (C5), 60.2 (OCH_3), 60.2 (OCH_3), 60.4 (OCH_3), 111.5 (C6′), 114.8 (C6a), 118.3 (C8), 121.1 (C10a), 126.9 (C1′), 127.7 (C3′), 127.9 (2×CH), 129.8 (2×CH), 133.9 (C1″), 140.6 (C2′), 144.8 (C10), 145.3 (C4″), 146.9 (C4′), 148.2 (C7), 149.8 (C9), 151.5 (C5′), 172.2 (C4); EIMS *m*/*z* 626 (M^+, 11), 472 (9), 471 (16), 235 (29), 234 (100); HREIMS *m*/*z* 626.2298 (M^+, calcd for $C_{32}H_{38}N_2O_9S$, 626.2297). Anal. Calcd for $C_{32}H_{38}N_2O_9S$: C, 61.33; H, 6.11; N, 4.47. Found: C, 61.21; H, 6.21; N, 4.50.

2.3.2. (6S,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-4-hydroxy-1,2,10,11-tetramethoxy-3,12,16-trimethyl-13-[(4-methylphenyl)sulfoxy]-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one (**24**).* Paraformaldehyde (15 mg, 0.5 mmol) was added to a stirred solution of **23** (31.3 mg, 0.05 mmol) in acetic acid–TFA (4/1; 4.0 mL) at 25 °C, and the reaction mixture was heated at 80 °C for 15 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (20 mL) and extracted with chloroform (3×20 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (15 g) column with dichloromethane–methanol (50/1) gave a solid, the recrystallization of which from ethyl acetate–ether gave **24** (21.1 mg, 66.0%) as colorless prisms, mp 198–200 °C. IR (KBr) 3300, 1628, 1412, 1300, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.82 (3H, s, 12-CH_3), 2.20 (1H, dd, *J*=16.5, 12.2 Hz, 14-Hβ), 2.16 (3H, s, 3-CH_3), 2.47 (3H, s, TsCH_3), 2.49 (3H, s, *N*CH_3), 2.92 (1H, d, *J*=17.2 Hz, 5-Hβ), 2.99 (1H, dd, *J*=17.2, 6.7 Hz, 5-Hα), 3.58 (1H, dd, *J*=16.3, 2.6 Hz, 14-Hα), 3.73 (3H, s, OCH_3), 3.77–3.79 (1H, m, 6-H), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.87–3.91 (1H, overlapped, 14a-H), 3.89 (3H, s, OCH_3), 4.30 (1H, d, *J*=4.3 Hz, 15-H), 4.55 (1H, d, *J*=18.6 Hz, 9-Hβ), 4.66 (1H, d, *J*=18.6 Hz, 9-Hα), 5.94 (1H, s, OH), 7.40 (2H, d, *J*=8.1 Hz, 2×ArH), 7.92 (2H, d, *J*=8.1 Hz, 2×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.9 (3′-CH_3), 10.4 (8-CH_3), 21.7 (TsCH_3), 22.7 (C5), 27.5 (C14), 39.9 (*N*CH_3), 40.4 (C9), 54.6 (C15), 56.3 (C14a), 58.6 (C6), 60.1 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 60.7 (OCH_3), 114.6 (C4a), 118.2 (C3), 121.4 (C15a), 124.2 (C9a), 125.3 (C13a), 126.0 (C13), 128.4 (2×CH), 129.8 (2×CH), 133.7 (C1′), 140.5 (C12), 145.0 (C1), 145.4 (C4′), 148.3 (C2), 148.3 (C4), 149.7 (C11), 149.9 (C10), 170.6 (C7); EIMS *m*/*z* 638 (M^+, 11), 484 (10), 483 (24), 235 (39), 234 (100); Anal. Calcd for $C_{33}H_{38}N_2O_9S$: C, 62.05; H, 6.00; N, 4.39. Found: C, 61.79; H, 6.13; N, 4.28.

2.3.3. (1R,2S*,5S*)-1,2,3,4,5,6-Hexahydro-7-hydroxy-2-[(2-hydroxy-3,4-dimethoxy-3-methylphenyl)methyl]-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,5-imino-3-benzazocine (**25**).* Hydrazine monohydrate (200 mL) was added to a stirred solution of **23** (2.57 g, 4.10 mmol) in methanol (240 mL) at 25 °C, and the reaction mixture was heated under reflux for 73 h. The reaction mixture was diluted with brine (1.2 L) and extracted with 5% methanol in chloroform (4×1.2 L). The combined extracts were washed with 5% aqueous $NaHCO_3$ solution (1.2 L), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (15 g) column with dichloromethane–methanol (40/1) gave **25** (1.54 g, 80.0%) as a pale yellow amorphous powder. IR (KBr) 3372, 2938, 1651, 1489, 1456, 1417, 1344, 1314, 1244, 1209, 1116, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.09 (3H, s, 3′-CH_3), 2.09–2.14 (1H, m, 2a-Hβ), 2.14 (3H, s, 8-CH_3), 2.47 (3H, s, *N*CH_3), 2.85 (1H, dd, *J*=17.6, 1.5 Hz, 6-Hβ), 2.93 (1H, dd, *J*=17.6, 6.6 Hz, 6-Hα), 3.24 (1H, dd, *J*=14.1, 2.0 Hz, 2a-Hα), 3.54 (1H, br d, *J*=6.6 Hz, 5-H), 3.75 (3H, s, 4′-OCH_3), 3.77 (6H, s, 5′-OCH_3 and 9-OCH_3), 3.81 (3H, s, 10-OCH_3), 4.23–4.27 (2H, m, 1-H and 2-H), 5.94 (1H, s, NH), 6.46 (1H, s, 6′-H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ 9.3 (3′-CH_3), 9.3 (8-CH_3), 23.6 (C6), 32.6 (C2a), 40.2 (*N*CH_3), 54.4 (C1), 56.1 (C2), 56.4 (OCH_3), 57.9 (C5), 60.3 (OCH_3), 60.4 (OCH_3), 60.5 (OCH_3), 112.2 (C6′), 115.5 (C6a), 118.7 (C1′), 118.8 (C8), 119.1 (C3′), 121.5 (C10a), 144.5 (C10), 146.3 (C2′), 146.8 (C5′), 146.9 (C4′), 148.1 (C7), 149.5 (C9), 172.4 (C4); EIMS *m*/*z* 472 (M^+, 47), 457 (12), 234 (100); HREIMS *m*/*z* 472.2210 (M^+, calcd for $C_{25}H_{32}N_2O_7$, 472.2208).

2.3.4. Ethyl (6S,9S*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-4,13-dihydroxy-1,2,10,11-tetramethoxy-3,12,16-trimethyl-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one-9-carboxylate (**26**).* TMSOTf (0.33 mL, 1.85 mmol) was added to a suspended solution of **25** (209.0 mg, 0.443 mmol) and ethyl diethoxyacetate (83.0 mL, 0.46 mmol) in dichloroethane (15 mL), and the reaction mixture was heated at 120 °C for 13 h. The reaction mixture was diluted with saturated $NaHCO_3$ (200 mL) and extracted with chloroform (3×200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (246 mg). Chromatography of this residue on a silica gel (120 g) column with dichloromethane–methanol (50/1) gave **26** (190.0 mg, 77.1%) as a pale yellow amorphous powder, the recrystallization of which from ethyl acetate–ether afforded **26** as colorless prisms, mp 253–254 °C. IR (KBr) 3399, 2940, 1732, 1639, 1460, 1422, 1350, 1281, 1192, 1117, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (3H, t, *J*=7.0 Hz, OC$H_2$$CH_3$), 2.06 (3H, s, 12-$CH_3$), 2.11 (3H, s, 3-$CH_3$), 2.30 (1H, dd, *J*=16.8, 10.4 Hz, 14-Hβ), 2.54 (3H, s, *N*CH_3), 2.77 (1H, d, *J*=17.7 Hz, 5-Hβ), 2.94 (1H, dd, *J*=16.8, 5.5 Hz, 14-Hα), 2.95 (1H, dd, *J*=17.7, 8.1 Hz, 5-Hα), 3.72 (3H, s, 2-OCH_3), 3.77 (3H, s, 10-OCH_3), 3.79 (3H, s, 11-OCH_3), 3.82 (1H, d, *J*=8.1 Hz, 6-H), 3.86 (3H, s, 1-OCH_3), 4.18 (1H, dq, *J*=10.7, 7.0 Hz, OC*H*CH_3), 4.25 (1H, dq, *J*=10.7, 7.0 Hz, OC*H*CH_3), 4.36 (1H, dd, *J*=5.5, 1.5 Hz, 15-H), 4.51 (1H, dt, *J*=10.4, 5.5 Hz, 14a-H), 4.80 (1H, br s, OH), 6.46 (1H, s, 9-H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.7 (3 or 12-CH_3), 8.8 (3 or 12-CH_3), 14.2 (OC$H_2$$CH_3$), 23.5 (C5), 24.8 (C14), 40.3 (*N*CH_3), 50.6 (C9), 52.3 (C14a), 54.6 (C15), 58.5 (C6), 60.1 (2-OCH_3), 60.2 (10 or 11-OCH_3), 60.3 (10 or 11-OCH_3), 60.7 (1-OCH_3), 61.7 (O$CH_2$$CH_3$), 114.7 (C4a), 115.3 (C9a), 117.5 (C3 or C12), 117.7 (C3 or C12), 121.8 (C13a), 122.9 (C15a), 143.8 (C10), 144.4 (C1), 146.9 (C13), 148.3 (C4), 149.3 (C2), 149.6 (C11), 169.9 (C7), 171.3 (C16); EIMS *m*/*z* 556 (M^+, 20), 484 (10), 234 (100); HREIMS *m*/*z* 556.2421 (M^+, calcd for $C_{29}H_{36}N_2O_9$, 556.2421). Anal. Calcd for $C_{29}H_{36}N_2O_9$: C, 62.58; H, 6.52; N, 5.03. Found: C, 62.79; H, 6.68; N, 4.98.

2.4. X-ray structure determination of compound 26[54]

All measurements were performed on a Rigaku AFC7S diffractometer with graphic-monochromated Cu Kα radiation (λ=1.54178 Å). The single crystal of **26** ($C_{29}H_{36}N_2O_6$) belongs to the triclinic space group *P*-1 (#2) with cell constants *a*=8.807 (5) Å, *b*=9.357 (4) Å, *c*=18.741 (6) Å, α=88.05 (3)°, β=86.28 (3)°, γ=66.65 (4)°, *V*=1415 (1) $Å^3$, *Z*=2, and D_c=1.306 g/cm^3. The data were collected at a temperature of −160.0 °C to a maximum 2θ value of 136.1°. A total of 5467 reflections were collected. The linear absorption coefficient, μ, for Cu Kα radiation was 8.097 cm^{-1}. The structure was solved by direct methods (SIR92)[55] and expanded using the Fourier technique. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but their positions were not refined: isotropic *B* values were refined. The final cycle of the full-matrix least-squares refinement was based on 5108 observed reflections [$I>2.00\sigma(I)$] and 398 variable parameters and converged with unweighted and weighted agreement factors of *R*=0.078, R_1=0.075, and *Rw*=0.212. Neutral atom scattering factors were taken from Cromer and Waber.[56] Anomalous dispersion effects were included in F_{calc};[57] the values for Δ*f*′ and Δ*f*″ were those of Creagh and McAuley.[58] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[59] All calculations were performed using the CrystalStructure[60,61] crystallographic software package. The drawing of the molecule was made by ORTEP.

2.4.1. Ethyl (6S,9S*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-4,13-[(4-methylphenyl)sulfoxy]-1,2,10,11-tetramethoxy-3,12,16-trimethyl-*

*6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one-9-carboxylate (**26a**).* TMSOTf (55.2 μL, 305 μmol) was added to a suspension of **23** (31.8 mg, 50.8 μmol) and ethyl diethoxyacetate (27.3 μL, 152 μmol) in dichloroethane (2 mL), and the reaction mixture was heated at 100 °C for 21.5 h. As a large amount of starting material still remained at this stage, TMSOTf (18.2 μL, 102 μmol) and ethyl diethoxyacetate (9.1 μL, 50.8 μmol) were added to the reaction mixture and the whole was heated at 100 °C for 20.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL) and extracted with chloroform (3×30 mL). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (60 mg). Chromatography of this residue on a silica gel (10 g) column with chloroform–methanol (100/1) gave **26a** (16.1 mg, 46%) as a pale yellow oil. IR (KBr) 3375, 2927, 2854, 1734, 1645, 1460, 1178, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.289 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.86 (3H, s, 12-CH_3), 2.11 (3H, s, 3-CH_3), 2.26 (1H, dd, *J*=17.1, 10.7 Hz, 14-Hβ), 2.50 (3H, s, TsCH_3), 2.55 (3H, s, *N*CH_3), 2.78 (1H, d, *J*=17.4 Hz, 5-Hβ), 2.97 (1H, dd, *J*=17.4, 7.6 Hz, 5-Hα), 3.26 (1H, dd, *J*=17.1, 4.2 Hz, 14-Hα), 3.69 (3H, s, 2-OCH_3), 3.74 (3H, s, 11-OCH_3), 3.83 (3H, s, 10-OCH_3), 3.87 (3H, s, 1-OCH_3), 3.86–3.90 (1H, overlapped, 6-H), 4.23 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 4.24–4.29 (1H, m, 14a-H), 4.31 (1H, br s, 15-H), 4.70 (1H, br s, OH), 6.34 (1H, s, 9-H), 7.38 (2H, d, *J*=8.2 Hz, 2×2′-H), 7.86 (2H, d, *J*=8.2 Hz, 2×3′-H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.7 (3-CH_3), 10.8 (12-CH_3), 14.2 (OCH_2CH_3), 21.4 (TsCH_3), 23.6 (C5), 26.5 (C14), 40.4 (*N*CH_3), 51.2 (C9), 52.4 (C14a), 54.2 (C15), 58.6 (C6), 59.9 (10-OCH_3), 60.0 (2-OCH_3), 60.3 (1-OCH_3), 60.6 (11-OCH_3), 61.7 (OCH_2CH_3), 114.3 (C4a), 117.3 (C3), 122.4 (C9a), 123.0 (C15a), 125.0 (C13a), 127.1 (C12), 128.6 (2×CH), 129.7 (2×CH), 133.6 (C1′), 141.0 (C13), 144.7 (C1), 145.3 (C4′), 147.8 (C4), 148.9 (C10), 149.3 (C2), 149.6 (C11), 169.8 (C7), 171.4 (C16); FABMS *m*/*z* 711 $[M+1]^+$; HRFABMS *m*/*z* 711.2585 (M^++1, calcd for $C_{36}H_{43}N_2O_{11}S$, 711.2588).

2.4.2. Ethyl (6S,9S*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-1,2,10,11-tetramethoxy-3,12,16-trimethyl-4,13-diphenylmethoxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one-9-carboxylate (**27**).* Benzyl bromide (0.114 mL. 0.955 mmol) was added to a suspension of **26** (177.0 mg, 0.318 mmol) and anhydrous K_2CO_3 (308.0 mg, 2.23 mmol) in acetone (20 mL), and the reaction mixture was heated under reflux for 12 h. The inorganic materials were removed by filtration and washed with chloroform (50 mL). The combined filtrates were concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (20 g) column with dichloromethane–methanol (100/1) gave **27** (205.5 mg, 87.7%) as a colorless oil. IR (KBr) 3443, 2838, 1732, 1663, 1456, 1418, 1371, 1341, 1281, 1267, 1251, 1211, 1115, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.16 (3H, s, 12-CH_3), 2.17 (3H, s, 3-CH_3), 2.22 (1H, dd, *J*=14.7, 10.8 Hz, 14-Hβ), 2.56 (3H, s, *N*CH_3), 2.95 (1H, d, *J*=18.1 Hz, 5-Hβ), 3.11 (1H, dd, *J*=18.1, 7.5 Hz, 5-Hα), 3.32 (1H, dd, *J*=14.7, 3.1 Hz, 14-Hα), 3.49 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.77 (1H, d, *J*=7.5 Hz, 6-H), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.17–4.29 (2H, m, $OCHCH_3$), 4.42 (1H, br s, 15-H), 4.40–4.47 (1H, m, 14a-H), 4.62 (1H, d, *J*=11.0 Hz, OCHAr), 4.72 (1H, d, *J*=11.0 Hz, OCHAr), 4.76 (1H, d, *J*=11.0 Hz, OCHAr), 4.78 (1H, d, *J*=11.0 Hz, OCHAr), 6.39 (1H, s, 9-H), 7.30–7.54 (10H, m, 10×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.7 (3 or 12-CH_3), 9.7 (3 or 12-CH_3), 14.3 (OCH_2CH_3), 24.5 (C5), 26.0 (C14), 40.6 (*N*CH_3), 51.3 (C9), 52.2 (C14a), 54.4 (C15), 58.8 (C6), 59.9 (OCH_3), 59.9 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 61.6 (OCH_2CH_3), 73.9 (OCH_2Ar), 74.0 (OCH_2Ar), 121.6 (C9a), 122.2 (C4a), 123.0 (C13a), 123.8 (C15a), 125.1 (C3), 125.2 (C12), 127.6 (C4″), 127.7 (C4′), 127.9 (C3″), 128.0 (C3′), 128.3 (C2″), 128.4 (C2′), 137.2 (C1′), 137.3 (C1″), 146.7 (C10), 147.2 (C1), 149.4 (C11), 149.7 (C2), 149.9 (C13), 151.1 (C4), 170.2 (C16), 171.2 (C7); EIMS *m*/*z* 736 (M^+, 1.4), 645 (100), 324 (38); HREIMS *m*/*z* 736.3360 (M^+, calcd for $C_{43}H_{48}N_2O_9$, 736.3361).

2.4.3. (6S,9S*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-9-hydroxymethyl-1,2,10,11-tetramethoxy-3,12,16-trimethyl-4,13-diphenylmethoxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one (**29a**).* Aqueous LiOH monohydrate (0.1 M, 15.8 mL, 1.58 mmol) was added to a stirred solution of **27** (529.0 mg, 0.72 mmol) in THF (48 mL) and methanol (16 mL), and the reaction mixture was stirred at 25 °C for 8 days. The reaction mixture was poured into saturated aqueous NH_4Cl solution (250 mL) and extracted with chloroform (3×500 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give corresponding carboxylic acid **28** as a solid, which was used in the next step without further purification. ^1H NMR (CD_3COD, 300 MHz) δ 2.13 (1H, m, 14-Hβ), 2.17 (6H, s, 3×ArCH_3), 2.55 (3H, s, *N*CH_3), 2.82 (1H, d, *J*=18.3 Hz, 5-Hβ), 3.07 (1H, dd, *J*=18.3, 7.7 Hz, 5-Hα), 3.36 (1H, dd, *J*=11.4, 3.3 Hz, 14-Hα), 3.49 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.75 (1H, d, *J*=7.5 Hz, 6-H), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.40–4.51 (1H, m, 14a-H), 4.51 (1H, br s, 15-H), 4.60–4.80 (4H, m, 2×OCH_2Ar), 6.21 (1H, s, 9-H), 7.22–7.55 (10H, m, 10×ArH); EIMS *m*/*z* 708 (M^+, 0.6), 631 (100), 325 (65).

Ethyl chloroformate (83 μL, 0.86 mmol) was added to a stirred solution of the above residue (**28**: 510.0 mg) and TEA (0.12 mL, 0.83 mmol) in THF (75 mL) at −7 °C, and the resulting mixture was stirred at the same temperature for 3 h. The precipitates were removed by filtration and the filter cake was carefully washed with THF (50 mL). The combined filtrates were stirred at 0 °C and sodium cyanoborohydride (60.6 mg, 1.60 mmol) was added. Then, the reaction mixture was stirred at 0 °C for 2 h, diluted with saturated aqueous NH_4Cl solution (500 mL), and extracted with chloroform (3×500 mL). The combined extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give a residue (520 mg). Chromatography of this residue on a silica gel (20 g) column with dichloromethane–methanol (100/1) gave **29a** (402.2 mg, 80.7%) as a colorless amorphous powder. IR (KBr) 3441, 1645, 1457, 1416, 1371, 1339, 1115, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.17 (6H, s, 2×ArCH_3), 2.20 (1H, dd, *J*=17.1, 12.2 Hz, 14-Hβ), 2.57 (3H, s, *N*CH_3), 2.96 (1H, d, *J*=18.2 Hz, 5-Hβ), 3.09 (1H, dd, *J*=18.2, 7.9 Hz, 5-Hα), 3.35 (1H, dd, *J*=17.1, 4.0 Hz, 14-Hα), 3.49 (3H, s, OCH_3), 3.77 (1H, overlapped, 6-H), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (1H, overlapped, 9-CH), 3.87 (3H, s, OCH_3), 4.06 (1H, dd, *J*=11.6, 3.7 Hz, 9-CH), 4.46 (1H, br d, *J*=4.3 Hz, 15-H), 4.55 (1H, m, 14a-H), 4.60 (1H, d, *J*=10.6 Hz, OCHAr), 4.73 (1H, d, *J*=11.3 Hz, OCHAr), 4.78 (1H, d, *J*=10.6 Hz, OCHAr), 4.79 (1H, d, *J*=11.3 Hz, OCHAr), 5.98 (1H, dd, *J*=7.6, 3.7 Hz, 9-H), 7.29–7.54 (10H, m, 10×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.5 (ArCH_3), 9.7 (ArCH_3), 23.6 (C5), 25.9 (C14), 40.2 (*N*CH_3), 50.6 (C9), 52.0 (C14a), 54.4 (C15), 58.6 (C6), 60.0 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 65.7 ($9CH_2$), 73.9 (OCH_2Ar), 73.9 (OCH_2Ar), 122.0 (C9a), 122.2 (C4a), 123.0 (C13a), 123.2 (C15a), 124.7 (C3), 125.3 (C12), 127.7 (C4″), 127.8 (C4′), 128.0 (C3″), 128.1 (C3′), 128.4 (C2″), 128.5 (C2′), 137.2 (C1′), 137.3 (C1″), 146.0 (C10), 147.6 (C1), 149.8 (C11), 149.8 (C2), 150.2 (C13), 151.2 (C4), 171.7 (C7); FABMS *m*/*z* 695 $[M+1]^+$; HRFABMS *m*/*z* 695.3334 (M^++1, calcd for $C_{41}H_{47}N_2O_8$, 695.3332).

2.4.4. (6S,9S*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-1,2,10,11-tetramethoxy-3,12,16-trimethyl-4,13-diphenylmethoxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one-9-carbaldehyde (**30a**).* Oxalyl chloride (0.53 mL, 6.18 mmol) was added to a stirred solution of DMSO (0.878 mL, 12.4 mmol) at −78 °C over 10 min and the resulting mixture was stirred at the same temperature for 10 min. Then, a solution of **29a** (536.0 mg, 0.772 mmol) in dichloromethane (30 mL) was added dropwise to the above mixture over 5 min. After being kept at the same temperature for 2 h, the temperature was increased to −60 °C and kept there for 2 h. TEA (2.2 mL, 15.4 mmol) was added to the reaction mixture and stirring was continued at −40 °C for 1 h, and then at 25 °C for 1.5 h. The reaction mixture was concentrated in vacuo and the residue was diluted with saturated aqueous $NaHCO_3$ solution (500 mL) and extracted with dichloromethane (3×500 mL). The combined

extracts were washed with brine (500 mL), dried, and concentrated in vacuo to give a residue. The residue (671.0 mg) was subjected to chromatography on a silica gel (20 g) column with ethyl acetate–hexane (2/1) to give **30a** (489.3 mg, 91.5%) as a colorless amorphous powder. IR (KBr) 3435, 2936, 1734, 1654, 1456, 1418, 1371, 1341, 1271, 1115, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.18 (3H, s, $ArCH_3$), 2.20 (3H, s, $ArCH_3$), 2.21 (1H, dd, J=16.8, 12.6 Hz, 14-Hβ), 2.72 (3H, s, NCH_3), 3.00 (1H, d, J=18.0 Hz, 5-Hβ), 3.17 (1H, dd, J=18.0, 8.0 Hz, 5-Hα), 3.37 (1H, dd, J=16.8, 3.7 Hz, 14-Hα), 3.54 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (1H, d, J=8.0 Hz, 6-H), 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.18 (1H, ddd, J=12.6, 4.6, 3.7 Hz, 14a-H), 4.39 (1H, br d, J=4.6 Hz, 15-H), 4.58 (1H, d, J=11.0 Hz, OCHAr), 4.73 (1H, d, J=11.3 Hz, OCHAr), 4.77 (1H, d, J=11.3 Hz, OCHAr), 4.78 (1H, d, J=11.0 Hz, OCHAr), 6.27 (1H, s, 9-H), 7.30–7.55 (10H, m, 10×ArH), 9.72 (1H, s, CHO); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.6 ($ArCH_3$), 9.7 ($ArCH_3$), 25.1 (C5), 25.7 (C14), 40.8 (NCH_3), 52.7 (C14a), 54.6 (C15), 58.6 (C6), 58.7 (C9), 60.0 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 60.1 (OCH_3), 73.8 (OCH_2Ar), 74.0 (OCH_2Ar), 118.5 (C9a), 122.4 (C4a), 123.2 (C13a), 125.2 (C3), 125.7 (C12), 127.6 (C15a), 127.6 (C4″), 127.8 (C4′), 128.0 (C3″), 128.2 (C3′), 128.5 (C2″), 128.5 (C2′), 137.1 (C1′), 137.3 (C1″), 145.8 (C10), 147.2 (C1), 149.8 (C11), 149.9 (C2), 150.6 (C4), 151.3 (C13), 172.0 (C7), 196.1 (CHO); FABMS m/z 693 $[M+1]^+$; HRFABMS m/z 693.3179 (M^++1, calcd for $C_{41}H_{45}N_2O_8$, 693.3176).

2.5. Transformation of 30a into 30b (epimerization of C9 position)

DBU (0.207 mL, 1.39 mmol) was added to a stirred solution of **30a** (930.0 mg, 1.39 mmol) in THF (250 mL), and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (1 L) and extracted with chloroform (3×1 L). The combined extracts were washed with brine (1 L), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (50 g) column with ethyl acetate–hexane (2/1) gave **30a** (290.4 mg, 31% recovery). Further elution with ethyl acetate–hexane (2/1)~ethyl acetate gave **30b** (571.8 mg, 62.0%).

Recovered **30a** (290.4 mg) was treated again with DBU (62.8 μL, 0.42 mmol) in THF (100 mL) at 25 °C for 1 h to give **30b** (158.9 mg) and **30a** (99.0 mg). Furthermore, recovered **30a** (99.0 mg) was treated with DBU (21.4 mL, 0.14 mmol) at 25 °C for 24 h, and performing the same work-up and separation described above afforded **30b** (60.0 mg) and **30a** (37.1%). Thus, 790.7 mg of **30b** (85.0%) could be obtained along with recovered **30a** (37.1 mg, 4.0%).

2.5.1. (6S,9R*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-1,2,10,11-tetramethoxy-3,12,16-trimethyl-4,13-diphenylmethoxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one-9-carbaldehyde (**30b**).* Colorless amorphous powder. IR (KBr) 3447, 2936, 1736, 1651, 1456, 1418, 1371, 1354, 1338, 1273, 1115, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.94 (1H, dd, J=15.4, 12.2 Hz, 14-Hβ), 2.20 (3H, s, $ArCH_3$), 2.23 (3H, s, $ArCH_3$), 2.50 (3H, s, NCH_3), 3.04 (1H, d, J=17.8 Hz, 5-Hβ), 3.14 (1H, dd, J=17.8, 6.2 Hz, 5-Hα), 3.59 (1H, dd, J=15.4, 2.1 Hz, 14-Hα), 3.69 (3H, s, OCH_3), 3.79 (1H, d, J=6.2 Hz, 6-H), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.92 (1H, dt, J=12.2, 2.1 Hz, 14a-H), 3.93 (3H, s, OCH_3), 4.28 (1H, br s, 15-H), 4.61 (1H, d, J=10.7 Hz, OCHAr), 4.69 (1H, d, J=10.7 Hz, OCHAr), 4.80 (1H, d, J=11.0 Hz, OCHAr), 4.83 (1H, d, J=11.0 Hz, OCHAr), 6.06 (1H, s, 9-H), 7.32–7.55 (10H, m, 10×ArH), 9.30 (1H, s, CHO); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.7 ($ArCH_3$), 9.7 ($ArCH_3$), 24.3 (C5), 25.79 (C14), 40.2 (NCH_3), 55.0 (C15), 56.9 (C14a), 58.6 (C6), 58.8 (C9), 60.1 (OCH_3), 60.1 (OCH_3), 60.2 (OCH_3), 60.7 (OCH_3), 74.5 (OCH_2Ar), 75.2 (OCH_2Ar), 119.1 (C9a), 122.5 (C4a), 125.3 (C3), 125.4 (C13a), 126.3 (C12), 128.0 (C15a), 128.0 (C3″), 128.0 (C2′), 128.2 (C4″), 128.4 (C4′), 128.5 (C3′), 128.6 (C2″), 136.1 (C1′), 137.4 (C1″), 146.7 (C10), 147.3 (C1), 149.9 (C11), 150.0 (C2), 150.2 (C13), 151.5 (C4), 170.4 (C7), 193.5 (CHO); FABMS m/z 693 $[M+1]^+$; HRFABMS m/z 693.3182 (M^++1, calcd for $C_{41}H_{45}N_2O_8$, 693.3176).

2.6. Reduction of 30b to generate 29b

Method A: Sodium cyanoborohydride (1.0 M THF solution, 88.0 μL, 88.0 μmol) was added to a stirred solution of **30b** (40.2 mg, 58.0 μmol) and acetic acid (0.43 mL, 7.2 mmol) in THF (8.0 mL) at 0 °C over 5 min, and the resulting mixture was stirred at 25 °C for 3.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with chloroform (3×100 mL). The combined extracts were washed with brine (100 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (10 g) column with chloroform~chloroform–methanol (50/1) gave **29b** (26.0 mg, 64.6%) as a colorless amorphous powder.

2.6.1. (6S,9R*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-9-hydroxymethyl-1,2,10,11-tetramethoxy-3,12,16-tri-methyl-4,13-diphenylmethoxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one (**29b**).* IR (KBr) 3431, 2935, 1645, 1630, 1456, 1416, 1371, 1337, 1279, 1250, 1115, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (1H, dd, J=15.3, 12.4 Hz, 14-Hβ), 2.22 (3H, s, $ArCH_3$), 2.25 (3H, s, $ArCH_3$), 2.44 (3H, s, NCH_3), 3.04 (1H, d, J=17.8 Hz, 5-Hβ), 3.12 (1H, dd, J=17.8, 6.5 Hz, 5-Hα), 3.27 (1H, dd, J=9.9, 6.5 Hz, 9-CH), 3.46 (1H, dd, J=9.9, 4.6 Hz, 9-CH), 3.51 (1H, dd, J=15.3, 2.2 Hz, 14-Hα), 3.72 (1H, d, J=6.5 Hz, 6-H), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.85 (1H, ddd, J=12.4, 3.1, 2.2 Hz, 14a-H), 3.89 (3H, s, OCH_3), 4.13 (1H, d, J=3.1 Hz, 15-H), 4.68 (1H, d, J=10.5 Hz, OCHAr), 4.73 (1H, d, J=10.5 Hz, OCHAr), 4.76 (1H, d, J=11.0 Hz, OCHAr), 4.79 (1H, d, J=11.0 Hz, OCHAr), 5.79 (1H, dd, J=6.5, 4.6 Hz, 9-H), 7.39–7.56 (10H, m, 10×ArH); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.7 ($ArCH_3$), 9.8 ($ArCH_3$), 25.0 (C5), 25.8 (C14), 40.2 (NCH_3), 52.5 (C9), 55.5 (C15), 58.3 (C14a), 59.6 (C6), 60.0 (OCH_3), 60.1 (OCH_3), 60.2 (OCH_3), 60.6 (OCH_3), 69.1 ($9CH_2$), 74.4 (OCH_2Ar), 75.4 (OCH_2Ar), 122.5 (C4a), 122.6 (C15a), 124.9 (C3), 125.1 (C13a), 125.2 (C9a), 125.3 (C12), 127.8 (C2″), 128.0 (C4″), 128.4 (C4′), 128.4 (C2′), 128.5 (C3″), 128.6 (C3′), 137.0 (C1′), 137.3 (C1″), 146.3 (C10), 147.3 (C1), 149.6 (C13), 150.0 (C2), 150.2 (C11), 151.4 (C4), 173.2 (C7); FABMS m/z 695 $[M+1]^+$; HRFABMS m/z 695.3327 (M^++1, calcd for $C_{41}H_{47}N_2O_8$, 695.3332).

Method B: A 0.5 M THF solution of $NaBH(HFIP)_3$ (0.258 mL, 0.129 mmol) was added to a stirred solution of **30b** (14.9 mg, 21.5 μmol) in dichloromethane (3.7 mL) at 0 °C over 5 min, and the resulting mixture was stirred at 25 °C for 32 h. The reaction mixture was diluted with saturated aqueous NH_4Cl solution (40 mL) and extracted with chloroform (3×40 mL). The combined extracts were washed with brine (40 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (7 g) column with chloroform gave **29b** (4.0 mg, 26.8%) as a colorless solid. Further elution with chloroform–methanol (20/1) gave **29a** (10.6 mg, 71.1%) as a colorless solid.

2.6.2. (6S,9R*,14aS*,15R*)-6,7,9,14,14a,15-Hexahydro-4,13-dihydroxy-9-hydroxymethyl-1,2,10,11-tetramethoxy-3,12,16-trimethyl-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one (**31**).* A solution of **29b** (103.0 mg, 0.148 mmol) in methanol (35 mL) was hydrogenated over 20% $Pd(OH)_2$–C (31.2 mg) at 25 °C for 2 h. The catalyst was removed by filtration and washed with methanol (50 mL) and then chloroform (50 mL). The combined filtrates were concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (6 g) column with chloroform–methanol (50/1) gave **31** (76.5 mg, 100%) as a colorless amorphous powder. IR (KBr) 3418, 2940, 1628, 1462, 1420, 1352, 1277, 1254, 1117, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (1H, dd, J=15.6, 12.8 Hz, 14-Hβ), 2.13 (6H, s, 2×$ArCH_3$), 2.44 (3H, s, NCH_3), 2.85 (1H, d, J=17.9 Hz, 5-Hβ), 3.05 (1H, dd, J=17.9, 6.8 Hz, 5-Hα), 3.13 (1H, dd,

J=10.7, 6.5 Hz, 9-CH), 3.34 (1H, dd, *J*=10.7, 4.5 Hz, 9-CH), 3.51 (1H, dd, *J*=15.6, 2.5 Hz, 14-Hα), 3.70 (1H, br d, *J*=6.8 Hz, 6-H), 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (1H, overlapped, 14a-H), 4.27 (1H, d, *J*=3.4 Hz, 15-H), 5.59 (1H, dd, *J*=6.5, 4.5 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 9.5 ($ArCH_3$), 9.6 ($ArCH_3$), 25.5 (C5), 26.7 (C14), 40.1 (*N*CH_3), 52.7 (C9), 56.7 (C15), 59.8 (C14a), 60.4 (OCH_3), 60.6 (C6), 60.8 (OCH_3), 61.0 (OCH_3), 61.1 (OCH_3), 65.7 ($9CH_2$), 117.1 (C4a), 120.1 (C3), 120.5 (C12), 121.8 (C13a), 122.6 (C15a), 125.8 (C9a), 145.2 (C10), 145.9 (C1), 148.6 (C13), 150.1 (C4), 151.1 (C2), 151.9 (C11), 173.2 (C7); FABMS *m*/*z* 515 $[M+1]^+$; HRFABMS *m*/*z* 515.2397 (M^++1, calcd for $C_{27}H_{35}N_2O_8$, 515.2393).

2.6.3. (6S,9R*,14aS*15R*)-6,7,9,14,14a,15-Hexahydro-9-hydroxymethyl-2,11-dimethoxy-3,12,16-trimethyl-1,4,7,10,13-pentaoxo-6,15-imino-4H-isoquino[3,2-b][3]benzazocin (**32**).* A solution of CAN (27.7 mg, 50.6 μL) was added to a stirred solution of **31** (5.2 mg, 10.1 μmol) in acetonitrile at 0 °C within 1 min, and the resulting mixture was stirred at the same temperature for 15 min. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (3×10 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (3 g) column with ethyl acetate–hexane (1/5) gave **32** (76.5 mg, 100%) as a colorless amorphous powder. IR (KBr) 3431, 2936, 1657, 1616, 1445, 1431, 1373, 1352, 1308, 1277, 1233, 1150, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.68 (1H, ddd, *J*=16.5, 12.2, 1.2 Hz, 14-Hβ), 1.94 (3H, s, $QuCH_3$), 1.95 (3H, s, $QuCH_3$), 2.38 (3H, s, *N*CH_3), 2.68 (1H, d, *J*=20.7 Hz, 5-Hβ), 2.89 (1H, dd, *J*=20.7, 6.6 Hz, 5-Hα), 3.06 (1H, dd, *J*=16.5, 2.7 Hz, 14-Hα), 3.44 (1H, dd, *J*=11.3, 4.3 Hz, 9-CH), 3.69 (1H, br d, *J*=6.6 Hz, 6-H), 3.74 (1H, dd, *J*=11.3, 3.4 Hz, 9-CH), 3.90 (1H, br d, *J*=12.2 Hz, 14a-H), 3.98 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.14 (1H, br s, 15-H), 5.30 (1H, ddd, *J*=4.3, 3.4, 1.2 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.9 ($QuCH_3$), 8.9 ($QuCH_3$), 24.3 (C5), 25.8 (C14), 39.9 (*N*CH_3), 52.5 (C9), 53.4 (C15), 57.0 (C14a), 59.2 (C6), 61.4 (OCH_3), 61.4 (OCH_3), 65.7 ($9CH_2$), 129.2 (C3), 129.7 (C12), 135.2 (C15a), 137.1 (C9a), 142.2 (C4a), 142.3 (C13a), 156.0 (C2), 156.0 (C11), 171.2 (C7), 181.2 (C10), 182.7 (C1), 185.7 (C13), 186.8 (C4); FABMS *m*/*z* 483 $[M+1]^+$; HRFABMS *m*/*z* 483.1768 (M^++1, calcd for $C_{25}H_{27}N_2O_8$, 483.1767).

2.7. Two-step synthesis of (±)-renieramycin G (1g) from 31 via 32

An aqueous (0.24 mL) solution of CAN (27.7 mg, 50.6 μL) was added to a stirred solution of **31** (5.2 mg, 10.1 μmol) in acetonitrile at 0 °C within 1 min, and the resulting mixture was stirred at the same temperature for 15 min. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (3×10 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give **32** (4.9 mg), which was used in the following step without further purification.

Angeloyl chloride (24.0 mg, 0.20 mmol) was added to a stirred solution of crude **32** described above in dichloromethane (1.0 mL), and the resulting mixture was stirred at 25 °C for 25 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (15 mL) and extracted with dichloromethane (3×15 mL). The combined extracts were washed with brine (15 mL), dried, and concentrated in vacuo to give a residue (17.2 mg). Chromatography of this residue on a silica gel (4 g) column with ethyl acetate–hexane (2/1) gave **1g** (2.1 mg, 36% in two steps) as a dark brown amorphous powder. IR (KBr) 2945, 1717, 1655, 1616, 1449, 1422, 1373, 1352, 1307, 1231, 1150 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 1.37 (3H, quint, *J*=1.4 Hz, C=CCH_3), 1.51 (1H, ddd, *J*=16.5, 12.2, 2.2 Hz, 14-Hβ), 1.55 (3H, dq, *J*=7.4, 1.4 Hz, C=CH*CH*$_3$), 1.81 (3H, s, *N*CH_3), 1.87 (3H, s, 3-CH_3), 1.90 (3H, s, 12-CH_3), 2.61 (1H, dd, *J*=21.0, 7.2 Hz, 5-Hα), 2.87 (1H, dd, *J*=20.7, 0.6 Hz, 5-Hβ), 3.10 (1H, dd, *J*=16.5, 3.2 Hz, 14-Hα), 3.38 (1H, dt, *J*=12.2, 3.2 Hz, 14a-H), 3.49 (1H, d, *J*=7.2 Hz, 6-H), 3.63 (3H, s, 2-OCH_3), 3.79 (3H, s, 11-OCH_3), 3.83 (1H, d, *J*=3.2 Hz, 15-H), 4.52 (1H, dd, *J*=11.6, 2.2 Hz, 9-CH), 4.92 (1H, dd, *J*=11.6, 2.2 Hz, 9-CH), 5.35 (1H, qq, *J*=7.4, 1.4 Hz, C=*CH*CH_3), 5.56 (1H, q, *J*=2.2 Hz, 9-H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.6 ($QuCH_3$), 8.6 ($QuCH_3$), 15.3 (C 4′), 20.3 (2′-CH_3), 23.6 (C5), 26.0 (C14), 39.3 (*N*CH_3), 50.8 (C9), 53.3 (C15), 56.0 (C14a), 59.2 (C6), 60.5 (2-OCH_3), 60.9 (11-OCH_3), 62.9 ($9CH_2$), 126.9 (C2′), 127.5 (C12), 128.8 (C3), 135.1 (C15a), 136.3 (C9a), 139.1 (C3′), 141.1 (C13a), 142.2 (C4a), 155.5 (C2), 156.4 (C11), 166.8 (C1′), 170.0 (C7), 180.4 (C10), 182.7 (C1), 185.0 (C13), 185.9 (C4); FABMS *m*/*z* 565 $[M+1]^+$; HRFABMS *m*/*z* 565.2183 (M^++1, calcd for $C_{30}H_{33}N_2O_9$, 565.2186).

2.8. Preparation of angelate 33 from 31

Oxalyl chloride (17.0 μL, 0.20 mmol) and DMF (1.5 μL, 19.8 μmol) were added to a stirred solution of commercially available angelic acid (20.2 mg, 0.20 mmol) in ether (1.0 mL) at 0 °C, and the resulting mixture was stirred at 25 °C for 2 h. A dichloromethane (0.5 mL) solution of **31** (5.0 mg, 9.7 μmol) was added to the above mixture over 5 min, the resulting mixture was concentrated in vacuo with a stream of argon gas to give a residue. Dichloroethane (1.0 mL) was added to the residue and the resulting mixture was heated at 80 °C for 3 h. After being concentrated, the crude product was subjected to chromatography [silica gel 4 g; elution with chloroform–methanol (30/1)] to give **33** (5.4 mg, 93%) as a colorless amorphous powder.

2.8.1. (6S,9R*,14aS*15R*)-6,7,9,14,14a,15-Hexahydro-4,13-dihydroxy-9-hydroxymethyl-1,2,10,11-tetramethoxy-3,12,16-trimethyl-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-7-one angelate (**33**).* IR (KBr) 3414, 2930, 1719, 1636, 1458, 1420, 1351, 1296, 1279, 1148, 1117, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (3H, quint, *J*=1.4 Hz, C=CH*CH*$_3$), 1.59 (3H, dq, *J*=7.1, 1.4 Hz, C=CCH_3), 2.04 (1H, dd, *J*=15.3, 11.5 Hz, 14-Hβ), 2.14 (3H, s, 12-CH_3), 2.15 (3H, s, 3-CH_3), 2.43 (3H, s, *N*CH_3), 2.81 (1H, d, *J*=17.3 Hz, 5-Hβ), 3.01 (1H, dd, *J*=17.3, 7.4 Hz, 5-Hα), 3.25 (1H, dd, *J*=15.3, 2.6 Hz, 14-Hα), 3.76 (3H, s, 2-OCH_3), 3.80 (1H, d, *J*=7.4 Hz, 6-H), 3.81 (3H, s, 11-OCH_3), 3.83 (3H, s, 10-OCH_3), 3.84 (3H, s, 1-OCH_3), 3.92 (1H, ddd, *J*=11.5, 2.8, 2.6 Hz, 14a-H), 4.14 (1H, dd, *J*=11.3, 2.9 Hz, 9-CH), 4.19 (1H, d, *J*=2.8 Hz, 15-H), 4.49 (1H, dd, *J*=11.3, 3.9 Hz, 9-CH), 5.70 (1H, dd, *J*=3.9, 2.9 Hz, 9-H), 5.73 (1H, qq, *J*=7.1, 1.4 Hz, *CH*=CCH_3); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 8.9 ($ArCH_3$), 8.9 ($ArCH_3$), 15.1 (C4′), 20.1 (2′-CH_3), 23.3 (C5), 25.5 (C14), 40.0 (*N*CH_3), 49.8 (C9), 55.4 (C15), 58.1 (C14a), 59.3 (C6), 60.1 (OCH_3), 60.3 (OCH_3), 60.6 (OCH_3), 60.7 (OCH_3), 64.7 ($9CH_2$), 114.9 (C4a), 117.0 (C12), 117.7 (C3), 118.7 (C13a), 124.2 (C9a), 127.5 (C2′), 128.1 (C15a), 137.1 (C3′), 143.7 (C10), 144.6 (C1), 146.1 (C13), 148.1 (C4), 149.5 (C11), 149.7 (C2), 167.0 (C1′), 171.0 (C7); EIMS *m*/*z* 596 (M^+, 16), 234 (100); HREIMS *m*/*z* 596.2736 (M^+, calcd for $C_{32}H_{40}N_2O_9$, 596.2734).

2.9. Preparation of (±)-renieramycin G (1g) from 33

An aqueous (0.53 mL) solution of CAN (43.7 mg, 79.7 μL) was added to a stirred solution of **33** (9.5 mg, 15.9 μmol) in acetonitrile at 0 °C in one portion, and the resulting mixture was stirred at the same temperature for 15 min. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (3×10 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue. Chromatography of this residue on a silica gel (6 g) column with ethyl acetate–hexane (2/1) gave **1g** (7.2 mg, 80.0%) as a colorless amorphous powder.

2.10. Cell growth inhibition assay (IC_{50})

A single-cell suspension (2×10^3 cells/well) was added to serially diluted test compounds in a microplate. The cells were then cultured for 4 days. Cells were enumerated with a cell counting kit (DOJINDO, Osaka, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with the untreated control.

Acknowledgements

This work was supported by a Grant-in Aid (No. 23590019) for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. This work was also partially supported by the Japan Society for the Promotion of Science (JSPS) Asia and Africa Science Platform Program (2010–2012), and a grant from the High-Tech Research Center Project, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan (No. S0801043). We are grateful to Dr. Takuo Tsukuda (Chugai Pharmaceutical Company, Kamakura Research Center) for conducting the cytotoxicity assay.

References and notes

1. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. Kubo, A.; Saito, N. *Studies in Natural Product Chemistry*; Elsevier: New York, NY, 1992; Vol. 10, pp 77–145.
3. Rinehart, K. L. *Med. Drug Rev.* **2000**, *102*, 1669–1730.
4. Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545–555.
5. Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265–269; Errata: **1982**, *104*, 5004.
6. He, H.-Y.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5822–5824.
7. Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721–3724.
8. Parameswaran, P. S.; Naik, C. G.; Kamat, S. Y.; Pramanik, B. N. *Indian J. Chem.* **1998**, *37B*, 1258–1263.
9. Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793–798.
10. Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305–7308.
11. Charupant, K.; Suwanborirux, K.; Amnuoypol, S.; Saito, E.; Kubo, A.; Saito, N. *Chem. Pharm. Bull.* **2007**, *55*, 81–86.
12. Lane, J. W.; Estevez, A.; Mortara, K.; Callan, O.; Spencer, J. R.; Williams, R. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3180–3183.
13. Wright, B. J. D.; Chan, C.; Danishefsky, S. J. *J. Nat. Prod.* **2008**, *71*, 409–414.
14. Suwanborirux, K.; Amnuoypol, S.; Plubrukarn, A.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2003**, *66*, 1441–1446.
15. Amnuoypol, S.; Suwanborirux, K.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2004**, *67*, 1023–1028.
16. Saito, N.; Tanaka, C.; Koizumi, Y.; Suwanborirux, K.; Amnuoypol, S.; Pummangura, S.; Kubo, A. *Tetrahedron* **2004**, *60*, 3873–3881.
17. Charupant, K.; Daikuhara, N.; Saito, E.; Amnuoypol, S.; Suwanborirux, K.; Owa, T.; Saito, N. *Bioorg. Med. Chem.* **2009**, *17*, 4548–4558.
18. Daikuhara, N.; Tada, Y.; Yamaki, S.; Charupant, K.; Amnuoypol, S.; Suwanborirux, K.; Saito, N. *Tetrahedron Lett.* **2009**, *50*, 4276–4278.
19. Saito, N.; Yoshino, M.; Charupant, K.; Suwanborirux, K. *Heterocycles* **2012**, *84*, 309–314.
20. Magnus, P.; Matthews, K. S. *Tetrahedron* **2012**, in press.
21. Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.
22. Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558–5561.
23. Liao, X. W.; Liu, W.; Dong, W. F.; Guan, B. H.; Chen, S. Z.; Liu, Z. Z. *Tetrahedron* **2009**, *65*, 5709–5715.
24. Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.
25. Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517–1520; Corrigendum: Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8458.
26. Chen, X.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3962–3965.
27. Yokoya, M.; Ito, H.; Saito, N. *Tetrahedron* **2011**, *67*, 9185–9192.
28. Yokoya, M.; Shinada-Fujino, K.; Saito, N. *Tetrahedron Lett.* **2011**, *52*, 2446–2449.
29. Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295–4310.
30. Saito, N.; Harada, S.; Inouye, I.; Yamaguchi, K.; Kubo, A. *Tetrahedron* **1995**, *51*, 8231–8246.
31. Saito, N.; Yamauchi, R.; Kubo, A. *Heterocycles* **1991**, *32*, 1203–1214.
32. Yokoya, M.; Kawachi, O.; Saito, N. *Heterocycles* **2008**, *76*, 1497–1509.
33. For simplicity, natural product numbering was used in this manuscript, but IUPAC names and numbers were used in the Experimental.
34. Our starting material for the E-ring portion of **1g** was the commercially available 3,4-dimethoxyphenol, the phenolic OH protection of which followed by three steps (a: *n*-BuLi, MeI, THF, 0 °C; b: HCl–EtOH; c: HMTA, AcOH) gave **7** in 68% overall yield: see Experimental.
35. Sasaki, T. *Chem. Ber.* **1921**, *54*, 163–168.
36. Kubo, A.; Saito, N.; Yamato, H.; Kawakami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525–2532.
37. Aldehyde **5b** was prepared from **7** in 95% yield: see Experimental.
38. Saito, N.; Yamauchi, R.; Nishioka, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391–5395.
39. Chang, Y.-A.; Sun, T.-H.; Chiang, M. Y.; Lu, F.-J.; Huang, Y.-T.; Liang, L.-C.; Ong, C. W. *Tetrahedron* **2007**, *63*, 8781–8787.
40. Ong, C. W.; Chang, Y. A.; Wu, J.-Y.; Cheng, C.-C. *Tetrahedron* **2003**, *59*, 8245–8249.
41. Ong, C. W.; Lee, H. C. *Aust. J. Chem.* **1990**, *43*, 773–775.
42. Saito, N.; Seki, R.; Kameyama, N.; Sugimoto, R.; Kubo, A. *Chem. Pharm. Bull.* **2003**, *51*, 821–831.
43. Treatment of **23** with trimethylsilyl chloride (TMSCl) and TEA in dichloroethane at 25 °C for 2 h, followed by treatment with ethyl diethoxyacetate in the presence of TMSOTf at the same temperature for 17 h, and finally refluxing for 42 h gave an inseparable mixture of many products. In contrast, the reaction of **23** with ethyl diethoxyacetate in the presence of TMSOTf in dichloroethane at 120 °C for 42 h gave **26a** in 46% yield (see Experimental), but the product yield and reproducibility of this transformation were surprisingly low.
44. Isomerization of 1,3-disubstituted 1,2,3,4-tetrahydroisoquinoline derivatives by DBU was reported in the synthetic studies on ecteinascidin 743 (**4a**).[45,46]
45. Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543–546.
46. Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408.
47. The isomerization ratio of **30a** could not be varied by changing the reaction conditions, such as the reaction time, or the ratio of substrate to base along with the concentration of the substrate.
48. Saito, N.; Harada, S.; Yamashita, M.; Saito, T.; Yamaguchi, K.; Kubo, A. *Tetrahedron* **1995**, *51*, 8213–8330.
49. The hydride reduction of **30b** with $NaBH_4$ in alcohol afforded only a polar polymeric material. In contrast, the reduction of **30b** with sodium tris(1,1,1,3,3,3-hexafluoroisopropoxy)borohydride $[NaBH(HFIP)_3]$[50] at 25 °C for 32 h gave **29a** and **29b** in 71% and 27% yields, respectively.
50. Kuroiwa, Y.; Matsumura, S.; Toshima, K. *Synlett* **2008**, 2523–2525.
51. Gladding, J. A.; Bacci, J. P.; Shaw, S. A.; Smith, A. B., III. *Tetrahedron* **2011**, *67*, 6697–6706.
52. Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1980**, *45*, 1218–1224.
53. Witty, T. R.; Remers, W. A. *J. Med. Chem.* **1973**, *16*, 1280–1284.
54. Details of the crystal structure have been deposited at the Cambridge Crystallographic Data Center and the allocated deposition number is CCDC 821424.
55. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burita, M. C.; Polidori, G.; Carmalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435–436.
56. Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; The Kynoch: Birmingham, England, 1974; Vol. IV; Table 2.2A.
57. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781–782.
58. Creagh, D. C.; McAuley, W. J. *International Tables for X-ray Crystallography*; Kluwer Academic: Boston, MA, 1992; Vol. C, pp 219–222, Table 4.2.6.8.
59. Creagh, D. C.; Hubbell, J. H. *International Tables for X-ray Crystallography*; Kluwer Academic: Boston, MA, 1992; Vol. C, pp 2200–2206, Table 4.2.4.3.
60. *Crystal Structure 4.0: Crystal Structure Analysis Package*; Rigaku Corporation: Tokyo, Japan, 2000–2010.
61. Carruthuthers, J. R.; Rollett, J. S.; Betteridge, P. W.; Kinna, D.; Pearce, L.; Larsen, A.; Gabe, E. *CRYSTALS Issue 11*; Chemical Crystallography Laboratory: Oxford, UK, 1999.