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Article

Chemistry of Renieramycins. Part 14: Total Synthesis of Renieramycin I and Practical Synthesis of Cribrostatin 4 (Renieramycin H)

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Abstract: The first total synthesis of (±)-renieramycin I, which was isolated from the Indian bright blue sponge *Haliclona cribricutis*, is described. The key step is the selenium oxide oxidation of pentacyclic bis-*p*-quinone derivative (**3**) stereo- and regioselectively. We also report a large-scale synthesis of cribrostatin 4 (renieramycin H) via the C3-C4 double bond formation in an early stage based on the Avendaño's protocol, from readily available 1-acetyl-3-(3-methyl-2,4,5-trimethylphenyl)methyl-piperazine-2,5-dione (**8**) in 18 steps (8.3% overall yield). The synthesis provides unambiguous evidence supporting the original structure of renieramycin I.

Keywords: cribrostatin 4 (renieramycin H); renieramycin I; total synthesis; structural determination; selenium oxide oxidation; marine natural product

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1. Introduction

Many tetrahydroisoquinoline antitumor natural products, such as renieramycins, saframycins, and ecteinascidins, have attracted considerable interest due to their extraordinary structures and meager availability in nature, as well as their potent antitumor activity [1,2]. Among them, renieramycins H (**1h**) and I (**1i**) were isolated from the methanol extract of the Indian bright blue sponge *Haliclona*

cribricutis collected from the intertidal region of Okha, Gujarat, in 1988 [3]. Original structures **1h** and **1i** were given the names renieramycins H and I, respectively. Thereafter, we revised the structure of renieramycin H to that of cribrostatin 4 (**2**) [4–6], which was independently isolated from the blue sponge *Cribrochalina* sp. collected from reef passages in the Republic of Maldives, based on ^{13}C NMR studies of several semi-synthetic models (Figure 1) [7,8]. Cribrostatin 4 (**2**) has attracted the interest of several medicinal chemistry experts because of its unique structure and cytotoxicity despite the lack of the hemiaminal or aminonitrile function at C-21. Three total syntheses of **2** have been reported [9–11]. Recently, we completed a 21-step stereocontrolled total synthesis of (±)-**2** from 1-acetyl-3-(3-methyl-2,4,5-trimethylphenyl)methyl-piperazine-2,5-dione (**8**) in 3.4% overall yield [12,13]. Furthermore, we have accomplished the total synthesis of renieramycin G (**1g**) [14,15]. The availability of **1g** and **2** has enabled us to prepare several renieramycin derivatives having a lactam carbonyl to understand the molecular basis of their impressive cytotoxicity profiles. We present herein an alternative large-scale approach for the total synthesis of **2**. This approach might yield a variety of novel analogs of cribrostatin 4 (**2**), as well as C3-C4 unsaturated bis-*p*-quinone derivatives, such as renieramycin I (**1i**), for detailed studies of structure activity relationships (SARs) of these classes of antitumor marine natural products.

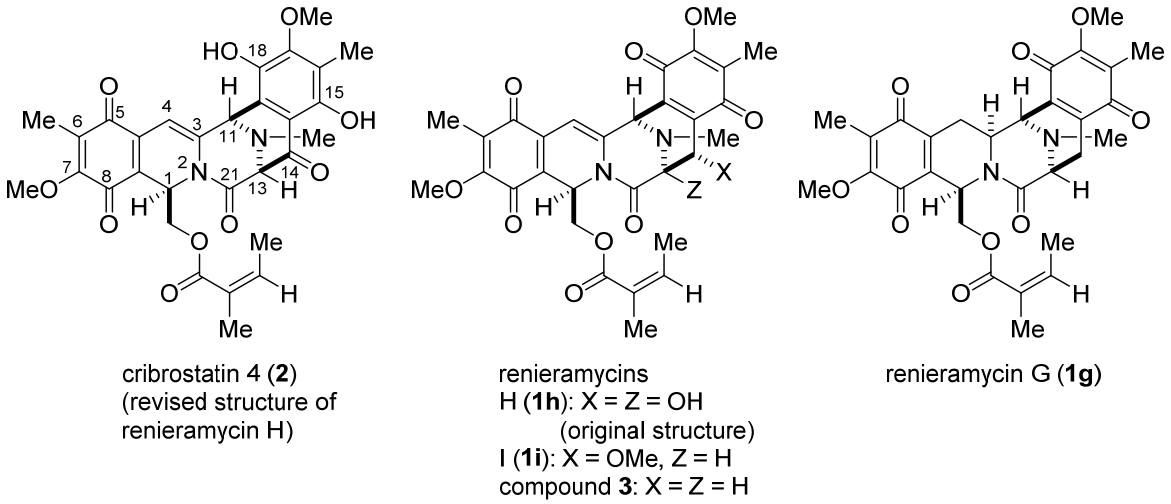


Figure 1. Structures of bis-1,2,3,4-tetrahydroisoquinoline marine natural products.

2. Results

The most serious problem in our previous cribrostatin 4 (**2**) synthesis was that 1-*epi*-pentacyclic alcohol (**4**) (Chart 1) might be formed, and the undesired stereochemistry had to be converted into the natural one at C-1 position via enolate formation through several cycles. Avendaño *et al*. reported that the stereocenter at C-3 of 1,3-*trans*-compound **5** [16] could be transformed into corresponding 1,3-*cis*-compound **7** via unsaturated compound **6** through regioselective radical bromination, followed by hydrogenation from the less hindered α-face in good yield [17]. They applied this protocol to the preparation of pentacyclic phthalascidin analogs [18]. We were very interested in this procedure for constructing the 1,3-*cis* relationships of renieramycins (Scheme 1) [19].

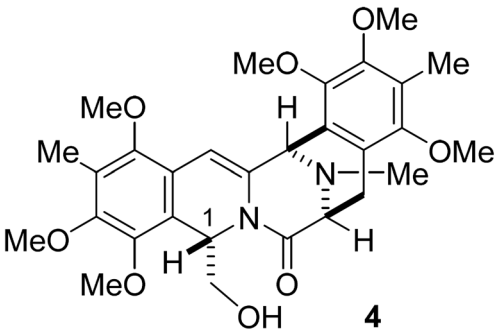
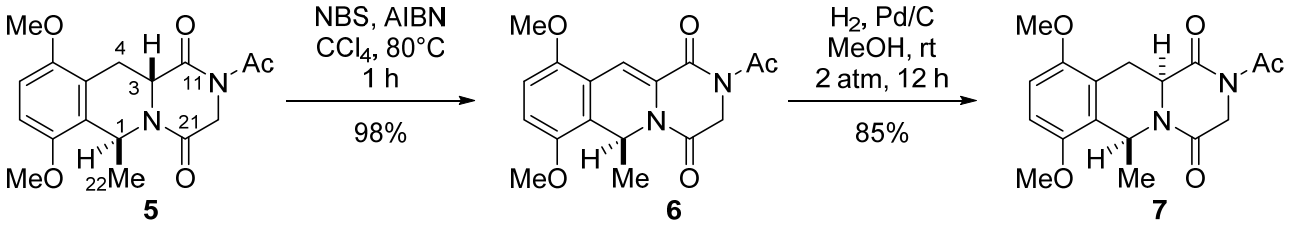
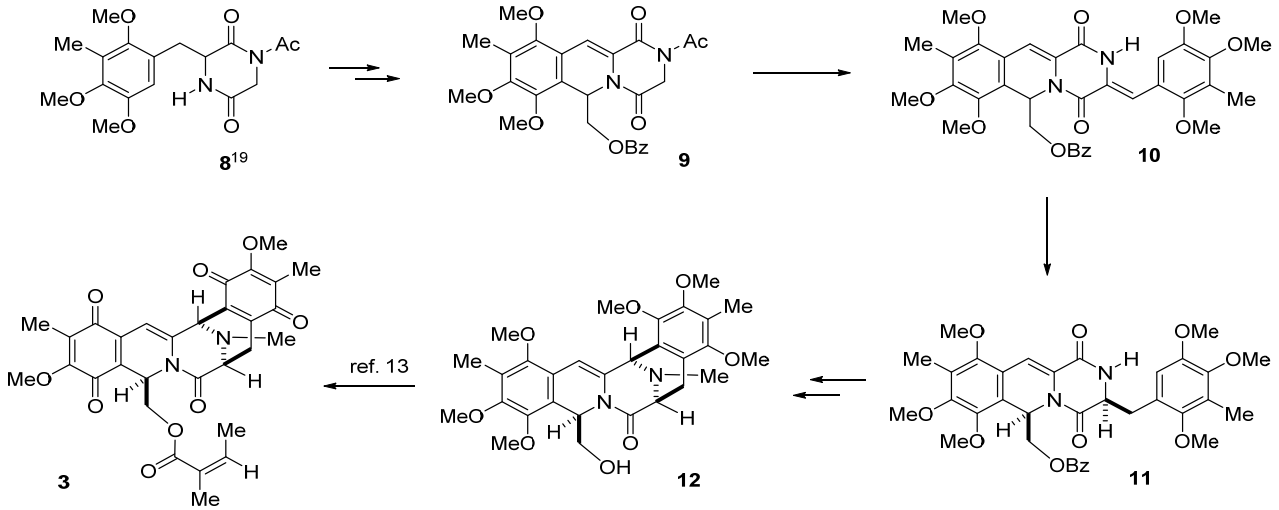


Chart 1. Structure of 1-*epi*-pentacyclic alcohol.



Scheme 1. Epimerization at C-3 through regioselective bromination at C-3 position and reduction sequences by Avendaño and co-workers.

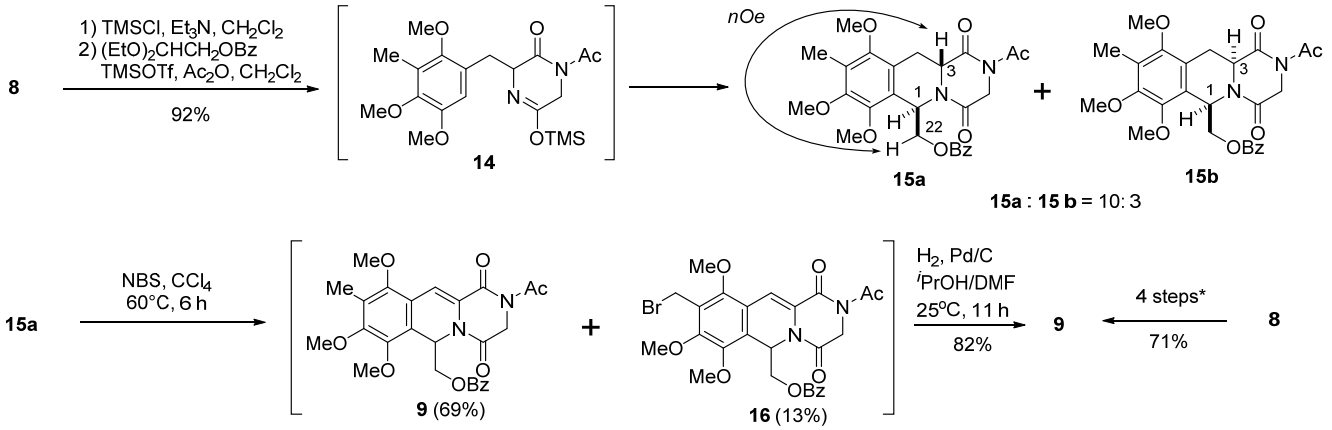
Based on Avendaño's protocol, we designed an alternative synthetic plan that involves the key transformations outlined in Scheme 2: (1) construction of tricyclic compound **9** having an α,β-unsaturated amide carbonyl from readily available compound **8** [20]; (2) condensation of **9** with benzaldehyde derivative and subsequent regio- and stereospecific hydrogenation leading to compound **11**; (3) construction of pentacyclic framework and conversion of ester into our intermediate **12**, which can be transformed into cribrostatin 4 intermediate **3** [13] (Scheme 2).



Scheme 2. Strategy for practical synthesis of compound **3**, which will be converted into **1i** and **2**.

According to the results of our previous studies [21,22], treatment of **8** with trimethylsilyl chloride (TMSCl) in the presence of triethylamine (TEA) in CH_2Cl_2 gave *O*-trimethylsilyl lactim intermediate **14**, which was treated with 2,2-diethoxyethyl benzoate in the presence of trimethylsilyl

triflate (TMSOTf) and acetic anhydride to give **15** as an inseparable mixture of diastereomers (**15a**:**15b** = 10:3) in 92% yield. After exerting a great deal of effort to separate this mixture by column chromatography several times, we obtained both isomers in their pure forms, and detailed 2D NMR studies confirmed the structures of **15a** (minor) and **15b** (major). The NMR spectrum of **15a** displayed H-1 and H-3 proton signals at δ 6.20 and δ 4.70, respectively, whereas the NMR spectrum of **15b** showed H-1 and H-3 proton signals appearing at δ 6.15 and δ 4.07, respectively. An observable nuclear Overhauser enhancement (NOE) between H-3 and H-22 revealed that compound **15a** has the *trans* form (Scheme 3).

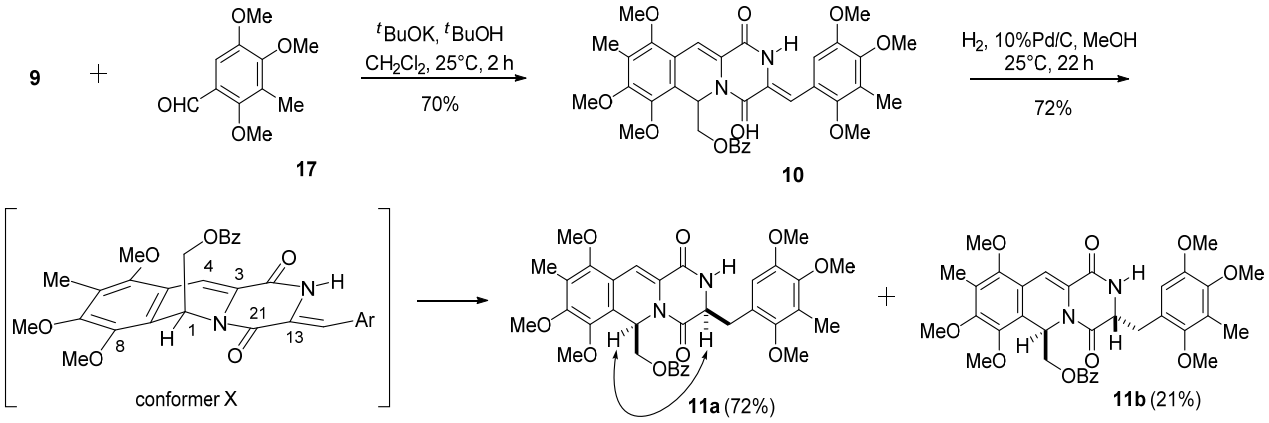


Scheme 3. 8 → 9: (1) TMSCl, TEA, CH_2Cl_2; (2) $(EtO)_2CHCH_2OBz$, TMSOTf, Ac_2O, CH_2Cl_2; (3) NBS, CCl_4, 60 °C, 3 h; (4) H_2, Pd/C, ^{i}PrOH/DMF, 25 °C, 11 h.

We then studied the conversion of **15** into unsaturated compound **9**, which is the first key step of our synthesis. A preliminary experiment was carried out using major isomer **15a**. According to the typical conditions of Avendaño *et al*. [17], **15a** was treated with *N*-bromosuccinimide (NBS: 1.0 equiv.) and 2,2′-azobisisobutyronitrile (AIBN: 0.1 equiv.) in CCl_4 at 80 °C for 6 h to generate **9** (55%) and **16** (4%) plus unreacted **15a** (33%). The ^{1}H NMR spectrum of **9** showed an H-4 olefinic proton signal that appeared as a singlet at δ 7.47. The ^{1}H NMR spectrum of **16** showed characteristic AB type doublet proton signals at δ 4.60 and δ 4.57 along with the H-4 olefinic singlet proton signal at δ 7.41. Accordingly, **16** might be a product of over-reaction product at C-6 aromatic methyl group. After extensive investigation of the reaction conditions, we found that the yield of our target **9** could be improved by slightly lowering the reaction temperature (60 °C) and excluding AIBN. Thus, the reaction of **15a** with NBS (2 equiv.) in CCl_4 at 60 °C for 6 h gave **9** (69%) and **16** (13%). It was extremely difficult to separate **9** and **16** in a large scale using silica gel column chromatography. However, catalytic reduction of the above mixture using 10% Pd/C in 2-propanol and DMF at 25 °C for 11 h gave **9** as the sole product in 82% overall yield. Accordingly, the transformation of **15a** into **9** without any purification of the intermediates was found to be the best choice in terms of overall yield (**9** in 71% yield in four steps).

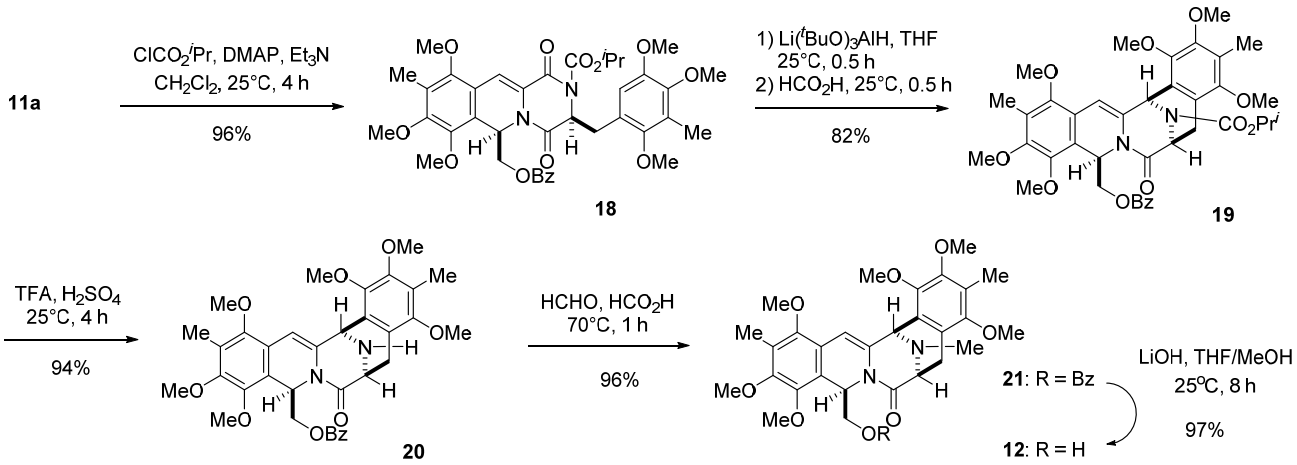
With key intermediate **9** in hand, we next looked into ways to design a practical transformation of **9** into **12**, which was the key intermediate in our previous total synthesis of cribrostatin 4 (**2**) (Schemes 4 and 5). Condensation of **9** with benzaldehyde derivative **17** [20] in the presence of potassium *tert*-butoxide gave (*Z*)-arylidenepiperazinedione **10** in 70% yield. Catalytic hydrogenation of the

trisubstituted double bond of **10** over 10% Pd on carbon in MeOH at 25 °C proceeded chemoselectively to give desired **11a** (72%) along with **11b** (21%). Detailed 2D NMR studies were performed to confirm the structures of **11a** and **11b**. The NMR spectrum of **11a** displayed H-1 and H-13 proton signals at δ 6.53 and δ 4.34, respectively, whereas the NMR spectrum of **11b** had H-1 and H-13 proton signals appearing δ 6.43 and δ 4.45, respectively. An NOE between H-1 and H-13 proton signals was observed in **11a** but not **11b**. Thus, the hydrogenation of **10** obviously occurred stereoselectively from the α-face to generate H-1 and H-13 cis isomer **11a**. It is proposed that the steric hindrance due to the C-8 methoxy group and the C-21 carbonyl group was responsible for the β-axial orientation of C-1 substituent as shown in conformer X of **10**.



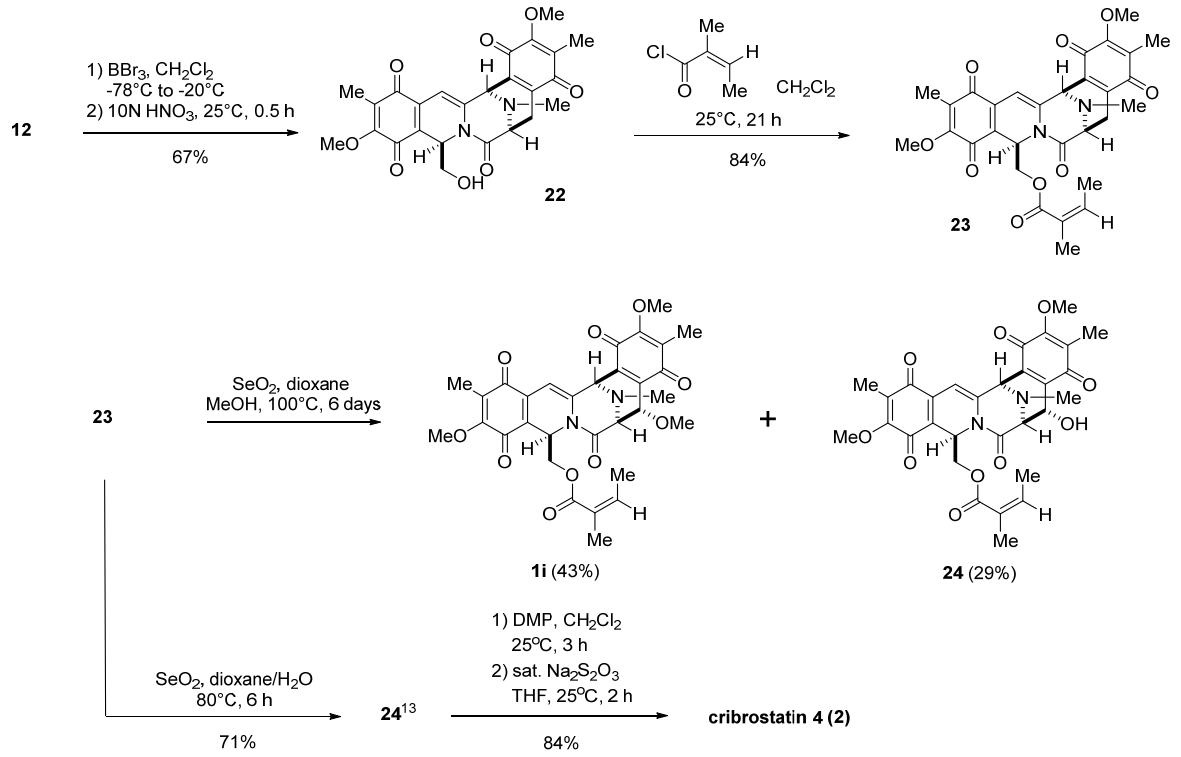
Scheme 4. Preparation of key intermediate **11a**.

The piperazinedione ring of **11a** was activated by introducing a 2-propyloxycarbonyl group to give imide **18** in 96% yield. Chemoselective reduction of **18** in the conventional manner afforded a hemiaminal, which was treated with formic acid at 25 °C for 0.5 h to afford **19** [23] in 82% yield. Deprotection of **19** with TFA and H_2SO_4 gave secondary amine **20**, which was transformed into **21** by reductive methylation in high yield. Hydrolysis of **21** with 10 N aqueous LiOH in THF/MeOH at 25 °C for 8 h gave primary alcohol **12** in 97% yield, which is identical to the intermediate in our previous total synthesis [13].



Scheme 5. Construction of pentacyclic primary alcohol **12**.

The conversion of **12** into **22** was accomplished by partial demethylation with boron tribromide (BBr_3), followed by oxidative demethylation to give bis-*p*-quinone **22** in 67% yield (Scheme 6). Acylation of **22** with in situ prepared angeloyl chloride in dichloromethane gave common intermediate **23** in 84% yield. Encouraged by the results of our extensive model studies, including the transformation of several natural products [24–26], the introduction of a methoxy group to the C-14 position of **23** was achieved using 10 equiv. of SeO_2 in a mixture of methanol and dioxane at 100 °C for six days to give **1i** in 43% yield along with secondary alcohol **24** in 29% yield. The orientation of the methoxy group of **1i** was assigned on the basis of the signal of 14-H (δ 4.34, d, J = 1.4 Hz). The spectroscopic properties of synthetic **1i** were in complete accord with those of natural renieramycin I (**1i**) [27].



Scheme 6. Transformation of compound **12** into renieramycin I (**1i**) and cribrostatin 4 (**2**) through compound **23**.

3. Experimental Section

IR spectra were obtained with a Shimadzu Prestige 21/IRAffinity-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 (ppm, J in Hz 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.

3.1. ((6R,11aR*)-2-Acetyl-7,8,10-trimethoxy-9-methyl-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2H-pyrazino-(1,2-b)isoquinolin-6-yl)methyl Benzoate (**15a**) and ((6R*,11aS*)-2-acetyl-7,8,10-trimethoxy-9-methyl- 1,4-dioxo-1,3,4,6,11,11a-hexahydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Benzoate (**15b**)*

TMSCl (498 μL, 3.9 mmol) was added to a stirred solution of **8** (1.05 g, 3.0 mmol) in dichloromethane (18 mL) and TEA (544 μL, 3.9 mmol), and stirring was continued at 25 °C for 2 h. A solution of 2,2-diethoxyethyl benzoate [28] (785.8 mg, 3.3 mmol) in dichloromethane (12 mL) followed by TMSOTf (2.71 mL, 15 mmol) was added dropwise for 5 min each, and then Ac_2O (283.6 μL, 3.0 mmol) was added in one portion at 25 °C and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (100 mL) and extracted with $CHCl_3$ (100 mL × 3). The combined extracts were washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1:2) to give **15** (1.37 g, 92%, **15a**:**15b** = 10:3) as a colorless amorphous powder, which was an inseparable mixture of diastereomers. Each authentic sample was obtained by chromatography on preparative layer silica gel plates (Merck 5715).

Compound **15a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (2H, m, Ar-H), 7.57 (1H, m, Ar-H), 7.44 (2H, m, Ar-H), 6.20 (1H, dd, *J* = 9.5, 3.9 Hz, C6-H), 4.75 (1H, dd, *J* = 11.7, 9.5 Hz, C12-H), 4.70 (1H, dd, *J* = 9.8, 5.4 Hz, C11a-H), 4.52 (1H, dd, *J* = 11.7, 3.9 Hz, C12-H), 4.36 (1H, d, *J* = 18.0 Hz, C3-H), 4.31 (1H, d, *J* = 18.0, C3-H), 3.95 (3H, s, C7-OMe), 3.80 (3H, s, C8-OMe), 3.72 (3H, s, C10-OMe), 3.40 (1H, dd, *J* = 16.6, 5.4 Hz, C11-Hα), 3.14 (1H, dd, *J* = 16.6, 9.8 Hz, C11-Hβ), 2.59 (3H, s, $COCH_3$), 2.21 (3H, s, C9-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.7 (s, $\underline{C}OCH_3$), 167.9 (s, C1), 166.6 (s, O$\underline{C}$OPh), 163.2 (s, C4), 152.4 (s, C10), 150.6 (s, C8), 146.2 (s, C7), 133.3 (d, Ph), 129.7 (d, Ph × 2), 129.6 (s, Ph), 128.5 (d, Ph × 2), 125.9 (s, C9), 122.6 (s, C6a), 121.4 (s, C10a), 63.6 (t, C12), 60.6 (q, C7-O$\underline{C}H_3$), 60.3 (q, C10-O$\underline{C}H_3$), 60.0 (q, C8-O$\underline{C}H_3$), 54.0 (d, C11a), 48.3 (d, C6), 45.7 (t, C3), 27.2 (q, CO$\underline{C}H_3$), 26.0 (t, C11), 9.5 (q, C9-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 1717, 1686, 1672, 1275, 714. EI-MS *m/z* (%): 496 (M^+, 11), 361 (100), 319 (13), 234 (15), 204 (8), 105 (7). HR-EI-MS: calcd for $C_{26}H_{28}N_2O_8$, 496.1846, found: 496.1841.

Compound **15b**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.93 (2H, m, Ar-H), 7.54 (1H, m, Ar-H), 7.42 (2H, m, Ar-H), 6.15 (1H, dd, *J* = 7.0, 4.6 Hz, C6-H), 5.10 (1H, d, *J* = 16.0 Hz, C3-H), 4.55 (1H, dd, *J* = 11.5, 7.0 Hz, C12-H), 4.37 (1H, dd, *J* = 11.5, 4.6 Hz, C12-H), 4.07 (1H, dd, *J* = 12.2, 4.9 Hz, C11a-H), 3.94 (3H, s, C7-OMe), 3.79 (3H, s, C8-OMe), 3.78 (1H, d, *J* =16.0 Hz, C3-H), 3.68 (1H, dd, *J* =15.9, 4.9 Hz, C11-Hα), 3.64 (3H, s, C10-OMe), 3.05 (1H, dd, *J* = 15.9, 12.2 Hz, C11-Hβ), 2.59 (3H, s, COMe), 2.22 (3H, s, C9-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.9 (s, $\underline{C}OCH_3$), 168.7 (s, C1), 166.4 (s, O$\underline{C}$OPh), 166.1 (s, C4), 151.7 (s, C10), 150.6 (s, C8), 146.2 (s, C7), 133.2 (d, Ph × 2), 129.7 (s, Ph), 129.6 (d, Ph), 128.4 (d, Ph × 2), 126.1 (s, C9), 123.6 (s, C6a), 121.8 (s, C10a), 66.1 (t, C12), 61.0 (q, C10-O$\underline{C}H_3$), 60.7 (q, C7-O$\underline{C}H_3$), 60.0 (q, C8-O$\underline{C}H_3$), 56.3 (d, C11a), 48.5 (d, C6), 45.6 (t, C3), 26.9 (q, CO$\underline{C}H_3$), 22.8 (t, C11), 9.4 (q, C9-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 1721, 1707, 1692, 1412, 1368, 1273. EI-MS *m/z* (%): 496 (M^+, 10), 361 (100), 319 (11), 234 (13), 204 (7), 105 (7). HR-EI-MS: calcd for $C_{26}H_{28}N_2O_8$, 496.1846, found: 496.1841.

*3.2. (2-Acetyl-7,8,10-trimethyl-1,4-dioxo-1,3,4,6-tetrahydro-2H-pyrazino(1,2-b)Isoquinoline-6-yl)methyl Beozoate (**9**) and (2-acetyl-9-(bromomethyl)-,7,8,10-trimethoxy-1,4-dioxo-1,3,4,6-tetrahydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Beozoate (**16**)*

NBS (106.8 mg, 0.6 mmol) was added to a stirred solution of **15a** (150.0 mg, 0.3 mmol) in dry CCl_4, and the reaction mixture was heated at 60 °C for 6 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was washed with CCl_4. The combined filtrates were concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel with ethyl acetate–hexane (1:3) as solvent to give **9** (102.0 mg, 69%) and **16** (17.7 mg, 13%).

Compound **9**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (2H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.47 (1H, s, C11-H), 7.42 (2H, m, Ar-H), 6.47 (1H, dd, *J* = 7.7, 3.8 Hz, C6-H), 4.93 (1H, d, *J* = 17.6 Hz, C3-H), 4.52 (1H, dd, *J* = 11.7, 7.7 Hz, C12-H), 4.27 (1H, dd, *J* = 11.7, 3.8 Hz, C12-H), 3.96 (3H, s, C7-OMe), 3.92 (1H, d, *J* =17.6 Hz, C3-H), 3.85 (3H, s, C8-OMe), 3.71 (3H, s, C10-OMe), 2.61 (3H, s, COMe), 2.21 (3H, s, C9-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.8 (s, $\underline{C}OCH_3$), 166.3 (s, O$\underline{C}$OPh), 162.7 (s, C4), 160.7 (s, C1), 154.1 (s, C8), 152.4 (s, C10), 146.0 (s, C7), 133.3 (d, Ph), 129.6 (d, Ph × 2), 129.4 (s, Ph), 128.5 (d, Ph × 2), 126.7 (s, C9), 125.8 (s, C11a or C10a), 121.5 (s, C6a), 118.9 (s, C11a or C10a), 114.7 (d, C11), 64.3 (t, C12), 62.1 (q, C10-O$\underline{C}H_3$), 60.8 (q, C7-O$\underline{C}H_3$), 60.2 (q, C8-O$\underline{C}H_3$), 47.9 (d, C6), 45.2 (t, C3), 26.7 (q, CO$\underline{C}H_3$), 9.4 (q, C9-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 1701, 1416, 1393, 1368, 1269, 1211, 1088, 1072, 1043, 1028, 1007, 964, 459. EI-MS *m*/*z* (%): 494 (M^+, 14), 359 (100), 260 (84), 232 (38), 217 (6), 202 (5), 105 (6). HR-EI-MS: calcd for $C_{26}H_{26}N_2O_8$, 494.1689, found: 494.1686.

Compound **16**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.90 (2H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.42 (2H, m, Ar-H), 7.41 (1H, s, C11-H), 6.49 (1H, dd, *J* = 7.7 Hz, 3.8 Hz, C6-H), 4.94 (1H, d, *J* =17.6 Hz, C3-H), 4.60 (1H, d, *J* =9.1 Hz, C9-C$\underline{H}_2$Br), 4.57 (1H, d, *J* = 9.1, C9-C$\underline{H}_2$Br), 4.55 (1H, dd, *J* = 11.6 Hz, 7.7 Hz, C12-H), 4.30 (1H, dd, *J* = 11.6 Hz, 3.8 Hz, C12-H), 4.03 (3H, s, C8-OMe), 3.97 (3H, s, C7-OMe), 3.90~3.95 (1H, overlapped, C3-H), 3.90 (3H, s, C10-OMe), 2.62 (3H, s, COC$\underline{H}_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.8 (s, $\underline{C}OCH_3$), 166.3 (s, O$\underline{C}$OPh), 162.7 (s, C4), 160.4 (s, C1), 153.9 (s, C8), 152.1 (s, C10), 146.0 (s, C7), 133.4 (d, Ph), 129.6 (d, Ph × 2), 129.3 (s, Ph), 128.5 (d, Ph × 2), 127.3 (s, C9), 126.3 (s, C10a or C11a), 125.1 (s, C6a), 119.4 (s, C10a or C11a), 113.6 (d, C11), 64.2 (t, C12), 63.4 (q, C10-O$\underline{C}H_3$), 60.7 (q, C7-O$\underline{C}H_3$ and C8-O$\underline{C}H_3$), 47.9 (d, C6), 45.2 (t, C3), 26.7 (q, CO$\underline{C}H_3$), 21.5 (t, C9-$\underline{C}H_2$Br). FT-IR (KBr) cm^{-1}: 1701, 1368, 1292, 1269, 1215. EI-MS *m*/*z* (%): 572 (M^+, 15), 493 (9), 439 (100), 417 (14), 393 (13), 375 (5), 371 (8), 364 (8), 359 (24), 339 (11), 310 (21), 274 (9), 260 (27), 231 (10), 105 (21). HR-EI-MS: calcd for $C_{26}H_{25}BrN_2O_8$, 572.0794, found: 572.0796.

*3.3. (2-Acetyl-7,8-10-trimethyl-1,4-dioxo-1,3,4,6-tetrahydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Benzoate (**9**) from **8** in Four Steps*

TMSCl (498 μL, 3.9 mmol) was added to a stirred solution of **8** (1.05 g, 3.0 mmol) in dichloromethane (18 mL) and TEA (544 μL, 3.9 mmol), and stirring was continued at 25 °C for 2 h. A solution of 2,2-diethoxyethyl benzoate (785.8 mg, 3.3 mmol) in dichloromethane (12 mL) followed by TMSOTf (2.71 mL, 15 mmol) was added dropwise respectively over 5 min. Then, Ac_2O (283.6 μL,

3.0 mmol) was added at 25 °C and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (100 mL) and extracted with $CHCl_3$ (100 mL × 3). The combined extracts were washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1:2) to give **15** (1.37 g, 92%, **15a**:**15b** = 10:3) as a colorless amorphous powder. Diastereomeric mixture **15** was dissolved in CCl_4 (90 mL) and NBS (106.8 mg, 5.46 nmol) was added at 25 °C, and the reaction mixture was heated at 60 °C for 3 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was washed with CCl_4. The combined filtrates were concentrated *in vacuo*, and the residue was used in the next step without further purification. The above residue was dissolved in 2-propanol/ DMF (1:0.2) (72 mL) and was hydrogenated over 10% Pd/C (980 mg) at 25 °C for 11 h. The catalyst was removed by filtration and washed with $CHCl_3$ and MeOH. The combined filtrates were diluted with H_2O (100 mL) and extracted with $CHCl_3$ (100 mL × 3). The combined extracts were washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1:4) to give **9** (1.05 g, 71% overall yield, 4 steps) as a colorless amorphous powder.

*3.4. (Z)-(7,8,10-Trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzylidene)-1,3,4,6-tetra-hydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Benzoate (**10**)*

A solution of ^{t}-BuOK in ^{t}-BuOH (1 M, 2.4 mL, 2.4 mmol) was added to a solution of **9** (988 mg, 2.0 mmol) and 2,4,5-trimethoxybenzaldehyde (**17**) (420 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) over 1 h at 0 °C, and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined extracts were washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1:2) to give **10** (901 mg, 70%) as a pale yellow amorphous powder.

Compound **10**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.40 (1H, s, N-H), 7.93 (2H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.36 (2H, m, Ar-H), 7.31 (1H, s, C11-H), 6.94 (1H, s, C3a-H), 6.68 (1H, dd, *J* = 6.8, 3.9 Hz, C6-H), 6.62 (1H, s, C6′-H), 4.52 (1H, dd, *J* = 11.7, 6.8 Hz, C12-H), 4.45 (1H, dd, *J* = 11.7, 3.9 Hz, C12-H), 3.98 (3H, s, C7-OMe), 3.84 (3H, s, C8-OMe), 3.83 (3H, s, C4′-OMe), 3.83 (3H, s, C5′-OMe), 3.69 (3H, s, C10-OMe), 3.58 (3H, s, C2′-OMe), 2.24 (3H, s, C3′-Me), 2.19 (3H, s, C9-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.1 (s, O<u>C</u>OPh), 157.4 (s, C4), 156.5 (s, C1), 153.3 (s, C8), 151.8 (s, C10), 149.6 (s, C5′), 149.2 (s, C2′), 149.0 (s, C4′), 146.0 (s, C7), 132.9 (d, Ph), 129.7 (s, Ph), 129.7 (d, Ph × 2), 128.2 (d, Ph × 2), 126.6 (s, C3′), 126.4 (s, C9), 126.2 (s, C11a), 125.4 (s, C3), 121.6 (s, C1′), 120.6 (s, C6a), 119.1 (s, C10a), 114.0 (d, C3a), 111.9 (d, C6′), 110.8 (d, C11), 65.0 (t, C12), 62.0 (q, C10-O<u>C</u>H$_3$), 60.9 (q, C2′-O<u>C</u>H$_3$), 60.7 (q, C7-O<u>C</u>H$_3$), 60.4 (q, C4′-O<u>C</u>H$_3$), 60.1 (q, C8-O<u>C</u>H$_3$), 55.9 (q, C5′-O<u>C</u>H$_3$), 48.7 (d, C6), 9.5 (q, C3′-<u>C</u>H$_3$), 9.3 (q, C9-<u>C</u>H$_3$). FT-IR (KBr) cm^{-1}: 3246, 1724, 1688, 1628, 1489, 1468, 1452, 1414, 1387, 1369, 1323, 1269, 1248, 1090, 1067, 1003, 712. EI-MS *m/z* (%): 644 (M^+, 7), 509 (100), 481 (5), 232 (10). HR-EI-MS: calcd for $C_{35}H_{36}N_2O_{10}$, 644.2370, found: 644.2369.

3.5. ((3S,6R*)-7,8,10-Trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,3,4,6-tetrahydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Benzoate (**11a**) and ((3R*,6R*)-7,8,10-trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,3,4,6-tetrahydro-2H-pyrazino-(1,2-b)isoquinolin-6-yl)methyl Benzoate (**11b**)*

A solution of **10** (644.0 mg, 1.0 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd/C (213.0 mg) at 25 °C for 22 h. The catalyst was removed by filtration and washed with $CHCl_3$ and MeOH. The combined filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1:2) to give **11b** (137.0 mg, 21%) as a pale yellow amorphous powder, and with ethyl acetate–hexane (2:1) to give **11a** (463.0 mg, 72%) as a pale yellow amorphous powder.

Compound **11a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (2H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.42 (2H, m, Ar-H), 7.25 (1H, s, C11-H), 6.53 (1H, dd, *J* = 7.5, 4.2 Hz, C6-H), 6.51 (1H, s, C6′-H), 6.22 (1H, s, *N*-H), 4.45 (1H, dd, *J* = 11.4, 7.5 Hz, C12-H), 4.34 (1H, dd, *J* = 10.3, 3.3 Hz, C3-H), 4.31 (1H, dd, *J* =11.4, 4.2 Hz, C12-H), 3.97 (3H, s, C7-OMe), 3.82 (3H, s, C8-OMe), 3.80 (3H, s, C5′-OMe), 3.78 (3H, s, C4′-OMe), 3.67 (3H, s, C10-OMe), 3.64 (3H, s, C2′-OMe), 3.52 (1H, dd, *J* =13.8, 3.3 Hz, C3a-H), 2.73 (1H, dd, *J* =13.8, 10.3 Hz, C3a-H), 2.20 (3H, s, C3′-Me), 2.19 (3H, s, C9-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.1 (s, O<u>C</u>OPh), 165.4 (s, C4), 160.7 (s, C1), 153.2 (s, C8), 151.8 (s, C10), 150.9 (s, C2′), 149.7 (s, C5′), 147.6 (s, C4′), 146.0 (s, C7), 133.1 (d, Ph), 129.9 (d, Ph × 2), 129.8 (s, Ph), 128.3 (d, Ph × 2), 126.4 (s, C9), 126.3 (s, C3′), 126.3 (s, C11a), 123.7 (s, C1′), 121.2 (s, C6a), 119.1 (s, C10a), 111.5 (d, C6′), 110.7 (d, C11), 64.6 (t, C12), 62.0 (q, C10-O<u>C</u>H$_3$), 60.8 (q, C7-O<u>C</u>H$_3$), 60.6 (q, C2′-O<u>C</u>H$_3$), 60.2 (q, C4′-O<u>C</u>H$_3$), 60.1 (q, C8-O<u>C</u>H$_3$), 56.0 (q, C5′-O<u>C</u>H$_3$) 55.3 (d, C3), 47.8 (d, C6), 33.5 (t, C3a), 9.7 (q, C3′-<u>C</u>H$_3$), 9.4 (q, C9-<u>C</u>H$_3$).

FT-IR (KBr) cm^{-1}: 3391, 1724, 1690, 1628, 1489, 1468, 1458, 1414, 1368, 1337, 1269, 1240, 1121, 1088. EI-MS *m/z* (%): 646 (M$^+$, 14), 511 (100), 509 (13), 483 (36), 260 (8), 232 (17), 195 (10). HR-EI-MS: calcd for $C_{35}H_{38}N_2O_{10}$, 646.2527, found: 646.2523.

Compound **11b**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.93 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.39 (2H, m, Ar-H), 6.91 (1H, s, C11-H), 6.43 (1H, dd, *J* = 7.1, 4.4 Hz, C6-H), 6.39 (1H, s, C6′-H), 4.45 (1H, dd, *J* = 8.9, 5.2 Hz, C3-H), 4.36 (1H, dd, *J* = 11.7, 7.1 Hz, C12-H), 4.31 (1H, dd, *J* =11.7, 4.4 Hz, C12-H), 3.98 (3H, s, C7-OMe), 3.83 (3H, s, C8-OMe), 3.66 (3H, s, C4′-OMe), 3.62 (3H, s, C5′-OMe), 3.61 (3H, s, C10-OMe), 3.57 (3H, s, C2′-OMe), 3.08 (1H, dd, *J* = 14.5, 8.9 Hz, C3a-H), 3.06 (1H, dd, *J* = 14.5, 5.2 Hz, C3a-H), 2.17 (3H, s, C9-Me), 2.05 (3H, s, C3′-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.2 (s, O<u>C</u>OPh), 165.0 (s, C4), 160.6 (s, C1), 153.0 (s, C8), 151.5 (s, C10), 151.5 (s, C2′), 149.1 (s, C5′), 147.7 (s, C4′), 145.9 (s, C7), 133.0 (d, Ph), 129.7 (s, Ph), 129.7 (d, Ph × 2), 128.3 (d, Ph × 2), 126.2 (s, C9), 125.8 (s, C3′), 125.4 (s, C11a or C10a), 121.9 (s, C1′), 120.7 (s, C6a), 119.0 (s, C11a or C10a), 112.0 (d, C6′), 109.3 (d, C11), 64.9 (t, C12), 61.9 (q, C10-O<u>C</u>H$_3$), 60.7 (q, C7-O<u>C</u>H$_3$), 60.5 (q, C2′-O<u>C</u>H$_3$), 60.2 (q, C4′-O<u>C</u>H$_3$), 60.1 (q, C8-O<u>C</u>H$_3$), 57.0 (d, C3), 55.8 (q, C5′-O<u>C</u>H$_3$), 47.9 (d, C6), 36.5 (t, C3a), 9.2 (q, C9-<u>C</u>H$_3$ and C3′-<u>C</u>H$_3$). FT-IR (KBr) cm^{-1}: 3300, 1724, 1692, 1628, 1487, 1468, 1414, 1379, 1321, 1271, 1119, 1088. EI-MS *m/z* (%): 646 (M$^+$, 11), 511 (100), 483 (39), 232 (16), 195 (9). HR-EI-MS: calcd for $C_{35}H_{38}N_2O_{10}$, 646.2527, found: 646.2521.

3.6. Isopropyl ((3S,6R*)-7,8,10-Trimethoxy-9-methyl-1,4-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,3,4,6-tetrahydro-2H-pyrazino(1,2-b)isoquinolin-6-yl)methyl Benzoate (**18**)*

A solution of **11a** (16.47 g, 25 mmol), TEA (28.10 mL, 200 mmol), and DMAP (12.21 g, 100 mmol) in dichloromethane (400 mL) was cooled with ice water, and isopropyl chloroformate (40.08 mL, 350 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 25 °C for 4 h. The organic layer was diluted with dichloromethane (500 mL), washed with 1 M aqueous HCl (500 mL ×2) and then water (500 mL), dried, and concentrated *in vacuo* to give a residue. The residue was subjected to column chromatography with ethyl acetate–hexane (2:5) to give **18** (17.5 g, 96%) as a yellow amorphous powder.

Compound **18**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.34 (2H, m, Ar-H), 7.19 (1H, s, C11-H), 6.53 (1H, t, *J* = 3.4 Hz, C6-H), 5.24 (1H, t, *J* = 6.1 Hz, C3-H), 4.96 (1H, sept, *J* = 6.3 Hz, $CO_2C\underline{H}(CH_3)_2$), 4.65 (1H, dd, *J* = 11.5, 3.4 Hz, C12-H), 4.36 (1H, dd, *J* = 11.5, 3.4 Hz, C12-H), 3.92 (3H, s, C7-OMe), 3.80 (3H, s, C4′-OMe or C5′-OMe), 3.78 (3H, s, C8-OMe), 3.63 (3H, s, C4′-OMe or C5′-OMe), 3.59 (3H, s, C2′-OMe), 3.44 (3H, s, C10-OMe), 3.34 (1H, dd, *J* = 13.7, 6.1 Hz, C3a-H), 3.17 (1H, dd, *J* = 13.7, 6.1 Hz, C3a-H), 2.10 (3H, s, C9-Me), 2.09 (3H, s, C3′-Me), 1.28 (3H, d, *J* = 6.3 Hz, $CO_2CH(C\underline{H}_3)_2$), 1.20 (3H, d, *J* = 6.3 Hz, $CO_2CH(C\underline{H}_3)_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.7 (s, O$\underline{C}$OPh), 163.4 (s, C4), 157.6 (s, C1), 153.4 (s, C8), 151.7 (s, $\underline{C}O_2CH(CH_3)_2$), 151.6 (s, C10), 151.4 (s, C2′), 149.0 (s, C4′ or C5′), 147.4 (s, C4′ or C5′), 145.8 (s, C7), 133.0 (d, Ph), 129.7 (d, Ph × 2), 129.6 (s, Ph), 128.3 (d, Ph × 2), 126.8 (s, C11a or C10a), 126.2 (s, C9), 125.6 (s, C3′), 122.5 (s, C1′), 120.0 (s, C6a), 119.3 (s, C11a or C12), 112.0 (d, C6′), 111.6 (d, C11), 71.8 (d, $CO_2\underline{C}H(CH_3)_2$), 66.3 (t, C12), 61.8 (q, C10-O$\underline{C}H_3$), 60.6 (q, C2′-O$\underline{C}H_3$), 60.5 (q, C7-O$\underline{C}H_3$), 60.0 (q, C4′-O$\underline{C}H_3$ or C5′-O$\underline{C}H_3$), 60.0 (q, C8-O$\underline{C}H_3$), 59.4 (d, C3), 55.9 (q, C4′-O$\underline{C}H_3$ or C5′-O$\underline{C}H_3$), 49.9 (d, C6), 35.8 (t, C3a), 21.6 (q, $CO_2CH(\underline{C}H_3)_2$), 21.5 (q, $CO_2CH(\underline{C}H_3)_2$), 9.7 (q, C3′-$\underline{C}H_3$), 9.2 (q, C9-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 2938, 1722, 1684, 1468, 1418, 1391, 1375, 1344, 1271, 1252, 1107, 1092, 1072, 712. EI-MS *m/z* (%): 732 (M^+, 12), 597 (100), 569 (19), 555 (6), 511 (8), 483 (21), 415 (9), 260 (13), 232 (19), 195 (13). HR-EI-MS: calcd for $C_{39}H_{44}N_2O_{12}$, 732.2894, found: 732.2889.

3.7. Isopropyl (6S,9R*,15R*)-9-((benzoyloxy)methyl)-1,2,4,10,11,13-hexamethoxy-3,12-dimethyl-7-oxo-6,7,9,15-tetrahydro-5H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinoline-16-carboxylate (**19**)*

A stirred solution of **18** (402.3 mg, 0.55 mmol) in THF (36 mL) was cooled with ice water and lithium tri-*tert*-butoxyaluminohydride (1.12 g, 4.4 mmol) was added over 10 min. After continued stirring at 25 °C for 30 min, anhydrous Na_2SO_4 (2 g) was added and the reaction mixture was quenched with water. The reaction mixture was filtered through Celite pad and then, the filtrate was diluted with brine (200 mL) and extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated *in vacuo* to give a residue, which was used in the next step without further purification. A solution of the residue as above in formic acid (36 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with saturated aqueous $NaHCO_3$ solution (80 mL) and extracted with $CHCl_3$ (3 × 80 mL). The combined extracts were washed with brine (80 mL), dried, and concentrated *in vacuo* to give a residue.

The residue was subjected to column chromatography with ethyl acetate–hexane (1:3) to give **19** (322.7 mg, 82%) as a pale yellow amorphous powder.

Compound **19**: ^{1}H-NMR (400 MHz, DMSO, 140 °C) δ: 7.58 (2H, m, Ar-H), 7.54 (1H, m, Ar-H), 7.41 (2H, m, Ar-H), 6.26 (1H, s, C14-H), 6.22 (1H, dd, *J* = 8.1, 4.2 Hz, C9-H), 5.93 (1H, d, *J* = 1.5, C15-H), 4.98 (1H, m, 1.5 Hz, C6-H), 4.86 (1H, sept, *J* = 6.2 Hz, $CO_2C\underline{H}(CH_3)$), 3.92 (1H, dd, *J* = 11.5, 4.2 Hz, C16-H), 3.87 (3H, s, C2-OMe or C11-OMe), 3.87 (3H, s, C10-OMe), 3.85 (1H, dd, *J* = 11.5, 8.1 Hz, C16-H), 3.75 (3H, s, C4-OMe or C13-OMe), 3.73 (3H, s, C2-OMe or C11-OMe), 3.67 (3H, s, C4-OMe or C13-OMe), 3.51 (3H, s, C1-OMe), 3.09 (1H, br d, *J* =17.6 Hz, C5-H), 3.04 (1H, dd, *J* =17.6, 3.9 Hz, C5-H), 2.15 (3H, s, C3-Me or C12-Me), 1.98 (3H, s, C3-Me or C12-Me), 1.23 (3H, d, *J* = 6.2 Hz, $CO_2CH(C\underline{H}_3)_2$), 1.21 (3H, d, *J* = 6.2 Hz, $CO_2CH(C\underline{H}_3)_2$). ^{13}C-NMR (100 MHz, DMSO, 140 °C) δ: 165.4 (s, C7), 164.4 (s, O$\underline{C}$OPh), 152.1 (s, $\underline{C}O_2CH(CH_3)_2$), 151.7 (s, C1), 150.2 (s, C2 or C11), 149.2 (s, C4 and C13), 145.0 (s, C2 or C11), 144.7 (s, C10), 132.3 (s, C14a), 131.9 (d, Ph), 128.7 (s, Ph), 128.3 (d, Ph × 2), 127.5 (d, Ph × 2), 124.5 (s, C3 or C12), 124.0 (s, C3 or C12), 123.7 (s, C4a), 119.9 (s, C15a), 118.8 (s, C13a), 118.2 (s, C9a), 100.0 (d, C14), 68.8 (d, $CO_2\underline{C}H(CH_3)_2$), 62.6 (t, C16), 60.3 (q, C4-O$\underline{C}H_3$ or C13-O$\underline{C}H_3$), 59.8 (q, C2-O$\underline{C}H_3$ or C10-O$\underline{C}H_3$ or C11-O$\underline{C}H_3$), 59.2 (q, C2-O$\underline{C}H_3$ or C10-O$\underline{C}H_3$ or C11-O$\underline{C}H_3$), 59.1 (q, q, C2-O$\underline{C}H_3$ or C10-O$\underline{C}H_3$ or C11-O$\underline{C}H_3$), 58.9 (q, C4-O$\underline{C}H_3$ or C13-O$\underline{C}H_3$), 58.6 (q, C1-O$\underline{C}H_3$), 52.5 (d, C6), 48.9 (d, C15), 45.5 (d, C9), 26.9 (t, C5), 20.9 (q, $CO_2CH(\underline{C}H_3)_2$), 20.9 (q, $CO_2CH(\underline{C}H_3)_2$), 8.24 (q, C3-$\underline{C}H_3$ or C12-$\underline{C}H_3$), 8.18 (q, C3-$\underline{C}H_3$ or C12-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 1717, 1707, 1686, 1647, 1466, 1414, 1362, 1344, 1298, 1269, 1109, 1070, 1007, 964, 712. EI-MS *m/z* (%): 716 (M^+, 22), 581 (100), 553 (67), 234 (21). HR-EI-MS: calcd for $C_{39}H_{44}N_2O_{11}$, 716.2945, found: 716.2942.

3.8. ((6S,9R*,15R*)-1,2,4,10,11,13-hexamethoxy-3,12-dimethyl-7-oxo-6,7,9,15-tetrahydro-5H-6, 15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-9-yl)methyl Benzoate (**20**)*

Concentrated H_2SO_4 (1.7 mL) was added to a stirred solution of **19** (322.7 mg, 0.45 mmol) in TFA (34 mL) at 0 °C over 5 min, and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was poured into water (40 mL) at 0 °C, basified with concentrated NH_4OH, and then extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were washed brine (100 mL), dried, and concentrated *in vacuo* to give a residue. The residue was subjected to column chromatography with ethyl acetate–hexane (1:3) to give **20** (267.6 mg, 94%) as a pale yellow amorphous powder.

Compound **20**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.70 (2H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.38 (2H, m, Ar-H), 6.41 (1H, dd, *J* = 8.1, 5.2 Hz, C9-H), 6.26 (1H, s, C14-H), 4.99 (1H, s, C15-H), 4.12 (1H, br d, *J* = 6.3 Hz, C6-H), 3.95~3.89 (2H, overlapped, C16-H), 3.90 (3H, s, C10-OMe), 3.87 (3H, s, C1-OMe), 3.76 (3H, s, C13-OMe), 3.76 (3H, s, C11-OMe), 3.67 (3H, s, C2-OMe), 3.44 (3H, s, C4-OMe), 3.19 (1H, dd, *J* = 17.0, 1.3 Hz, C5-H), 3.07 (1H, dd, *J* = 17.0, 6.3 Hz, C5-H), 2.19 (3H, s, C12-Me), 1.88 (3H, s, C3-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.5 (s, C7), 166.0 (s, O$\underline{C}$OPh), 152.5 (s, C4), 150.8 (s, C11), 149.9 (s, C2), 149.8 (s, C13), 146.3 (s, C1), 146.0 (s, C10), 136.1 (s, C13a or C14a), 132.5 (d, Ph), 129.6 (d, Ph), 129.4 (s, Ph), 128.3 (d, Ph), 125.7 (s, C12), 125.3 (s, C15a), 125.0 (s, C3), 121.5 (s, C4a), 120.4 (s, C13a or C14a), 119.5 (s, C9a), 99.8 (d, C14), 63.4 (t, C16), 61.4 (q, C13-O$\underline{C}H_3$), 60.8 (q, C10-O$\underline{C}H_3$), 60.2 (q, C1-O$\underline{C}H_3$), 60.1 (q, C11-O$\underline{C}H_3$), 59.9

(q, C2-O$\underline{C}H_3$), 59.3 (q, C4-O$\underline{C}H_3$), 53.9 (d, C6), 50.1 (d, C15), 45.7 (d, C9), 29.0 (t, C5), 9.3 (q, C12-$\underline{C}H_3$), 9.1 (q, C3-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 2938, 1722, 1680, 1638, 1466, 1412, 1362, 1271, 1248, 1115, 1070, 1009, 964, 712. EI-MS *m/z* (%): 630 (M^+, 22), 495 (48), 467 (100), 234 (39), 204 (18). HR-EI-MS: calcd for $C_{35}H_{38}N_2O_9$, 630.2577, found: 630.2581.

3.9. ((6S,9R*,15R*)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-7-oxo-6,7,9,15-tetrahydro-5H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-9-yl)methyl Benzoate (**21**)*

A 37% aqueous solution of formaldehyde (6 mL) was added to a stirred solution of **20** (251.2 mg, 0.4 mmol) in formic acid (7.0 mL) at 60 °C, and the reaction mixture was heated at 70 °C for 1 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (80 mL) and extracted with $CHCl_3$ (3 × 80 mL). The combined extracts were washed brine (80 mL), dried, and concentrated *in vacuo* to give a residue. The residue was subjected to column chromatography with ethyl acetate–hexane (1:1) to give **21** (247.3 mg, 96%) as a colorless amorphous powder.

Compound **21**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.71 (2H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.38 (2H, m, Ar-H), 6.43 (1H, t, *J* = 6.4 Hz, C9-H), 6.30 (1H, s, C14-H), 4.63 (1H, s, C15-H), 3.92 (3H, s, C10-OMe), 3.91 (2H, d, *J* = 6.4 Hz, C17-H), 3.87 (3H, s, C1-OMe), 3.76 (6H, s, C11-OMe and C13-OMe), 3.68 (1H, overlapped, C6-H), 3.67 (3H, s, C2-OMe), 3.43 (3H, s, C4-OMe), 3.15 (1H, dd, *J* = 17.6, 4.1 Hz, C5-H), 3.11 (1H, br d, *J* = 17.6 Hz, C5-H), 2.55 (3H, s, *N*-Me), 2.20 (3H, s, C12-Me), 1.89 (3H, s, C3-Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.1 (s, C7), 166.0 (s, O$\underline{C}$OPh), 152.4 (s, C4), 150.7 (s, C11), 149.8 (s, C2), 149.5 (s, C13), 146.1 (s, C1), 145.9 (s, C10), 132.7 (s, C14a), 132.5 (d, Ph), 129.6 (d, Ph × 2), 129.3 (s, Ph), 128.3 (d, Ph × 2), 126.0 (s, C15a), 125.7 (s, C12), 124.7 (s, C3), 121.1 (s, C4a), 119.9 (s, C13a), 119.6 (s, C9a), 102.7 (d, C14), 63.6 (t, C17), 61.3 (q, C11-O$\underline{C}H_3$ or C13-O$\underline{C}H_3$), 60.7 (q, C10-O$\underline{C}H_3$), 60.5 (d, C6), 60.1 (q, C1-O$\underline{C}H_3$), 60.0 (q, C11-O$\underline{C}H_3$ or C13-O$\underline{C}H_3$), 59.8 (q, C2-O$\underline{C}H_3$), 59.2 (q, C4-O$\underline{C}H_3$), 56.8 (d, C15), 45.5 (d, C9), 41.6 (q, *N*-CH_3), 29.2 (t, C5), 9.2 (q, C12-$\underline{C}H_3$), 9.0 (q, C3-$\underline{C}H_3$). FT-IR (KBr) cm^{-1}: 1722, 1678, 1638, 1464, 1412, 1358, 1341, 1271, 1126, 1113, 1099, 1067, 1007, 712. EI-MS *m/z* (%): 644 (M^+, 17), 509 (20), 481 (100), 248 (37), 218 (15). HR-EI-MS: calcd for $C_{36}H_{40}N_2O_9$, 644.2734, found: 644.2733.

3.10. (6S,9R*,15R*)-9-(hydroxymethyl)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-5,6,9,15-tetrahydro-7H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-7-one (**12**)*

A 10 M aqueous solution of lithium hydroxide monohydrate (77 µL, 0.77 mmol) was added to a stirred solution of **21** (226.3 mg, 0.35 mmol) in THF (2.0 mL) and MeOH (0.7 mL), and stirring was continued at 25 °C for 8 h. The reaction mixture was diluted with water (80 mL), and the mixture was extracted with $CHCl_3$ (3 × 80 mL). The combined extracts were washed with brine (80 mL), dried, and concentrated *in vacuo* to give a residue. The residue was subjected to column chromatography with ethyl acetate–hexane (2:1) to give **12** (184.1 mg, 97%) as a colorless amorphous powder.

Compound **12**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.27 (1H, s, C14-H), 6.08 (1H, dd, *J* = 7.9, 5.1 Hz, C9-H), 4.70 (1H, brs, C15-H), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.77 (3H, s, OMe), 3.75 (3H, s, OMe) 3.72 (1H, br t, C6-H), 3.66 (3H, s, OMe), 3.32 (1H, dt, *J* = 11.5, 5.1 Hz,

C17-H), 3.22 (1H, dt, *J* = 11.5, 7.9 Hz, C17-H), 3.21 (2H, d, *J* = 4.4 Hz, C5-H), 2.57 (3H, s, *N*-Me), 2.19 (3H, s, C12-Me), 2.18 (3H, s, C3-Me), 1.37 (1H, t, *J* = 6.1 Hz, -OH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.1 (C7), 152.6 (C4), 150.7 (C11), 150.1 (C2), 149.7 (C13), 146.3 (C1), 145.8 (C10), 132.8 (C14a), 126.0 (C15a), 125.4 (C12), 125.1 (C3), 121.1 (C4a), 120.6 (C9a), 119.5 (C13a), 102.9 (14), 64.6 (C17), 61.3 (-OCH_3), 60.6 (-OCH_3), 60.6 (C6), 60.1 (-OCH_3), 60.1 (-OCH_3), 60.0 (-OCH_3), 59.8 (-OCH_3), 56.5 (C15), 49.1 (C9), 41.6 (*N*-CH_3), 29.3 (C5), 9.4 (-CH_3), 9.2 (-CH_3). FT-IR (KBr) cm^{-1}: 3468, 2940, 1672, 1636, 1466, 1412, 1341, 1248, 1113, 1065, 1007, 964. EI-MS *m/z* (%): 540 (M^+, 9), 509 (27), 481 (100), 248 (51). HR-EI-MS: calcd for $C_{29}H_{36}N_2O_8$, 540.2472, found: 540.2473.

3.11. ((6S,9R*,15R*)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-7-oxo-6,7,9,15-tetrahydro-5H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-9-yl)methyl Benzoate (**22**)*

To a stirred solution of **12** (216.0 mg, 0.4 mmol) in CH_2Cl_2 (24 mL) at −78 °C was added a CH_2Cl_2 solution of BBr_3 (1.0 M, 2.40 mL, 2.4 mmol) over 5 min. Stirring was continued at the same temperature for 1 h, and then at −20 °C for 14.5 h. The reaction mixture was diluted with water (200 mL) and extracted with 5% MeOH in $CHCl_3$ (4 × 200 mL). The combined extracts were washed with 5% $NaHCO_3$ solution (200 mL), dried, and concentrated *in vacuo* to give a residue. A solution of the above residue in 10 N HNO_3 (5.0 mL) was stirred at 25 °C for 30 min. The reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with brine (200 mL), dried, and concentrated *in vacuo*. The residue was subjected to purification by silica gel chromatography with ethyl acetate to give **22** (130.0 mg, 67%) as a dark purple amorphous powder.

Compound **22**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.26 (1H, s, 14-H), 5.96 (1H, dd, *J* = 7.1, 4.5 Hz, 9-H), 4.55 (1H, s, 15-H), 4.02 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.74 (1H, dt, *J* = 6.5, 1.5 Hz, 6-H), 3.50 (1H, dd, *J* = 11.4, 4.5 Hz, 17-H), 3.36 (1H, dd, *J* = 11.4, 7.1 Hz, 17-H), 2.96 (1H, dd, *J* = 19.8, 6.5 Hz, 5-Hα), 2.89 (1H, dd, *J* = 19.8, 1.5 Hz, C5-Hβ), 2.51 (3H, s, *N*-CH_3), 1.96 (3H, s, 3-CH_3 or 12-CH_3), 1.94 (3H, s, 3-CH_3 or 12-CH_3), 1.62 (1H, br s, OH). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 186.6 (s, C-4), 185.0 (s, C-13), 180.5 (s, C-10 and C-1), 168.0 (s, C-7), 156.0 (s, C-11), 155.4 (s, C-2), 140.7 (s, C-14a), 140.0 (s, C-4a), 136.5 (s, C-15a), 134.5 (s, C-13a), 129.1 (s, C-3), 127.6 (s, C-12), 125.0 (s, C-9a), 101.8 (d, C-14), 62.9 (t, C-17), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 59.6 (d, C-6), 54.4 (d, C-15), 48.4 (d, C-9), 41.2 (q, *N*-CH_3), 28.7 (t, C-5), 8.8 (q, Ar-CH_3), 8.7 (q, Ar-CH_3). FT-IR (KBr) cm^{-1}: 3347, 2951, 2855, 1654, 1616, 1568, 1450, 1373, 1310. LR-MS (FAB^+): 481 $[M + H]^+$. HR-MS (FAB^+): calcd for $C_{25}H_{25}N_2O_8$, 481.1611, found: 481.1623.

3.12. ((6S,9R*,15R*)-2,11-dimethoxy-3,12,16-trimethyl-1,4,7,10,13-pentaoxo-1,5,6,7,9,10,13,15-octa-hydro-4H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-9-yl)methyl (Z)-2-methylbut-2-enoate (**23**)*

A solution of angelic acid (601.0 mg, 6.0 mmol) in ether (30 mL) was cooled with ice water, and a solution of oxalyl chloride (0.5 mL, 5.9 mmol) in DMF (46.0 μL, 592 mmol) was added dropwise over 5 min. The resulting solution was stirred at 25 °C for 2 h. Then, a solution of **22** (142.0 mg, 0.3 mmol)

in CH_2Cl_2 (15 mL) was added over 5 min. The reaction mixture was concentrated to approximately 3.0 mL with a stream of argon, and CH_2Cl_2 (8.0 mL) was added. The resulting mixture was stirred at 25 °C for 21 h. The reaction mixture was directly purified by silica gel chromatography with ethyl acetate–hexane (2:1) to afford **23** (139.0 mg, 84%) as a dark purple film.

Compound **23**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.24 (1H, s, 14-H), 6.12 (1H, dd, *J* = 5.7, 2.9 Hz, 9-H), 5.92 (1H, qq, *J* = 7.4, 1.4 Hz, 21-H), 4.50 (1H, br s, 15-H), 4.21 (1H, dd, *J* = 11.9, 5.7 Hz, 17-H), 4.05 (3H, s, C11-OCH_3), 4.01 (3H, s, 2-OCH_3), 4.01 (1H, dd, *J* = 11.9, 2.9 Hz, 17-H), 3.72 (1H, dt, *J* = 6.8, 1.4 Hz, 6-H), 2.95 (1H, dd, *J* = 19.8, 6.8 Hz, 5-Hβ), 2.84 (1H, dd, *J* = 19.8, 1.4 Hz, 5-H), 2.47 (3H, s, *N*-CH_3), 1.96 (3H, s, 12-CH_3), 1.92 (3H, s, 3-CH_3), 1.75 (3H, dq, *J* = 7.4, 1.4 Hz, 21-CH_3), 1.57 (1H, quint, *J* = 1.4 Hz, 20-CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 186.5 (s, C-4), 184.9 (s, C-13), 180.5 (s, C-1), 180.1 (s, C-10), 167.1 (s, C-7 and C-19), 156.2 (s, C-11), 155.2 (s, C-2), 140.6 (s, C-14a), 139.8 (s, C-4a), 139.3 (d, C-21), 136.2 (s, C-15a), 134.6 (s, C-13a), 128.5 (s, C-3), 127.3 (s, C-12), 126.8 (s, C-20), 124.2 (s, C-9a), 101.3 (d, C-14), 62.4 (t, C-17), 61.1 (q, 11-OCH_3), 61.0 (q, 2-OCH_3), 59.5 (d, C-6), 54.3 (d, C-15), 47.1 (d, C-9), 41.1 (q, *N*-CH_3), 28.3 (t, C-5), 20.2 (q, C-23), 15.5 (q, C-22), 8.7 (q, 3-CH_3), 8.6 (q, 12-CH_3). FT-IR (KBr) cm^{-1}: 2949, 1653, 1616, 1570, 1458, 1309, 1228, 1153. EI-MS *m*/*z* (%): 562 (M^+, 5), 421 (100), 218 (40). HR-EI-MS: calcd for $C_{30}H_{30}N_2O_9$, 562.1951, found: 562.1952.

*3.13. Renieramycin I (**1i**)*

A suspension of **23** (15.0 mg, 0.027 mmol) and SeO_2 (29.6 mg, 0.27 mmol) in dioxane (3.0 mL) and MeOH (1.0 mL) was heated at 100 °C for 6 days. The reaction mixture was filtered and the filter cake was washed with ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a residue. Flash column chromatography on silica gel with ethyl acetate–hexane (2:3) afforded **1i** (6.8 mg, 43%) as a dark red film and **24** (4.4 mg, 29%).

Renieramycin I (**1i**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.26 (1H, s, 4-H), 6.07 (1H, dd, *J* = 5.5, 2.7 Hz, 1-H), 5.92 (1H, qq, *J* = 7.3, 1.4 Hz, 26-H), 4.54 (1H, d, *J* = 0.9 Hz, 11-H), 4.34 (1H, d, *J* = 1.4 Hz, 14-H), 4.16 (1H, dd, *J* = 12.1, 5.5 Hz, 22-H), 4.06 (3H, s, 7-OCH_3), 4.02 (1H, dd, *J* = 12.1, 2.7 Hz, 22-H), 3.98 (3H, s, 17-OCH_3), 3.74 (1H, br t, *J* = 1.4 Hz, 13-H), 3.62 (3H, s, 14-OCH_3), 2.55 (3H, s, *N*-CH_3), 1.96 (3H, s, 6-CH_3), 1.94 (3H, s, 16-CH_3), 1.73 (3H, dq, *J* = 7.3, 1.4 Hz, 26-CH_3), 1.55 (3H, quint, *J* = 1.4 Hz, 25-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 185.8 (s, C-15), 184.7 (s, C-5), 180.9 (s, C-18), 180.1 (s, C-8), 167.1 (s, C-24), 164.1 (s, C-21), 156.1 (s, C-7), 155.2 (s, C-17), 139.2 (d, C-26), 138.6 (s, C-3), 137.4 (s, C-19), 137.0 (s, C-20), 134.2 (s, C-10), 129.3 (s, C-16), 127.4 (s, C-6), 126.7 (s, C-25), 124.9 (s, C-9), 102.2 (d, C-4), 73.4 (d, C-14), 64.7 (d, C-13), 62.6 (t, C-22), 61.2 (q, 7-OCH_3), 60.9 (q, 17-OCH_3), 59.4 (q, 14-OCH_3), 54.5 (d, C-11), 47.3 (d, C-1), 41.7 (q, *N*-CH_3), 20.2 (q, 25-CH_3), 15.5 (q, 26-CH_3), 8.9 (q, Ar-CH_3), 8.7 (q, Ar-CH_3). FT-IR (KBr) cm^{-1}: 3429, 2949, 1717, 1684, 1655, 1614, 1570, 1454, 1342, 1306, 1233, 1209, 1153, 1096. EI-MS *m*/*z* (%): 594 ($[M + 2H]^+$, 0.7), 593 ($[M + H]^+$, 2), 592 (M^+, 6), 479 (19), 452 (26), 451 (100), 421 (20), 248 (25), 218 (11). HR-EI-MS: calcd for $C_{30}H_{30}N_2O_{10}$, 592.2057, found: 592.2056.

3.14. ((6S,9R*,15R*)-5-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-1,4,7,10,13-pentaoxo-1,5,6,7,9,10,13,15-octahydro-4H-6,15-epiminobenzo(4,5)azocino(1,2-b)isoquinolin-9-yl) methyl (Z)-2-methylbut-2-enoate (**24**)*

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.28 (1H, s, 4-H), 6.09 (1H, dd, *J* = 6.0, 2.9 Hz, 1-H), 5.93 (1H, qq, *J* = 7.3, 1.5 Hz, 26-H), 4.86 (1H, br d, *J* = 7.0 Hz, 14-H), 4.52 (1H, d, *J* = 1.1 Hz, 11-H), 4.19 (1H, dd, *J* = 12.0, 6.0 Hz, 22-H), 4.06 (3H, s, 7-OCH_3), 4.01 (3H, s, 17-OCH_3), 3.99 (1H, dd, *J* = 12.0, 2.9 Hz, 22-H), 3.75 (1H, dd, *J* = 1.7, 1.1 Hz, 13-H), 2.88 (1H, br d, *J* = 7.0 Hz, OH), 2.55 (3H, s, *N*-CH_3), 1.96 (3H, s, 6-CH_3), 1.93 (3H, s, 16-CH_3), 1.75 (3H, dq, *J* = 7.3, 1.5 Hz, 26-CH_3), 1.56 (3H, quint, *J* = 1.5 Hz, 25-CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 186.7 (s, C-15), 184.7 (s, C-5), 181.0 (s, C-18), 180.0 (s, C-8), 167.1 (s, C-24), 163.9 (s, C-21), 156.1 (s, C-7), 155.4 (s, C-17), 139.3 (d, C-26), 138.4 (s, C-10 or C-20), 138.3 (s, C-10 or C-20), 136.9 (s, C-19), 134.3 (s, C-3), 128.8 (s, C-16), 127.4 (s, C-6), 126.7 (s, C-25), 124.8 (s, C-9), 102.2 (d, C-4), 67.1 (d, C-13), 64.8 (d, C-14), 62.3 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 54.7 (d, C-11), 47.2 (d, C-1), 41.5 (q, *N*-CH_3), 20.2 (q, 25-CH_3), 15.5 (q, 26-CH_3), 8.7 (q, Ar-CH_3), 8.7 (q, Ar-CH_3). FT-IR (KBr) cm^{-1}: 3446, 2930, 2857, 1654, 1616, 1570, 1456, 1307, 1233, 1211, 1153. EI-MS *m/z* (%): 578 (M^+, 5), 437 (100), 421 (48), 218 (20). HR-EI-MS: calcd for $C_{30}H_{30}N_2O_{10}$, 578.1900, found: 578.1899.

*3.15. Cribrostatin 4 (**2**) via **24***

A suspension of **23** (112.4 mg, 0.2 mmol) and SeO_2 (110.9 mg, 1.0 mmol) in dioxane (30 mL) and water (3.0 mL) was heated at 80 °C for 6 h. The reaction mixture was filtered and the filter cake was washed with ethyl acetate (200 mL). The combined filtrates were concentrated *in vacuo* to give a residue (248.3 mg). Flash column chromatography on silica gel (70 g) with hexane–ethyl acetate (1:1) afforded **24** (72.5 mg, 63%) along with recovered **23** (16.2 mg, 14%). Dess-Martin periodinane (DMP, 445.3 mg, 1.05 mmol) was added to a stirred solution of **24** (57.8 mg, 0.1 mmol) in dichloromethane (15 mL), and the mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with THF (50 mL), saturated aqueous $Na_2S_2O_3$ solution (50 mL) was added, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined extracts were washed with brine (100 mL), dried, and concentrated *in vacuo*. The residue (230 mg) was purified by silica gel (9 g) flash column chromatography with hexane–ethyl acetate (1:2) to give cribrostatin 4 (**2**: 81.0 mg, 70.0% from **23**) as a dark red film. 1H-, 13C NMR, and also IR spectral charts of synthetic renieramycin **I** and cribrostatin **4** are available in the supplementary information.

4. Conclusions

In summary, we have succeeded in reducing the number of steps in our first version of the total synthesis of cribrostatin 4 through key intermediate **12**, from 21 steps in 3.4% overall yield to 18 steps in 8.3% overall yield. The main point of this alternative total synthesis is based on the Avendano's protocol introducing C3-C4 double bond in the early stage. We have completed the first total synthesis of renieramycin I (**1i**), and the spectroscopic data provide unambiguous evidence that supports the original structure of the natural product. The development of ways to utilize this approach for the

synthesis of other members of the C3-C4 unsaturated renieramycin family, and the examination of their biological activities to evaluate the mechanism of action, are undergoing in our laboratory.

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Author Contributions

Masashi Yokoya Keiichiro Kobayashi, and Mitsuhiro Sato: conducted the experimental. Naoki Saito and Masashi Yokoya: wrote the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References and Notes

1. Scott, J.D.; Williams, R.M. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. Avendaño, C.; de la Cuesta, E. Synthetic Chemistry with *N*-Acyliminium Ions Derived from Piperazine-2,5-Diones and Related Compounds. *Curr. Org. Synth.* **2009**, *6*, 143–168.
3. Parameswaran, P.S.; Naik, C.G.; Kamat, S.Y.; Pramanik, B.N. Renieramycins H and I, Two Novel Alkaloids from the Sponge *Haliclona cribricutis* Dendy. *Indian J. Chem.* **1998**, *37B*, 1258–1263.
4. Pettit, G.R.; Collins, J.C.; Herald, D.L.; Doubek, D.L.; Boyd, M.R.; Schmidt, J.M.; Hooper, J.N.A.; Tackett, L.P. Isolation and Structure of Cribrostatins 1 and 2 from the Blue Marine Sponge *Cribrochalina* sp. *Can. J. Chem.* **1992**, *70*, 1170–1175.
5. Pettit, G.R.; Knight, J.C.; Collins, J.C.; Herald, D.L.; Pettit, R.K.; Boyd, M.R.; Young, V.G. Antineoplastic Agents 430. Isolation and Structure of Cribrostatins 3, 4, and 5 from the Republic of Maldives *Cribrochalina* Species. *J. Nat. Prod.* **2000**, *63*, 793–798.
6. Pettit, G.R.; Collins, J.C.; Knight, J.C.; Herald, D.L.; Nieman, R.A.; Williams, M.D.; Pettit, R.K. Antineoplastic Agents. 485. Isolation and Structure of Cribrostatin 6, a Dark Blue Cancer Cell Growth Inhibitor from the Marine Sponge *Cribrochalina* sp. *J. Nat. Prod.* **2003**, *66*, 544–547.
7. Kubo, A.; Saito, N.; Sakai, H.; Takai, E.; Muranaka, R.; Itabashi, M.; Yazawa, K.; Mikami, Y. Synthesis and Antitumor Evaluation of Octahydro-5-hydroxy-1,5-imino-3-benzazocin-4,7,10-triones. *Heterocycles* **1997**, *46*, 309–320.
8. Saito, N.; Sakai, H.; Suwanborirux, K.; Pummangura, S.; Kubo, A. ^{13}C-NMR Spectral Assignment of 5-Hydroxy-1,5-imino-3-benzazocin-4,7,10-trione Derivatives: The Revised Structure of Renieramycin H. *Heterocycles* **2001**, *55*, 21–28.
9. Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S.J. Total Synthesis of Cribrostatin IV: Fine-tuning the Character of an Amide Bond by Remote Control. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.

10. Vincent, G.; Williams, R.M. Asymmetric Total Synthesis of (−)-Cribrostatin 4 (Renieramycin H). *Angew. Chem. Int. Ed.* **2007**, *46*, 1517–1520.
11. Chen, X.; Zhu, J. Total Synthesis of the Marine Natural Product (−)-Cribrostatin 4 (Renieramycin H). *Angew. Chem. Int. Ed.* **2007**, *46*, 3962–3965.
12. Yokoya, M.; Ito, H.; Saito, N. Synthesis of Renieramycins: Construction of the Core Ring System of Cribrostatin 4 through Modified Pictet-Spengler Cyclization of 3,6-Bisarylpiperazine-2,5-diones with Diethoxyethyl Benzoate. *Chem. Pharm. Bull.* **2011**, *59*, 787–792.
13. Yokoya, M.; Ito, H.; Saito, N. Chemistry of Renieramycins. Part 11: Total Synthesis of (±)-Cribrostatin 4. *Tetrahedron* **2011**, *67*, 9185–9192.
14. Yokoya, M.; Shinada-Fujino, K.; Saito, N. Chemistry of Renieramycins. Part 9: Stereocontrolled Total Synthesis of (±)-Renieramycin G. *Tetrahedron Lett.* **2011**, *52*, 2446–2449.
15. Yokoya, M.; Shinada-Fujino, K.; Yoshida, S.; Mimura, M.; Takada, H.; Saito, N. Chemistry of Renieramycins. Part 12: An Improved Total Synthesis of (±)-Renieramycin G. *Tetrahedron* **2012**, *68*, 4166–4181.
16. For simplicity, natural product numbering was used in the manuscript, but IUPAC names and numbers were used in the Experimental.
17. González, J.F.; de la Cuesta, E.; Avendaño, C. Short Stereocontrolled Synthesis of *trans* and *cis*-Tetrahydro-pyrazinoisoquinolinediones. *Tetrahedron Lett.* **2003**, *44*, 4395–4398.
18. González, J.F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. Synthesis of Phthalascidin Analogs. *Tetrahedron* **2005**, *61*, 7447–7455.
19. Ortín, I.; González, J.F.; de la Cuesta, E.; Avendaño, C. Reactions Promoted by (Hydroxy(tosyloxy)iodo)benzene in Pyrazino(1,2-*b*)isoquinolines. *Tetrahedron* **2010**, *66*, 646–652.
20. Kubo, A.; Saito, N.; Yamato, H.; Yamauchi, R.; Hiruma, K.; Inoue, S. Synthesis of Saframycins. II. Preparations and Reactions of *N*-Methyl-2,5-piperazinediones. *Chem. Pharm. Bull.* **1988**, *36*, 2607–2614.
21. Yokoya, M.; Kawachi, O.; Saito, N. Synthesis of Tetrahydroisoquinoline Antitumor Natural Products: Construction of Tricyclic Lactams through Pictet-Spengler-type Cyclization of *N*-methyl-3-arylmethylpiperazine-2,5-dione with Ethyl diethoxyacetate. *Heterocycles* **2008**, *76*, 1497–1509.
22. Nakai, K.; Kubo, K.; Yokoya, M.; Saito, N. Preparation of Renieramycin Left-half Model Compounds. *Tetrahedron* **2014**, *70*, 6529–6545.
23. The signal in the NMR spectrum ($CDCl_3$, at 20 °C) of **19** was not split, which was a mixture of two rotational isomers.
24. Saito, N.; Ōhira, Y.; Wada, N.; Kubo, A. Synthesis of saframycins. V. Selenium Oxide Oxidation of Hexahydro-1,5-imino-3-benzazocin-7,10-dione; a Useful Method for Constructing Saframycins C and D from Saframycin B. *Tetrahedron* **1990**, *46*, 7711–7728.
25. Saito, N.; Harada, S.; Inouye, I.; Yamaguchi, K.; Kubo, A. Synthesis of Saframycins. XII. Total Synthesis of (−)-*N*-Acetylsaframycin Mx 2 and its *epi*-(+)-Enantiomer. *Tetrahedron* **1995**, *51*, 8231–8246.

26. Mori, M.; Daikuhara, N.; Yamada, J.; Saito N. Selenium Oxide Oxidation of Hexahydro-1,5-imino-3-benzazocine-7,10-dione in Aliphatic Alcohol for Conversion of Renieramycin Marine Natural Products. *Heterocycles* **2012**, *86*, 317–330.
27. We cannot obtain any ^{13}C NMR spectral data of natural renieramycin I (**1i**); see reference [3].
28. Du, J.; Watanabe, K.A. Facile Preparation of α-Acyloxyacetaldehyde, a Versatile Intermediate in the Synthesis of Antiviral Nucleosides. *Synth. Commun.* **2004**, *34*, 1925–1930.

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