Synthesis of Renieramycins: Construction of the Core Ring System of Cribrostatin 4 through Modified Pictet–Spengler Cyclization of 3,6-Bisarylpiperazine-2,5-dione with Diethoxyethyl Benzoate

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A nine-step synthesis of pentacyclic key intermediate 11 of cribrostatin 4 (2) along with renieramycin I (1i) from 3,6-bisarylpiperazine-2,5-dione derivative 3 is described. The key step of this synthesis is the stereoselective cyclization of lactam nitrogen with diethoxyethyl benzoate, followed by the stereoselective hydrogenation to generate ABC ring system 6.

Key words cribrostatin 4; marine natural product; Pictet–Spengler cyclization; tetrahydroisoquinoline; preparation

In the course of our chemical studies on marine-derived tetrahydroisoquinoline alkaloids (Fig. 1),[1] we recently succeeded in preparing the ABC ring model compound of renieramycin G (**1g**) through the stereoselective Pictet–Spengler-type cyclization of *N*-methyl-3-arylmethylpiperazine-2,5-dione with ethyl diethoxyacetate.[2] Encouraged by the results of model studies, we report here a nine-step synthesis of the pentacyclic framework for the total synthesis of cribrostatin 4 (**2**) along with renieramycin I (**1i**).

A mixture of 3-arylidene-6-arylmethylpiperazinedione **3**[3] and 3 eq of triethylamine (TEA) was treated with trimethylsilyl chloride (TMSCl, 3 eq) in dichloroethane at 25 °C for 1 h to afford the *O*-trimethylsilyllactim intermediate. This intermediate was treated with ethyl diethoxyacetate (1.5 eq) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 25 °C for 19 h, and then refluxed for 1 h to give **4** in 72% yield as a single isomer (Chart 1). The stereochemistry of **4** was undetermined at this stage, but ^{1}H-NMR measurement showed a C-1[4] proton signal at δ 6.60.

Then, we studied the chemoselective reduction of the ester carbonyl of **4** to the hydroxymethyl group at C1 position. Encouraged by the results of our model studies,[2] we applied the three-step transformation of **4** to corresponding alcohol **5** (1, hydrolysis; 2, mixed anhydride preparation; 3, $NaBH_4$ reduction), but the overall yield was 53%. For the reduction step, we found it best to establish a direct method for the construction of a 1-hydroxymethyl derivative from **3**. Cyclization of **3** with 2,2-diethoxyethyl benzoate[5] using the above two steps afforded **5** in 83% overall yield. X-ray crystallographic analysis of **5** proved that the stereochemistry was *trans* between C1 and C3 protons (Fig. 2). This stereoselective cyclization would proceed from the less hindered α-face to the (*E*)-iminium isomer.

The next stage of our investigation involved the establishment of a method to construct the *cis* stereochemistry between C3 and C13. Catalytic reduction of the double bond of **5** in the presence of 10% Pd/C gave **6a** in 93% yield along

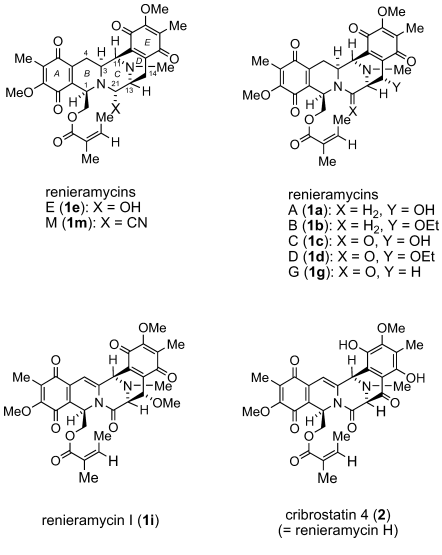
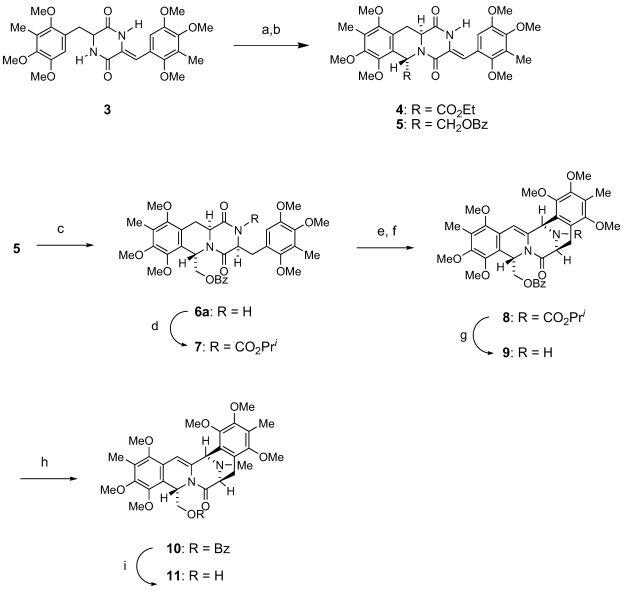


Fig. 1. Structure of Renieramycins and Related Marine Natural Products



4: (a) TMSCl (3 eq), TEA (3 eq), $(CH_2Cl)_2$, 25 °C, 1 h; (b) $(EtO)_2CHCO_2Et$ (1.5 eq), TMSOTf (6 eq), 25 °C 19 h, and then reflux, 1 h (72%, 2 steps); **5**: (a) TMSCl (3 eq), TEA (3 eq), $(CH_2Cl)_2$, 25 °C. 1 h; (b) $(EtO)_2CHCH_2OBz$ (1.5 eq), TMSOTf (6 eq), 25 °C, 19 h (83%, 2 steps); (c) H_2, 10% Pd/C, MeOH, 25 °C, 40 h (93%); (d) $ClCO_2Pr^i$, TEA, DMAP, CH_2Cl_2, 25 °C, 8 h (82%); (e) $LiAl(OBu^t)_3H$, THF, 0 °C, 2.5 h; (f) HCO_2H, 60 °C, 14 h (80%, 2 steps); (g) H_2SO_4/TFA (1 : 20), 25 °C, 10 h (96%); (h) 37% HCHO–H_2O, HCO_2H, 70 °C, 1 h (97%); (i) 1 M LiOH aq, THF/MeOH, 25 °C, 2 h (100%).

Chart 1. A Nine-Step Synthesis of **11** from **3**

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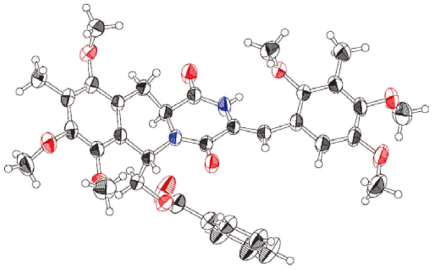

Fig. 2. ORTEP Drawing of Compound **5**

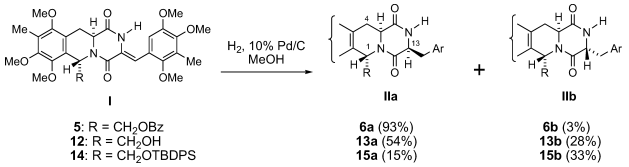

Chart 2. Catalytic Hydrogenation of Compound **I**

with corresponding *trans* diastereomer **6b** in 3% yield. The *cis* stereochemical assignment of **6a** is based on ^{1}H-NMR spectral evidence. The δ value of β-axial proton at C4 position of **6a** (δ 1.94) indicates that this proton is positioned in the deshielding zone of the aromatic ring of the side chain at C13 position, and differs from the δ values of δ 2.87 and δ 2.92 appearing in the ^{1}H-NMR spectra of **5** and **6b**, respectively. Thus, the hydrogenation of **5** has obviously occurred stereoselectively from the α-face to generate *cis* isomer **6a**. The bulky substituents at C1 would exert enough steric influence on the course of the reduction (Chart 2). The catalytic reduction of **12**, which was obtained from **5** by hydrolysis in 96% yield, gave *cis* isomer **13a** (δ 1.88 at 4-Hβ; 54%) and *trans* isomer **13b** (δ 2.73 at 4-Hβ; 28%). On the contrast, the catalytic reduction of **14**, which was prepared from **12** by silylation in 80% yield, afforded mainly *trans* isomer **15b** (δ 2.71 at 4-Hβ) in 33% yield along with *cis* isomer **15a** (δ 1.94 at 4-Hβ; 15%). The structures of these products (**6a**, **13a**, **15a**) were confirmed by direct comparison chemically transformed compounds.[6,7]

Finally, we studied the construction of the D ring to generate the pentacyclic framework of renieramycins. The piperazine ring of **6a** was activated by the introduction of a 2-propyloxycarbonyl group to give imide **7** in 82% yield. The chemoselective reduction of **7** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran (THF) afforded a diastereomeric mixture of aminals, which was converted into a cyclized product by exposure to formic acid at 60 °C for 14 h. Surprisingly, it was unexpected dehydrogenated compound **8** (80%). The mechanistic pathway for this transformation is unclear at this stage, but it can be presumed that after the dehydration of the aminals (i) to generate an iminium ion species (ii), rapid isomerization followed by a spontaneous oxidation of iii and cyclization sequence afforded **8** (Chart 3).[8,9] The deprotection of **8** with trifluoroacetic acid (TFA) and H_2SO_4 at 25 °C for 10 h gave secondary amine **9** (96%), the stereochemical structure of which was confirmed by X-ray crystallographic analysis (Fig. 3). Reductive methylation of **9** with formaldehyde and formic acid at 70 °C for 1 h afforded compound **10** (97%). Hydrolysis of **10** with 1 M LiOH/H_2O in THF and MeOH at 25 °C for 2 h gave alcohol **11** in quantitative yield.

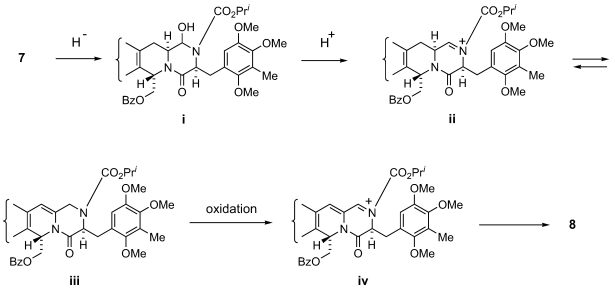

Chart 3. One Possible Mechanism of Acid-Catalyzes Cyclization Including Isomerization and Unexpected Oxidation Sequence

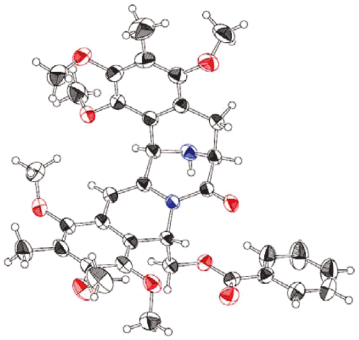

Fig. 3. ORTEP Drawing of Compound **9**

In summary, we have succeeded in the nine-step transformation of pentacyclic compound **11** from readily available **3** in high yield. To date, a number of elegant total syntheses of renieramycins A (**1a**),[10] G (**1g**),[11—14] and cribrostatin 4 (**2**)[15—17] have been reported and almost all of them include the construction of the bicyclic AB ring system with a *cis* relationship at C1 and C3 positions, followed by condensation of the E ring part and elaboration of the central bridged CD ring. Our strategy for the total synthesis of **2** along with renieramycin I (**1i**) might be prepare 1-*epi*-pentacycles, but, undesired stereochemistry might be inverted to natural one at C-1 position on the basis of our previous synthetic studies on saframycin antibiotics.[18,19] Our route might be provided both natural and unnatural derivatives as part of a broad study of this family of biologically active compounds. Efforts to investigate the isomerization at C1 position of **11** and its application to the total synthesis of cribrostatin **4** along with its derivatives are under way.

Experimental[20]

Ethyl (6*S,11a*S**)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione-6-carboxylate (4)** TMSCl (38.3 μl, 0.3 mmol) was added to a stirred solution of **3**[3] (50.0 mg, 0.1 mmol) in $ClCH_2CH_2Cl$ (1 ml) and TEA (41.8 μl, 0.3 mmol), and the stirring was continued at 25 °C for 1 h. A solution of ethyl diethoxyacetate (26.7 μl, 0.15 mmol) in $ClCH_2CH_2Cl$ (1 ml) followed by TMSOTf (108.6 μl, 0.6 mmol) was added dropwise respectively over 5 min, and the reaction mixture was stirred at 25 °C for 19 h. After TLC monitoring revealed that all of starting material **3** had been consumed, the reaction mixture was refluxed for 1 h. Then, the reaction mixture was diluted with water (10 ml), made alkaline with saturated $NaHCO_3$ solution, and extracted with $CHCl_3$ (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1 : 3) to give **4** (42.0 mg, 72%) as a yellow amorphous powder. ^{1}H-NMR δ: 1.31

(3H, t, J=7.2 Hz, $CO_2CH_2C\underline{H}_3$), 2.20 (3H, s, $ArCH_3$), 2.25 (3H, s, $ArCH_3$), 2.92 (1H, dd, J=16.8, 11.3 Hz, C11-H), 3.42 (1H, dd, J=16.8, 4.8 Hz, C11-H), 3.65 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.26 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.64 (1H, dd, J=11.3, 4.8 Hz, C11a-H), 6.60 (1H, s, C6-H), 6.65 (1H, s, C6′-H), 6.97 (1H, s, C3a-H), 9.40 (1H, s, NH). ^{13}C-NMR δ: 9.6 (CH_3), 9.7 (CH_3), 14.3 ($CO_2CH_2\underline{C}H_3$), 28.1 (C11), 52.2 (C6), 54.1 (C11a), 56.0 (OCH_3), 60.0 (OCH_3×2), 60.1 (OCH_3), 60.4 (OCH_3), 61.2 (OCH_3), 62.0 ($CO_2\underline{C}H_2CH_3$), 111.8 (C6′), 114.5 (C3a), 121.2 (C10a), 121.4 (C1′), 122.1 (C6a), 124.6 (C3), 125.5 (C9), 126.4 (C3′), 146.3 (C7), 148.7 (C2′ or C4′), 148.8 (C2′ or C4′), 149.5 (C5′), 149.9 (C8), 151.8 (C10), 157.6 (C4), 164.4 (C1), 169.0 ($\underline{C}O_2CH_2CH_3$). IR (KBr) cm^{-1}: 2941, 2837, 1735, 1697, 1633, 1456, 1400, 1257, 1085. Electron ionization (EI)-MS m/z (%): 584 (M^+, 27), 553 (20), 511 (100), 234 (18). High-resolution EI-MS Calcd for $C_{30}H_{36}O_{10}N_2$: 584.2370. Found: 584.2374.

(6*S,11a*S**)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-6-phenylcarbonyloxymethyl-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (5)**[2)] Three-Step Preparation of **5** from **4**: Lithium hydroxide monohydrate (6.9 mg, 0.164 mmol) was added to a stirred solution of **4** (40.0 mg, 0.068 mmol) in THF (0.46 ml) and MeOH (0.14 ml), and the resulting solution was stirred at 25 °C for 48 h. The reaction mixture was poured into water (20 ml), acidified with 1 N HCl, and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a carboxylic acid (39.4 mg), which was used in the next step without further purification. Ethyl chloroformate (0.008 ml, 0.082 mmol) was added to a stirred solution of the above residue and TEA (0.011 ml, 0.079 mmol) in THF (1.2 ml) at 25 °C. The reaction mixture was stirred at +5 °C for 4 h, and then at 25 °C for 13 h. After filtration of the mixture with THF (3 ml), a suspension of sodium borohydride (3.1 mg, 0.082 mmol) in water (0.04 ml) was added to the combined filtrate at 0 °C and stirring was continued for 5 h at the same temperature. The reaction mixture was poured into saturated aqueous NH_4Cl solution (30 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated *in vacuo* to give a residue (39.2 mg). The residue was subjected to column chromatography with ethyl acetate–hexane (1 : 2) to give **5** (19.7 mg, 53%) as a pale yellow solid.

Direct Transformation of **5** from **3**: TMSCl (0.38 ml, 3.0 mmol) was added to a stirred solution of **3** (500.0 mg, 1.0 mmol) in dichloroethane (10 ml) and TEA (0.42 ml, 3.0 mmol), and the stirring was continued at 25 °C for 1 h. A solution of 2,2-diethoxyethyl benzoate[5)] (327.0 mg, 1.5 mmol) in $ClCH_2CH_2Cl$ (10 ml) followed by TMSOTf (0.11 ml, 6.0 mmol) was added dropwise respectively over 5 min, and the reaction mixture was stirred at 25 °C for 19 h. The reaction mixture was diluted with water (50 ml), made alkaline with saturated $NaHCO_3$ solution, and extracted with $CHCl_3$ (200 ml×3). The combined extracts were washed with brine (200 ml), dried, and concentrated *in vacuo*. The residue was subjected to column chromatography with ethyl acetate–hexane (1 : 4—1 : 3) to give **5** (533.0 mg, 83%) as a colorless solid, the recrystallization of which from ethyl acetate–hexane gave **5** as colorless prisms, mp 194—194.5 °C. ^{1}H-NMR δ: 2.21 (3H, s, C9-CH_3), 2.25 (3H, s, C3′-CH_3), 2.83 (1H, dd, J=16.8, 12.6 Hz, C11-H), 3.49 (3H, s, OCH_3), 3.57 (1H, dd, J=16.8, 4.2 Hz, C11-H), 3.67 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.68 (1H, dd, J=11.6, 3.7 Hz, C6-CHO), 4.75 (1H, dd, J=12.6, 4.2 Hz, C11a-H), 4.80 (1H, dd, J=11.6, 9.2 Hz, C6-CHO), 6.41 (1H, dd, J=9.2, 3.7 Hz, C6-H), 6.55 (1H, s, C6′-H), 6.87 (1H, s, C3a-H), 7.39 (2H, m, ArH), 7.51 (1H, m, ArH), 7.98 (2H, m, ArH), 9.27 (1H, s, NH). ^{13}C-NMR δ: 9.5 (CH_3), 9.6 (CH_3), 28.9 (C11), 48.9 (C6), 52.7 (C11a), 55.9 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 60.4 (OCH_3), 60.5 (OCH_3), 60.8 (OCH_3), 63.9 (CH_2O), 111.7 (C6′), 113.7 (C3a), 121.4 (C1′), 121.6 (C10a), 122.3 (C6a), 124.6 (C3), 125.3 (C9), 126.4 (C3′), 128.2 (Ph×2), 129.6 (Ph×2), 129.7 (Ph), 132.8 (Ph), 146.0 (C7), 148.5 (C4′), 148.8 (C2′), 149.4 (C5′), 150.2 (C8), 152.1 (C10), 157.4 (C4), 164.4 (C-1), 166.0 ($\underline{C}$OPh). IR (KBr) cm^{-1}: 3447, 2940, 1717, 1697, 1627, 1273, 1074. EI-MS m/z (%): 646 (M^+, 26), 615 (19), 511 (100), 234 (16). High-resolution EI-MS Calcd for $C_{35}H_{38}N_2O_{10}$: 646.2526. Found: 646.2524. *Anal.* Calcd for $C_{35}H_{38}N_2O_{10}$: C, 65.00; H, 5.92; N, 4.33. Found: C, 65.09; H, 5.94; N 4.24.

Hydrogenation of Compound 5 A solution of **5** (1.29g, 2 mmol) in MeOH (50.0 ml) was hydrogenated over 10% Pd/C (640 mg) at 25 °C for 40 h. The catalyst was removed by filtration and washed with MeOH. The combined filtrates were concentrated *in vacuo* to give a solid, the recrystallization of which from $CHCl_3$–hexane gave **6a** (1.20 g, 93%) as colorless prisms. After the mother liquor was concentrated, the resulting residue was purified by silica gel chromatography with from hexane–ethyl acetate=1 : 1.5 to ethyl acetate–MeOH=10 : 1 to give **6b** (39.0 mg, 3%) as a colorless amorphous powder.

(3*S**,6*S**,11a*S**)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-6-phenylcarbonyloxymethyl-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**6a**): mp 99.5—101.5 °C ($CHCl_3$–hexane). ^{1}H-NMR δ: 1.94 (1H, dd, J=16.9, 11.8 Hz, C11), 2.16 (3H, s, C3′-CH_3), 2.18 (3H, s, C9-CH_3), 3.01 (1H, dd, J=13.7, 6.4 Hz, C3a-H), 3.24 (1H, dd, J=13.7, 4.6 Hz, C3a-H), 3.25 (1H, dd, J=16.9, 4.6 Hz, C11-H), 3.47 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.30 (1H, m, C3-H), 4.39 (1H, dd, J=11.8, 4.6 Hz, C11a-H), 4.57 (1H, dd, J=11.7, 4.6 Hz, C6-CHO), 4.65 (1H, dd, J=11.7, 8.3 Hz, C6-CHO), 6.29 (1H, dd, J=8.3, 4.6 Hz, C6-H), 6.33 (1H, s, NH), 6.43 (1H, s, C6′-H), 7.43 (2H, m, ArH), 7.55 (1H, m, ArH), 7.99 (2H, m, ArH). ^{13}C-NMR δ: 9.5 (CH_3), 9.9 (CH_3), 27.9 (C11), 35.1 (C3a), 48.3 (C6), 51.5 (C11a), 55.5 (OCH_3), 56.2 (C3), 60.0 (OCH_3), 60.1 (OCH_3), 60.2 (OCH_3), 60.5 (OCH_3), 60.6 (OCH_3), 63.7 (CH_2O), 111.1 (C6′), 121.9 (C10a), 122.0 (C6a), 122.7 (C1′), 125.3 (C9), 125.8 (C3′), 128.3 (Ph×2), 129.5 (Ph×2), 129.7 (Ph), 132.9 (Ph), 145.8 (C7), 147.2 (C4′), 149.1 (C5′), 150.0 (C8), 151.2 (C2′), 152.1 (C10), 164.1 (C4), 166.0 (s, $\underline{C}$OPh), 166.3 (C1). IR (KBr) cm^{-1}: 2940, 1719, 1694, 1663, 1456, 1273, 1117. EI-MS m/z (%): 648 (M^+, 28), 513 (100), 195 (33). High-resolution EI-MS Calcd for $C_{35}H_{40}O_{10}N_2$: 648.2683. Found: 648.2684.

(3*R**,6*S**,11a*S**)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-6-phenylcarbonyloxymethyl-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**6b**): ^{1}H-NMR δ: 2.19 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.88 (1H, dd, J=14.2, 10.2 Hz, C3a-H), 2.92 (1H, dd, J=15.9, 12.6 Hz, C11-H), 3.46 (1H, dd, J=14.2, 3.3 Hz, C3a-H), 3.58 (3H, s, OCH_3), 3.63 (1H, dd, J=15.9, 4.4 Hz, C11-H), 3.68 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.86 (1H, dd, J=12.6, 4.4 Hz, C11a-H), 3.93 (3H, s, OCH_3), 4.12 (1H, dd, J=10.2, 3.3 Hz, C3-H), 4.42 (1H, dd, J=11.2, 5.0 Hz, C6-CHO), 4.54 (1H, dd, J=11.2, 5.7 Hz, C6-CH_2O), 6.12 (1H, m, C6-H), 6.59 (1H, s, C6′-H), 6.78 (1H, s, NH), 7.40 (2H, m, ArH), 7.49 (1H, m, ArH), 7.96 (2H, m, ArH). ^{13}C-NMR δ: 9.6 (CH_3), 9.9 (CH_3), 23.4 (C11), 31.5 (C3a), 49.3 (C6), 55.0 (C11a), 56.0 (C3), 56.0 (OCH_3), 60.0 (OCH_3), 60.3 (OCH_3), 60.7 (OCH_3), 60.7 (OCH_3), 61.0 (OCH_3), 66.4 (CH_2O), 111.3 (C6′), 122.7 (C10a), 123.8 (C6a), 124.2 (C1′), 125.5 (C9), 125.9 (C3′), 128.1 (Ph×2), 129.6 (Ph×2), 129.8 (Ph), 132.8 (Ph), 146.1 (C7), 147.2 (C4′), 149.6 (C8), 150.2 (C2′), 150.4 (C5′), 151.4 (C10), 165.8 ($\underline{C}$OPh), 168.5 (s, C4), 168.6 (s, C1). IR (KBr) cm^{-1}: 3474, 2940, 1722, 1686, 1450, 1273, 1117, 1072. EI-MS m/z (%): 648 (M^+, 28), 513 (100), 195 (48). High-resolution EI-MS Calcd for $C_{35}H_{40}O_{10}N_2$: 648.2683. Found: 648.2686.

Hydrogenation of Compound 12 The same procedure as described above but using **12** (40 mg, 0.077 mmol) and 10% Pd/C (25.0 mg) in MeOH (1 ml) at 25 °C for 5.5 h gave **13a** (22.8 mg, 54.0%) and **13b** (11.7 mg, 28.0%).

(3*S**,6*S**,11a*S**)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**13a**): Colorless amorphous powder. ^{1}H-NMR δ: 1.88 (1H, dd, J=16.9, 11.8 Hz, C11-H), 2.15 (3H, s, C4′-CH_3), 2.16 (3H, s, C9-CH_3), 3.03 (1H, dd, J=13.7, 6.2 Hz, C3a-H), 3.19 (1H, dd, J=16.9, 4.7 Hz, C11-H), 3.28 (1H, dd, J=13.7, 4.6 Hz, C3a-H), 3.47 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.73 (1H, dd, J=11.7, 8.9 Hz, C$\underline{H}$OH), 3.78 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.01 (1H, dd, J=11.7, 3.9 Hz, C$\underline{H}$OH), 4.38 (1H, dd, J=11.8, 4.7 Hz, C11a-H), 4.47 (1H, m, C3-H), 5.97 (1H, dd, J=8.9, 3.9 Hz, C6-H), 6.45 (1H, s, C7′-H), 6.58 (1H, s, NH). ^{13}C-NMR δ: 9.5 (CH_3), 9.9 (CH_3), 27.8 (C11), 35.1 (C3a), 51.2 (C6), 51.5 (C11a), 55.5 (OCH_3), 56.3 (C3), 60.0 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 60.5 (OCH_3), 60.6 (OCH_3), 63.4 (CH_2OH), 111.2 (C6′), 121.7 (C10a), 122.8 (C-1′), 122.9 (C6a), 124.9 (C9), 125.7 (C3′), 145.7 (C7), 147.2 (C4′), 149.1 (C5′), 150.0 (C8), 151.2 (C2′), 152.1 (C10), 165.1 (C4), 166.8 (C1). IR (KBr) cm^{-1}: 3404, 2940, 1670, 1639, 1458, 1409, 1340, 1261, 1074. EI-MS m/z (%): 544 (M^+, 11), 513 (100), 485 (20), 195 (19). High-resolution EI-MS Calcd for $C_{28}H_{36}N_2O_9$: 544.2421. Found: 544.2418.

(3*R**,6*S**,11a*S**)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**13b**): Amorphous powder. ^{1}H-NMR δ: 2.18 (3H, s, C9-CH_3), 2.22 (3H, s, C3′-CH_3), 2.73 (1H, dd, J=16.8, 12.5 Hz, C11-H), 3.06 (1H, dd, J=13.9, 8.4 Hz, C3a-H), 3.41 (1H, dd, J=16.8, 4.4 Hz, C11-H), 3.49 (1H, dd, J=13.9, 3.8 Hz, C3a-H), 3.65 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.76 (1H, dd, J=11.5, 8.6 Hz, C$\underline{H}$OH), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.04 (1H, dd, J=11.5, 3.9 Hz, C$\underline{H}$OH), 4.36 (1H, dd, J=8.4, 3.8 Hz, C3-H), 4.40 (1H, dd, J=12.5, 4.4 Hz, C11a-H), 5.98 (1H, dd, J=8.6, 3.9 Hz, C6-H), 6.36 (1H, s,

NH), 6.62 (1H, s, C6′-H). ^{13}C-NMR δ: 9.5 (CH_3), 9.9 (CH_3), 27.8 (C11), 34.7 (C3a), 51.5 (C6), 52.2 (C11a), 55.5 (C3), 56.1 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 60.3 (OCH_3), 60.4 (OCH_3), 60.7 (OCH_3), 63.8 (CH_2OH), 111.6 (C6′), 121.7 (C10a), 123.2 (C6a), 123.4 (C1′), 125.0 (C9), 126.0 (C3′), 145.9 (s, C7), 147.3 (C4′), 149.4 (C5′), 150.2 (C8), 150.7 (C2′), 152.2 (C10), 165.2 (C4), 166.7 (C1). IR (KBr) cm^{-1}: 3443, 2939, 1681, 1458. EI-MS *m/z* (%): 544 (M^+, 8), 513 (100), 485 (12), 195 (16). High-resolution EI-MS Calcd for $C_{28}H_{36}N_2O_9$: 544.2421. Found: 544.2418.

Hydrogenation of Compound 14 The same procedure as described above but using **14** (19.5 mg, 0.025 mmol) and 10% Pd/C (8.1 mg) in MeOH (1 ml) at 2 MPa for 5.5 h gave **15a** (2.9 mg, 15.0%) and **15b** (6.4 mg, 33.0%).

(3*S**,6*S**,11a*S**)-6-*tert*-Butyldiphenylsilyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**15a**): Colorless amorphous powder. ^{1}H-NMR δ: 0.98 (9H, s, C(CH_3)$_3$), 1.94 (1H, dd, *J*=17.0, 12.3 Hz, C11-H), 2.15 (3H, s, C9-CH_3), 2.20 (3H, s, C3′-CH_3), 3.04 (1H, dd, *J*=13.7, 6.6 Hz, C3a-H), 3.19 (1H, dd, *J*=17.0, 4.8 Hz, C11-H), 3.32 (1H, dd, *J*=13.7, 4.2 Hz, C3a-H), 3.46 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.81 (1H, dd, *J*=10.8, 7.8 Hz, C6-CHO), 4.03 (1H, dd, *J*=10.8, 3.8 Hz, C6-CHO), 4.42 (1H, m, C-3), 4.45 (1H, dd, *J*=12.3, 4.8 Hz, C-11a), 6.08 (1H, dd, *J*=7.8, 3.8 Hz, C-6), 6.12 (1H, s, NH), 6.46 (1H, s, C6′-H), 7.69—7.29 (10H, m, SiPh×2). ^{13}C-NMR δ: 9.5 (CH_3), 9.9 (CH_3), 19.2 (C(CH_3)$_3$), 26.8 (C(CH_3)$_3$), 28.1 (C11), 35.2 (C3a), 50.3 (C6), 51.6 (C11a), 55.5 (OCH_3), 56.4 (C-3), 59.9 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 60.2 (OCH_3), 60.6 (OCH_3), 64.2 (CH_2O), 111.1 (C6′), 122.0 (C10a), 123.0 (C1′), 123.5 (C6a), 124.6 (C3′), 125.8 (C9), 127.5 (SiPh×2), 127.6 (SiPh×2), 129.5 (SiPh), 129.6 (SiPh), 133.0 (SiPh), 133.1 (SiPh), 135.3 (SiPh×2), 135.4 (SiPh×2), 145.7 (C7), 147.2 (C5′), 149.1 (C4′), 149.8 (C8), 151.2 (C2′), 152.1 (C10), 163.8 (C1), 166.7 (C4). IR (KBr) cm^{-1}: 3447, 2936, 1684, 1655, 1458, 1115. Positive FAB-MS: 783 [M+H$^+$]. High-resolution positive FAB-MS Calcd for $C_{44}H_{54}N_2O_9Si$: 783.3670. Found: 783.3677.

(3*R**,6*S**,11a*S**)-6-*tert*-Butyldiphenylsilyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**15b**): Pale yellow oil. ^{1}H-NMR δ: 1.03 (9H, s, C(CH_3)$_3$), 2.16 (3H, s, C9-CH_3), 2.23 (3H, s, C3′-CH_3), 2.71 (1H, dd, *J*=17.0, 12.7 Hz, C11-H), 2.85 (1H, dd, *J*=13.8, 10.5 Hz, C3a-H), 3.38 (1H, dd, *J*=17.0, 4.4 Hz, C11-H), 3.66 (1H, m, C3a-H), 3.62 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.87 (1H, dd, *J*=10.5, 8.3 Hz, C6-CHO), 4.08 (1H, dd, *J*=10.5, 3.7 Hz, C6-CHO), 4.33 (1H, dd, *J*=10.5, 2.4 Hz, C3-H), 4.57 (1H, dd, *J*=12.7, 4.4 Hz, C11a-H), 6.11 (1H, dd, *J*=8.3, 3.7 Hz, C6-H), 6.23 (1H, s, N-H), 6.57 (1H, s, C7′-H), 7.32—7.73 (10H, m, SiPh×2). ^{13}C-NMR δ: 9.5 (CH_3), 9.9 (CH_3), 19.4 (C(CH_3)$_3$), 26.9 (C(CH_3)$_3$), 28.0 (C11), 35.6 (C3a), 50.8 (C6), 52.3 (C11a), 55.4 (C3), 56.0 (OCH_3), 60.0 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 60.3 (OCH_3), 60.9 (OCH_3), 64.1 (CH_2O), 111.3 (C6′), 121.9 (C10a), 123.8 (C6a), 124.0 (C1′), 124.6 (C9), 126.2 (C3′), 127.6 (SiPh×4), 129.6 (SiPh), 129.7 (SiPh), 133.0 (SiPh), 133.2 (SiPh), 135.3 (d, SiPh×2), 135.5 (d, SiPh×2), 146.0 (C7), 147.3 (C4′), 149.5 (C5′), 150.0 (C8), 150.8 (C2′), 152.1 (C10), 164.3 (C4), 166.9 (C1). IR (KBr) cm^{-1}: 3431, 2934, 1686, 1668, 1464, 1114. Positive FAB LR-MS: 783 [M+H$^+$]. High-resolution positive FAB-MS Calcd for $C_{44}H_{54}N_2O_9Si$: 783.3670. Found: 783.3677.

(6*S,11a*S**)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (12)** An aqueous 0.1 M solution of lithium hydroxide monohydrate (11.6 ml, 1.16 mmol) was added to a solution of **6b** (600 mg, 0.93 mmol) in THF (35 ml) and MeOH (12 ml), and the reaction mixture was stirred at 25 °C for 7 h. The reaction mixture was diluted with water (200 ml) and extracted with $CHCl_3$ (200 ml×3). The combined extracts were washed with brine (200 ml), dried, and concentrated *in vacuo* and the residue was purified by silica gel chromatography with MeOH–$CHCl_3$ (1 : 100) to give **12** (383.8 mg, 96%) as a colorless amorphous powder. ^{1}H-NMR δ: 2.19 (3H, s, C9-CH_3), 2.25 (3H, s, C3′-CH_3), 2.81 (1H, dd, *J*=17.1, 12.2 Hz, C11-H), 3.52 (1H, dd, *J*=17.1, 4.6 Hz, C11-H), 3.65 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.82—3.93 (1H, m, CHOH), 3.93 (3H, s, OCH_3), 4.15 (1H, dd, *J*=11.5, 3.7 Hz, CHOH), 4.73 (1H, dd, *J*=12.2, 4.6 Hz, C11a-H), 6.10 (1H, dd, *J*=8.1, 3.7 Hz, C6-H), 6.64 (1H, s, C6′-H), 6.94 (1H, s, C3a-H), 9.41 (1H, s, NH). ^{13}C-NMR δ: 9.5 (CH_3), 9.7 (CH_3), 28.9 (C11), 51.8 (C6), 52.7 (C11a), 55.9 (OCH_3), 60.0 (OCH_3), 60.0 (OCH_3), 60.4 (OCH_3), 60.4 (OCH_3), 61.1 (OCH_3), 63.9 (CH_2OH), 111.8 (C6′), 113.8 (C3a), 121.5 (C10a), 121.5 (C1′), 123.2 (C6a), 124.8 (C9), 124.9 (C3), 126.4 (C3′), 145.8 (C7), 148.5 (C4′), 148.8 (C2′), 149.4 (C5′), 150.2 (C8), 152.1 (C10), 158.2 (C4), 164.8 (C1). IR (KBr) cm^{-1}: 3447, 2938, 1690, 1624, 1458, 1406. EI-MS *m/z* (%): 542 (M^+, 12), 511 (100), 234 (12). High-resolution EI-MS Calcd for $C_{28}H_{34}N_2O_9$: 542.2264. Found: 542.2261.

(6*S,11a*S**)-6-*tert*-Butyldiphenylsilyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (14)** *tert*-Butyl diphenylchlorosilane (TBDPSCl) (42.0 μl, 0.164 mmol) was added to a stirred solution of **5** (19.7 mg, 0.036 mol), *N*,*N*-dimethylaminopyridine (DMAP) (6.6 mg, 0.055 mol), and imidazole (18.6 mg, 0.27 mmol) in dry THF (1.0 ml) at 25 °C, and the reaction mixture was heated under reflux for 3 h. After cooling, the reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a residue (60.2 mg). Chromatography on a silica gel column with hexane–ethyl acetate (4 : 1—3 : 1) gave **14** (22.7 mg, 80.2%) as a pale yellow amorphous powder. ^{1}H-NMR δ: 0.98 (9H, s, C(CH_3)$_3$), 2.17 (3H, s, C9-CH_3), 2.26 (3H, s, C3′-CH_3), 2.76 (1H, dd, *J*=16.9, 12.4 Hz, C11-H), 3.47 (1H, dd, *J*=16.9, 4.7 Hz, C11-H), 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.91 (1H, dd, *J*=10.7, 7.7 Hz, C6-CHO), 4.14 (1H, dd, *J*=10.7, 3.4 Hz, C6-CHO), 4.74 (1H, dd, *J*=12.4, 4.7 Hz, C11a-H), 6.20 (1H, dd, *J*=7.7, 3.4 Hz, C6-H), 6.69 (1H, s, C6′-H), 6.98 (1H, s, C3a-H), 7.30—7.70 (10H, m, SiPh×2), 9.35 (1H, s, NH). ^{13}C-NMR δ: 9.5 (C9-CH_3), 9.7 (C3′-CH_3), 19.3 (C(CH_3)$_3$), 26.8 (C(CH_3)$_3$), 29.0 (C11), 51.0 (C6), 52.8 (C11a), 55.9 (OCH_3), 60.0 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 60.4 (OCH_3), 60.9 (OCH_3), 64.4 (CH_2O), 111.7 (C6′), 113.4 (C3a), 121.7 (C10a), 121.7 (C1′), 123.8 (C6a), 124.5 (C9), 125.1 (C3), 126.4 (C3′), 127.5 (SiPh×2), 127.6 (SiPh×2), 129.5 (SiPh), 129.6 (SiPh), 133.0 (SiPh), 133.4 (SiPh), 135.2 (SiPh×2), 135.4 (SiPh×2), 145.9 (C7), 148.4 (C2′), 148.8 (C4′), 149.4 (C5′), 150.0 (C8), 152.0 (C10), 157.2 (C4), 164.8 (C1). IR (KBr) cm^{-1}: 3437, 2936, 2857, 1697, 1630, 1458, 1398, 1338, 1256. Positive FAB-MS: 781 [M+H$^+$]. High-resolution positive FAB-MS Calcd for $C_{44}H_{53}N_2O_9Si$: 781.3516. Found: 781.3520.

Conversion of 13a into 6a Benzoyl chloride (4.0 mg, 0.028 mmol) was added to a stirred solution of **13a** (15.0 mg, 0.023 mmol) with TEA (0.004 ml, 0.028 mmol) and DMAP (0.7 mg, 0.0055 mmol) in dichloromethane (1.0 ml) at 25 °C, and this mixture was stirred at the same temperature for 1.5 h. The reaction mixture was concentrated *in vacuo* and chromatography on a silica gel column with hexane–ethyl acetate (3 : 1) afforded **6a** (16.3 mg, 91%) as colorless prisms, whose spectral data were in complete agreement with those of the authentic sample described above.

Conversion of 13a into 15a The same procedure as described above (from **5** to **14**) but using **13a** (20.0 mg, 36.8 mmol) gave TBDPS derivative (28.3 mg, 99%) as a pale yellow oil, whose spectral data were in complete agreement with those of minor product **15a**.

(3*S,6*S**,11a*S**)-2-Isopropyloxycarbonyl-6-phenylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6*H*-pyrazino[1,2-*b*]soquinoline-1,4-dione (7)** A solution of **6a** (500 mg, 0.772 mmol), TEA (0.21 ml, 1.54 mmol), and DMAP (188.0 mg, 1.54 mmol) in dichloromethane (15 ml) was cooled with ice-water and isopropyl chloroformate ($ClCO_2Pr^i$, 0.425 ml, 3.09 mmol) was added dropwise over 10 min. After stirring at 25 °C for 8 h, the reaction mixture was diluted with CH_2Cl_2 (200 ml) and washed with 1 N HCl (50 ml×2). The combined extracts were washed with water (100 ml), dried, and concentrated *in vacuo*. The residue was purified by silica gel chromatography with hexane–ethyl acetate (1 : 4) to afford **7** (462.0 mg, 82%) as a colorless amorphous powder. ^{1}H-NMR δ: 1.23 (1H, dd, *J*=16.9, 12.6 Hz, C-11), 1.35 (3H, d, *J*=6.4 Hz, $CO_2CH(CH_3)_2$), 1.38 (3H, d, *J*=6.4 Hz, $CO_2CH(CH_3)_2$), 2.06 (3H, s, C9-CH_3), 2.15 (3H, s, C3′-CH_3), 3.11 (1H, dd, *J*=16.9, 4.8 Hz, C11-H), 3.13 (1H, dd, *J*=13.9, 4.2 Hz, C3a-H), 3.36 (3H, s, OCH_3), 3.47 (1H, dd, *J*=13.9, 4.9 Hz, C3a-H), 3.53 (3H, s, OCH_3), 3.53 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.49 (1H, dd, *J*=12.6, 4.8 Hz, C11a-H), 4.55 (1H, dd, *J*=11.5, 4.2 Hz, C6-CHO), 4.59 (1H, dd, *J*=11.5, 8.3 Hz, C6-CHO), 4.99 (1H, dd, *J*=4.9, 4.2 Hz, C3-H), 5.11 (1H, sept, *J*=6.4 Hz, $CO_2CH(CH_3)_2$), 6.23 (1H, dd, *J*=8.3, 4.2 Hz, C6-H), 6.34 (1H, s, C6′-H), 7.42 (2H, m, ArH), 7.55 (1H, m, ArH), 7.95 (2H, m, ArH). ^{13}C-NMR δ: 9.5 (C9-CH_3), 9.8 (C3′-CH_3), 21.9 ($CO_2CH(CH_3)_2$×2), 27.1 (C11), 33.6 (C3a), 48.2 (C6), 53.0 (C11a), 55.3 (OCH_3), 59.5 (C3), 60.0 (OCH_3), 60.0 (OCH_3), 60.1 (OCH_3), 60.3 (OCH_3), 60.5 (OCH_3), 64.0 (t, C6-CH_2O), 72.0 ($CO_2CH(CH_3)_2$), 111.9 (C6′), 121.5 (C6a), 121.9 (C10a), 122.4 (C1′), 125.3 (C9), 125.8 (C3′), 128.3 (Ph×2), 129.5 (Ph×2), 129.5 (Ph), 132.9 (Ph), 145.7 (C7), 147.3 (C4′), 148.9 (C5′), 150.0 (C8), 151.5 ($CO_2CH(CH_3)_2$), 151.6 (C2′), 152.1 (C10), 163.7 (C1), 165.3 (C4), 166.0 (COPh). IR (KBr) cm^{-1}: 2939, 1724, 1274, 1111. Positive FAB MS: 735

[M+H$^+$]. High-resolution positive FAB-MS Calcd for $C_{39}H_{46}N_2O_{12}$: 735.3129 [M+H$^+$]. Found: 735.3124.

Isopropyl 1,2,4,10,11,13-Hexamethoxy-3,12-dimethyl-7-oxo-9-phenylcarbonyloxymethyl-(6*S,9*S**,15*R**)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-*b*]3-benzazocine-16-carboxylate (8)** A stirred solution of **7** (230.0 mg, 0.313 mmol) in dry THF (9 ml) was cooled with ice-water and lithium tri-*tert*-butoxyaluminohydride (319.0 mg, 1.25 mmol) was added over 10 min. After continued stirring at 0 °C for 2.5 h, Na_2SO_4 was added and the reaction mixture was quenched with water (5 ml). The reaction mixture was filtered through Celite pad and the filtrate was concentrated *in vacuo* to give a residue that was used in the next step without further purification. A solution of the above residue in formic acid (5 ml) was stirred at 60 °C for 14 h. After the reaction mixture was concentrated *in vacuo*, the residue was dissolved with $CHCl_3$ (80 ml) and 5% aqueous $NaHCO_3$ solution (80 ml). The phases were allowed to separate and the aqueous phase was extracted with $CHCl_3$ (80 ml×3). The combined extracts were washed with brine (80 ml), dried, and concentrated *in vacuo* to give a residue, the purification of which by silica gel column chromatography with ethyl acetate to ethyl acetate–MeOH (20 : 1) gave **8** (179.0 mg, 80%) as a pale yellow amorphous powder. ^{1}H-NMR δ[22]: 1.17 (6H, m, $CO_2CH(\underline{CH}_3)_2$), 2.13 (6H, s, Ar-$CH_3$×2), 3.09 (2H, m), 3.62 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.34 (1H, dd, *J*=11.2, 7.1 Hz), 4.43 (1H, m), 4.83 (1H, m), 5.23 (1H, m), 6.30 (1H, m), 6.37 (1H, s), 6.45 (1H, m), 7.43 (2H, m, ArH), 7.53 (1H, m, ArH), 7.99 (2H, m, ArH). IR (KBr) cm^{-1}: 2939, 1707, 1647, 1466, 1269. EI-MS *m/z* (%): 716 (M$^+$, 8), 581 (100), 553 (77), 234 (29). High-resolution EI-MS Calcd for $C_{39}H_{44}N_2O_{11}$: 716.2945. Found: 716.2944.

1,2,4,10,11,13-Hexamethoxy-3,12-dimethyl-7-oxo-9-phenylcarbonyloxymethyl-(6*S,9*S**,15*R**)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-*b*]3-benzazocine (9)**[23] Concentrated H_2SO_4 (1.5 ml) was added over 5 min to a stirred solution of **8** (1.10 g, 1.54 mmol) in TFA (30 ml) at 0 °C, and the reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was poured into water (100 ml) at 0 °C and basified with NH_4OH. The solution was extracted with $CHCl_3$ (200 ml×3). The combined extracts were washed with brine (200 ml), dried, and concentrated *in vacuo*, and the residue was purified by silica gel chromatography with hexane–ethyl acetate (3 : 1) to ethyl acetate to afford **9** (933.0 mg, 96%) as a solid. Recrystallization from hexane–ethyl acetate gave **9** as colorless prisms, mp 200—201 °C. ^{1}H-NMR δ: 2.12 (3H, s, C3-CH_3), 2.15 (3H, s, C12-CH_3), 2.99 (1H, dd, *J*=17.7, 2.7 Hz, C5-H), 3.06 (1H, dd, *J*=17.7, 6.2 Hz, C5-H), 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.03 (1H, ddd, *J*=6.2, 2.7, 1.7 Hz, C6-H), 4.49 (1H, dd, *J*=11.3, 6.5 Hz, C9-CH), 4.58 (1H, dd, *J*=11.3, 3.3 Hz, C9-CH), 5.13 (1H, br s, C15-H), 6.20 (1H, d, *J*=0.6 Hz, C14-H), 6.46 (1H, dd, *J*=6.5, 3.3 Hz, C9-H), 7.44 (2H, m, ArH), 7.57 (1H, m, ArH), 8.00 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 9.18 (C3-CH_3), 9.23 (C12-CH_3), 25.7 (C5), 47.9 (C15), 48.8 (C9), 53.7 (C6), 59.7 (OCH_3), 59.7 (OCH_3), 60.0 (OCH_3), 60.2 (OCH_3), 60.6 (OCH_3), 61.0 (OCH_3), 65.4 (C9$\underline{C}H_2$), 97.1 (C14), 119.0 (C6a), 121.1 (C13a), 121.2 (C4a), 124.6 (C3), 125.5 (C12), 127.4 (s, C15a), 128.4 (Ph×2), 129.7 (Ph×2), 129.8 (Ph), 133.2 (Ph), 137.0 (C14a), 145.7 (C10), 145.9 (C1), 149.2 (C13), 149.9 (C2), 150.1 (C12), 152.2 (C4), 167.3 (CO), 172.3 (C7). IR (KBr) cm^{-1}: 2939, 1716, 1676, 1635, 1465, 1271, 1168. EI-MS *m/z* (%): 630 (M$^+$, 23), 495 (48), 467 (100), 234 (41). High-resolution EI-MS Calcd for $C_{35}H_{38}N_2O_9$: 630.2577. Found: 630.2579. *Anal.* Calcd for $C_{35}H_{38}N_2O_9$: C, 66.65; H, 6.07; N, 4.44. Found: C, 66.56; H, 6.15; N, 4.39.

1,2,4,10,11,13-Hexamethoxy-9-phenylcarbonyloxymethyl-3,12,16-trimethyl-7-oxo-(6*S,9*S**,15*R**)-5,6,9,15-tetrahydro-6,15-iminoisoquino-[3,2-*b*]3-benzazocine (10)** Formaldehyde (37% wt% solution water, 19.4 ml) was added to a solution of **9** (820.0 mg, 1.30 mmol) in formic acid (22.7 ml) at 60 °C, and the reaction mixture was stirred at 70 °C for 1 h. After reaction mixture was diluted with water (200 ml), the resulting solution was extracted with $CHCl_3$ (200 ml×3). The combined extracts were washed with aqueous 5% $NaHCO_3$ solution (200 ml), dried, and concentrated *in vacuo* and the residue was subjected to silica gel chromatography with hexane–ethyl acetate=3 : 1 to ethyl acetate to afford **10** (813.0 mg, 97%) as a colorless amorphous powder. ^{1}H-NMR δ: 2.12 (3H, s, C12-CH_3), 2.14 (3H, s, C3-CH_3), 2.55 (3H, s, $\underline{N}CH_3$), 3.05 (1H, dd, *J*=17.7, 1.7 Hz, C5H), 3.16 (1H, dd, *J*=17.7, 7.2 Hz, C5H), 3.63 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.82 (1H, m, C6-H), 3.90 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.44 (1H, dd, *J*=11.4, 3.8 Hz, C9CH), 4.50 (1H, dd, *J*=11.4, 6.0 Hz, C9CH), 4.92 (1H, d, *J*=1.8 Hz, C15H), 6.37 (1H, d, *J*=0.6 Hz, C14-H), 6.48 (1H, dd, *J*=6.0, 3.8 Hz, C9-H), 7.44 (2H, m, ArH), 7.56 (1H, m, ArH), 8.03 (2H, m, ArH). ^{13}C-NMR δ: 9.3 (C12-CH_3), 9.5 (q, C3-CH_3), 26.5 (C5), 41.5 (NCH_3), 48.2 (C9), 54.9 (C15), 59.8 (OCH_3), 59.8 (OCH_3), 60.0 (OCH_3), 60.3 (OCH_3), 60.4 (C6), 60.6 (OCH_3), 61.1 (OCH_3), 65.9 (C9$\underline{C}H_2$), 99.6 (C14), 118.8 (C9a), 120.7 (C4a), 120.8 (C13a), 124.6 (C3), 125.4 (C12), 127.2 (C15a), 128.2 (Ph×2), 129.6 (Ph×2), 129.8 (Ph), 132.8 (Ph), 134.7 (C14a), 145.7 (C1), 145.7 (C18), 148.8 (C13), 149.8 (C2), 150.1 (C11), 152.2 (C4), 166.0 (CO), 169.8 (C7). IR (KBr) cm^{-1}: 3447, 2940, 2833, 1724, 1676, 1638, 1466, 1414, 1354, 1271, 1248, 1113, 1067, 1007. Positive FAB-MS: 645 [M+H$^+$]. High-resolution positive FAB-MS Calcd for $C_{36}H_{40}N_2O_9$: 645.2812 [M+H$^+$]. Found: 645.2814.

1,2,4,10,11,13-Hexamethoxy-9-hydroxymethyl-3,12,16-trimethyl-7-oxo-(6*S,9*S**,15*R**)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-*b*]3-benzazocine (11)** An aqueous 1 M solution of lithium hydroxide monohydrate (2.5 ml, 2.5 mmol) was added to a stirred solution of **10** (738.0 mg, 1.15 mmol) in THF (6.7 ml) and MeOH (2.2 ml), and stirring was continued at 25 °C for 2 h. After the reaction mixture was diluted with water (200 ml), the resulting mixture was extracted with $CHCl_3$ (200 ml×3). The combined extracts were washed with brine (200 ml), dried, and concentrated *in vacuo* to give a residue. Purification by silica gel chromatography with $CHCl_3$–MeOH (50 : 1) gave **11** (619.0 mg, 100%) as a colorless amorphous powder. ^{1}H-NMR δ: 2.13 (6H, s, C3-CH_3 and C12-CH_3), 2.67 (3H, s, $\underline{N}CH_3$), 3.01 (1H, dd, *J*=17.9, 0.7 Hz, C5-H), 3.16 (1H, dd, *J*=17.9, 7.7 Hz, C5-H), 3.66 (3H, s, OCH_3), 3.66—3.81 (2H, m, C9CH) 3.69 (6H, s, OCH_3×2), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.91 (1H, m, C6-H), 3.96 (3H, s, OCH_3), 4.90 (1H, d, *J*=1.7 Hz, C15-H), 6.22 (1H, dd, *J*=7.2, 4.5 Hz, C9-H), 6.32 (1H, s, C14-H). ^{13}C-NMR δ: 9.4 (C3-CH_3 or C12-CH_3), 9.5 (C3-CH_3 or C12-CH_3), 25.8 (C5), 41.4 ($\underline{N}CH_3$), 51.0 (C9), 54.7 (C15), 59.8 (OCH_3), 59.8 (OCH_3), 60.0 (OCH_3), 60.1 (C6), 60.3 (OCH_3), 60.6 (OCH_3), 61.1 (OCH_3), 65.6 (C9$\underline{C}H_2$), 99.4 (C14), 119.6 (C9a or C13a), 120.6 (C9a or C13a), 120.6 (C5a), 124.5 (C3 or C12), 125.2 (C3 or C12), 127.4 (C15a), 134.8 (C14a), 145.6 (C10), 145.7 (C1), 148.9 (C13), 149.9 (C2 or C11), 150.0 (s, C2 or C11), 152.0 (C4), 170.8 (C7). IR (KBr) cm^{-1}: 3421, 2940, 1670, 1632, 1466, 1412. EI-MS *m/z* (%): 540 (M$^+$, 11), 509 (24), 481 (100), 248 (49). High-resolution EI-MS Calcd for $C_{29}H_{36}N_2O_8$: 540.2472 [M+H$^+$]. Found: 540.2478.

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References and Notes

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20) All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Shimadzu IRAffinity-1 Fourier Transform Infrared Spectrometer. ^{1}H-NMR spectra were recorded at 300 MHz on a JEOL AL-300 spectrometer and at 400 MHz on a JEOL AL-400 spectrometer. ^{13}C-NMR was recorded at 100 MHz (multiplicities were determined from distortionless enhancement by polarization transfer (DEPT) spectra). NMR spectra were measured in $CDCl_3$ and the chemical shifts were recorded in δ_H values relative to $(CH_3)_4Si$ as the internal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.
21) X-Ray crystallographic analysis of **5**. All measurements were performed on a Rigaku AFC7S diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.54178 Å). Crystal data: Colorless prismatic crystal, triclinic, $C_{35}H_{38}N_2O_{10}$ (Mr±646.69), space group P-1 (#2) with a=9.234(3) Å, b=11.313(4) Å, c=16.658(6) Å, α=77.21(3)°, β=76.14(3)°, γ=85.33(3)°, V=1647(1) Å^3, Z=2, and D_{calcd}=1.304 g/cm^3. The final cycle of the full-matrix least-squares refinement was based on 5802 unique reflections (2θ<136.0°) and 428 variable parameters and converged with unweighted and weighted agreement factors of R=0.0578, R_w=0.1481, and R_1=0.0526 for $I>2.0\sigma(I)$ data.
22) The signals in the ^{1}H-NMR spectra of **8** were not split, which indicated that there was a mixture of rotational isomers.
23) X-Ray crystallographic analysis of **9**. All measurements were performed on a Rigaku AFC7S diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.54178 Å). Crystal data: Colorless prismatic crystal, monoclinic, $C_{35}H_{38}N_2O_9$ (Mr=630.69), space group Pc (#7) with a=16.319(5) Å, b=9.560(3) Å, c=22.170(6) Å, β=108.62(2)°, V =3278(2) Å^3, Z=4, and D_{calcd}=1.278 g/cm^3. The final cycle of the full-matrix least-squares refinement was based on 6105 unique reflections (2θ<135.9°) and 906 variable parameters and converged with unweighted and weighted agreement factors of R=0.0437, R_w=0.0949, and R_1=0.0363 for $I>2.0\sigma(I)$ data.