PREPARATION OF TRICYCLIC ANALOG AS CDE RING MODEL OF RENIERAMYCIN MARINE NATURAL PRODUCT BY NOVEL PHOTO-INDUCED TRANSFORMATION OF 6-METHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE-5,8-DIONE

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – 2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2H-pyrazino[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (11a) was prepared as the CDE ring model of renieramycins, and its novel photo-induced transformation was demonstrated to construct a 1,3-dioxol ring.

INTRODUCTION

Renieramycin-type marine natural products exhibit potent antitumor activity, the mechanism of action of which may involve the reaction of the iminium ion that is formed from the elimination of the cyano group or the hydroxy group at C-21 position with the guanine residue of DNA. As a result of intensive efforts channeled into the research of renieramycin marine natural products, about 30 compounds have been isolated from nature. Cell proliferation inhibition tests using human cancer cell lines have revealed that the substitution pattern of the characteristic E-ring greatly affects the inhibitory activity of renieramycins obtained from nature. However, there are only two reports of the synthesis of target compounds having a variety of E-ring substitution patterns for SAR study. Those reports have used chiral amino acids as the starting material to prepare natural products.

We were able to identify minor metabolites 1t, 1u, and 1x from Thai and Philippine blue sponge Xestospongia sp. We have also completed the first asymmetric total synthesis of (-)-1t along with a large-scale synthetic route to (±)-1t. Guo’s group was able to isolate and elucidate the structure of fennebricin B (2) from the skin of South China Sea nudibranch Jorunna funebris and its possible
sponge-prey *Xestospongia* sp. All of these compounds have a common aromatic ring along with a fused 1,3-dioxole that is also present in the E-ring of ecteinascidin 3. Recently, we found that synthesized model compound 4 was converted directly into 5 by photo-chemical transformation in high yield. To our knowledge, there are only two established precedents for such a photo cyclization reaction, and thereafter it had not been applied to total synthesis. Recently Gademann *et al.* reported the total synthesis of natural products effectively utilizing this photo reaction. We are very interested in the reaction mechanisms underlying a transformation to construct a fascinating ring system. In this paper, we present the preparation of diastereomers 11a–c and their photochemical transformation into 34a–c. We also show the photo-induced transformation of 11a into cis-12a and discuss the reaction mechanism.

**Figure 1.** Structures of 1,2,3,4-tetrahydroisoquinoline natural products having 1,3-dioxol ring at E-ring

**Scheme 1.** A fantastic photo-induced 1,3-dioxol ring formation reaction

The synthesis of 11 was performed by the following strategy (Figure 2). *p*-Quinones 11a–c would be obtained from corresponding 10a–c by removing the TBS group and a subsequent oxidative demethylation. Alkoxy compounds 10a–c would be prepared by the alkylation of phenol 9, and 9 would be produced by a modified Pictet-Spengler reaction of lactam 8. This compound would be generated from highly substituted benzaldehyde 7 by employing our previous strategy where we adopted the modified Gallina method. 7 was obtained from 6 over six steps by using Hibino’s protocol. Thus, we started the preparation of left-half model compounds 11a–c via compound 8.
RESULTS AND DISCUSSION

2,6-Dihydroxytoluene 6 was converted into compound 7\textsuperscript{11} in six steps. 7 was protected with TBS to produce ether 13 in 83% yield (Scheme 2). Condensation of aldehyde 13 with 1,4-diacetylpiperazine-2,5-dione 14 by the modified Gallina and Liberatori method gave 15 in 69% yield. The catalytic hydrogenation of 15 proceeded smoothly where 15 was completely consumed. Purification of the crude material by SiO\textsubscript{2} column chromatography gave an inseparable mixture of two products (1:0.3). It was confirmed that the major product was compound 16, which might be produced by the debenzylation of 15, followed by the transfer of the TBS group from C-2' into C-3'. It was very difficult to obtain 8 in high yield, we should try an alternative route which involved benzyl protection of the phenolic hydroxy group (Scheme 3).

According to the published method,\textsuperscript{12} monobenzyl derivative 19 was obtained from commercially available 3,5-dihydroxy-4-methylbenzoic acid (17) in 27% yield. Over-reacted compound 20 (31%) and
methyl ester 18 (27%) were also obtained. Product 20 underwent deprotection under catalytic hydrogenation conditions to form 18 in 94% yield. Methylation of 19 gave ether 21 in 93% yield. Hydride reduction of 21 produced alcohol 22, the oxidation of which with PCC gave aldehyde 23 in 91% overall yield. Condensation of 23 with diacetate 14 under the same conditions as those described above afforded 24 in 81% yield. Finally, the catalytic reduction of 24 was carried out to generate 25 in 98% yield.

Scheme 3. 7 Seven Steps transformation of 17 into 25

Phenol 25 was subjected to our modified Pictet-Spengler cyclization to construct 1,2,3,4-tetrahydroisoquinoline. The reaction of 25 with trimethylsilyl chloride (2.6 eq.) in the presence of triethylamine (2.6 eq.) in dichloromethane gave O-trimethylsilyllactim intermediate 27. Treatment of 27 with 2,2-diethoxyethyl benzoate (26) in the presence of trimethylsilyl trifluoromethanesulfonate at 25 °C for 15 h gave 28 as a single diastereomer. The yield of 28 was very low; its structure was confirmed from the HMBC correlations between the common carbon signal (δ 158.1 ppm) and the methyl proton signal of the methoxy group and the aryl proton signal at C-10 position. The stereochemistry of 28 could not be determined at this stage. The salcomine oxidation of 28 under oxygen atmosphere gave methoxy p-quinone 11a in 78% yield. Conversion of 25 by the modified Pictet-Spengler cyclization gave 28 with a maximum yield of only 19%.
Scheme 4. Synthesis of methoxy p-quinone 11 via modified Pictet-Spengler reaction

These observations indicated that we should try a third synthetic route via catechol lactam 31 (Scheme 5). The conversion of 17 into bisalkylated compound 29 was accomplished in four steps in 79% overall yield using Borchardt’s procedure. The condensation of benzaldehyde 29 with 14 in the same manner as that described above yielded 30 (82%). The reaction of 30 under catalytic hydrogenation followed by deprotection produced 31 in 83% yield. Then, we reinvestigated the conversion of 31 into cyclized compound 32. The two-step conversion of 31 provided 32 in 64% overall yield. This approach solves both problems of regioselectivity and reactivity. Product 32 was a 1:1 diastereomeric mixture. It was separated by SiO2 column chromatography and the relative configuration of cis-32 was confirmed by X-ray crystallographic analysis (Figure 3).

Scheme 5. Synthesis of 1,2,3,4-tetrahydroisoquinoline 32 from compound 17
Figure 3. X-Ray structure of compound cis-32

The oxidation of cis-32 and trans-32 with salconine gave p-quinones cis-33 and trans-33 in 66% and 44% yields, respectively (Scheme 6). cis-11a was obtained by the methylation of cis-33 in 68% yield, and its relative configuration was confirmed by comparison with an authentic product.

Scheme 6. Synthesis of alkoxy p-quinones 11a-c

With tricyclic model cis-11a in hand, we turned our attention to the establishment of a method for converting p-quinones 11 into dioxolanes 12 by a photo-induced reaction (Scheme 7). In a preliminary experiment, we found that the photochemical conversion of cis-11a produced cis-12a in only 34% yield. The low yield was because the reaction proceeded slowly due to the low solubility of the reactants. After numerous attempts using a variety of solvents, we found that the combination of acetylation and this photo-induced reaction resulted in improved yields. Thus, the photo-induced reaction of cis-11a in the presence of acetic anhydride in pyridine generated cis-34a in 69% yield.
Scheme 7. Photo-induced 1,3-dioxole ring formation from cis/trans alkoxy p-quinones 11a-c

As the photo-induced transformation of cis-11a into corresponding cyclized acetate cis-34a proceeded in good yield, we applied this novel reaction to other alkoxy p-quinones. Substrates trans-11a, cis/trans-11b, and cis/trans-11c were prepared from cis/trans-33 in 46–77% yields (Scheme 6). The photo-induced reaction of trans-11a in acetic anhydride and pyridine produced trans-34a in 58% yield. In the case of propyl substrate, the reaction proceeded within 1 h to afford corresponding cis-34c and trans-34c in 86% and 76% yields, respectively. The photocyclization reaction of the ethoxy substrate was complicated by the formation of an additional stereo-center with much lower reactivity. Desired photocyclized compounds cis-34b and trans-34b were obtained as a diastereomeric mixture in 34% (2:1) and 19% (1.3:1) yields, respectively. The formation of 35 was confirmed by the following experiment: cis-11b
was stirred with acetic anhydride in the presence of pyridine in the dark for 51 h to generate 35 in 35% yield.\textsuperscript{18}

In summary, we succeeded in the synthesis of 1,3-dioxoles from cis-\textbf{11a} by using the photo-induced ring closing reaction. By adding an acetylation agent to the reaction, solubility and reaction yield were improved. We were able to prepare other alkylated products with improved yields. Efforts are being made to uncover the reaction mechanism of the novel photo-induced transformation for application to the total synthesis of ecteinascidin and renieramycin T marine natural products.

**EXPERIMENTAL**

**General:** IR spectra were obtained with a Shimadzu Prestige 21/IRAffinity-1 FT-IR spectrometer. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for \textsuperscript{1}H and 100 MHz for \textsuperscript{13}C; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for \textsuperscript{1}H and 75 MHz for \textsuperscript{13}C (ppm, \textit{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-(Benzyloxy)-2-[(\textit{tert}-butyldimethylsilyloxy]-5-methoxy-4-methylbenzaldehyde (13): TBSCI (7.32 g, 49.0 mmol, 1.6 eq.) and imidazole (6.60 g, 97.0 mmol, 3.1 eq.) were added to a solution of aldehyde 7 (8.33 g, 31.0 mmol) in DMF (170 mL), and the reaction was stirred at ambient temperature for 2 h. The reaction was quenched by the slow addition (15 min) of H\textsubscript{2}O (370 mL) at 0 °C. The solution was extracted with Et\textsubscript{2}O (3 × 200 mL). The combined organic layer was washed with brine (200 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO\textsubscript{2} flash column chromatography (\textit{n}-hexane–EtOAc = 30 : 1) to give 13 (9.89 g, 83%) as a pale yellow solid. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ}: 10.37 (1H, s, 1-CHO), 7.26-7.41 (5H, m, Bn-H), 7.05 (1H, s, 6-H), 4.93 (2H, s, 3-OCH\textsubscript{2}Ph), 3.82 (3H, s, 5-OCH\textsubscript{3}), 2.07 (3H, s, 4-CH\textsubscript{3}), 1.02 (9H, s, TBS), 0.15 (6H, s, TBS); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) \textit{δ}: 189.5 (d, 1-CHO), 152.9 (s, C-5), 149.5 (s, C-3), 147.3 (s, C-2), 137.1 (s, Bn), 130.2 (s, C-4), 128.4 (d, Bn), 128.0 (d, Bn), 127.9 (d, Bn), 125.9 (s, C-1), 102.3 (d, C-6), 74.5 (t, 3-OCH\textsubscript{2}Ph), 55.7 (q, 5-OCH\textsubscript{3}), 25.9 (q, TBS), 18.5 (s, TBS), 10.30 (q, 4-CH\textsubscript{3}), −4.4 (q, TBS); IR (KBr): 2959, 2930, 1678, 1391 cm\textsuperscript{-1}; EIMS \textit{m/z} (%): 386 (M\textsuperscript{+}, 0.1), 330 (24), 329 (100), 301 (10), 238 (8), 210 (5), 91 (8); HREIMS: calcd for C\textsubscript{22}H\textsubscript{30}O\textsubscript{4}Si 386.1913; found 386.1910.
(Z)-1-Acetyl-3-{3-[benzyloxy]-2-[(tert-butylidemethylsilyloxy)-5-methoxy-4-methylbenzyldiene]-piperazine-2,5-dione (15): A 1.0 M solution of potassium tert-butoxide in tert-butyl alcohol (23.0 mL, 23.0 mmol, 1.1 eq.) was added to a solution of 13 (7.77 g, 20.0 mmol) and 1,4-diacylpirazarine-2,5-dione 14 (4.73 g, 24.0 mmol, 1.2 eq.) in CH2Cl2 (50 mL) at 0 °C over 2 min, and the mixture was refluxed for 5 h. The reaction mixture was poured into saturated aqueous NH4Cl solution (200 mL) and extracted with CH2Cl2 (3 × 150 mL). The combined organic layer was washed with brine (200 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO2 flash column chromatography (n-hexane–EtOAc = 3 : 1) to give 15 (7.19 g, 69%) as a pale yellow amorphous, and 13 (182 mg, 2% recovery) as a yellow solid. 1H-NMR (400 MHz, CDCl3) δ: 8.40 (1H, s, 4-NH), 7.29-7.44 (5H, m, Bn-H), 7.15 (1H, s, 3a-H), 6.46 (1H, s, 6'-H), 4.96 (2H, s, 3'-OCH2-Ph), 4.48 (2H, s, 6'-H), 3.79 (3H, s, 5'-OCH3), 2.65 (3H, s, 1-COCH3), 2.09 (3H, s, 4'-CH3), 0.94 (9H, s, TBS), 0.06 (6H, s, TBS); 13C-NMR (100 MHz, CDCl3) δ: 172.5 (s, 1-COCH3), 162.3 (s, C-5), 160.2 (s, C-2), 153.2 (s, C-5'), 150.1 (s, C-3'), 140.1 (s, C-2'), 137.1 (s, Bn), 128.4 (d, Bn), 127.9 (d, Bn), 127.8 (d, Bn), 125.6 (s, C-3), 123.9 (s, C-4'), 122.6 (s, C-1'), 118.8 (d, C-3a), 106.0 (d, C-6'), 74.5 (t, 3'-OCH2-Ph), 55.8 (q, 5'-OCH3), 46.2 (t, C-6), 27.2 (q, 1-COCH3) 25.9 (q, TBS), 18.3 (s, TBS), 9.8 (q, 4'-CH3), −4.3 (q, TBS); IR (KBr): 2932, 1701, 1368, 1256 cm−1; EI-MS m/z (%): 524 (M+, 13), 468 (14), 467 (46), 425 (18), 392 (8), 391 (30), 377 (36), 376 (58), 375 (12), 351 (16), 335 (18), 334 (32), 249 (10), 234 (10), 92 (8), 91 (100), 73 (14); HR-EI-MS: calcd for C28H36O6N2Si 524.2343; found 524.2338.

1-Acetyl-3-[(tert-butylidemethylsilyloxy)-3-hydroxy-5-methoxy-4-methylbenzyl]piperazine-2,5-dione (8) and 1-Acetyl-3-[(tert-butylidemethylsilyloxy)-2-hydroxy-5-methoxy-4-methylbenzyl]piperazine-2,5-dione (16): A solution of 15 (100 mg, 280 μmol) in 1PrOH (1.0 mL) and DMF (1.0 mL) was hydrogenated over 10% Pd/C (22.9 mg) at ambient temperature for 3.5 h. The catalyst was removed by filtration and washed with 1PrOH and CHCl3. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO2 flash column chromatography (n-hexane–EtOAc = 1 : 1) to give regio isomeric mixture 8 & 16 (0.3 : 1, 82.0 mg, 94%) as a red amorphous. 1H-NMR (400 MHz, CDCl3) (major, 16) δ: 6.40 (1H, br s, 4-NH), 6.29 (1H, s, 6'-H), 5.09 (1H, s, 2'-OH), 4.39 (1H, ddd, J = 7.7, 4.4, 1.7 Hz, 3-H), 4.23 (1H, d, J = 17.7 Hz, 6-H), 4.13 (1H, d, J = 17.7 Hz, 6-H), 3.73 (3H, s, 5'-OCH3), 3.38 (1H, dd, J = 14.0, 4.4 Hz, 3a-H), 3.09 (1H, dd, J = 14.0, 7.7 Hz, 3a-H), 2.56 (3H, s, 1-COCH3), 2.05 (3H, s, 4'-CH3), 1.06 (9H, s, TBS), 0.20 (3H, s, TBS), 0.19 (3H, s, TBS). (minor, 8) δ: 6.16 (1H, s, 6'-H), 6.08 (1H, br s, 4-NH), 5.15 (1H, s, 3'-OH), 4.30 (1H, ddd, J = 9.2, 3.2, 1.5 Hz, 3-H), 4.30 (1H, d, J = 17.9 Hz, 6-H), 4.09 (1H, d, J = 17.9 Hz, 6-H), 3.75 (3H, s, 5'-OCH3), 3.39 (1H, dd, J = 14.0, 3.2 Hz, 3a-H), 2.94 (1H, dd, J = 14.0, 9.2 Hz, 3a-H), 2.56 (3H, s, 1-COCH3), 2.10 (3H, s, 4'-CH3), 1.05 (9H, s, TBS), 0.23 (3H, s, TBS), 0.21 (3H, s, TBS); 13C-NMR (100
MHz, CDCl₃) (major, 16) δ: 171.7 (s, 1-COCH₃), 168.8 (s, C-2), 166.1 (s, C-5), 152.0 (s, C-5’), 141.6 (s, C-3’), 140.1 (s, C-2’), 117.8 (s, C-4’), 117.5 (s, C-1’), 105.9 (d, C-6’), 57.3 (d, C-3), 55.9 (q, 5’-OCH₃), 45.7 (t, C-6), 32.7 (t, C-3a), 27.2 (q, 1-COCH₃), 25.9 (q, TBS), 18.5 (s, TBS), 10.6 (q, 4’-CH₃), −3.9 (q, TBS), −3.9 (q, TBS). (minor, 8) δ: 171.7 (s, 1-COCH₃), 168.5 (s, C-2), 166.0 (s, C-5), 153.4 (s, C-5’), 146.6 (s, C-3’), 135.0 (s, C-2’), 122.1 (s, C-1’), 113.4 (s, C-4’), 103.6 (d, C-6’), 56.8 (d, C-3), 55.8 (q, 5’-OCH₃), 45.8 (t, C-6), 33.6 (t, C-3a), 27.2 (q, 1-COCH₃), 25.9 (q, TBS), 18.5 (s, TBS), 8.6 (q, 4’-CH₃), −3.9 (q, TBS), −4.0 (q, TBS); EIMS m/z (%): 436 (M⁺, 6), 379 (26), 378 (8), 337 (27), 265 (16), 252 (31), 224 (18), 223 (100), 180 (8); HREIMS: calcd for C₂₁H₂₂O₆N₂Si 436.2030; found 436.2028.

Methyl 3-(benzyloxy)-5-hydroxy-4-methylbenzoate (19)овал: 3,5-Dihydroxy-4-methylbenzoic acid (17) (4.90 g, 29.2 mmol, 1.0 eq) and PTSA (1.12 g, 5.84 mmol, 0.2 eq.) were dissolved in MeOH (50 mL), and the mixture was heated to reflux for 6 h. MeOH was evaporated. The resultant solid was dissolved with 10% aqueous NaHCO₃ (200 mL), and the aqueous solution was extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 18, which was used in the next step without further purification. To a solution of crude 18 in DMF (300 mL) was added K₂CO₃ (3.84 g, 27.7 mmol, 0.95 eq.). To this stirred suspension, benzyl bromide (3.30 mL, 27.7 mmol, 0.95 eq.) was added dropwise over a period of 3 h. The solution was stirred at ambient temperature for 8 h. Then DMF was removed under reduced pressure. The residue was diluted with water (200 mL) and the product was extracted with CH₂Cl₂ (3 × 200 mL). The combined organic layer were washed with brine (600 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 4 : 1) to provide benzoate 19 (2.13 g, 27%) as a colorless solid, and with n-hexane–EtOAc = 9 : 1 to give 20 (3.29 g, 31%) as a pale yellow solid, and with n-hexane–EtOAc = 1 : 1 to give 18 (1.56 g, 27% recovery) as a colorless solid.

Methyl 3,5-dihydroxy-4-methylbenzoate (18): ¹H-NMR (300 MHz, DMSO-d₆) δ: 9.51 (2H, s, 3-OH and 5-OH), 6.92 (2H, s, 2-H and 6-H), 3.76 (3H, s, 1-CO₂CH₃), 1.97 (3H, s, 4-CH₃).

Methyl 3-(benzylxylo)-5-hydroxy-4-methylbenzoate (19): ¹H-NMR (400 MHz, DMSO-d₆) δ: 9.75 (1H, s, 5-OH), 7.46 (2H, d, J = 7.4 Hz, Bn-H), 7.39 (2H, t, J = 7.4 Hz, Bn-H), 7.32 (1H, t, J = 7.4 Hz, Bn-H), 7.13 (1H, s, 2-H or 6-H), 7.08 (1H, s, 2-H or 6-H), 5.30 (2H, s, 3-OCH₂-Ph), 3.80 (3H, s, 1-CO₂CH₃), 2.07 (3H, s, 4-CH₃).

Methyl 3,5-bis(benzylxylo)-4-methylbenzoate (20): ¹H-NMR (400 MHz, DMSO-d₆) δ: 7.31-7.50 (10H, m, Bn-H), 7.29 (2H, s, 2-H and 6-H), 5.17 (4H, s, 3-OCH₂-Ph and 5-OCH₂-Ph), 3.82 (3H, s, 1-CO₂CH₃), 2.15 (3H, s, 4-CH₃).
Methyl 3,5-dihydroxy-4-methylbenzoate (18) from 20: A solution of 20 (100 mg, 280 μmol) in EtOH (2.4 mL) and DMF (2.4 mL) was hydrogenated over 10% Pd/C (59.6 mg) at ambient temperature for 3 h. The catalyst was removed by filtration and washed with MeOH and CHCl₃. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 4 : 1 ~ 1 : 1) to provide 18 (48.0 mg, 94%) as a colorless solid.

Methyl 3-(benzyloxy)-5-methoxy-4-methylbenzoate (21): Methyl iodide (1.16 mL, 18.4 mmol, 5.0 eq.) was added to a suspension of ester 19 (1.00 g, 3.68 mmol) and anhydrous K₂CO₃ (1.53 g, 11.0 mmol, 3.0 eq.) in acetone (50 mL), and the reaction mixture was stirred at ambient temperature for 22 h. The insoluble materials were removed by filtration and washed with CHCl₃. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 4 : 1) to give 21 (978 mg, 93%) as a pale yellow solid. ¹H-NMR (400 MHz, CDCl₃) δ: 7.33-7.47 (5H, m, Bn-H), 7.32 (1H, s, 2-H), 7.24 (1H, s, 6-H), 5.12 (2H, s, 3-OCH₂-Ph), 3.91 (3H, s, 1-CO₂CH₃), 3.88 (3H, s, 5-OCH₃), 2.20 (3H, s, 4-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 167.2 (s, 1-CO₂CH₃), 158.2 (s, C-5), 157.2 (s, C-3), 137.1 (s, Bn), 128.5 (d, Bn), 128.2 (s, C-1), 127.9 (d, Bn), 127.2 (d, Bn), 120.9 (s, C-4), 106.1 (d, C-2), 104.9 (d, C-6), 70.4 (t, 3-OCH₂-Ph), 55.8 (q, 5-OCH₃), 52.1 (q, 1-CO₂CH₃), 8.9 (q, 4-CH₃); IR (KBr): 3034, 2932, 1720, 1587, 1317, 1231, 1126, 999, 693 cm⁻¹; EIMS m/z (%): 286 (M⁺, 45), 255 (13), 254 (14), 91 (100)); HREIMS: calcd for C₁₇H₁₈O₄ 286.1205; found 286.1208.

[3-(Benzyloxy)-5-methoxy-4-methylphenyl]methanol (22): A 1.0 M solution of LiAlH₄ in THF (3.50 mL, 3.50 mmol, 1.55 eq.) was added to a solution of 21 (650 mg, 2.27 mmol) in THF (5.0 mL) at 0 °C over 5 min. After stirring for 2 h at 60 °C, the reaction was quenched by the slow addition of 1 M aqueous HCl solution (50 mL) at 0 °C. The solution was extracted with CHCl₃ (3 × 50 mL). The combined organic layer were washed with brine (150 mL), dried over sodium sulfate, and concentrated in vacuo to give 22 (580 mg), which was used in the next step without further purification. ¹H-NMR (400 MHz, CDCl₃) δ: 7.31-7.49 (5H, m, Bn-H), 6.62 (1H, s, 2-H or 6-H), 6.56 (1H, s, 2-H or 6-H), 5.07 (2H, s, 3-OCH₂-Ph), 4.62 (2H, s, 1-CH₂OH), 3.83 (3H, s, 5-OCH₃), 2.16 (3H, s, 4-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 158.5 (s, C-5), 157.5 (s, C-3), 139.4 (s, C-1), 137.4 (s, Bn), 128.5 (d, Bn), 127.7 (d, Bn), 127.1 (d, Bn), 114.3 (s, C-4), 103.6 (d, C-2 or C-6), 102.4 (d, C-2 or C-6), 70.2 (t, 3-OCH₂-Ph), 65.6 (t, 1-CH₂OH), 55.7 (q, 5-OCH₃), 8.3 (q, 4-CH₃); IR (CHCl₃): 3011, 1589, 1423, 1134 cm⁻¹; EIMS m/z (%): 258 (M⁺, 38), 227 (14), 92 (8), 91 (100), 65 (6); HREIMS: calcd for C₁₆H₁₆O₃ 258.1256; found 258.1255.
3-(Benzyloxy)-5-methoxy-4-methylbenzaldehyde (23): To a solution of crude 22 in CH₂Cl₂ (40 mL) were added celite (6.0 g) and PCC (990 mg, 4.50 mmol, 2.0 eq.). The reaction mixture was stirred at ambient temperature for 1.5 h and then diluted with Et₂O (150 mL). The reaction mixture was stirred at ambient temperature for 30 min. The insoluble materials were removed by filtration and washed Et₂O. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 19 : 1 ~ 9 : 1) to give 23 (524 mg, 91%, 2 steps from 21) as a pale yellow solid. ¹H-NMR (400 MHz, CDCl₃) δ: 9.88 (1H, s, 1-CHO), 7.31-7.46 (5H, m, Bn-H), 7.11 (1H, s, 2-H), 7.06 (1H, s, 6-H), 5.14 (2H, s, 3-OCH₂-Ph), 3.89 (3H, s, 5-OCH₃), 2.22 (3H, s, 4-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 191.8 (d, 1-CHO), 158.8 (s, C-5), 157.7 (s, C-3), 136.8 (s, Bn), 135.0 (s, C-1), 128.6 (d, Bn), 127.9 (d, Bn), 127.1 (d, Bn), 123.0 (s, C-4), 106.2 (d, C-2), 104.6 (d, C-6), 70.4 (t, 3-OCH₂-Ph), 55.8 (q, 5-OCH₃), 9.2 (q, 4-CH₃); IR (KBr) cm⁻¹: 2999, 2841, 1684, 1589, 1383, 1310, 1140, 729; EIMS m/z (%): 256 (M⁺, 43), 91 (100), 65 (6); HREIMS: calcd for C₁₆H₁₆O₃ 256.1099; found 256.1096.

(Z)-1-Acetyl-3-[3-(benzyloxy)-5-methoxy-4-methylbenzylidene]piperazine-2,5-dione (24): A 1.0 M solution of potassium tert-butoxide in tert-butyl alcohol (2.10 mL, 2.10 mmol, 1.2 eq.) was added to a solution of 23 (450 mg, 1.76 mmol) and 1,4-diacetylpiperazine-2,5-dione 14 (349 mg, 1.76 mmol, 1.0 eq.) in CH₂Cl₂ (9.0 mL) at 0 °C over 2 min, and stirring was continued at ambient temperature for 2.5 h. The reaction mixture was poured into saturated aqueous NH₄Cl solution (60 mL) and extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layer was washed with brine (180 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 2 : 1 ~ 1 : 1) to give 24 (565 mg, 81%) as a yellow solid, and with n-hexane–EtOAc = 4 : 1 to provide aldehyde 23 (13.7 mg, 3% recovery) as a yellow solid. ¹H-NMR (400 MHz, CDCl₃) δ: 7.91 (1H, s, 4-NH), 7.31-7.44 (5H, m, Bn-H), 7.12 (1H, s, 3a-H), 6.57 (1H, s, 2'-H), 6.52 (1H, s, 6'-H), 5.10 (2H, s, 3'-OCH₂-Ph), 4.51 (2H, s, 6-H), 3.84 (3H, s, 5'-OCH₃), 2.65 (3H, s, 1-COCH₃), 2.18 (3H, s, 4'-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 172.5 (s, 1-COCH₃), 162.5 (s, C-5), 160.0 (s, C-2), 159.2 (s, C-5’), 158.1 (s, C-3’), 136.8 (s, Bn), 130.5 (s, C-3 or C-1’), 128.7 (d, Bn), 128.0 (d, Bn), 127.1 (d, Bn), 125.3 (s, C-3 or C-1’), 120.6 (d, C-3a), 117.4 (s, C-4’), 105.1 (d, C-2’), 103.9 (d, C-6’), 70.5 (t, 3'-OCH₂-Ph), 55.9 (q, 5'-OCH₃), 46.1 (t, C-6), 27.2 (q, 1-COCH₃), 8.6 (q, 4'-CH₃); IR (KBr) cm⁻¹: 3304, 2940, 1692, 1213; EIMS m/z (%): 394 (M⁺, 43), 91 (100), 65 (6); HREIMS: calcd for C₂₂H₂₂N₂O₅ 394.1529; found 394.1530.

1-Acetyl-3-(3-hydroxy-5-methoxy-4-methylbenzyl)piperazine-2,5-dione (25): A solution of 24 (492 mg, 1.25 mmol) in EtOH (10.0 mL) and DMF (10.0 mL) was hydrogenated over 10% Pd/C (133 mg) at
ambient temperature for 1.5 h. The catalyst was removed by filtration and washed with MeOH and CHCl₃.

The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (n-hexane–EtOAc = 1 : 1 ~ 1 : 2) to provide 25 (375 mg, 98%) as a colorless powder. ¹H-NMR (400 MHz, CD₃OD) δ: 6.24 (2H, s, 2'-H and 6'-H), 4.38 (1H, br t, J = 4.9, 4.3 Hz, 3-H), 4.09 (1H, d, J = 18.0 Hz, 6-H), 3.72 (3H, s, 5'-OCH₃), 3.14 (1H, dd, J = 13.5, 4.3 Hz, 3a-H), 2.92 (1H, dd, J = 13.5, 4.9 Hz, 3a-H), 2.80 (1H, d, J = 18.0 Hz, 6-H), 2.50 (3H, s, 1-COCH₃), 1.99 (3H, s, 4'-CH₃); ¹³C-NMR (100 MHz, CD₃OD) δ: 173.4 (s, 1-ÇOCH₃), 170.4 (s, C-2), 168.6 (s, C-5), 160.2 (s, C-3'), 157.4 (s, C-5'), 134.1 (s, C-1'), 112.9 (s, C-4'), 110.5 (d, C-2' or C-6'), 105.1 (d, C-2' or C-6'), 59.4 (d, C-3), 56.1 (q, 5'-OCH₃), 46.4 (t, C-6), 41.7 (t, C-3a), 27.2 (q, 1-COCH₃), 8.2 (q, 4'-CH₃); IR (KBr): 3362, 3192, 3144, 3075, 3007, 2957, 2926, 2855, 1686, 1601, 1427, 1223, 1115 cm⁻¹; EIMS m/z (%): 306 (M⁺, 22), 152 (20), 151 (100); HREIMS: calcd for C₁₃H₁₈N₂O₅ 306.1216; found 306.1217.

(6R⁺,11aS⁻)–2-Acetyl-7-hydroxy-6-[benzoyloxy)methyl]-9-methoxy-8-methyl-2,3,11a-tetrahydro-4H-pyrazino[1,2-b]isoquinoline-1,4(6H)-dione (28): TMSCl (33.0 µL, 255 µmol, 2.6 eq.) was added to a solution of 25 (30.0 mg, 98.0 µmol) in CH₂Cl₂ (1.0 mL) and Et₃N (36.0 µL, 255 µmol, 2.6 eq.) and stirring was continued at ambient temperature for 4 h. A solution of 2,2-diethoxyethyl benzoate 26 (30.2 mg, 127 µmol, 1.3 eq.) in CH₂Cl₂ (0.7 mL) followed by TMSOTf (49.5 µL, 269 µmol, 2.7 eq.) was added dropwise for 1 min, and the reaction mixture was stirred for 15 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ (40 mL) and extracted with CHCl₃ (3 × 10 mL). The combined organic layer were washed with brine (40 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue.

The residue was purified by SiO₂ flash column chromatography (CHCl₃–EtOH = 99 : 1) to provide benzoate 28 (8.50 mg, 19%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ: 7.90 (2H, br d, J = 7.8 Hz, 2'-H and 6'-H), 7.54 (1H, br t, J = 7.8 Hz, 4'-H), 7.40 (2H, br t, J = 7.8 Hz, 3'-H and 5'-H), 6.41 (1H, s, 10-H), 6.23 (1H, dd, J = 6.7, 4.8 Hz, 6-H), 5.10 (1H, d, J = 17.1 Hz, 3-H), 4.47 (1H, dd, J = 11.2, 6.7 Hz, 12-H), 4.43 (1H, dd, J = 11.2, 4.8 Hz, 12-H), 4.17 (1H, dd, J = 12.0, 4.9 Hz, 11a-H), 3.84 (3H, s, 9-OCH₃), 3.78 (1H, d, J = 17.1 Hz, 3-H), 3.35 (1H, dd, J = 15.5, 12.0 Hz, 11-H), 3.25 (1H, dd, J = 15.5, 4.9 Hz, 11-H), 2.60 (3H, s, 2-COCH₃), 2.14 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 171.0 (s, 2-ÇOCH₃), 168.7 (s, C-1), 166.9 (s, C-14), 166.4 (s, C-4), 158.1 (s, C-9), 151.6 (s, C-7), 133.2 (d, C-4'), 131.5 (s, C-10a), 129.7 (s, C-1'), 129.6 (d, C-2' and C-6'), 128.4 (d, C-3' and C-5'), 111.7 (s, C-6a), 111.0 (s, C-8), 102.6 (d, C-10), 66.4 (t, C-12), 56.8 (d, C-11a), 55.8 (q, 9-OCH₃), 48.6 (d, C-6), 45.6 (t, C-3), 29.8 (t, C-11), 27.0 (q, 2-COCH₃), 8.1 (q, 8-CH₃); IR (KBr): 3366, 3302, 2959, 2932, 1717, 1667, 1269, 1132 cm⁻¹; EIMS m/z (%): 452 (M⁺, 1), 318 (17), 317 (100), 275 (21), 190 (27), 175 (5), 105 (7); HREIMS: calcd for C₂₄H₂₄N₂O₇ 452.1584; found 452.1580.
(6R+,11aS)-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2H-pyrazino-[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (cis-11a): A salcomine (6.10 mg, 19.0 µmol, 1.0 eq.) was added to a solution of 28 (8.40 mg, 19.0 µmol) in THF (1.0 mL) and stirring was continued at ambient temperature for 3 h under O2 atmosphere. The reaction mixture was filtered through a cellulose pad and washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was purified by SiO2 flash column chromatography (benzene−EtOAc = 3 : 1 ~ 1 : 1) to provide p-quinone cis-11a (6.80 mg, 78%) as a yellow oil.

1H-NMR (400 MHz, CDCl3) δ: 7.84 (2H, br d, J = 7.9 Hz, 2’-H and 6’-H), 7.58 (1H, br t, J = 7.9 Hz, 4’-H), 7.43 (2H, br t, J = 7.9 Hz, 3’-H and 5’-H), 5.80 (1H, br td, J = 3.5, 1.4 Hz, 6-H), 5.19 (1H, d, J = 17.3 Hz, 3-H), 4.67 (1H, dd, J = 11.7, 3.9 Hz, 12-H), 4.53 (1H, dd, J = 11.7, 3.5 Hz, 12-H), 4.13 (1H, dd, J = 11.4, 5.2 Hz, 11a-H), 4.03 (3H, s, 9-OCH3), 3.84 (1H, d, J = 17.3 Hz, 3-H), 3.50 (1H, dd, J = 17.7, 11-H), 2.64 (1H, d, J = 17.7, 11.4, 1.4 Hz, 11-H), 2.59 (3H, s, 2-COCH3), 2.00 (3H, s, 8-CH3); 13C-NMR (100 MHz, CDCl3) δ: 184.5 (s, C-7), 180.4 (s, C-10), 170.9 (s, 2-COCH3), 167.3 (s, C-1), 166.2 (s, C-14), 165.9 (s, C-4), 155.5 (s, C-9), 137.6 (s, C-6a), 133.6 (d, C-4’), 129.5 (d, C-2’ and C-6’), 129.3 (s, C-8), 129.1 (s, C-10a), 128.7 (d, C-3’ and C-5’), 64.9 (t, C-12), 61.1 (q, 9-OCH3), 54.9 (d, C-11a), 49.4 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-COCH3), 21.6 (t, C-11), 8.9 (q, 8-CH3); IR (KBr) cm⁻¹: 2951, 2849, 1705, 1694, 1368, 1273; FABMS m/z: 467 [M+H]+; HRFABMS: calcd for C24H23N2O8 467.1458; found 467.1456.

From 17 to 29

Methyl 3,5-bis(benzyloxy)-4-methylbenzoate (20): 3,5-Dihydroxy-4-methylbenzoic acid (17) (5.24 g, 31.2 mmol) and PTSA (1.19 g, 6.24 mmol, 0.2 eq.) were dissolved in MeOH (50 mL), and the mixture was heated to reflux for 6 h. MeOH was evaporated. The resultant solid was diluted with 10% NaHCO3 (100 mL), and the aqueous solution was extracted with EtOAc (3 × 200 mL). The combined organic layer were washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give 18, which was used in the next step without further purification. To a solution of crude 18 in acetone (100 mL) was added K2CO3 (21.6 g, 156 mmol, 5.0 eq.). To this stirred suspension, benzyl bromide (11.1 mL, 93.6 mmol, 3.0 eq.) was added dropwise over a period of 3 h. The solution was stirred at ambient temperature for 24 h. Then acetone was removed under reduced pressure. The residue was diluted with water (100 mL) and the product was extracted with Et2O (3 × 100 mL). The combined organic layer were washed with H2O (100 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO2 flash column chromatography (n-hexane−EtOAc = 10 : 1) to provide 20 (9.98 g, 88%, 2 steps) as a pale yellow solid.
Methyl 3,5-bis(benzyloxy)-4-methylbenzoate (20): $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.31-7.50 (10H, m, Bn-H), 7.29 (2H, s, 2-H and 6-H), 5.17 (4H, s, 3-OCH$_2$-Ph and 5-OCH$_2$-Ph), 3.82 (3H, s, 1-CO$_2$CH$_3$), 2.15 (3H, s, 4-CH$_3$).

3,5-Bis(benzyloxy)-4-methylphenylmethanol: A 1.0 M solution of LiAlH$_4$ in THF (42.0 mL, 42.0 mmol, 1.55 eq.) was added to a solution of 20 (9.98 g, 29.5 mmol) in THF (50 mL) at 0 °C over 5 min, and the mixture was stirred at 60 °C for 1.5 h. The reaction mixture was diluted with saturated aqueous NH$_4$Cl solution (100 mL) at 0 °C and extracted with 1% MeOH in CH$_2$Cl$_2$ (3 × 200 mL). The combined organic layer were washed with brine (300 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO$_2$ flash column chromatography ($n$-hexane–EtOAc = 2 : 1) to give alcohol (8.8 g, 96%) as a yellow solid. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.29-7.47 (10H, m, Bn-H), 6.69 (2H, s, 2'-H and 6'-H), 5.15 (1H, t, $J = 5.7$ Hz, 1-OH), 5.08 (4H, s, 3'-OCH$_2$-Ph and 5'-OCH$_2$-Ph), 4.43 (2H, d, $J = 5.7$ Hz, 1-H), 2.07 (3H, s, 4'-CH$_3$).

3,5-Bis(benzyloxy)-4-methylbenzaldehyde (29): To a solution of alcohol (10.6 g, 31.6 mmol) in CH$_2$Cl$_2$ (530 mL) were added celite (40.0 g) and PCC (13.9 g, 63.2 mmol, 2.0 eq.). The reaction mixture was stirred at ambient temperature for 1 h and then diluted with Et$_2$O (350 mL). The reaction mixture was stirred at ambient temperature for 30 min. The insoluble materials were removed by filtration and washed Et$_2$O. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO$_2$ flash column chromatography ($n$-hexane–EtOAc = 19 : 1 ~ 4 : 1) to give 29 (9.81 g, 93%) as a yellow solid. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 9.87 (1H, s, 1-CHO), 7.31-7.60 (10H, m, Bn-H), 7.13 (2H, s, 2-H and 6-H), 5.16 (4H, s, 3-OCH$_2$-Ph and 5-OCH$_2$-Ph), 2.28 (3H, s, 4'-CH$_3$).

1-Acetyl-3-[3,5-bis(benzyloxy)-4-methylbenzylidene]piperazine-2,5-dione (30): A 1.0 M solution of potassium tert-butoxide in tert-butyl alcohol (34.0 mL, 34.0 mmol, 1.2 eq.) was added to a solution of 29 (9.25 g, 27.8 mmol) and 1,4-diacetyl piperazine-2,5-dione 14 (5.51 g, 27.8 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (220 mL) at 0 °C over 2 min, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was poured into saturated aqueous NH$_4$Cl solution (250 mL) and extracted with CHCl$_3$ (3 × 200 mL). The combined organic layer were washed with brine (200 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO$_2$ flash column chromatography (CHCl$_3$–EtOH = 99 : 1) to give 30 (10.8 g, 82%) as a yellow solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 7.85 (1H, s, 4-NH), 7.31-7.45 (10H, m, Bn-H), 7.08 (1H, s, 3a-H), 6.54 (2H, s, 2'-H and 6'-H), 5.10 (4H, s, 3'-OCH$_2$Ph and 5'-OCH$_2$Ph), 4.50 (2H, s, 6-H), 2.64 (3H, s, 1-COCH$_3$), 2.25 (3H, s, 4'-CH$_3$); $^{13}$C-NMR (100MHz, CDCl$_3$) $\delta$: 172.5 (s, 1-COCH$_3$), 162.4 (s, C-5), 160.0 (s, C-2), 158.2 (s, C-3’ and C-5’), 136.7
1-Acetyl-3-(3,5-dihydroxy-4-methylbenzyl)piperazine-2,5-dione (31): A solution of 30 (2.00 g, 4.25 mmol) in EtOH (34.0 mL) and DMF (136 mL) was hydrogenated over 10% Pd/C (4.50 g) at ambient temperature for 2 h. The catalyst was removed by filtration and washed with MeOH and CHCl₃. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (CHCl₃−MeOH = 19 : 1) to give 31 (1.03 g, 83%) as a colorless solid.

(6S*,11aS*)-2-Acetyl-7,9-dihydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-4H-pyrazino[1,2-b]isoquinoline-1,4(6H)-dione (trans-32) and (6R*,11aS*)-2-Acetyl-7,9-dihydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-4H-pyrazino[1,2-b]isoquinoline-1,4(6H)-dione (cis-32): TMSCl (85.0 µL, 665 µmol, 3.9 eq.) was added to a solution of 31 (50.0 mg, 170 µmol) in CH₂Cl₂ (2.0 mL) and Et₃N (93.0 µL, 663 µmol, 3.9 eq.) and stirring was continued at ambient temperature for 3 h. A solution of 2,2-diethoxyethyl benzoate 26 (47.6 mg, 200 µmol, 1.2 eq.) in CH₂Cl₂ (0.8 mL) followed by TMSOTf (155 µL, 856 µmol, 5.0 eq.) was added dropwise for 1 min, and the reaction mixture was stirred for 14 h. The reaction mixture was diluted with saturated aqueous NaHCO₃ (40 mL) and extracted with 10% MeOH in CHCl₃ (4 × 10 mL). The combined organic layer were washed with brine (40 mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (CHCl₃−MeOH = 49 : 1) to provide benzoate trans-32 (23.5 mg, 32%) as a pale yellow amorphous, and with CHCl₃−MeOH = 49 : 1−19 : 1 to give cis-32 (23.5 mg, 32%) as a pale brown amorphous. Compound cis-32 was obtained as a colorless prisms by recrystallization from MeOH. trans-32: ¹H-NMR (400 MHz, CD₃OD) δ: 7.97 (2H, d, J = 7.9 Hz, Bz-H), 7.59 (1H, t, J = 7.9 Hz, Bz-H), 7.45 (2H, t, J = 7.9 Hz, Bz-H), 6.27 (1H, s, 10-H), 6.13 (1H, dd, J = 9.5, 3.8 Hz, 6-H), 4.81-4.86 (1H, 11a-H overlapped with H₂O), 4.75 (1H, dd, J = 11.6, 9.5 Hz, 12-H),
4.60 (1H, dd, J = 11.6, 3.8 Hz, 12-H), 4.34 (1H, d, J = 18.0 Hz, 3-H), 4.23 (1H, d, J = 18.0 Hz, 3-H), 3.20 (2H, d, J = 7.3 Hz, 11-H), 2.50 (3H, s, 2-COCH₃), 2.06 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CD₃OD) δ: 173.2 (s, 2-COCH₃), 169.4 (s, C-1), 168.2 (s, C-14), 165.8 (s, C-4), 157.0 (s, C-9), 153.9 (s, C-7), 134.4 (d, Bz), 132.2 (s, Bz), 131.2 (s, C-10a), 130.7 (d, Bz), 129.6 (d, Bz), 111.4 (s, C-6a), 111.4 (s, C-8), 107.9 (d, C-10), 64.5 (t, C-12), 55.7 (d, C-11a), 50.2 (d, C-6), 46.7 (t, C-3), 32.1 (t, C-11), 27.0 (q, 2-COCH₃), 8.7 (q, 8-CH₃); IR (KBr): 3410, 3391, 1713, 1659, 1273, 1099 cm⁻¹; EIMS m/z (%): 438 (M⁺, 2), 346 (5), 345 (25), 304 (11), 303 (67), 281 (6), 262 (15), 261 (100), 260 (5), 239 (5), 233 (5), 176 (25), 105 (17); HREIMS: calcld for C₂₃H₂₂N₂O₇ 438.1427; found 438.1428.

**cis-32:** mp 243-245 °C (MeOH); ¹H-NMR (400 MHz, CD₃OD) δ: 7.87 (2H, br d, J = 7.8 Hz, Bz-H), 7.56 (1H, br t, J = 7.8 Hz, Bz-H), 7.41 (2H, br t, J = 7.8 Hz, Bz-H), 6.35 (1H, s, 10-H), 6.12 (1H, dd, J = 7.9, 4.7 Hz, 6-H), 4.84 (1H, d, J = 16.8 Hz, 3-H), 4.50 (1H, dd, J = 10.9, 7.9 Hz, 12-H), 4.33 (1H, dd, J = 10.9, 4.7 Hz, 12-H), 4.30 (1H, dd, J = 12.1, 5.0 Hz, 11α-H), 3.89 (1H, d, J = 16.8 Hz, 3-H), 3.25 (1H, dd, J = 15.5, 12.1 Hz, 11-H), 3.07 (1H, dd, J = 15.5, 5.0 Hz, 11-H), 2.49 (3H, s, 2-COCH₃), 2.07 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CD₃OD) δ: 172.4 (s, 2-COCH₃), 170.7 (s, C-1), 168.9 (s, C-14), 168.1 (s, C-4), 157.2 (s, C-9), 153.8 (s, C-7), 134.4 (d, Bz), 133.0 (s, C-10a), 131.1 (s, Bz), 130.6 (d, Bz), 129.5 (d, Bz), 112.1 (s, C-6a), 111.4 (s, C-8), 107.5 (d, C-10), 66.6 (t, C-12), 57.8 (d, C-11a), 50.2 (d, C-6), 46.3 (t, C-3), 30.1 (t, C-11), 26.9 (q, 2-COCH₃), 8.8 (q, 8-CH₃); IR (KBr): 3383, 3366, 2924, 1717, 1678, 1368, 1271, 1198, 1099 cm⁻¹; EIMS m/z (%): 438 (M⁺, 1), 346 (6), 345 (12), 305 (14), 304 (54), 303 (100), 263 (5), 262 (18), 261 (31), 177 (16), 176 (33), 105 (13), 77 (5); HREIMS m/z: calcld for C₂₃H₂₂N₂O₇ 438.1427; found 438.1422; *Anal.* Calcd for C₂₃H₂₂N₂O₇: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.78; H, 4.95; N, 6.33.

**X-Ray Structure Determination of Compound cis-32:** Crystals of cis-32 (C₂₃H₂₂N₂O₇) belong to orthorhombic space group Pbcₐ (#61) with a = 15.0927(3) Å, b = 16.1542(3) Å, c = 16.3805(3) Å, V = 3993.72(13) Å³, Z = 8, and Dcalcd = 1.458 g/cm³. X-Ray intensities were measured with a Rigaku R-Axis Rapid diffractometer in the graphite-monochromatic CuKα radiation mode (λ = 1.54187 Å). The final cycle of the full-matrix least-squares refinement was based on 3650 unique reflections (20 < 136.4°) and 294 variable parameters, and converged with unweighted and weighted agreement factors of R = 0.0338, Rw = 0.0850, and R1 = 0.0327 for I > 2.0 σ (I) data. The drawing of the molecule was made by ORTEP as shown here. CCDC-No. (1870093) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(6R⁺,11aS⁺)-2-Acetyl-9-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2H-pyrazino[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (cis-33): A salcomine (15.3 mg, 47 μmol, 1.0 eq.) was added
to a solution of cis-32 (20.5 mg, 109 μmol) in THF (3.0 mL) and stirring was continued at ambient temperature for 4 h under O₂ atmosphere. The reaction mixture was filtered through a cellulose pad and washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was purified by SiO₂ flash column chromatography (benzene–EtOAc = 1 : 1) to provide quinone cis-33 (13.7 mg, 66%) as a dark red amorphous, and (benzene–EtOAc = 4 : 1 ~ 1 : 1) to recover the starting material cis-32 (3.00 mg, 15%) as a yellow oil. ¹H-NMR (400 MHz, CDCl₃) δ: 7.84 (2H, br d, J = 7.6 Hz, Bz-H), 7.57 (1H, br t, J = 7.6 Hz, Bz-H), 7.43 (2H, br t, J = 7.6 Hz, Bz-H), 6.93 (1H, s, 9-OH), 5.83 (1H, br td, J = 3.7, 1.8 Hz, 6-H), 5.19 (1H, d, J = 17.4 Hz, 3-H), 4.70 (1H, dd, J = 11.7, 3.7 Hz, 12-H), 4.52 (1H, dd, J = 11.7, 3.7 Hz, 12-H), 4.14 (1H, dd, J = 11.4, 5.2 Hz, 11a-H), 3.85 (1H, d, J = 17.4 Hz, 3-H), 3.48 (1H, dd, J = 17.9, 5.2 Hz, 11-H), 2.69 (1H, dd, J = 17.9, 11.4, 1.8 Hz, 11-H), 2.59 (3H, s, 2-COCH₃), 2.01 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 183.9 (s, C-7), 180.5 (s, C-10), 170.8 (s, 2-ÇOCH₃), 167.3 (s, C-1), 166.2 (s, C-14), 165.9 (s, C-4), 151.0 (s, C-9), 140.0 (s, C-6a), 135.4 (s, C-10a), 133.6 (d, Bz), 129.5 (d, Bz), 129.1 (s, Bz), 128.7 (d, Bz), 118.2 (s, C-8), 65.0 (t, C-12), 54.7 (d, C-11a), 49.7 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-ÇOCH₃), 21.4 (t, C-11), 8.2 (q, 8-CH₃); IR (KBr): 3206, 2924, 1720, 1657, 1323, 1269, 1233, 1196 cm⁻¹; FABMS m/z: 453 [M+H⁺]; HRFABMS: calecd for C₂₃H₂₁N₂O₈ 453.1298; found 453.1303.

(6S,11aS)-2-Acetyl-9-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2H-pyrazino[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetrione (trans-33): A salomine (2.90 mg, 8.80 μmol, 0.1 eq.) was added to a solution of trans-32 (38.5 mg, 88.0 μmol) in THF (5.0 mL) and stirring was continued at ambient temperature for 3 h under O₂ atmosphere. The reaction mixture was filtered through a cellulose pad and washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was purified by SiO₂ flash column chromatography (benzene–EtOAc = 2 : 1) to provide benzoate trans-33 (17.5 mg, 44%) as a dark red amorphous, and with CH₂Cl₂-EtOH = 19 : 1 to give trans-32 (14.3 mg, 37% recovery) as a yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ: 7.93 (2H, dd, J = 7.8, 1.6 Hz, Bz-H), 7.59 (1H, tt, J = 7.8, 1.6 Hz, Bz-H), 7.45 (2H, t, J = 7.8 Hz, Bz-H), 6.91 (1H, s, 9-OH), 6.07 (1H, m, 6-H), 4.87 (1H, dd, J = 11.9, 6.8 Hz, 12-H), 4.73 (1H, dd, J = 11.1, 4.8 Hz, 11a-H), 4.57 (1H, dd, J = 11.9, 3.2 Hz, 12-H), 4.42 (1H, d, J = 18.8 Hz, 3-H), 4.23 (1H, d, J = 18.8 Hz, 3-H), 3.33 (1H, ddd, J = 19.0, 4.8, 1.0 Hz, 11-H), 2.69 (1H, dd, J = 19.0, 11.1, 2.4 Hz, 11-H), 2.60 (3H, s, 2-COCH₃), 2.00 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 184.6 (s, C-7), 181.1 (s, C-10), 171.6 (s, 2-ÇOCH₃), 166.5 (s, C-1), 166.3 (s, C-14), 162.4 (s, C-4), 151.0 (s, C-9), 139.1 (s, C-10a), 136.1 (s, C-6a), 133.6 (d, Bz), 129.6 (d, Bz), 129.0 (s, Bz), 128.7 (d, Bz), 118.4 (s, C-8), 64.4 (t, C-12), 53.4 (d, C-11a), 48.6 (d, C-6), 45.6 (t, C-3), 27.2 (q, 2-ÇOCH₃), 26.6 (t, C-11), 8.2 (q, 8-CH₃); IR (KBr): 3181, 2970, 1713, 1655, 1294, 1260, 1240, 1231, 1211 cm⁻¹; EIMS m/z (%): 452 (M⁺, 2), 423 (12), 422 (47), 330 (15), 288 (10), 204 (5), 203 (7), 190 (5), 106 (9), 105 (100), 77 (14); HREIMS: calecd for C₂₉H₂₂N₂O₈ 452.1220; found 452.1217.
(6R\(^{+}\),11aS\(^{-}\))-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2H-pyrazino-
[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (cis-11a): A TMSCHN\(_2\) (0.6 M in Hex., 154 \(\mu\)L, 92.0
\(\mu\)mol, 2.0 eq.) was added to a solution of cis-33 (20.6 mg, 46.0 \(\mu\)mol) in THF : MeOH (9 : 1, 1.0 mL) at
0 \(^{\circ}\)C in the dark, and stirring was continued for 2 h under Ar atmosphere. Then reaction mixture was
concentrated under reduced pressure. The residue was diluted with 5% aqueous NaHCO\(_3\) (10 mL) and the
product was extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 10 mL). The combined organic layer were washed with brine (30
mL), dried over sodium sulfate, and concentrated in vacuo to give a residue. The residue was purified by
SiO\(_2\) flash column chromatography (benzene–EtOAc = 5 : 1) to provide benzoate cis-11a (14.6 mg, 68%)
as a pale yellow amorphous. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.84 (2H, br d, \(J = 7.9\) Hz, Bz-H), 7.58 (1H,
br t, \(J = 7.9\) Hz, Bz-H), 7.43 (2H, br t, \(J = 7.9\) Hz, Bz-H), 5.80 (1H, br td, \(J = 3.5, 1.4\) Hz, 6-H), 5.19 (1H,
d, \(J = 17.3\) Hz, 3-H), 4.67 (1H, dd, \(J = 11.7, 3.9\) Hz, 12-H), 4.53 (1H, dd, \(J = 11.7, 3.5\) Hz, 12-H), 4.13
(1H, dd, \(J = 11.4, 5.2\) Hz, 11a-H), 4.03 (3H, s, 9-OCH\(_3\)), 3.84 (1H, d, \(J = 17.3\) Hz, 3-H), 3.50 (1H, dd, \(J =
17.7, 5.2\) Hz, 11-H), 2.64 (1H, ddd, \(J = 17.7, 11.4, 1.4\) Hz, 11-H), 2.59 (3H, s, 2-COCH\(_3\)), 2.00 (3H, s,
8-CH\(_3\)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\): 184.5 (s, C-7), 180.4 (s, C-10), 179.0 (s, 2-COCH\(_3\)), 167.3 (s,
C-1), 166.2 (s, C-14), 165.9 (s, C-4), 155.5 (s, C-9), 137.6 (s, C-6a), 133.6 (d, Bz), 129.5 (d, Bz), 129.3 (s,
C-8), 129.1 (s, C-10a), 129.1 (s, Bz), 128.7 (d, Bz), 64.9 (t, C-12), 61.1 (q, 9-OCH\(_3\)), 54.9 (d, C-11a),
49.4 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-COCH\(_3\)), 21.6 (t, C-11), 8.9 (q, 8-CH\(_3\)); IR (KBr): 2951, 2849,
1705, 1694, 1663, 1368, 1273 cm\(^{-1}\); FABMS \(m/z\): 467 [M+H]\(^{+}\); HRFABMS: calcd for C\(_{24}\)H\(_{23}\)N\(_2\)O\(_8\)
467.1458; found 467.1456.

(6S\(^{+}\),11aS\(^{-}\))-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2H-pyrazino-
[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (trans-11a): The same procedure for cis-33 was used. The
residue was purified by SiO\(_2\) flash column chromatography (benzene–EtOAc = 6 : 1) to provide benzoate
trans-11a (5.60 mg, 55%) as a yellow amorphous. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.94 (2H, d, \(J = 7.6\)
Hz, Bz-H), 7.58 (1H, t, \(J = 7.6\) Hz, Bz-H), 7.45 (2H, t, \(J = 7.6\) Hz, Bz-H), 6.03 (1H, m, 6-H), 4.85 (1H, dd, \(J =
11.9, 7.3\) Hz, 12-H), 4.70 (1H, dd, \(J = 11.5, 4.8\) Hz, 11a-H), 4.55 (1H, dd, \(J = 11.9, 3.2\) Hz, 12-H), 4.43
(1H, d, \(J = 18.5\) Hz, 3-H), 4.20 (1H, d, \(J = 18.5\) Hz, 3-H), 4.03 (3H, s, 9-OCH\(_3\)), 3.31 (1H, dd, \(J = 19.0,
4.8\) Hz, 11-H), 2.64 (1H, ddd, \(J = 19.0, 11.5, 2.0\) Hz, 11-H), 2.60 (3H, s, 2-COCH\(_3\)), 1.99 (3H, s, 8-CH\(_3\));
\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\): 185.2 (s, C-7), 181.0 (s, C-10), 171.7 (s, 2-COCH\(_3\)), 166.6 (s, C-1), 166.3
(s, C-14), 162.3 (s, C-4), 155.5 (s, C-9), 138.4 (s, C-10a), 136.8 (s, C-6a), 133.6 (d, Bz), 129.6 (d, Bz),
129.3 (s, C-8), 129.0 (s, Bz), 128.7 (d, Bz), 64.2 (t, C-12), 61.1 (q, 9-OCH\(_3\)), 53.6 (d, C-11a), 48.3 (d,
C-6), 45.6 (t, C-3), 27.2 (q, 2-COCH\(_3\)), 27.0 (t, C-11), 8.8 (q, 8-CH\(_3\)); IR (KBr) cm\(^{-1}\): 2941, 2928, 2855,
1717, 1679, 1317, 1271, 1215; EI-MS \(m/z\) (%): 466 (M\(^{+}\), 4), 437 (13), 436 (48), 434 (7), 333 (8), 331 (22),
329 (7), 289 (7), 259 (7), 232 (8), 204 (11), 202 (8), 106 (9), 105 (100), 77 (14). HREIMS calc'd for 
C_{24}H_{22}N_{2}O_{8} 466.1377; found 466.1372.

(6R',11aS')-2-Acetyl-9-ethoxy-6-[(benzoyloxy)methyl]-8-methyl-11a-dihydro-2H-pyrazino[1,2-
6b]isoquinoline-1,4,7,10(3H,6H)-tetaone (cis-11b): Ethyl iodide (13.0 μL, 165 μmol, 5.0 eq.) was added to a suspension of cis-33 (15.0 mg, 33.0 μmol) and Ag₂O (38.2 mg, 165 μmol, 5.0 eq.) in CH₂Cl₂ (1.0 mL), and the reaction mixture was stirred at 45 ℃ for 1 h. The insoluble materials were removed by filtration and washed with CH₂Cl₂. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (CH₂Cl₂–MeOH = 19 : 1) to give cis-11b (12.2 mg, 77%) as a yellow amorphous. \(^{1}H\)-NMR (400 MHz, CDCl₃) δ: 7.84 (2H, d, J = 7.9 Hz, Bz-H), 7.57 (1H, t, J = 7.9 Hz, Bz-H), 7.42 (2H, t, J = 7.9 Hz, Bz-H), 5.79 (1H, br td, J = 3.6, 1.9 Hz, 6-H), 5.18 (1H, d, J = 17.2 Hz, 3-H), 4.66 (1H, dd, J = 11.7, 3.6 Hz, 12-H), 4.53 (1H, dd, J = 11.7, 3.6 Hz, 12-H), 4.29 (1H, quin, J = 7.0 Hz, 9-OCH₂CH₃), 4.28 (1H, quin, J = 7.0 Hz, 9-OCH₂CH₃), 4.13 (1H, dd, J = 11.3, 5.2 Hz, 11a-H), 3.84 (1H, d, J = 17.2 Hz, 3-H), 3.49 (1H, dd, J = 17.6, 5.2 Hz, 11-H), 2.63 (1H, ddd, J = 17.6, 11.3, 1.9 Hz, 11-H), 2.59 (3H, s, 2-COCH₃), 2.01 (3H, s, 8-CH₃), 1.37 (3H, t, J = 7.0 Hz, 9-OCH₂CH₃); \(^{13}C\)-NMR (100 MHz, CDCl₃) δ: 184.5 (s, C-7), 180.5 (s, C-10), 170.8 (s, 2-COCH₃), 167.3 (s, C-1), 166.1 (s, C-14), 165.9 (s, C-4), 155.0 (s, C-9), 137.6 (s, C-6a), 137.6 (s, C-10a), 133.5 (d, Bz), 129.9 (s, C-8), 129.5 (d, Bz), 129.1 (s, Bz), 128.6 (d, Bz), 69.6 (t, 9-OCH₂CH₃), 64.9 (t, C-12), 54.9 (d, C-11a), 49.4 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-COCH₃), 21.6 (t, C-11), 15.9 (q, 9-OCH₂CH₃), 9.0 (q, 8-CH₃); IR (KBr): 2978, 2934, 1717, 1690, 1663, 1368, 1269 cm⁻¹; MS m/z: 481 [M+H]⁺; HRFABMS: calc'd for C₂₅H₂₈N₂O₈ 481.1611; found 481.1619.

(6S',11aS')-2-Acetyl-9-ethoxy-6-[(benzoyloxy)methyl]-8-methyl-11a-dihydro-2H-pyrazino[1,2-
b]isoquinoline-1,4,7,10(3H,6H)-tetaone (trans-11b): The same procedure for cis-33 was used. The residue was purified by SiO₂ flash column chromatography (benzene–EtOAc = 5 : 1) to provide benzoate trans-11b (17.9 mg, 67%) as a yellow amorphous. \(^{1}H\)-NMR (400 MHz, CDCl₃) δ: 7.94 (2H, d, J = 7.9 Hz, Bz-H), 7.58 (1H, t, J = 7.9 Hz, Bz-H), 7.44 (2H, t, J = 7.9 Hz, Bz-H), 6.03 (1H, br t, J = 3.4 Hz, 6-H), 4.85 (1H, dd, J = 11.8, 7.2 Hz, 12-H), 4.70 (1H, dd, J = 11.4, 4.8 Hz, 11a-H), 4.55 (1H, dd, J = 11.8, 3.4 Hz, 12-H), 4.43 (1H, d, J = 18.5 Hz, 3-H), 4.30 (2H, q, J = 7.0 Hz, 9-OCH₂CH₃), 4.20 (1H, d, J = 18.5 Hz, 3-H), 3.31 (1H, dd, J = 19.0, 4.8 Hz, 11-H), 2.63 (1H, ddd, J = 19.0, 11.4, 2.3 Hz, 11-H), 2.60 (3H, s, 2-COCH₃), 2.00 (3H, s, 8-CH₃), 1.37 (3H, t, J = 7.0 Hz, 9-OCH₂CH₃); \(^{13}C\)-NMR (100 MHz, CDCl₃) δ: 185.3 (s, C-7), 181.1 (s, C-10), 171.7 (s, 2-COCH₃), 166.6 (s, C-1), 166.3 (s, C-14), 162.3 (s, C-4), 155.0 (s, C-9), 138.4 (s, C-10a), 136.8 (s, C-6a), 133.6 (d, Bz), 130.0 (s, C-8), 129.6 (d, Bz), 129.1 (s, Bz), 128.7 (d, Bz), 69.6 (t, 9-OCH₂CH₃), 64.2 (t, C-12), 53.6 (d, C-11a), 48.3 (d, C-6), 45.6 (t, C-3), 27.2 (t,
C-11), 27.1 (q, 2-COCH₃), 15.9 (q, 9-OCH₂-CH₃), 9.0 (q, 8-CH₃); IR (KBr): 2976, 2938, 1717, 1684, 1663, 1271, 1227 cm⁻¹; FABMS m/z: 481 [M+H]⁺; HRFABMS: calcd for C₂₅H₂₅N₂O₈ 481.1611; found 481.1611.

(6R,11aS⁺)-2-Acetyl-6-[(benzoyloxy)methyl]-9-isopropoxy-8-methyl-11,11a-dihydro-2H-pyrazino-[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (cis-11c): Isopropyl iodide (33.0 µL, 330 µmol, 5.0 eq.) was added to a suspension of cis-33 (30.0 mg, 66.0 µmol) and Ag₂O (76.0 mg, 330 µmol, 5.0 eq.) in CH₂Cl₂ (3.0 mL), and the reaction mixture was stirred at 42 °C for 1 h. The insoluble materials were removed by filtration and washed with CH₂Cl₂. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash column chromatography (benzene–EtOAc = 4 : 1) to give cis-11c (15.0 mg, 46%) as a yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ: 7.84 (2H, d, J = 7.8 Hz, Bz-H), 7.57 (1H, t, J = 7.8 Hz, Bz-H), 7.42 (2H, t, J = 7.8 Hz, Bz-H), 5.80 (1H, td, J = 3.6, 1.8 Hz, 6-H), 5.19 (1H, d, J = 17.3 Hz, 3-H), 4.79 (1H, sept, J = 6.1 Hz, 9-OCH-(CH₃)₂), 4.67 (1H, dd, J = 11.7, 3.6 Hz, 12-H), 4.51 (1H, dd, J = 11.7, 3.6 Hz, 12-H), 4.13 (1H, dd, J = 11.3, 5.2 Hz, 11a-H), 3.84 (1H, d, J = 17.3 Hz, 3-H), 3.49 (1H, dd, J = 17.5, 5.2 Hz, 11-H), 2.63 (1H, dd, J = 17.5, 11.3, 1.8 Hz, 11-H), 2.60 (3H, s, 2-COCH₃), 2.01 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 184.6 (s, C-7), 180.6 (s, C-10), 170.9 (s, 2-COCH₃), 167.3 (s, C-1), 166.2 (s, C-14), 165.9 (s, C-4), 154.4 (s, C-9), 137.6 (s, C-6a), 137.6 (s, C-10a), 133.6 (d, Bz), 131.2 (s, C-8), 129.5 (d, Bz), 129.1 (s, Bz), 128.6 (d, Bz), 76.5 (d, 9-OCH-(CH₃)₂), 64.9 (t, C-12), 54.9 (d, C-11a), 49.5 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-COCH₃), 22.9 (q, 9-OCH-(CH₃)₂), 21.7 (t, C-11), 9.3 (q, 8-CH₃); IR (KBr): 2976, 2926, 2855, 1717, 1690, 1668, 1369, 1271 cm⁻¹; FABMS m/z: 495 [M+H]⁺; HRFABMS: calcd for C₂₆H₂₇N₂O₈ 495.1767; found 495.1766.

(6S⁺,11aS⁺)-2-Acetyl-6-[(benzoyloxy)methyl]-9-isopropoxy-8-methyl-11,11a-dihydro-2H-pyrazino-[1,2-b]isoquinoline-1,4,7,10(3H,6H)-tetraone (trans-11c): The same procedure for cis-33 was used. The residue was purified by SiO₂ flash column chromatography (benzene–EtOAc = 5 : 1) to provide benzoate trans-11c (16.5 mg, 50%) as a yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ: 7.93 (2H, d, J = 7.7 Hz, Bz-H), 7.58 (1H, t, J = 7.7 Hz, Bz-H), 7.44 (2H, t, J = 7.7 Hz, Bz-H and 5'-H'), 6.03 (1H, br d, J = 7.1 Hz, 6-H), 4.86 (1H, dd, J = 11.7, 7.1 Hz, 12-H), 4.81 (1H, sept, J = 6.1 Hz, 9-OCH-(CH₃)₂), 4.70 (1H, dd, J = 11.4, 4.8 Hz, 11a-H), 4.56 (1H, dd, J = 11.7, 2.9 Hz, 12-H), 4.44 (1H, d, J = 18.5 Hz, 3-H), 4.20 (1H, d, J = 18.5 Hz, 3-H), 3.30 (1H, dd, J = 19.0, 4.8 Hz, 11-H), 2.63 (1H, ddd, J = 19.0, 11.4, 2.1 Hz, 11-H), 2.60 (3H, s, 2-COCH₃), 1.99 (3H, s, 8-CH₃), 1.31 (6H, d, J = 6.1 Hz, 9-OCH-(CH₃)₂); ¹³C-NMR (100 MHz, CDCl₃) δ: 185.3 (s, C-7), 181.3 (s, C-10), 171.7 (s, 2-COCH₃), 166.7 (s, C-1), 166.3 (s, C-14), 162.3 (s, C-4), 154.5 (s, C-9), 138.5 (s, C-10a), 136.9 (s, C-6a), 133.6 (d, Bz), 130.3 (s, C-8), 129.6 (d, Bz), 129.1
(6R<sup>+</sup>,11αS<sup>−</sup>)-2-Acetyl-7-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6H-[15,17]-dioxolo[4,5-f]pyrazino[1,2-b]isoquinoline-8,11-dione (cis-12a): A solution of cis-11a (7.10 mg, 15.0 μmol) in CH₂Cl₂ (40 mL) was stirred at ambient temperature adjacent to an 18-W compact fluorescent light bulb. After 1.5 h, the reaction mixture was concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash chromatography (CH₂Cl₂ – 10% NH₄OH contained MeOH = 19 : 1) to provide compound cis-12a (2.40 mg, 34%) as a yellow amorphous. <sup>1</sup>H-NMR (400 MHz, CDCl₃) δ: 7.93 (2H, d, J = 7.6 Hz, Bz-H), 7.56 (1H, t, J = 7.6 Hz, Bz-H), 7.42 (2H, t, J = 7.6 Hz, Bz-H), 6.18 (1H, dd, J = 7.3, 5.0 Hz, 6-H), 5.96 (1H, d, J = 1.2 Hz, 16-H), 5.94 (1H, d, J = 1.2 Hz, 16-H), 5.12 (1H, d, J = 17.1 Hz, 3-H) 4.43 (1H, dd, J = 11.6, 7.3 Hz, 12-H), 4.38 (1H, dd, J = 11.6, 5.0 Hz, 12-H), 4.13 (1H, dd, J = 12.3, 4.9 Hz, 11a-H), 3.77 (1H, d, J = 17.1 Hz, 3-H), 3.51 (1H, dd, J = 12.3, 4.9 Hz, 11-H), 3.05 (1H, dd, J = 12.3, 12.3 Hz, 11-H), 2.61 (3H, s, 2-COCH₃), 2.15 (3H, s, 8-CH₃); <sup>13</sup>C-NMR (100 MHz, CDCl₃) δ: 171.3 (s, 2-ÇOCH₃), 168.6 (s, C-1), 167.3 (s, C-14), 166.8 (s, C-4), 146.4 (s, C-9), 146.4 (s, C-7), 138.2 (s, C-10), 133.6 (d, Bz), 129.9 (d, Bz), 129.8 (s, Bz), 128.8 (d, Bz), 111.4 (s, C-10a), 111.2 (s, C-6a), 106.9 (s, C-8), 101.6 (t, C-16), 67.0 (t, C-12), 56.5 (d, C-11a), 48.8 (d, C-6), 45.9 (t, C-3), 27.3 (q, 2-ÇOCH₃), 23.0 (t, C-11), 9.1 (q, 8-ÇH₃); IR (CHCl₃): 3385, 2928, 2359, 1717, 1273 cm<sup>−¹</sup>; EIMS m/z (%): 466 (M<sup>+</sup>, 7), 344 (5), 332 (17), 331, (100), 329 (6), 317 (5), 289 (19), 204 (21), 105 (13); HREIMS: calcd for C₂₄H₂₂N₂O₈ 466.1376; found 466.1371.

(6R<sup>+</sup>,11αS<sup>−</sup>)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6H-[15,17]-dioxolo[4,5-f]pyrazino[1,2-b]isoquinoline-8,11-dione (cis-34a): An Ac₂O (69.0 μL, 730 μmol, 50 eq.) and pyridine (59.0 μL, 730 μmol, 50 eq.) were added to a solution of cis-11a (6.80 mg, 15 μmol) in CH₂Cl₂ (1.0 mL), and the reaction mixture were stirred at ambient temperature adjacent to an 18-W compact fluorescent light bulb. After 1.5 h, the reaction mixture was concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash chromatography (CH₂Cl₂ – MeOH = 19 : 1) to provide compound cis-34a (5.10 mg, 69%) as a pale yellow amorphous. <sup>1</sup>H-NMR (400 MHz, CDCl₃) δ: 7.91 (2H, br d, J = 7.6 Hz, Bz-H), 7.55 (1H, br t, J = 7.6 Hz, Bz-H), 7.42 (2H, br t, J = 7.6 Hz, Bz-H), 6.06 (1H, d, J = 1.4 Hz, 16-H), 6.03 (1H, d, J = 1.4 Hz, 16-H), 5.88 (1H, m, 6-H), 5.06 (1H, d, J = 17.1 Hz, 3-H) 4.35 (1H, dd, J = 11.0, 7.3 Hz, 12-H), 4.30 (1H, dd, J = 11.0, 5.0 Hz, 12-H), 4.13 (1H, dd, J = 12.4, 4.9 Hz, 11a-H), 3.73 (1H, d, J = 17.1 Hz, 3-H), 3.53 (1H, dd, J = 15.9, 4.9 Hz, 11-H), 3.14 (1H, dd, J = 15.9, 12.4
Hz, 11-H), 2.58 (3H, s, 2-COCH₃), 2.44 (3H, s, 7-OCOCH₃), 2.03 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 170.8 (s, 2-COCH₃), 169.6 (s, 7-OCOCH₃), 168.3 (s, C-1), 166.5 (s, C-14), 165.9 (s, C-4), 146.4 (s, C-9), 142.2 (s, C-10), 141.0 (s, C-7), 133.2 (d, Bz), 129.5 (s, Bz), 129.6 (d, Bz), 128.5 (d, Bz), 117.5 (s, C-6a), 112.6 (s, C-8), 111.7 (s, C-10a), 102.0 (t, C-16), 65.9 (t, C-12), 55.8 (d, C-11a), 48.3 (d, C-6), 45.5 (t, C-3), 26.9 (q, 2-COCH₃), 22.5 (t, C-11), 20.6 (q, 7-OCOCH₃), 9.6 (q, 8-CH₃); IR (CHCl₃): 3022, 2928, 2855, 1719, 1271, 1198 cm⁻¹; EIMS m/z (%): 508 (M⁺, 5), 466 (9), 374 (10), 373 (49), 360 (5), 359 (27), 332 (17), 331 (100), 317 (17), 289 (13), 204 (17), 190 (6), 105 (15); HREIMS: calcd for C₂₆H₂₄N₂O₉ 508.1482; found 508.1481.

(6S*,11aS*)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6H-[15,17]-dioxolo[4,5-f]pyrazino[1,2-b]isoquinoline-8,11-dione (trans-34a): Ac₂O (142 μL, 1.50 mmol, 50 eq.) and pyridine (121 μL, 1.50 mmol, 50 eq.) were added to a solution of trans-11a (14.0 mg, 0.03 mmol) in CH₂Cl₂ (2.0 mL), and the reaction mixture were stirred at ambient temperature adjacent to an 18-W compact fluorescent light bulb. After 2.5 h, the reaction mixture was concentrated in vacuo to give a residue. The residue was purified by SiO₂ flash chromatography (CH₂Cl₂−EtOAc = 9 : 1) to provide compound trans-34a (8.80 mg, 58%) as a colorless amorphous. ¹H-NMR (400 MHz, CDCl₃) δ: 7.98 (2H, dd, J = 7.9, 1.3 Hz, Bz-H), 7.57 (1H, tt, J = 7.9, 1.3 Hz, Bz-H), 7.44 (2H, t, J = 7.9 Hz, Bz-H), 6.04 (1H, d, J = 1.3 Hz, 16-H), 6.03 (1H, d, J = 1.3 Hz, 16-H), 5.99 (1H, dd, J = 9.9, 3.9 Hz, 6-H), 4.70 (1H, br t, J = 6.6 Hz, 11a-H) 4.55 (1H, dd, J = 11.9, 9.9 Hz, 12-H), 4.46 (1H, dd, J = 11.9, 3.9 Hz, 12-H), 4.44 (1H, d, J = 18.0 Hz, 3-H), 4.20 (1H, d, J = 18.0 Hz, 3-H), 3.33 (1H, dd, J = 16.3, 6.6 Hz, 11-H), 3.26 (1H, br s, 11-H), 2.58 (3H, s, 2-COCH₃), 2.47 (3H, s, 7-OCOCH₃), 2.02 (3H, s, 8-CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ: 171.5 (s, 2-COCH₃), 169.4 (s, 7-OCOCH₃), 167.5 (s, C-1), 166.5 (s, C-14), 163.3 (s, C-4), 146.1 (s, C-9), 142.7 (s, C-10), 141.0 (s, C-7), 133.3 (d, Bz), 129.7 (d, Bz), 129.5 (s, Bz), 128.5 (d, Bz), 116.6 (s, C-6a), 112.6 (s, C-8), 111.2 (s, C-10a), 102.3 (t, C-16), 63.1 (t, C-12), 53.4 (d, C-11a), 48.1 (d, C-6), 45.7 (t, C-3), 27.2 (q, 2-COCH₃), 24.7 (t, C-11), 20.7 (q, 7-OCOCH₃), 9.6 (q, 8-CH₃); IR (KBr): 3414, 2955, 2926, 2855, 1719, 1721, 1701, 1676, 1275, 1198 cm⁻¹; EIMS m/z (%): 508 (M⁺, 2), 466 (11), 374 (5), 373 (26), 344 (20), 332 (17), 331 (100), 302 (5), 289 (27), 217 (5), 204 (19), 105 (14); HREIMS: calcd for C₂₆H₂₄N₂O₉ 508.1482; found 508.1483.

(6R*,11aS*)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16-dimethyl-2,3,11,11a-tetrahydro-6H-[15,17]-dioxolo[4,5-f]pyrazino[1,2-b]isoquinoline-8,11-dione (cis-34b): The same procedure for cis-11a was used (1 h). The residue was purified by SiO₂ flash column chromatography (benzene−EtOAc = 4 : 1 ~ 1 : 1) to provide inseparable diastereomer mixture cis-34b (dr = 2 : 1, 9.10 mg, 34%) as a pale yellow amorphous, and with benzene−EtOAc = 6 : 1 to give 35 (4.50 mg, 16%) as a yellow oil. cis-34b:
$^1$H-NMR (400 MHz, CDCl$_3$) (major) $\delta$: 7.91 (2H, d, $J = 7.5$ Hz, Bz-H), 7.55 (1H, t, $J = 7.5$ Hz, Bz-H), 7.42 (2H, t, $J = 7.5$ Hz, Bz-H), 6.31 (1H, q, $J = 4.9$ Hz, 16-H), 5.87 (1H, br s, 6-H), 5.06 (1H, d, $J = 17.1$ Hz, 3-H), 4.41 (1H, br d, $J = 11.5$ Hz, 12-H), 4.29 (1H, dd, $J = 11.5$, 5.2 Hz, 12-H), 4.12 (1H, dd, $J = 12.2$, 4.9 Hz, 11a-H), 3.72 (1H, d, $J = 17.1$ Hz, 3-H), 3.51 (1H, dd, $J = 15.6$, 4.9 Hz, 11-H), 3.11 (1H, dd, $J = 15.6$, 12.2 Hz, 3-H), 2.57 (3H, s, 2-COCH$_3$), 2.42 (3H, s, 7-OCOCH$_3$), 2.00 (3H, s, 8-CH$_3$), 1.74 (3H, d, $J = 4.9$ Hz, 16-CH$_3$). (minor) $\delta$: 7.91 (2H, d, $J = 7.5$ Hz, Bz-H), 7.55 (1H, t, $J = 7.5$ Hz, Bz-H), 7.42 (2H, t, $J = 7.5$ Hz, Bz-H), 6.34 (1H, q, $J = 5.0$ Hz, 16-H), 5.87 (1H, br s, 6-H), 5.06 (1H, d, $J = 17.1$ Hz, 3-H), 4.41 (1H, br d, $J = 11.5$ Hz, 12-H), 4.29 (1H, dd, $J = 11.5$, 5.2, 12-H), 4.13 (1H, dd, $J = 12.2$, 4.9 Hz, 11a-H), 3.72 (1H, d, $J = 17.1$ Hz, 3-H), 3.51 (1H, dd, $J = 15.6$, 4.9 Hz, 11-H), 3.11 (1H, dd, $J = 15.6$, 12.2, 11-H), 2.57 (3H, s, 2-COCH$_3$), 2.42 (3H, s, 7-OCOCH$_3$), 2.00 (3H, s, 8-CH$_3$), 1.72 (3H, d, $J = 5.0$ Hz, 16-CH$_3$); $^{13}$C-NMR (100 MHz, CDCl$_3$) (major) $\delta$: 170.9 (s, 2-COCH$_3$), 169.6 (s, 7-OCOCH$_3$), 168.3 (s, C-1), 166.5 (s, C-14), 165.9 (s, C-4), 146.6 (s, C-9), 142.5 (s, C-10), 140.7 (s, C-7), 133.2 (d, Bz), 129.6 (d, Bz), 129.6 (s, Bz), 128.4 (d, Bz), 117.2 (s, C-6a), 112.2 (s, C-8), 111.3 (s, C-10a), 110.7 (d, C-16), 66.0 (t, C-12), 55.9 (d, C-11a), 48.3 (d, C-6), 45.5 (t, C-3), 26.9 (q, 2-COCH$_3$), 22.5 (t, C-11), 20.9 (q, 16-CH$_3$), 20.6 (q, 7-OCOCH$_3$), 9.6 (q, 8-CH$_3$). (minor) $\delta$: 170.9 (s, 2-COCH$_3$), 169.6 (s, 7-OCOCH$_3$), 168.3 (s, C-1), 166.5 (s, C-14), 165.9 (s, C-4), 146.7 (s, C-9), 142.5 (s, C-10), 140.8 (s, C-7), 133.2 (d, Bz), 129.6 (d, Bz), 129.6 (s, Bz), 128.4 (d, Bz), 117.1 (s, C-6a), 112.2 (s, C-8), 111.3 (s, C-10a), 110.6 (d, C-16), 66.0 (t, C-12), 55.8 (d, C-11a), 48.3 (d, C-6), 45.5 (t, C-3), 26.9 (q, 2-COCH$_3$), 22.5 (t, C-11), 20.8 (q, 16-CH$_3$), 20.6 (q, 7-OCOCH$_3$), 9.6 (q, 8-CH$_3$); IR (KBr): 2955, 2924, 2853, 1722, 1707, 1366, 1271, 1196 cm$^{-1}$; EIMS m/z (%): 522 (M$^+$, 3), 480 (8), 389 (5), 388 (9), 387 (44), 346 (18), 345 (100), 303 (15), 218 (14), 105 (12); HREIMS: calcd for C$_27$H$_{26}$N$_2$O$_9$ 522.1638; found 522.1641.

35: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 7.90 (2H, d, $J = 7.9$ Hz, Bz-H), 7.56 (1H, t, $J = 7.9$ Hz, Bz-H), 7.42 (2H, t, $J = 7.9$ Hz, Bz-H), 7.20 (1H, s, 11-H), 6.32 (1H, br s, 6-H), 4.88 (1H, d, $J = 17.6$ Hz, 3-H), 4.34 (1H, br d, $J = 8.6$ Hz, 12-H), 4.30 (1H, br d, $J = 8.6$, 12-H), 3.97 (1H, quin, $J = 7.0$ Hz, 9-OC$_2$H$_2$-CH$_3$), 3.96 (1H, quin, $J = 7.0$ Hz, 9-OC$_2$H$_2$-CH$_3$), 3.90 (1H, d, $J = 17.6$ Hz, 3-H), 2.63 (3H, s, 2-COCH$_3$), 2.52 (3H, s, 7-OCOCH$_3$ or 10-OCOCH$_3$), 2.42 (3H, s, 7-OCOCH$_3$ or 10-OCOCH$_3$), 2.13 (3H, s, 8-CH$_3$), 1.38 (3H, t, $J = 7.0$ Hz, 9-OC$_2$H$_2$-CH$_3$); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$: 171.7 (s, 2-COCH$_3$), 168.9 (s, 7-OCOCH$_3$ or 10-OCOCH$_3$), 168.3 (s, 7-OCOCH$_3$ or 10-OCOCH$_3$), 166.3 (s, C-14), 162.4 (s, C-4), 160.1 (s, C-1), 150.5 (s, C-9), 144.4 (s, C-7), 139.1 (s, C-10), 133.3 (d, Bz), 129.6 (d, Bz), 129.4 (s, Bz), 129.3 (s, C-8), 128.5 (d, Bz), 127.2 (s, C-6a or C-10a or C-11a), 121.8 (s, C-6a or C-10a or C-11a), 117.9 (s, C-6a or C-10a or C-11a), 112.3 (d, C-11), 69.8 (t, 9-OC$_2$H$_2$-CH$_3$), 63.3 (t, C-12), 47.8 (d, C-6), 45.2 (t, C-3), 26.9 (q, 2-COCH$_3$), 20.6 (q, 7-OCOCH$_3$ or 10-OCOCH$_3$), 20.5 (q, 7-OCOCH$_3$ or 10-OCOCH$_3$), 15.7 (q, 9-OC$_2$H$_2$-CH$_3$), 10.9 (q, 8-CH$_3$); IR (KBr): 2934, 1705, 1369, 1271, 1184 cm$^{-1}$; EIMS m/z (%): 564 (M$^+$, 2), 431 (5), 430 (22), 429 (100), 388 (6), 387 (26), 345 (13), 331 (8), 330 (44), 303 (5), 302 (10),
288 (20), 260 (11), 246 (6), 245 (5), 218 (16), 217 (6), 189 (5), 105 (15), 77 (5); HREIMS: calcd for C_{29}H_{28}N_{2}O_{10} 564.1744; found 564.1748.

2-Acetyl-6-[(benzoyloxy)methyl]-9-ethoxy-8-methyl-1,4-dioxo-1,3,4,6-tetrahydro-2H-pyrazino-[1,2-b]isoquinoline-7,10-diyl diacetate (35): Ac_{2}O (360 µL) was added to a solution of quinone cis-11b (13.6 mg, 29.0 µmol) in pyridine (1.5 mL) and stirring was continued at 25 °C in the dark for 51 h. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by SiO_{2} flash column chromatography (benzene−EtOAc = 6 : 1) to provide a 35 (5.70 mg, 35%) as a pale yellow amorphous, and with benzene−EtOAc = 5 : 1 to give cis-11b (3.60 mg, 27% recovery) as a yellow oil.

(6S*,11aS*)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16-dimethyl-2,3,11,11a-tetrahydro-6H-[15,17]dioxolo[4,5-f]pyrazino[1,2-b]isoquinoline-8,11-dione (trans-34b): The same procedure for cis-11a was used (1 h). The residue was purified by SiO_{2} flash column chromatography (benzene−EtOAc = 4 : 1 ~ 1 : 1) to provide inseparable diastereomer mixture trans-34b (dr = 1.3 : 1, 3.30 mg, 19%) as a colorless amorphous, and with benzene−EtOAc = 9 : 1 to give 35 (1.60 mg, 9%) as a yellow oil.

1^H-NMR (400 MHz, CDCl_{3}) (major) δ: 7.98 (2H, d, J = 7.6 Hz, Bz-H), 7.57 (1H, t, J = 7.6 Hz, Bz-H), 7.44 (2H, t, J = 7.6 Hz, Bz-H), 6.33 (1H, q, J = 5.0 Hz, 16-H), 5.99 (1H, br s, 6-H), 4.69 (1H, dd, J = 13.4, 6.1 Hz, 11a-H), 4.47-4.58 (2H, m, 12-H), 4.36 (1H, d, J = 18.5 Hz, 3-H), 4.25 (1H, d, J = 18.5 Hz, 3-H), 3.33 (1H, dd, J = 15.7, 6.1 Hz, 11-H), 3.15 (1H, br d, J = 15.7 Hz, 11-H), 2.59 (3H, s, 2-COCH_{3}), 2.46 (3H, s, 7-OCOCH_{3}), 1.99 (3H, s, 8-CH_{3}), 1.72 (3H, d, J = 5.0 Hz, 16-CH_{3}). (minor) δ: 7.98 (2H, d, J = 7.6 Hz, Bz-H), 7.57 (1H, t, J = 7.6 Hz, Bz-H), 7.44 (2H, t, J = 7.6 Hz, Bz-H), 6.31 (1H, q, J = 4.8 Hz, 16-H), 5.99 (1H, br s, 6-H), 4.69 (1H, dd, J = 6.0, 3.2 Hz, 11a-H), 4.47-4.58 (2H, m, 12-H), 4.44 (1H, d, J = 18.8 Hz, 3-H), 4.19 (1H, d, J = 18.8 Hz, 3-H), 3.29 (1H, dd, J = 12.7, 6.0 Hz, 11-H), 3.12 (1H, br d, J = 12.7 Hz, 11-H), 2.58 (3H, s, 2-COCH_{3}), 2.46 (3H, s, 7-OCOCH_{3}), 1.99 (3H, s, 8-CH_{3}), 1.71 (3H, d, J = 4.8 Hz, 16-CH_{3}); 13^C-NMR (100 MHz, CDCl_{3}) (major) δ: 171.6 (s, 2-COCH_{3}), 169.5 (s, 7-OCOCH_{3}), 167.6 (s, C-1), 166.5 (s, C-14), 163.0 (s, C-4), 146.3 (s, C-9), 143.0 (s, C-10), 140.9 (s, C-7), 133.3 (d, Bz), 129.7 (d, Bz), 129.5 (s, Bz), 128.5 (d, Bz), 115.9 (s, C-6a), 112.3 (s, C-8), 110.9 (s, C-10a), 110.8 (d, C-16), 63.1 (t, C-12), 53.5 (d, C-11a), 48.2 (d, C-6), 45.7 (t, C-3), 27.1 (q, 2-COCH_{3}), 24.5 (t, C-11), 20.9 (q, 16-CH_{3}), 20.7 (q, 7-OCOCH_{3}), 9.6 (q, 8-CH_{3}). (minor) δ: 171.5 (s,2-COCH_{3}), 169.5 (s, 7-OCOCH_{3}), 167.5 (s, C-1), 166.5 (s, C-14), 163.0 (s, C-4), 146.3 (s, C-9), 143.0 (s, C-10), 140.8 (s, C-7), 133.3 (d, Bz), 129.7 (d, Bz), 129.5 (s, Bz), 128.5 (d, Bz), 115.9 (s, C-6a), 112.3 (s, C-8), 110.9 (s, C-10a), 110.8 (d, C-16), 63.0 (t, C-12), 53.2 (d, C-11a), 48.2 (d, C-6), 45.7 (t, C-3), 27.1 (q, 2-COCH_{3}), 24.5 (t, C-11), 20.8 (q, 16-CH_{3}), 20.7 (q, 7-OCOCH_{3}), 9.6 (q, 8-CH_{3}); IR (KBr): 2957, 2924, 2855, 1721, 1705, 1676, 1273,
(6R',11aS')-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16,16-trimethyl-2,3,11,11a-tetrahydro-6H-15,17[dioxolo[4,5-f]pyrazino[1,2-b]isonicotinol-8,11-dione (cis-34c): The same procedure for cis-11a was used (1 h). The residue was purified by SiO2 flash column chromatography (benzene–EtOAc = 5 : 1 ~ 4 : 1) to provide a cis-34c (10.2 mg, 86%) as a pale red amorphous. 1H-NMR (400 MHz, CDCl3) δ: 7.91 (2H, d, J = 7.9 Hz, Bz-H), 7.55 (1H, t, J = 7.9 Hz, Bz-H), 7.41 (2H, t, J = 7.9 Hz, Bz-H), 5.87 (1H, br s, 6-H), 5.05 (1H, d, J = 17.1 Hz, 3-H), 4.34 (1H, br t, J = 10.3 Hz, 12-H), 4.28 (1H, dd, J = 10.3, 5.2 Hz, 12-H), 4.41 (1H, dd, J = 12.4, 4.9 Hz, 11a-H), 3.72 (1H, d, J = 17.1 Hz, 3-H), 3.50 (1H, dd, J = 16.0, 4.9 Hz, 11-H), 3.10 (1H, dd, J = 16.0, 12.4 Hz, 11-H), 2.58 (3H, s, 2-COCH3), 2.43 (3H, s, 7-COCH3), 1.99 (3H, s, 8-CH3), 1.72 (3H, s, 16-CH3), 1.69 (3H, s, 16-CH3); 13C-NMR (100 MHz, CDCl3) δ: 170.9 (s, 2-COCH3), 169.7 (s, 7-COCH3), 168.4 (s, C-1), 166.5 (s, C-14), 165.9 (s, C-4), 164.2 (s, C-9), 142.0 (s, C-10), 141.5 (s, C-7), 133.2 (d, Bz), 129.6 (s, Bz), 129.6 (d, Bz), 128.4 (d, Bz), 119.5 (s, C-16), 116.6 (s, C-6a), 112.0 (s, C-8), 111.1 (s, C-10a), 66.1 (t, C-12), 55.9 (d, C-11a), 48.3 (d, C-6), 45.5 (t, C-3), 26.9 (q, 2-COCH3), 26.1 (q, 16-CH3), 22.5 (t, C-11), 20.6 (q, 7-COCH3), 9.6 (q, 8-CH3); IR (KBr): 2924, 2853, 1722, 1709, 1688, 1366, 1273, 1198 cm⁻¹; EIMS m/z (%): 536 (M⁺, 3), 494 (8), 402 (8), 401 (38), 372 (9), 360 (19), 359 (100), 330 (5), 317 (30), 232 (8), 105 (13); HREIMS: calcd for C₂₈H₂₈N₂O₉ 536.1795; found 536.1791.

(6S',11aS')-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16,16-trimethyl-2,3,11,11a-tetrahydro-6H-15,17[dioxolo[4,5-f]pyrazino[1,2-b]isonicotinol-8,11-dione (trans-34c): The same procedure for trans-11a was used (1 h). The residue was purified by SiO2 flash column chromatography (benzene–EtOAc = 6 : 1) to provide a trans-34c (13.5 mg, 76%) as a yellow amorphous. 1H-NMR (400 MHz, CDCl3) δ: 7.97 (2H, d, J = 7.6 Hz, Bz-H), 7.57 (1H, t, J = 7.6 Hz, Bz-H), 7.44 (2H, t, J = 7.6 Hz, Bz-H), 5.99 (1H, br s, 6-H), 4.69 (1H, dd, J = 9.5, 5.7 Hz, 11a-H) 4.56 (1H, br d, J = 11.7 Hz, 12-H), 4.52 (1H, br d, J = 11.7 Hz, 12-H), 4.35 (1H, d, J = 18.0 Hz, 3-H), 4.26 (1H, d, J = 18.0 Hz, 3-H), 3.31 (1H, dd, J = 16.3, 5.7 Hz, 11-H), 3.11 (1H, m, 11-H), 2.58 (3H, s, 2-COCH3), 2.46 (3H, s, 7-COCH3), 1.98 (3H, s, 8-CH3) 1.70 (3H, s, 16-CH3), 1.69 (3H, s, 16-CH3); 13C-NMR (100 MHz, CDCl3) δ: 171.6 (s, 2-COCH3), 169.4 (s, 7-COCH3), 167.5 (s, C-1), 166.4 (s, C-14), 163.0 (s, C-4), 145.8 (s, C-9), 142.5 (s, C-10), 140.6 (s, C-7), 133.3 (d, Bz), 129.6 (d, Bz), 129.5 (s, Bz), 128.5 (d, Bz), 119.5 (s, C-16), 115.4 (s, C-6a), 112.1 (s, C-8), 110.8 (s, C-10a), 63.0 (t, C-12), 53.2 (d, C-11a), 48.2 (d, C-6), 45.7 (t, C-3), 27.1 (q, 2-COCH3), 26.1 (q, 16-CH3), 26.1 (q, 16-CH3), 25.2 (t, C-11), 20.7 (q, 7-COCH3), 9.6 (q, 8-CH3); IR (KBr): 2992, 2938, 1769, 1716, 1680, 1371, 1271, 1198 cm⁻¹; EIMS m/z (%): 536 (M⁺, 4), 494 (12), 402
(5), 401 (23), 373 (6), 372 (26), 360 (19), 359 (100), 330 (9), 318 (7), 317 (36), 232 (8), 105 (14), 77 (5); HREIMS m/z: calcd for C_{28}H_{28}N_{2}O_{9} 536.1795; found 536.1796.

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REFERENCES AND NOTES
16. CCDC-No. 1870093 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via WWW.ccdc.cam.ac.uk/data_request/cif.
17. As a result of detailed analysis about crude material, the formation of by-product 34 was confirmed. Thus, it was expected that the desired reaction progressed slowly and competing reactions that do not involve light are competing.