HETEROCYCLES, Vol. 99, No. 2, 2019, pp. 1276 - 1303. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 30th October, 2018, Accepted, 19th November, 2018, Published online, 14th February, 2019
DOI: 10.3987/COM-18-S(F)100

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-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-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.[1] As a result of intensive efforts channeled into the research of renieramycin marine natural products, about 30 compounds have been isolated from nature.[2] 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.[3] 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.[4] We have also completed the first asymmetric total synthesis of (-)-**1t**[5a] along with a large-scale synthetic route to (±)-**1t**.[5b] 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.[6] 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.[7] 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.[8] Recently Gademann *et al.* reported the total synthesis of natural products effectively utilizing this photo reaction.[9] 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.

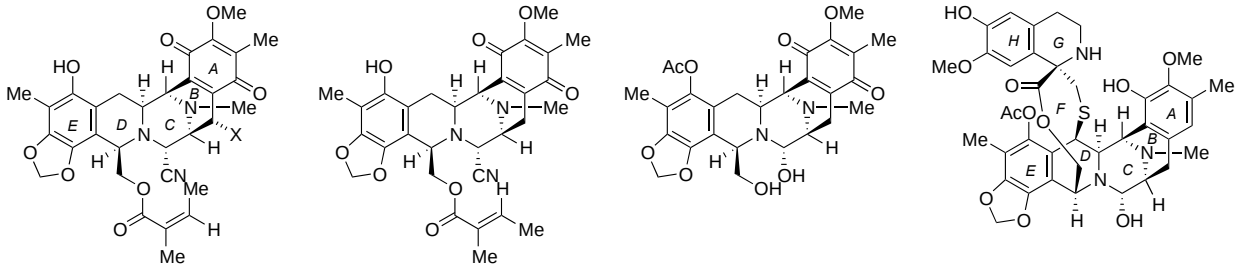
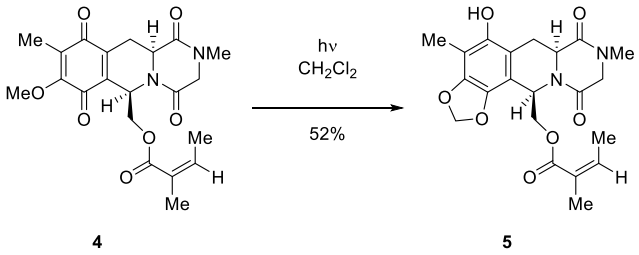


Figure 1. Structures of 1,2,3,4-tetrahydroisoquinoline natural products having 1,3-dioxol ring at E-ring



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.[10] **7** was obtained from **6** over six steps by using Hibino's protocol.[11] Thus, we started the preparation of left-half model compounds **11a–c** via compound **8**.

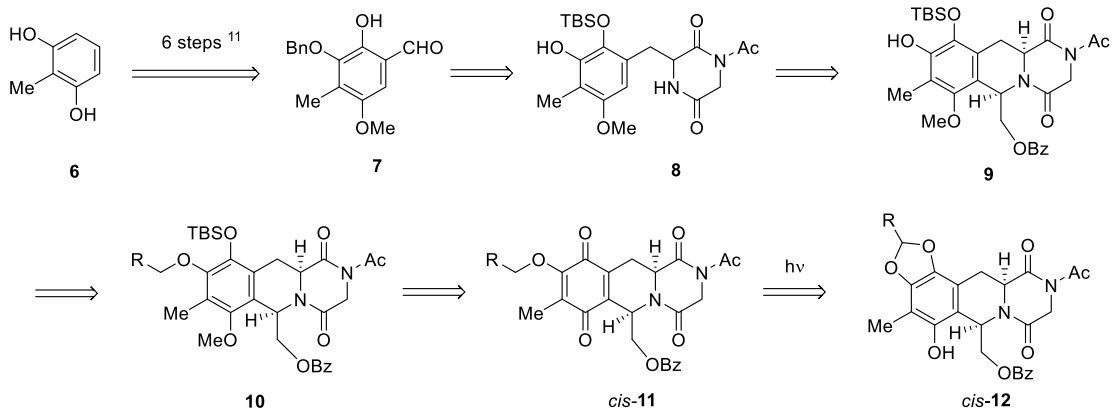
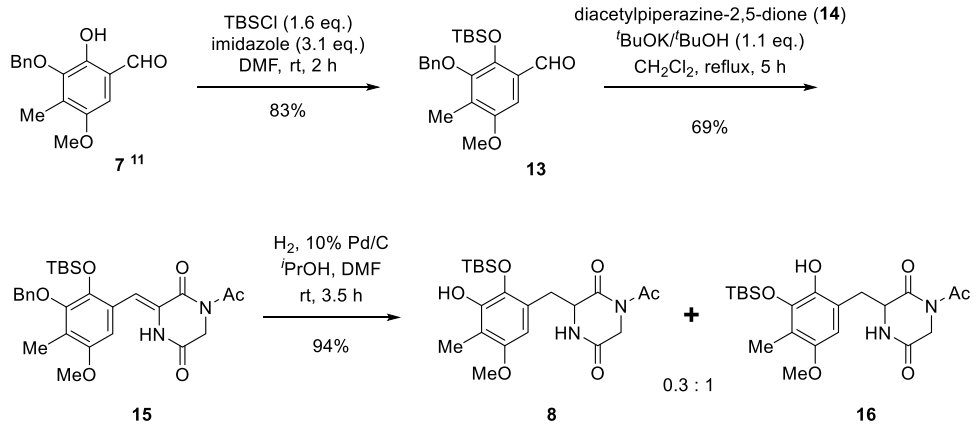


Figure 2. Outline for the synthesis of targeted CDE ring model compounds *cis*-**12** using the novel photo-induced transformation

RESULTS AND DISCUSSION

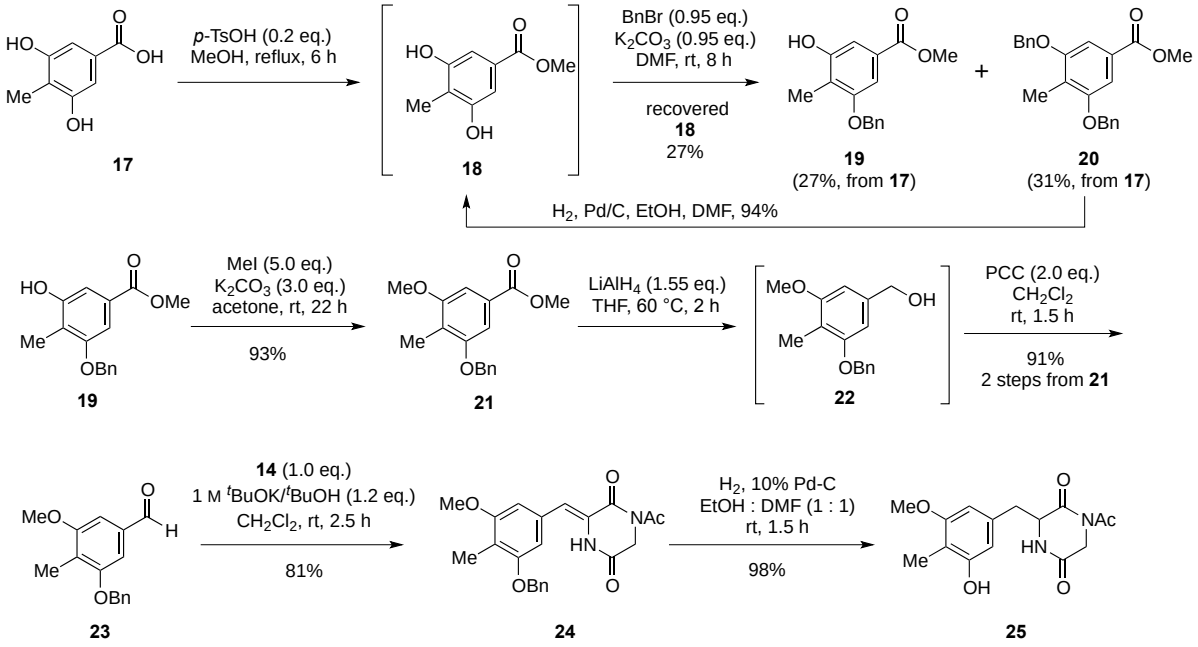
2,6-Dihydroxytoluene **6** was converted into compound **7**[11] in six steps. **7** was protected with TBS to produce ether **13** in 83% yield (Scheme 2). Condensation of aldehyde **13** with 1,4-diacetylpiperazine-2,5-dione **14** by the modified Gallina and Liberatori method gave **15** in 69% yield. The catalytic hydrogenation of **15** proceeded smoothly where **15** was completely consumed. Purification of the crude material by SiO_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).



Scheme 2. Three steps preparation of **8** from **7**

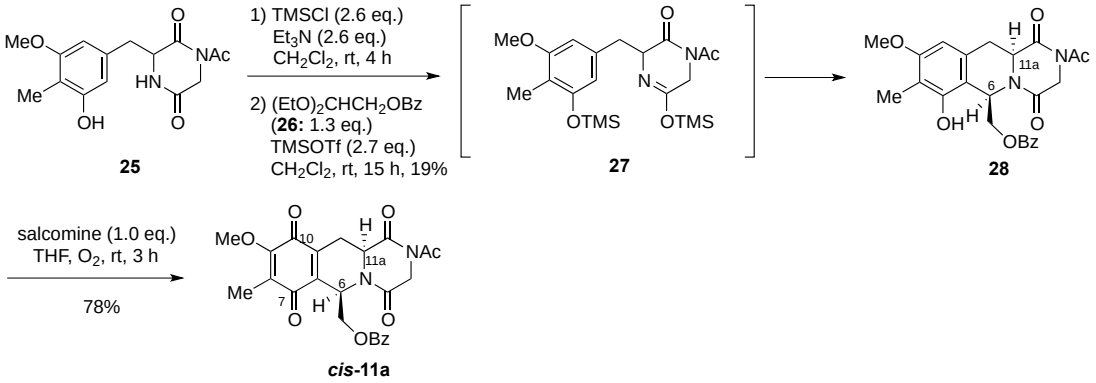
According to the published method,[12] monobenzyl derivative **19** was obtained from commercially available 3,5-dihydroxy-4-methylbenzoic acid (**17**) in 27% yield. Over-reacted compound **20** (31%) and

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.



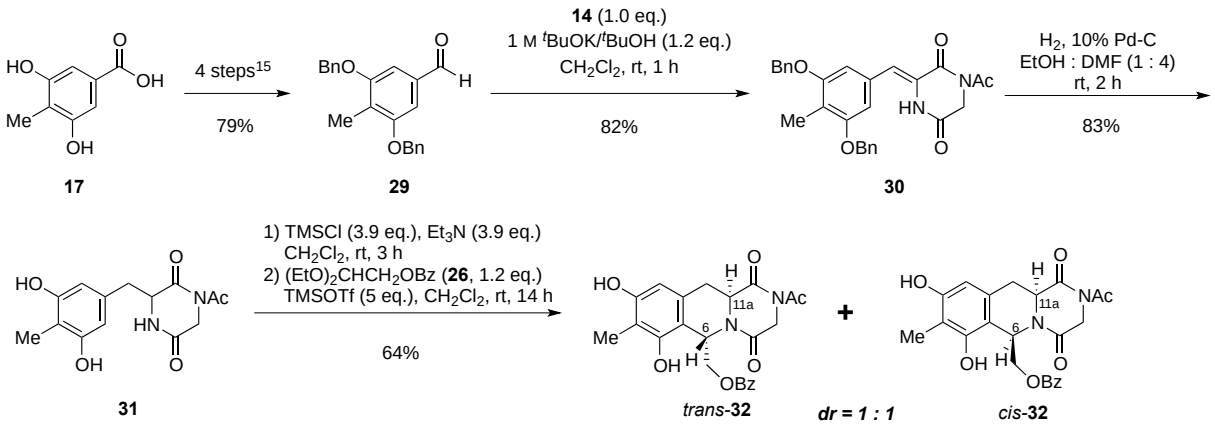
Scheme 3. 7 Seven Steps transformation of **17** into **25**

Phenol **25** was subjected to our modified Pictet-Spengler cyclization to construct 1,2,3,4-tetrahydroisoquinoline.[13] 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**)[14] 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.[15] 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 SiO_2 column chromatography and the relative configuration of *cis*-**32** was confirmed by X-ray crystallographic analysis (Figure 3).[16]



Scheme 5. Synthesis of 1,2,3,4-tetrahydroisoquinoline **32** from compound **17**

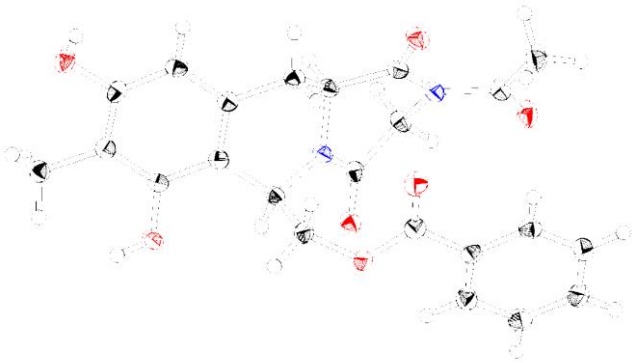
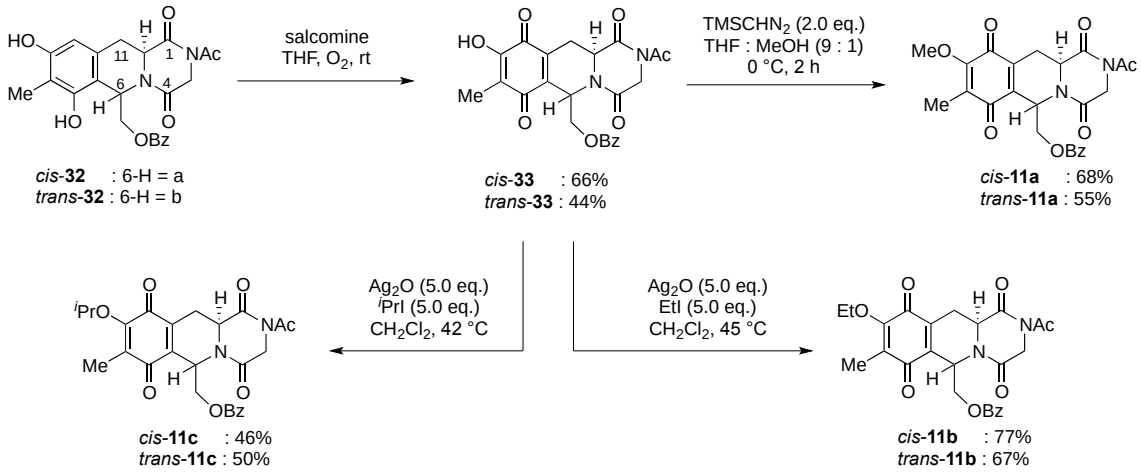


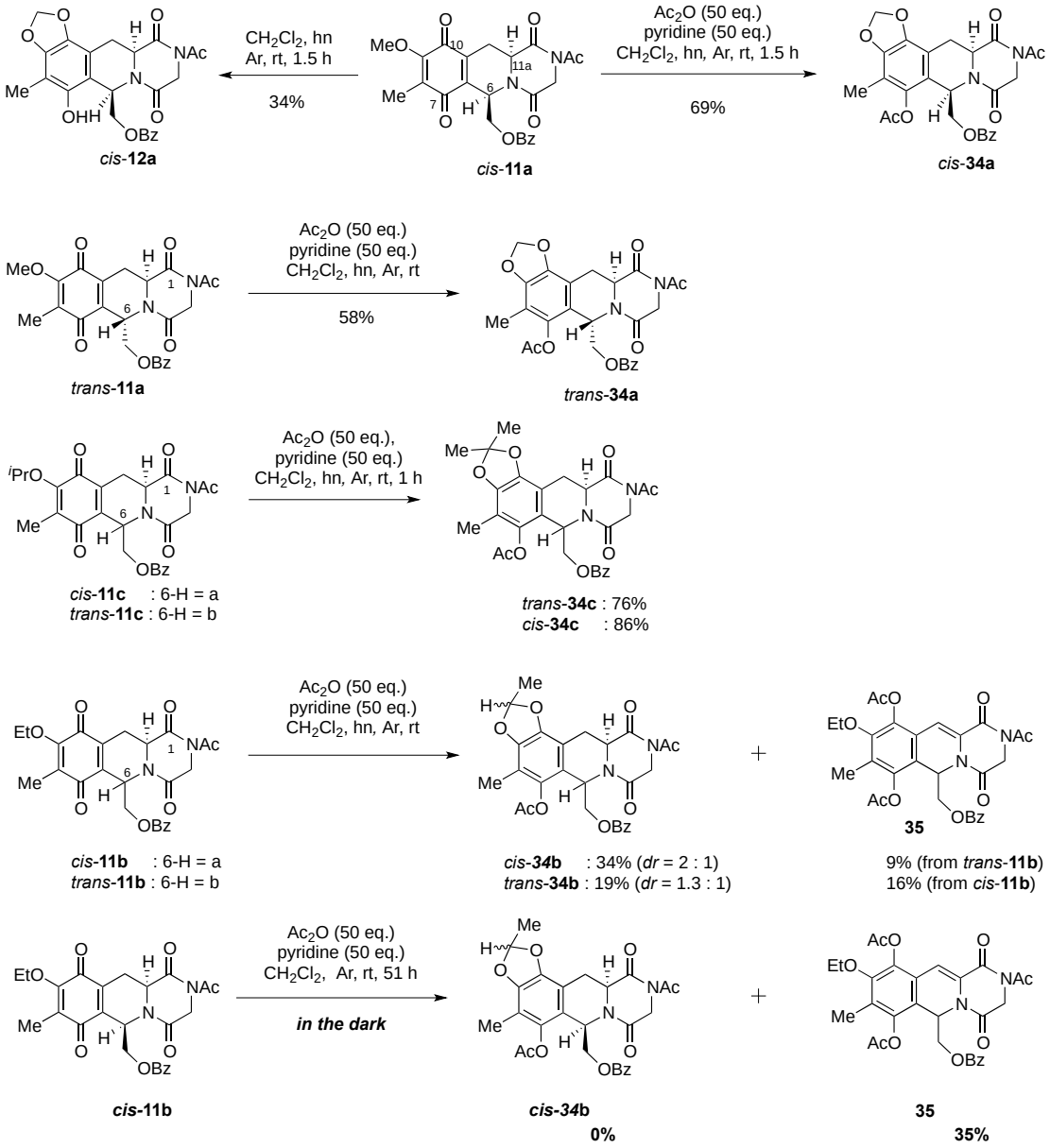
Figure 3. X-Ray structure of compound *cis*-**32**

The oxidation of *cis*-**32** and *trans*-**32** with salcomine 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 tricyclized 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.[17] 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.[18]

In summary, we succeeded in the synthesis of 1,3-dioxoles from *cis*-**11a** by using the photo-induced ring closing reaction. By adding an acetylating 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. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C (ppm, *J* in Hz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.

3-(Benzyloxy)-2-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-4-methylbenzaldehyde (13): TBSCl (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_2O (370 mL) at 0 °C. The solution was extracted with Et_2O (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 (*n*-hexane−EtOAc = 30 : 1) to give **13** (9.89 g, 83%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O$\underline{CH_2}$Ph), 3.82 (3H, s, 5-OCH_3), 2.07 (3H, s, 4-CH_3), 1.02 (9H, s, TBS), 0.15 (6H, s, TBS); ^{13}C-NMR (100 MHz, $CDCl_3$) 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-O$\underline{CH_2}$Ph), 55.7 (q, 5-OCH_3), 25.9 (q, TBS), 18.5 (s, TBS), 10.30 (q, 4-CH_3), −4.4 (q, TBS); IR (KBr): 2959, 2930, 1678, 1391 cm^{-1}; EIMS *m/z* (%): 386 (M^+, 0.1), 330 (24), 329 (100), 301 (10), 238 (8), 210 (5), 91 (8); HREIMS: calcd for $C_{22}H_{30}O_4Si$ 386.1913; found 386.1910.

(*Z*)-1-Acetyl-3-{3-[benzyloxy]-2-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-4-methylbenzylidene}-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-diacetylpiperazine-2,5-dione **14** (4.73 g, 24.0 mmol, 1.2 eq.) in CH_2Cl_2 (50 mL) at 0 °C over 2 min, and the mixture was refluxed for 5 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (200 mL) and extracted with CH_2Cl_2 (3 × 150 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 (*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. ^{1}H-NMR (400 MHz, $CDCl_3$) 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'-O$\underline{CH_2}$-Ph), 4.48 (2H, s, 6-H), 3.79 (3H, s, 5'-OCH_3), 2.65 (3H, s, 1-$COCH_3$), 2.09 (3H, s, 4'-CH_3), 0.94 (9H, s, TBS), 0.06 (6H, s, TBS); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.5 (s, 1-$\underline{C}OCH_3$), 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'-O$\underline{CH_2}$-Ph), 55.8 (q, 5'-OCH_3), 46.2 (t, C-6), 27.2 (q, 1-CO$\underline{C}H_3$) 25.9 (q, TBS), 18.3 (s, TBS), 9.8 (q, 4'-CH_3), −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 $C_{28}H_{36}O_6N_2Si$ 524.2343; found 524.2338.

1-Acetyl-3-{2-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-5-methoxy-4-methylbenzyl}piperazine-2,5-dione (8) and 1-Acetyl-3-{3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-5-methoxy-4-methylbenzyl}piperazine-2,5-dione (16): A solution of **15** (100 mg, 280 μmol) in ^{i}PrOH (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 ^{i}PrOH and $CHCl_3$. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 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. ^{1}H-NMR (400 MHz, $CDCl_3$) (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'-OCH_3), 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-$COCH_3$), 2.05 (3H, s, 4'-CH_3), 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'-OCH_3), 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-$COCH_3$), 2.10 (3H, s, 4'-CH_3), 1.05 (9H, s, TBS), 0.23 (3H, s, TBS), 0.21 (3H, s, TBS); ^{13}C-NMR (100

MHz, $CDCl_3$) (major, **16**) δ: 171.7 (s, 1-$\underline{C}OCH_3$), 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'-OCH_3), 45.7 (t, C-6), 32.7 (t, C-3a), 27.2 (q, 1-CO$\underline{C}H_3$), 25.9 (q, TBS), 18.5 (s, TBS), 10.6 (q, 4'-CH_3), −3.9 (q, TBS), −3.9 (q, TBS). (minor, **8**) δ: 171.7 (s, 1-$\underline{C}OCH_3$), 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'-OCH_3), 45.8 (t, C-6), 33.6 (t, C-3a), 27.2 (q, 1-$COCH_3$), 25.9 (q, TBS), 18.5 (s, TBS), 8.6 (q, 4'-CH_3), −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 $C_{21}H_{32}O_6N_2Si$ 436.2030; found 436.2028.

Methyl 3-(benzyloxy)-5-hydroxy-4-methylbenzoate (19)[12]: 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 diluted with 10% aqueous $NaHCO_3$ (200 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 DMF (300 mL) was added K_2CO_3 (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 CH_2Cl_2 (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 SiO_2 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): ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 9.51 (2H, s, 3-OH and 5-OH), 6.92 (2H, s, 2-H and 6-H), 3.76 (3H, s, 1-CO_2CH_3), 1.97 (3H, s, 4-CH_3).

Methyl 3-(benzyloxy)-5-hydroxy-4-methylbenzoate (19): ^{1}H-NMR (400 MHz, DMSO-d_6) 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-O$\underline{CH_2}$-Ph), 3.80 (3H, s, 1-CO_2CH_3), 2.07 (3H, s, 4-CH_3).

Methyl 3,5-bis(benzyloxy)-4-methylbenzoate (20): ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.31-7.50 (10H, m, Bn-H), 7.29 (2H, s, 2-H and 6-H), 5.17 (4H, s, 3-O$\underline{CH_2}$-Ph and 5-O$\underline{CH_2}$-Ph), 3.82 (3H, s, 1-CO_2CH_3), 2.15 (3H, s, 4-CH_3).

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 $CHCl_3$. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 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 K_2CO_3 (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 $CHCl_3$. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (*n*-hexane−EtOAc = 4 : 1) to give **21** (978 mg, 93%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O$\underline{CH_2}$-Ph), 3.91 (3H, s, 1-CO_2CH_3), 3.88 (3H, s, 5-OCH_3), 2.20 (3H, s, 4-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.2 (s, 1-$\underline{C}O_2CH_3$), 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-O$\underline{C}H_2$-Ph), 55.8 (q, 5-OCH_3), 52.1 (q, 1-$CO_2\underline{C}H_3$), 8.9 (q, 4-CH_3); 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 $C_{17}H_{18}O_4$ 286.1205; found 286.1208.

[3-(Benzyloxy)-5-methoxy-4-methylphenyl]methanol (22): A 1.0 M solution of $LiAlH_4$ 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 sttiring 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 $CHCl_3$ (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. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O$\underline{CH_2}$-Ph), 4.62 (2H, s, 1-$\underline{CH_2}$OH), 3.83 (3H, s, 5-OCH_3), 2.16 (3H, s, 4-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) 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-O$\underline{C}H_2$-Ph), 65.6 (t, 1-CH_2OH), 55.7 (q, 5-OCH_3), 8.3 (q, 4-CH_3); IR ($CHCl_3$): 3011, 1589, 1423, 1134 cm^{-1}; EIMS *m/z* (%): 258 (M^+, 38), 227 (14), 92 (8), 91 (100), 65 (6); HREIMS: calcd for $C_{16}H_{18}O_3$ 258.1256; found 258.1255.

3-(Benzyloxy)-5-methoxy-4-methylbenzaldehyde (23): To a solution of crude **22** in CH_2Cl_2 (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 Et_2O (150 mL). The reaction mixture was stirred at ambient temperature for 30 min. The insoluble materials were removed by filtration and washed Et_2O. 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 ~ 9 : 1) to give **23** (524 mg, 91%, 2 steps from **21**) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O$\underline{C}H_2$-Ph), 3.89 (3H, s, 5-OCH_3), 2.22 (3H, s, 4-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) 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-O$\underline{C}H_2$-Ph), 55.8 (q, 5-OCH_3), 9.2 (q, 4-CH_3); IR (KBr): 2999, 2841, 1684, 1589, 1383, 1310, 1140, 729 cm^{-1}; EIMS *m/z* (%): 256 (M^+, 43), 91 (100), 65 (6); HREIMS: calcd for $C_{16}H_{16}O_3$ 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 CH_2Cl_2 (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 NH_4Cl solution (60 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layer were washed with brine (180 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 ~ 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.
^{1}H-NMR (400 MHz, $CDCl_3$) 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'-O$\underline{C}H_2$-Ph), 4.51 (2H, s, 6-H), 3.84 (3H, s, 5'-OCH_3), 2.65 (3H, s, 1-$COCH_3$), 2.18 (3H, s, 4'-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.5 (s, 1-$\underline{C}OCH_3$), 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'-O$\underline{C}H_2$-Ph), 55.9 (q, 5'-OCH_3), 46.1 (t, C-6), 27.2 (q, 1-CO$\underline{C}H_3$), 8.6 (q, 4'-CH_3); IR (KBr) cm^{-1}: 3304, 2940, 1692, 1213; EIMS *m/z* (%): 394 (M^+, 60), 261 (17), 91 (100); HREIMS: calcd for $C_{22}H_{22}N_2O_5$ 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 $CHCl_3$. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (*n*-hexane−EtOAc = 1 : 1 ~ 1 : 2) to provide **25** (375 mg, 98%) as a colorless powder. ^{1}H-NMR (400 MHz, CD_3OD) 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'-OCH_3), 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-$COCH_3$), 1.99 (3H, s, 4'-CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.4 (s, 1-$\underline{C}OCH_3$), 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'-OCH_3), 46.4 (t, C-6), 41.7 (t, C-3a), 27.2 (q, 1-CO$\underline{C}H_3$), 8.2 (q, 4'-CH_3); 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 $C_{15}H_{18}N_2O_5$ 306.1216; found 306.1217.

(6*R,11a*S**)-2-Acetyl-7-hydroxy-6-[(benzoyloxy)methyl]-9-methoxy-8-methyl-2,3,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-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 CH_2Cl_2 (1.0 mL) and Et_3N (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 CH_2Cl_2 (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 $NaHCO_3$ (40 mL) and extracted with $CHCl_3$ (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 SiO_2 flash column chromatography ($CHCl_3$−EtOH = 99 : 1) to provide benzoate **28** (8.50 mg, 19%) as a pale yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-OCH_3), 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-$COCH_3$), 2.14 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.0 (s, 2-$\underline{C}OCH_3$), 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-OCH_3), 48.6 (d, C-6), 45.6 (t, C-3), 29.8 (t, C-11), 27.0 (q, 2-CO$\underline{C}H_3$), 8.1 (q, 8-CH_3); 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 $C_{24}H_{24}N_2O_7$ 452.1584; found 452.1580.

(6*R,11a*S**)-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-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 O_2 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 SiO_2 flash column chromatography (benzene−EtOAc = 3 : 1 ~ 1 : 1) to provide *p*-quinone ***cis*-11a** (6.80 mg, 78%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-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, $CDCl_3$) δ: 184.5 (s, C-7), 180.4 (s, C-10), 170.9 (s, 2-$\underline{C}OCH_3$), 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, C-4'), 129.5 (d, C-2' and C-6'), 129.3 (s, C-8), 129.1 (s, C-10a), 129.1 (s, C-1'), 128.7 (d, C-3' and C-5'), 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-$CO\underline{C}H_3$), 21.6 (t, C-11), 8.9 (q, 8-CH_3); IR (KBr) cm^{-1}: 2951, 2849, 1705, 1694, 1663, 1368, 1273; FABMS *m/z*: 467 $[M+H]^+$; HRFABMS: calcd for $C_{24}H_{23}N_2O_8$ 467.1458; found 467.1456.

From **17** to **29**[13]

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% $NaHCO_3$ (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 K_2CO_3 (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 Et_2O (3 × 100 mL). The combined organic layer were washed with H_2O (100 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 = 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) δ: 7.31-7.50 (10H, m, Bn-H), 7.29 (2H, s, 2-H and 6-H), 5.17 (4H, s, 3-O$\underline{CH_2}$-Ph and 5-O$\underline{CH_2}$-Ph), 3.82 (3H, s, 1-CO_2CH_3), 2.15 (3H, s, 4-CH_3).

(3,5-Bis(benzyloxy)-4-methylphenyl)methanol: 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_4Cl solution (100 mL) at 0 °C and extracted with 1% MeOH in CH_2Cl_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) δ: 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'-O$\underline{CH_2}$-Ph and 5'-O$\underline{CH_2}$-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_2Cl_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_2O (350 mL). The reaction mixture was stirred at ambient temperature for 30 min. The insoluble materials were removed by filtration and washed Et_2O. 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, $CDCl_3$) δ: 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-O$\underline{CH_2}$-Ph and 5-O$\underline{CH_2}$-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-diacetylpiperazine-2,5-dione **14** (5.51 g, 27.8 mmol, 1.0 eq.) in CH_2Cl_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_4Cl aolution (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, $CDCl_3$) δ: 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'-O$\underline{CH_2}$Ph and 5'-O$\underline{CH_2}$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, $CDCl_3$) δ: 172.5 (s, 1-$\underline{C}OCH_3$), 162.4 (s, C-5), 160.0 (s, C-2), 158.2 (s, C-3' and C-5'), 136.7

(s, Bn), 130.5 (s, C-1'), 128.7 (d, Bn), 128.0 (d, Bn), 127.1 (d, Bn), 125.3 (s, C-3), 120.5 (d, C-3a), 117.9 (s, C-4'), 105.4 (d, C-2' and C-6'), 70.5 (t, 3'-O$\underline{C}H_2$Ph and 5'-O$\underline{C}H_2$Ph), 46.1 (t, C-6), 27.2 (q, 1-CO$\underline{C}H_3$), 8.9 (q, 4'-CH_3); IR (KBr): 3316, 3021, 1694, 1356 cm^{-1}; EIMS *m/z* (%): 470 (M^+, 54), 337 (10), 181 (5), 91 (100); HREIMS: calcd for $C_{28}H_{26}N_2O_5$ 470.1842; found 470.1844.

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 $CHCl_3$. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 19 : 1) to give **31** (1.03 g, 83%) as a colorless solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 6.03 (2H, s, 2'-H and 6'-H), 4.23 (1H, dd, *J* = 4.9, 4.4 Hz, 3-H), 4.02 (1H, d, *J* = 17.8 Hz, 6-H), 2.97 (1H, dd, *J* = 13.8, 4.9 Hz, 3a-H), 2.82 (1H, d, *J* = 17.8 Hz, 6-H), 2.74 (1H, dd, *J* = 13.8, 4.4 Hz, 3a-H), 2.41 (3H, s, 1-$COCH_3$), 1.90 (3H, s, 4'-CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.4 (s, 1-$\underline{C}OCH_3$), 170.3 (s, C-2), 168.6 (s, C-5), 157.7 (s, C-3' and C-5'), 133.9 (s, C-1'), 111.5 (s, C-4'), 109.1 (d, C-2' and C-6'), 59.3 (d, C-3), 46.3 (t, C-6), 41.5 (t, C-3a), 27.2 (q, 1-CO$\underline{C}H_3$), 8.3 (q, 4'-CH_3); IR (KBr): 3375, 2926, 1684, 1223 cm^{-1}; EIMS *m/z* (%): 292 (M^+, 29), 250 (15), 138 (21), 137 (100); HREIMS: calcd for $C_{14}H_{16}N_2O_5$ 292.1059; found 292.1065.

(6*S,11a*S**)-2-Acetyl-7,9-dihydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-dione (*trans*-32) and (6*R**,11a*S**)-2-Acetyl-7,9-dihydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-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 CH_2Cl_2 (2.0 mL) and Et_3N (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 CH_2Cl_2 (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 $NaHCO_3$ (40 mL) and extracted with 10% MeOH in $CHCl_3$ (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 SiO_2 flash column chromatography ($CHCl_3$−MeOH = 49 : 1) to provide benzoate *trans*-**32** (23.5 mg, 32%) as a pale yellow amorphous, and with $CHCl_3$−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**: ^{1}H-NMR (400 MHz, CD_3OD) 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 H_2O), 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-$COCH_3$), 2.06 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.2 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 8.7 (q, 8-CH_3); 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: calcd for $C_{23}H_{22}N_2O_7$ 438.1427; found 438.1428.

cis-**32:** mp 243-245 °C (MeOH); ^{1}H-NMR (400 MHz, CD_3OD) 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, 11a-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-$COCH_3$), 2.07 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ: 172.4 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 8.8 (q, 8-CH_3); 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*: calcd for $C_{23}H_{22}N_2O_7$ 438.1427; found 438.1422; *Anal.* Calcd for $C_{23}H_{22}N_2O_7$: 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** ($C_{23}H_{22}N_2O_7$) 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) Å^3, Z = 8, and D_{calcd} = 1.458 g/cm^3. X-Ray intensities were measured with a Rigaku R-AXIS RAPID diffractometer in the graphite-monochromatic CuKα radiation mode (λ = 1.54187 Å). The final cycle of the full-matrix least-squares refinement was based on 3650 unique reflections (2θ < 136.4^o) 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.

(6*R,11a*S**)-2-Acetyl-9-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-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 O_2 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 SiO_2 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. ^{1}H-NMR (400 MHz, $CDCl_3$) 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, ddd, *J* = 17.9, 11.4, 1.8 Hz, 11-H), 2.59 (3H, s, 2-$COCH_3$), 2.01 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 183.9 (s, C-7), 180.5 (s, C-10), 170.8 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 21.4 (t, C-11), 8.2 (q, 8-CH_3); IR (KBr): 3206, 2924, 1720, 1657, 1323, 1269, 1233, 1196 cm^{-1}; FABMS *m/z*: 453 $[M+H]^+$; HRFABMS: calcd for $C_{23}H_{21}N_2O_8$ 453.1298; found 453.1303.

(6*S,11a*S**)-2-Acetyl-9-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-tetraone (*trans*-33):** A salcomine (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 O_2 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 SiO_2 flash column chromatography (benzene−EtOAc = 2 : 1) to provide benzoate *trans*-**33** (17.5 mg, 44%) as a dark red amorphous, and with CH_2Cl_2-EtOH = 19 : 1 to give *trans*-**32** (14.3 mg, 37% recovery) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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, ddd, *J* = 19.0, 11.1, 2.4 Hz, 11-H), 2.60 (3H, s, 2-$COCH_3$), 2.00 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 184.6 (s, C-7), 181.1 (s, C-10), 171.6 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 26.6 (t, C-11), 8.2 (q, 8-CH_3); 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: calcd for $C_{24}H_{22}N_2O_8$ 452.1220; found 452.1217.

(6*R,11a*S**)-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-tetraone (*cis*-11a):** A $TMSCHN_2$ (0.6 M in Hex., 154 μL, 92.0 μmol, 2.0 eq.) was added to a solution of *cis*-**33** (20.6 mg, 46.0 μmol) in THF : MeOH (9 : 1, 1.0 mL) at 0 °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_2Cl_2 (3 × 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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 184.5 (s, C-7), 180.4 (s, C-10), 170.9 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 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 $C_{24}H_{23}N_2O_8$ 467.1458; found 467.1456.

(6*S,11a*S**)-2-Acetyl-6-[(benzyloxy)methyl]-9-methoxy-8-methyl-11,11a-dihydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 185.2 (s, C-7), 181.0 (s, C-10), 171.7 (s, 2-$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 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 calcd for $C_{24}H_{22}N_2O_8$ 466.1377; found 466.1372.

(6*R,11a*S**)-2-Acetyl-9-ethoxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-tetraone (*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 Ag_2O (38.2 mg, 165 μmol, 5.0 eq.) in CH_2Cl_2 (1.0 mL), and the reaction mixture was stirred at 45 °C for 1 h. The insoluble materials were removed by filtration and washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (CH_2Cl_2−MeOH = 19 : 1) to give *cis*-**11b** (12.2 mg, 77%) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O$\underline{CH_2}$CH$_3$), 4.28 (1H, quin, *J* = 7.0 Hz, 9-O$\underline{CH_2}$CH$_3$), 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-COCH$_3$), 2.01 (3H, s, 8-CH$_3$), 1.37 (3H, t, *J* = 7.0 Hz, 9-OCH$_2\underline{CH_3}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 184.5 (s, C-7), 180.5 (s, C-10), 170.8 (s, 2-$\underline{C}$OCH$_3$), 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-O$\underline{CH_2}$CH$_3$), 64.9 (t, C-12), 54.9 (d, C-11a), 49.4 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-CO$\underline{C}$H$_3$), 21.6 (t, C-11), 15.9 (q, 9-OCH$_2\underline{CH_3}$), 9.0 (q, 8-CH$_3$); IR (KBr): 2978, 2934, 1717, 1690, 1663, 1368, 1269 cm^{-1}; MS *m/z*: 481 $[M+H]^+$; HRFABMS: calcd for $C_{25}H_{25}N_2O_8$ 481.1611; found 481.1619.

(6*S,11a*S**)-2-Acetyl-9-ethoxy-6-[(benzoyloxy)methyl]-8-methyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-tetraone (*trans*-11b):** The same procedure for *cis*-**33** was used. The residue was purified by SiO_2 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, $CDCl_3$) 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-O$\underline{CH_2}$-CH$_3$), 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-COCH$_3$), 2.00 (3H, s, 8-CH$_3$), 1.37 (3H, t, *J* = 7.0 Hz, 9-OCH$_2$-$\underline{CH_3}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 185.3 (s, C-7), 181.1 (s, C-10), 171.7 (s, 2-$\underline{C}$OCH$_3$), 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-O$\underline{C}$H$_2$-CH$_3$), 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-CO<u>C</u>H$_3$), 15.9 (q, 9-OCH$_2$-<u>C</u>H$_3$), 9.0 (q, 8-CH$_3$); IR (KBr): 2976, 2938, 1717, 1684, 1663, 1271, 1227 cm^{-1}; FABMS *m/z*: 481 [M+H]$^+$; HRFABMS: calcd for $C_{25}H_{25}N_2O_8$ 481.1611; found 481.1611.

(6*R,11a*S**)-2-Acetyl-6-[(benzoyloxy)methyl]-9-isopropoxy-8-methyl-11,11a-dihydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-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 Ag_2O (76.0 mg, 330 μmol, 5.0 eq.) in CH_2Cl_2 (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 CH_2Cl_2. The combined filtrates were concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (benzene−EtOAc = 4 : 1) to give *cis*-**11c** (15.0 mg, 46%) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O<u>C</u>H-(CH$_3$)$_2$), 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, ddd, *J* = 17.5, 11.3, 1.8 Hz, 11-H), 2.60 (3H, s, 2-COCH$_3$), 2.01 (3H, s, 8-CH$_3$), 1.31 (6H, t, *J* = 6.1 Hz, 9-OCH-(<u>C</u>H$_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 184.6 (s, C-7), 180.6 (s, C-10), 170.9 (s, 2-<u>C</u>OCH$_3$), 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-O<u>C</u>H-(CH$_3$)$_2$), 64.9 (t, C-12), 54.9 (d, C-11a), 49.5 (d, C-6), 45.5 (t, C-3), 27.0 (q, 2-CO<u>C</u>H$_3$), 22.9 (q, 9-OCH-(<u>C</u>H$_3$)$_2$), 21.7 (t, C-11), 9.3 (q, 8-CH$_3$); IR (KBr): 2976, 2926, 2855, 1717, 1690, 1668, 1369, 1271 cm^{-1}; FABMS *m/z* : 495 [M+H]$^+$; HRFABMS: calcd for $C_{26}H_{27}N_2O_8$ 495.1767; found 495.1766.

(6*S,11a*S**)-2-Acetyl-6-[(benzoyloxy)methyl]-9-isopropoxy-8-methyl-11,11a-dihydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-1,4,7,10(3*H*,6*H*)-tetraone (*trans*-11c):** The same procedure for *cis*-**33** was used. The residue was purified by SiO_2 flash column chromatography (benzene−EtOAc = 5 : 1) to provide benzoate *trans*-**11c** (16.5 mg, 50%) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-O<u>C</u>H-(CH$_3$)$_2$), 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-COCH$_3$), 1.99 (3H, s, 8-CH$_3$), 1.31 (6H, d, *J* = 6.1 Hz, 9-OCH-(<u>C</u>H$_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 185.3 (s, C-7), 181.3 (s, C-10), 171.7 (s, 2-<u>C</u>OCH$_3$), 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

(s, Bz), 128.7 (d, Bz), 76.5 (d, 9-O<u>C</u>H-(CH_3)$_2$), 64.3 (t, C-12), 53.6 (d, C-11a), 48.4 (d, C-6), 45.6 (t, C-3), 27.2 (q, 2-CO<u>C</u>H$_3$), 27.1 (t, C-11), 22.9 (q, 9-OCH-(<u>C</u>H$_3$)$_2$), 9.0 (q, 8-CH$_3$); IR (KBr): 2978, 2938, 1717, 1682, 1663, 1269, 1225, 1209 cm^{-1}; FABMS *m/z* : 495 $[M+H]^+$; HRFABMS: calcd for $C_{26}H_{27}N_2O_8$ 495.1767; found 495.1772.

(6*R,11a*S**)-2-Acetyl-7-hydroxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6*H*-[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 CH_2Cl_2 (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 SiO_2 flash chromatography (CH_2Cl_2−10% NH_4OH contained MeOH = 19 : 1) to provide compound *cis*-**12a** (2.40 mg, 34%) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-COCH$_3$), 2.15 (3H, s, 8-CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.3 (s, 2-<u>C</u>OCH$_3$), 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-CO<u>C</u>H$_3$), 23.0 (t, C-11), 9.1 (q, 8-CH$_3$); IR ($CHCl_3$): 3385, 2928, 2359, 1717, 1273 cm^{-1}; EIMS *m/z* (%): 466 (M^+, 7), 344 (5), 332 (17), 331, (100), 329 (6), 317 (5), 289 (19), 204 (21), 105 (13); HREIMS: calcd for $C_{24}H_{22}N_2O_8$ 466.1376; found 466.1371.

(6*R,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6*H*-[15,17]-dioxolo[4,5-*f*]pyrazino[1,2-*b*]isoquinoline-8,11-dione (*cis*-34a):** An Ac_2O (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 CH_2Cl_2 (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 SiO_2 flash chromatography (CH_2Cl_2−MeOH = 19 : 1) to provide compound *cis*-**34a** (5.10 mg, 69%) as a pale yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-$COCH_3$), 2.44 (3H, s, 7-$OCOCH_3$), 2.03 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.8 (s, 2-$\underline{C}OCH_3$), 169.6 (s, 7-$O\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 22.5 (t, C-11), 20.6 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); IR ($CHCl_3$): 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 $C_{26}H_{24}N_2O_9$ 508.1482; found 508.1481.

(6*S,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8-methyl-2,3,11,11a-tetrahydro-6*H*-[15,17]-dioxolo[4,5-*f*]pyrazino[1,2-*b*]isoquinoline-8,11-dione (*trans*-34a):** Ac_2O (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 CH_2Cl_2 (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 SiO_2 flash chromatography (CH_2Cl_2−EtOAc = 9 : 1) to provide compound *trans*-**34a** (8.80 mg, 58%) as a colorless amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-$COCH_3$), 2.47 (3H, s, 7-$OCOCH_3$), 2.02 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5 (s, 2-$\underline{C}OCH_3$), 169.4 (s, 7-$O\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 24.7 (t, C-11), 20.7 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); IR (KBr): 3414, 2955, 2926, 2855, 1757, 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 $C_{26}H_{24}N_2O_9$ 508.1481; found 508.1483.

(6*R,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16-dimethyl-2,3,11,11a-tetrahydro-6*H*-[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 SiO_2 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) δ: 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, 11-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) δ: 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) δ: 170.9 (s, 2-$\underline{C}OCH_3$), 169.6 (s, 7-O$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 22.5 (t, C-11), 20.9 (q, 16-CH_3), 20.6 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3). (minor) δ: 170.9 (s, 2-$\underline{C}OCH_3$), 169.6 (s, 7-O$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 22.5 (t, C-11), 20.8 (q, 16-CH_3), 20.6 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); IR (KBr): 2955, 2924, 2853, 1722, 1707, 1689, 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 $C_{27}H_{26}N_2O_9$ 522.1638; found 522.1641.

35: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 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-O$\underline{CH_2}$-CH_3), 3.96 (1H, quin, *J* = 7.0 Hz, 9-O$\underline{CH_2}$-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-OCH_2-$\underline{CH_3}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.7 (s, 2-$\underline{C}OCH_3$), 168.9 (s, 7-O$\underline{C}OCH_3$ or 10-O$\underline{C}OCH_3$), 168.3 (s, 7-O$\underline{C}OCH_3$ or 10-O$\underline{C}OCH_3$), 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-O$\underline{CH_2}$-CH_3), 63.3 (t, C-12), 47.8 (d, C-6), 45.2 (t, C-3), 26.9 (q, 2-CO$\underline{C}H_3$), 20.6 (q, 7-OCO$\underline{C}H_3$ or 10-OCO$\underline{C}H_3$), 20.5 (q, 7-OCO$\underline{C}H_3$ or 10-OCO$\underline{C}H_3$), 15.7 (q, 9-OCH_2-$\underline{C}H_3$), 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 $C_{29}H_{28}N_2O_{10}$ 564.1744; found 564.1748.

2-Acetyl-6-[(benzoyloxy)methyl]-9-ethoxy-8-methyl-1,4-dioxo-1,3,4,6-tetrahydro-2*H*-pyrazino-[1,2-*b*]isoquinoline-7,10-diyl diacetate (35): Ac_2O (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.

(6*S,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16-dimethyl-2,3,11,11a-tetrahydro-6*H*-[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-$\underline{C}OCH_3$), 169.5 (s, 7-O$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 24.5 (t, C-11), 20.9 (q, 16-CH_3), 20.7 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3). (minor) δ: 171.5 (s,2-$\underline{C}OCH_3$), 169.5 (s, 7-O$\underline{C}OCH_3$), 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), 112.2 (s, C-8), 110.9 (s, C-10a), 110.7 (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-CO$\underline{C}H_3$), 24.5 (t, C-11), 20.8 (q, 16-CH_3), 20.7 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); IR (KBr): 2957, 2924, 2855, 1721, 1705, 1676, 1273,

1198 cm^{-1}; EIMS *m/z* (%): 522 (M^+, 3), 480 (11), 388 (6), 387(28), 358 (20), 346 (18), 345 (100), 316 (8), 304 (6), 303 (35), 218 (17), 105 (15), 77 (5); HREIMS: calcd for $C_{27}H_{26}N_2O_9$ 522.1638; found 522.1638.

(6*R,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16,16-trimethyl-2,3,11,11a-tetrahydro-6*H*-[15,17]dioxolo[4,5-*f*]pyrazino[1,2-*b*]isoquinoline-8,11-dione (*cis*-34c):** The same procedure for *cis*-**11a** was used (1 h). The residue was purified by SiO_2 flash column chromatography (benzene−EtOAc = 5 : 1 ~ 4 : 1) to provide a *cis*-**34c** (10.2 mg, 86%) as a pale red amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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), 4.14 (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-$COCH_3$), 2.43 (3H, s, 7-$OCOCH_3$), 1.99 (3H, s, 8-CH_3), 1.72 (3H, s, 16-CH_3), 1.69 (3H, s, 16-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.9 (s, 2-$\underline{C}OCH_3$), 169.7 (s, 7-O$\underline{C}OCH_3$), 168.4 (s, C-1), 166.5 (s, C-14), 165.9 (s, C-4), 146.2 (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-CO$\underline{C}H_3$), 26.1 (q, 16-CH_3), 26.1 (q, 16-CH_3), 22.5 (t, C-11), 20.6 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); 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 $C_{28}H_{28}N_2O_9$ 536.1795; found 536.1791.

(6*S,11a*S**)-2-Acetyl-7-acetoxy-6-[(benzoyloxy)methyl]-8,16,16-trimethyl-2,3,11,11a-tetrahydro-6*H*-[15,17]dioxolo[4,5-*f*]pyrazino[1,2-*b*]isoquinoline-8,11-dione (*trans*-34c):** The same procedure for *trans*-**11a** was used (1 h). The residue was purified by SiO_2 flash column chromatography (benzene−EtOAc = 6 : 1) to provide a *trans*-**34c** (13.5 mg, 76%) as a yellow amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) 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-$COCH_3$), 2.46 (3H, s, 7-$OCOCH_3$), 1.98 (3H, s, 8-CH_3) 1.70 (3H, s, 16-CH_3), 1.69 (3H, s, 16-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.6 (s, 2-$\underline{C}OCH_3$), 169.4 (s, 7-O$\underline{C}OCH_3$), 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-CO$\underline{C}H_3$), 26.1 (q, 16-CH_3), 26.1 (q, 16-CH_3), 25.2 (t, C-11), 20.7 (q, 7-OCO$\underline{C}H_3$), 9.6 (q, 8-CH_3); 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 $C_{28}H_{28}N_2O_9$ 536.1795; found 536.1796.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid (No. 18K06561) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. We would like to thank Professor Kazuhiko Takatori of Meiji Pharmaceutical University for the X-ray crystallographic analysis of *cis*-**32a**.

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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.
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