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SYNTHESIS OF TETRAHYDROISOQUINOLINE ANTITUMOR NATURAL PRODUCTS: CONSTRUCTION OF TRICYCLIC LACTAMS THROUGH PICTET-SPENGLER-TYPE CYCLIZATION OF *N*-METHYL-3-ARYLMETHYLPIPERAZINE-2,5-DIONE WITH ETHYL DIETHOXYACETATE

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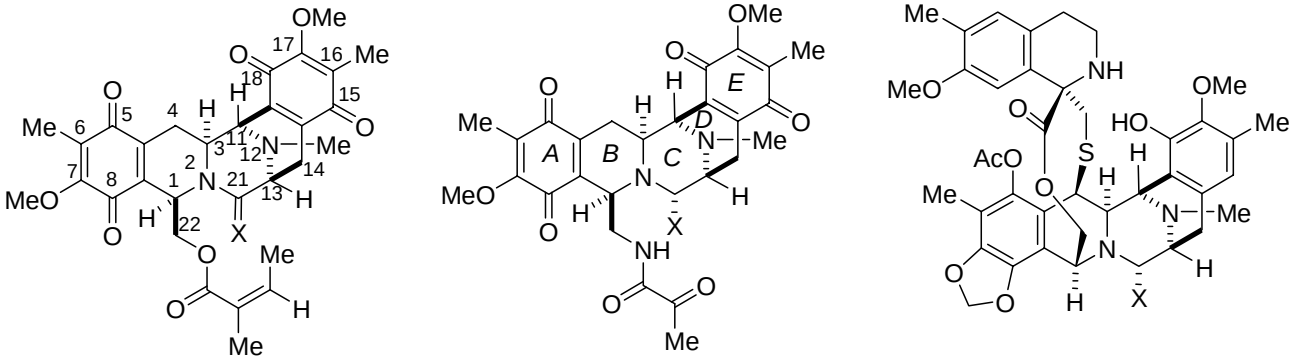
Abstract – 6-Hydroxymethyl-7,8,10-trimethoxy-2,6-dimethyl-3,6,11,11a-tetrahydro-2H-pyrazino[1,2-b]isoquinoline-1,4-dione (**10**) was prepared stereoselectively by Pictet-Spengler-type cyclization of the *O,N*-acetal of 3-arylmethylpiperazine-2,5-dione (**8**) in high yield. This procedure provides an efficient route for the total synthesis of renieramycin G and cribrostatin 4.

This paper is dedicated to Professor Ryoji Noyori (2001 Nobel Laureate in Chemistry) on the occasion of his 70th birthday.

INTRODUCTION

The tetrahydroisoquinoline family of natural products, including renieramycins, saframycins, and ecteinascidins, has elicited much excitement both for their novel structures and meager availability in nature, and for their unique mechanisms of action (Figure 1).[1] Although the detailed molecular mechanism of action remains unclear, it has been speculated that the hydroxyl or cyano substituent at C21 position is essential, suggesting that the elimination of the functional group at this position leads to the formation of a potent, electrophilic iminium ion species that has been implicated in the formation of covalent bonds with DNA.[2] Previous studies have ignited in the structures of renieramycin G (**4**)[3] and cribrostatin 4 (**5**),[4] because both natural products maintained cytotoxicity despite lack of the hemiaminal

or aminonitrile function at C21 (Figure 2). In 2005, Magnus and Matthews[5a] and Williams and co-workers[5b] independently accomplished the first total synthesis of (-)-renieramycin G (**4**). The first total synthesis of cribrostatin 4 (**5**) was achieved by Danishefsky and co-workers also in 2005,[6a] and two years later, Vincent and Williams[6b] and Chen and Zhu[6c] completed two total syntheses. However, structure-activity relationship (SAR) studies remain relatively few, because most studies have focused on the total synthesis.



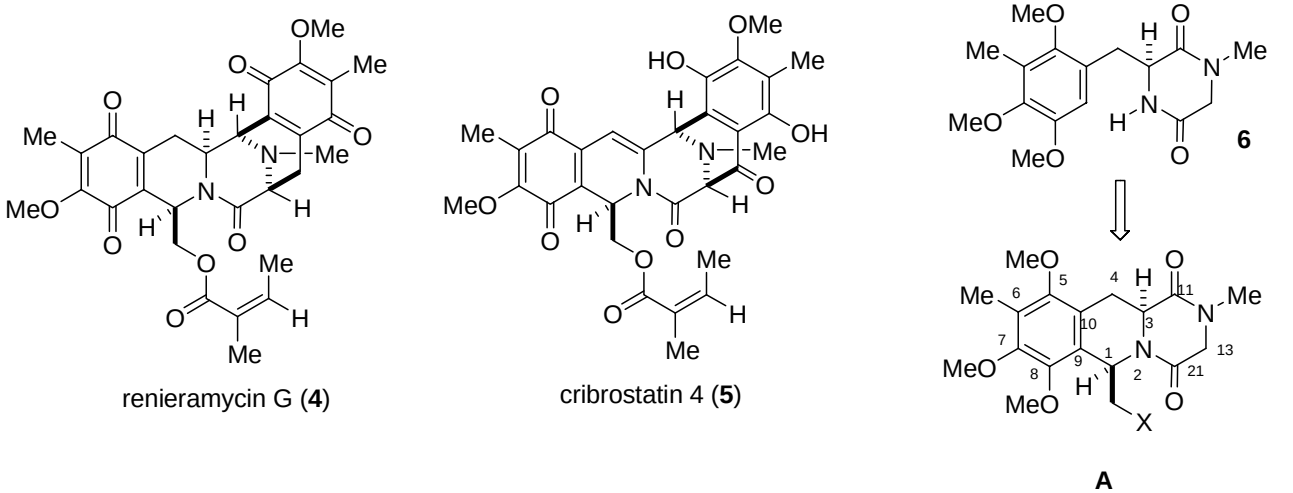
renieramycins
E (**1a**): X = OH
M (**1b**): X = CN

saframycins
S (**2a**): X = OH
A (**2b**): X = CN

ecteinascidins
743 (**3a**): X = OH
770 (**3b**): X = CN

Figure 1. Structures of tetrahydroisoquinoline antitumor natural products

We are very interested in the efficient synthesis of 3,6,11,11a-tetrahydro-2*H*-pyrazino-[*1,2-b*]isoquinoline-1,4-diones (**A**)[7] for the preparation of various derivatives, along with the total synthesis of renieramycin G (**4**). In this paper, we report recent progress in the construction of the ABC ring core from 3-arylpiperazine-2,5-dione derivative (**6**).[8]



renieramycin G (**4**)

cribrostatin 4 (**5**)

6

A

Figure 2. Structures of renieramycin G and cribrostatin 4 along with our target (**A**).

RESULTS AND DISCUSSION

Except for a few examples, it was generally difficult to construct the tetrahydroisoquinoline core with the Pictet-Spengler cyclization of non-basic nitrogen of the secondary amide that could not react with aldehyde to produce an iminium ion species. Thus, all successful total syntheses of **4** and **5** employed the same strategy that included coupling of the tetrahydroisoquinoline core (AB ring core) with amino acid derivatives to afford tertiary amide (Figure 3).[5,6]

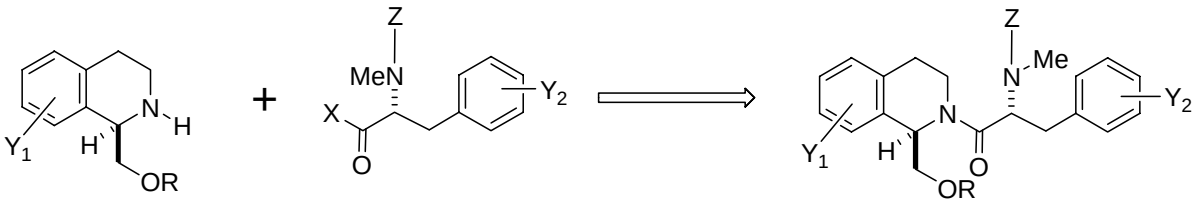


Figure 3. Strategy for the total synthesis of renieramycin G and cribrostatin 4

Treatment of compound **6** with paraformaldehyde in acetic acid and trifluoroacetic acid (TFA) (1:4 v/v) under reflux for 1 h gave **7a** in 85% yield according to the procedure of Ong et al. (Table 1, entry 1).[9a,b] The reaction of **6** with acetaldehyde under similar conditions for 6 h afforded **7b** in 54% yield as a single isomer. The *trans* stereochemical assignment between C1 and C3 protons was based on nuclear Overhauser enhancement (NOE) between the C-1 methyl protons (δ 1.47) and the proton at C3 (δ 4.35). The structure of compound **7b** was subsequently confirmed by single-crystal X-ray analysis (Figure 4). The stereochemical course of this reaction is rationalized to proceed through (*E*)-iminium isomer. Thus, this cyclization would proceed from the less hindered α-face.

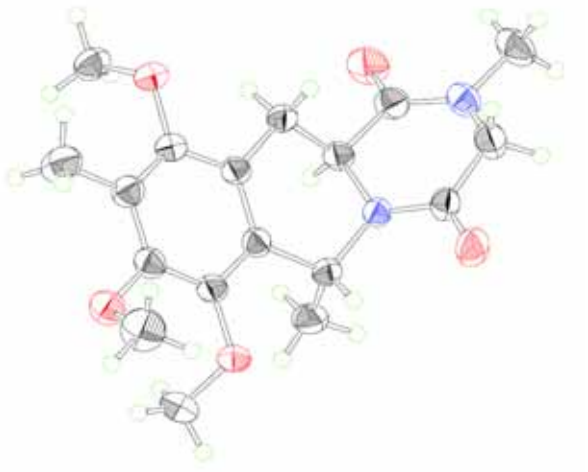
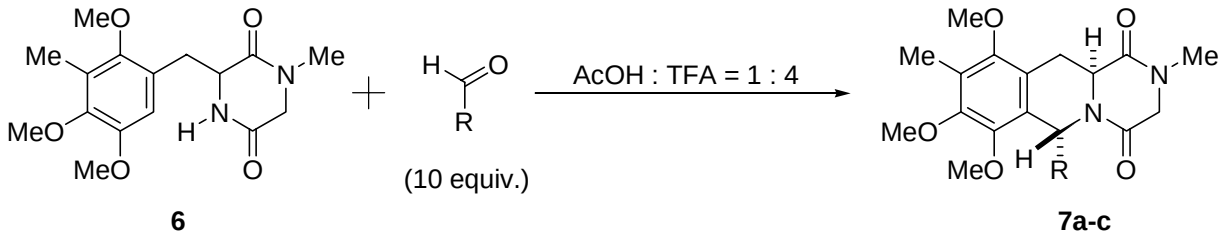


Figure 4. X-Ray structure of compound **7b**

The next step of the investigation was to establish a method for the preparation of a tricyclic compound having a hydroxymethyl or an aminomethyl functionality at C1. The transformation of **6** with ethyl glyoxylate was carried out under similar conditions for 4 h, but only a trace amount of product **7c** (2%) was obtained and 82% of the starting material was recovered. Numerous efforts to improve the yield of product **7c** under several conditions were also unsuccessful (Table 1, entries 3 and 4).[10,11]

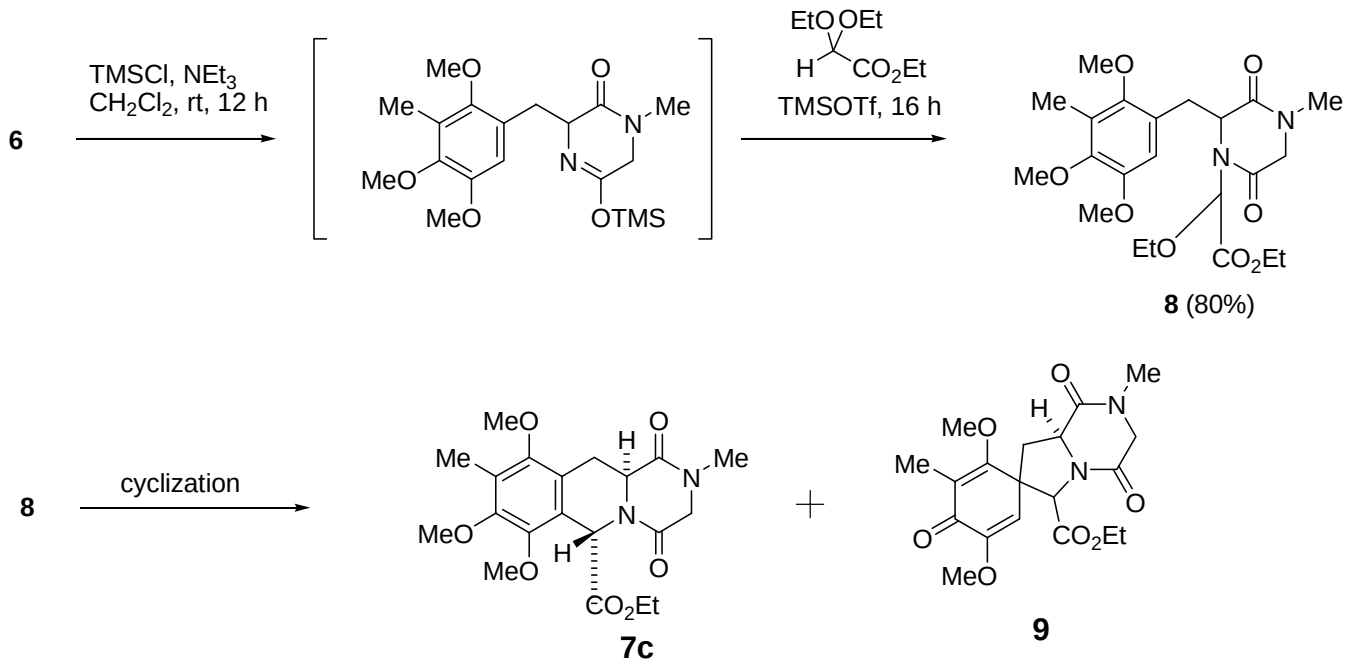


6 **7a-c**

Entry	Aldehyde	Time (h)	Temp (^{o}C)	Product (%)		Recovery of **6** (%)
1	$(CH_2O)n$	1	75	**7a** (R = H)	85	0
2	MeCHO	6	75	**7b** (R = Me)	54	0
3	$CHOCO_2Et$	4	75	**7c** (R = CO_2Et)	2	82
4	$CHOCO_2Et$	48	75	**7c** (R = CO_2Et)	6	0
5	$CHOCO_2Et$	120	100	**7c** (R = CO_2Et)	8	0

Table 1

This problem was solved with the procedure of Avendaño and co-workers.[12] Treatment of **6** with ethyl 2-chloro-2-ethoxy acetate in the presence of sodium hydride in DMF at 0^{o}C for 2.5 h afforded *N*-alkyl compound **8** (71%) as an inseparable mixture of diastereomers (3:2) along with recovered **6** (12%). It is well known that trimethylsilyl triflate catalyzes effectively the aldol-type *N*-alkylation of lactam through *O*-trimethylsilyllactims. Thus, the reaction of **6** with trimethylsilyl chloride in the presence of triethylamine in dichloromethane gave the *O*-trimethylsilyllactim intermediate. Subsequent treatment with ethyl diethoxyacetate in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded **8** as an inseparable mixture of diastereoisomers (3:2) in 80% yield (Scheme 1). Treatment of **8** in TFA at 70^{o}C for 5 h afforded desired product **7c** (24%); however, the main product was spiro compound **9**[13] that was obtained in 32% yield as a single isomer, and restored **6** in 35% yield. After extensive investigation of the reaction conditions, the following procedure was found to be optimum in terms of product yield and reproducibility of the reaction. Treatment of **8** with 1.2 equiv. of *p*-toluenesulfonic acid in $ClCH_2CH_2Cl$ under reflux for 36 h gave **7c** in 93% yield (Table 2). Furthermore, the conversion of **6** into **7c** in a one-pot procedure was performed by acid-catalyzed cyclization *via* **8** with TMSOTf in 93% yield.



Scheme 1

Run	Acid (equiv.)	Condition	Yield of **7c** (%)	**9** (%)	Restored **6** (%)
1	TFA	70°C, 5 h, neat	24	32	35
2	$BF_3 \cdot OEt_2$ (1.5)	reflux, 22 h, CH_2Cl_2	64	0	0
3	*p*-TsOH (1.2)	reflux, 36 h, $ClCH_2CH_2Cl$	93	0	0

Table 2

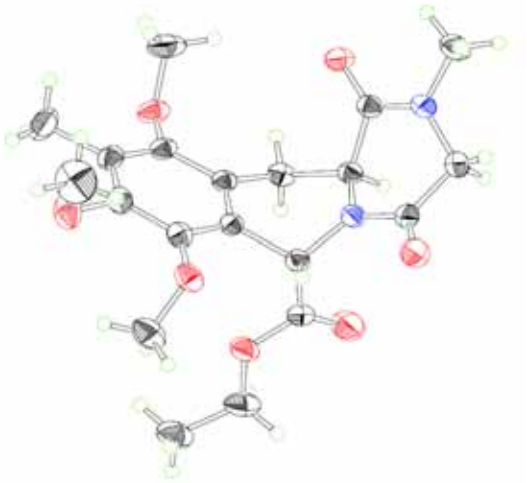
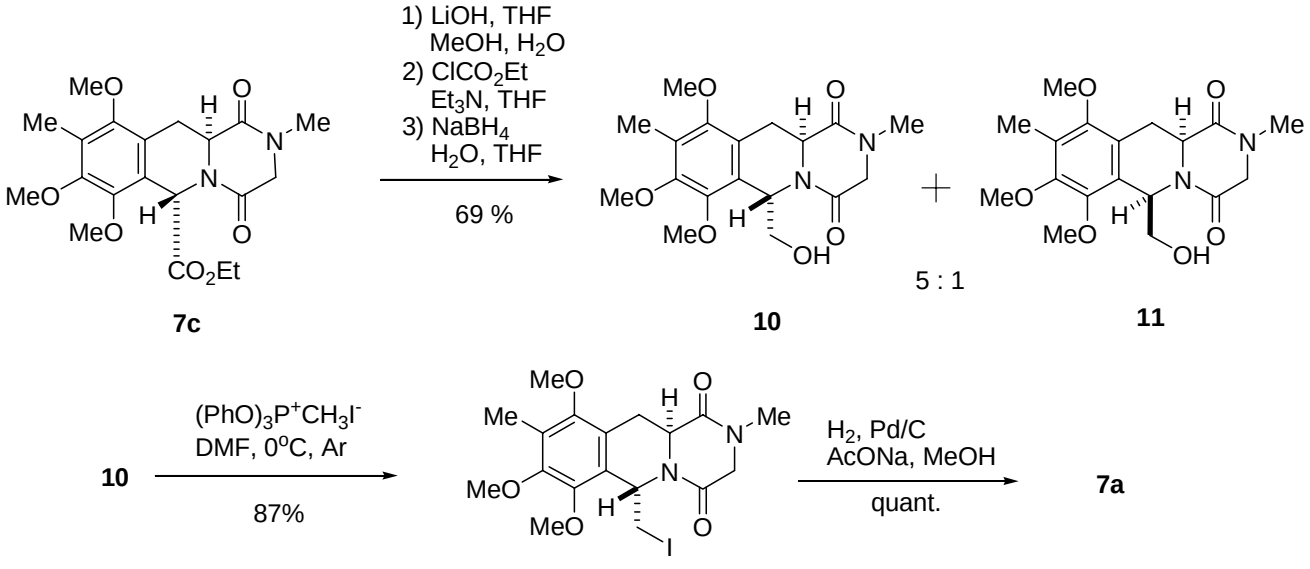


Figure 5. X-Ray structure of compound **7c**

X-Ray crystallographic analysis of **7c** proved that the stereochemistry was *trans* between C1 and C3 protons (Figure 5). Thus, this stereoselective cyclization would also proceed from the less hindered α-face to the (*E*)-iminium isomer.

In the next step of the investigation, we were able to establish that the chemoselective reduction of the ester carbonyl of **7c** gave hydroxymethyl compound **10** (Scheme 2). Reduction of **7c** with DIBAL in toluene at -78°C was unsuccessful, and only polar polymeric material was produced.[14] In contrast, reduction of **7c** with $LiBH_4$ in the presence of an equimolar amount of MeOH in THF at 50°C promoted the ester reduction;[11a,15] however, reduction of one of the lactam carbonyls also proceeded to generate an inseparable mixture of products. Accordingly, the sequence of reactions in Scheme 2 was studied. Hydrolysis of the ester group of **7c** with 10% aqueous NaOH in EtOH afforded desired carboxylic acids in 65% yield as a 1:1 diastereomeric mixture. Alternatively, hydrolysis with LiOH in THF, MeOH, and H_2O afforded a 5:1 mixture of diastereomers. According to Kakinuma and co-workers,[16] the major isomer was treated with ethyl chloroformate and triethylamine in THF to give a mixed anhydride, which was reduced with sodium borohydride in aqueous THF solution to furnish alcohols **10** and **11** in 52% and 17% overall yields, respectively. The stereochemistry of both compounds could not be determined because no information could be acquired from NOE experiments. Thus, major product **10** was transformed into the corresponding 1-methyl compound. Alcohol **10** was treated with $(PhO)_3P^+CH_3I^-$ in DMF to give alkyl iodide **12** in 87% yield.[17] This compound was then hydrogenated with Pd/C to afford **7a** in quantitative yield. This product was identical with the authentic one as described above. Thus, we conclude that the relative stereochemistry of major alcohol **7b** might be *trans* between C1 proton and C3a proton.



Scheme 2

In summary, 6-substituted 7,8,10-trimethoxy-2,6-dimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino-[1,2-*b*]-isoquinoline-1,4-diones were prepared stereoselectively by Pictet-Spengler-type cyclization of *O*,*N*-acetal of 3-arylmethylpiperazine-2,5-dione in high yields. Efforts to investigate the isomerization from *trans* to *cis* and its application to the total synthesis of renieramycins are under way.

EXPERIMENTAL

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Shimadzu IRAffinity-1 Fourier Transform Infrared Spectrometer. ^{1}H-NMR spectra were recorded at 300 MHz on a JEOL-AL-300 spectrometer and at 400 MHz on a JEOL-AL-400 spectrometer. ^{13}C-NMR was recorded at 100 MHz (multiplicity determined from distortionless enhancement by polarization transfer (DEPT) spectra). NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to $(CH_3)_4Si$ as the internal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.

7,8,10-Trimethoxy-2,9-dimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**7a,** entry 1) Paraformaldehyde (120.0 mg, 1.00 mmol) was added to a solution of compound **6** (131.4 mg, 0.40 mmol) in acetic acid and TFA (1:4, v/v, 3 mL), and this mixture was heated at 75°C for 1 h. The reaction mixture was poured into water (80 mL) and extracted with $CHCl_3$ (80 mL x 3). The combined extracts were washed with 5% aqueous $NaHCO_3$ (80 mL), dried, and concentrated *in vacuo* and the residue was subjected to chromatography on silica gel with CH_2Cl-MeOH (80:1) to give **7a**, which was recrystallized from EtOAc-*n*-hexane to give **7a** (113.1 mg, 85%) as colorless prisms.

mp 145-146°C. IRν_{max} (KBr) 2932, 1656 cm^{-1}. δ_H 2.19 (3H, s, Ar-CH_3), 2.72 (1H, dd, *J* = 16.4, 12.1 Hz, C11-H), 3.04 (3H, s, *N*-CH_3), 3.57 (1H, dd, *J* = 16.4, 3.7 Hz, C11-H), 3.67 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.06 (2H, s, C3-H x 2), 4.12 (1H, dd, *J* = 12.1, 3.7 Hz, C11a-H), 4.12 (1H, d, *J* = 17.4 Hz, C6-H), 5.41 (1H, d, *J* = 17.4 Hz, C6-H). δ_C 9.3 (q, Ar-CH_3), 28.6 (t, C11), 33.4 (q, *N*-CH_3), 40.2 (t, C6), 51.4 (t, C3), 55.4 (d, C11a), 60.1 (q, Ar-OCH_3 x 2), 60.2 (q, Ar-OCH_3), 121.5 (s), 123.2 (s), 124.1 (s), 145.8 (s), 150.2 (s), 152.2 (s), 161.8 (s), 165.1 (s). EI-MS *m/z* (%): 335 (M^+ + 1, 19), 334 (M^+, 100), 319 (20), 193 (14). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.99; H, 6.77; N, 8.35.

(6*S**, 11a*R**)-7,8,10-Trimethoxy-2,6,9-trimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**7b**, entry 2) Acetaldehyde (230.0 mg, 4.00 mmol) was added to a solution of compound **6** (131.4 mg, 0.40 mmol) in acetic acid and TFA (1:4, v/v, 3 mL), and this mixture was heated at 75°C for 6 h. The reaction mixture was poured into water (40 mL) and extracted with $CHCl_3$ (40 mL x 3). The

combined extracts were washed with 5% aqueous $NaHCO_3$ (40 mL), dried, and concentrated *in vacuo* and the residue was subjected to chromatography on silica gel with CH_2Cl_2-MeOH (100:1) to give **7b**, which was recrystallized from EtOAc-*n*-hexane to give **7b** (111.4 mg, 80%) as yellow prisms.

mp 140-141°C. IRν_{max} (KBr) 2932, 1666 cm^{-1}. δ_H 1.47 (3H, d, *J* = 7.0 Hz, C12-H), 2.18 (3H, s, Ar-CH_3), 2.71 (1H, dd, *J* = 16.8, 12.5 Hz, C11-H), 3.04 (3H, s, *N*-CH_3), 3.49 (1H, dd, *J* = 16.8, 4.1 Hz, C11-H), 3.67 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.99 (1H, d, *J* = 17.5 Hz, C3-H), 4.07 (1H, d, *J* = 17.5 Hz, C3-H), 4.35 (1H, dd, *J* = 12.5, 4.1 Hz, C11a-H), 5.85 (1H, q, *J* = 7.0 Hz, C6-H). δ_C 9.27 (q, Ar-CH_3), 19.7 (q, C12), 28.7 (t, C11), 33.4 (q, *N*-CH_3), 44.9 (d, C6), 51.1 (t, C3), 51.4 (d, C11a), 55.4 (q ×2, Ar-OCH_3), 60.2 (q, Ar-OCH_3), 120.7 (s), 124.3 (s), 128.5 (s), 145.9 (s), 150.4 (s), 152.1 (s), 160.8 (s), 165.5 (s). EI-MS *m/z* (%): 349 (M^+ + 1, 11), 348 (M^+, 52), 334 (19), 333 (100), 305 (12), 234 (10). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.07; H, 7.12; N, 8.04.

X-Ray crystallographic analysis of **7b** All measurements were performed on a Rigaku AFC7S diffractometer with graphite-monochromated CuKα radiation (λ=1.54178 Å). Crystal data: Colorless prismatic crystal, monoclinic, $C_{18}H_{24}N_2O_5$ (M_r=348.40), space group C2/c with *a*=15.562(2) Å, *b*=13.914(2) Å, *c*=32.244(4) Å, β=91.730(10)°, *V*=7197(1) $Å^3$, *Z*=16, and D_{calcd}=1.286 g/cm^3. The structure was solved by direct methods (SHELXS-97[18]) and expanded using Fourier techniques (DIRDIF94[19]). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions but were not refined. The final cycle of full-matrix least-squares refinement was based on 6486 unique reflections (2θ<135.98°) and 451 variable parameters and converged with unweighted and weighted agreement factors of *R*=0.096, R_w=0.197, and R_1=0.047 for $I > 2.0\sigma(I)$ data. CCDC-No. 687,437 contains supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

(6*S**, 11a*R**)-Ethyl 7,8,10-trimethoxy-2,9-dimethyl-3,6,11,11a-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione-6-carboxylate (**7b**, entry 4) Ethyl glyoxylate (204.0 mg, 2.00 mmol) was added to a solution of compound **6** (64.4 mg, 0.20 mmol) in acetic acid and TFA (1:4, v/v, 2 mL), and this mixture was heated at 75°C for 48 h. The reaction mixture was poured into water (10 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with 5% aqueous $NaHCO_3$ (20 mL), dried, and concentrated *in vacuo* and the residue was subjected to chromatography on silica gel with CH_2Cl_2-MeOH (120:1) to give **7c** (5.0 mg, 6%) as a pale yellow syrup.

Ethyl 2-ethoxy-2-{4-methyl-3,6-dioxo-2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]piperazin-1-yl}-acetate (**8**) Trimethylsilyl chloride (26.0 μL, 0.20 mmol) was added to a solution of **6** (32.8 mg, 0.10 mmol) with triethylamine (28.4 μL, 0.20 mmol) in CH_2Cl_2 (1 mL) and this reaction mixture was stirred at rt for 2 h. A solution of ethyl diethoxyacetate (36.4 μL, 0.20 mmol) in dry CH_2Cl_2 (1 mL),

followed by TMSOTf (184.4 μL, 1.02 mmol), was added dropwise respectively over 5 min, and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with 10% aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (20 mL x 3). The combined extracts were washed with water (20 mL), dried, and concentrated *in vacuo*, and the residue was subjected to chromatography on silica gel with $CHCl_3$ to give **8** (37.0 mg, 80%) as an inseparable mixture of diastereoisomers (1:0.7).

LRMS (FAB^+): 453 (M^+ + H). HRMS (FAB^+): calcd for $C_{22}H_{33}N_2O_8$: 453.2159 (M^+ +H); found: 453.2237 (M^+ + H).

Major diastereoisomer δ_H 1.25 (3H, t, *J* = 7.1 Hz, C2-$OCH_2\underline{CH_3}$), 1.38 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2\underline{CH_3}$), 2.19 (3H, s, Ar-Me), 2.60 (1H, d, *J* = 17.3 Hz, C5-H), 2.76 (3H, s, *N*-CH_3), 2.81 (1H, dd, *J* = 13.9, 5.9 Hz, C2-$\underline{CH_2}$), 3.34 (1H, dd, *J* = 13.9, 3.6 Hz, C2-$\underline{CH_2}$), 3.39 (1H, d, *J* = 17.3 Hz, C5-H), 3.50 (2H, q, *J* = 7.1 Hz, C2-$O\underline{CH_2}CH_3$), 3.62, 3.79, 3.80 (each 3H, s, Ar-OCH_3), 4.2-4.3 (2H, m, -$CO_2\underline{CH_2}CH_3$), 4.58 (1H, dd, *J* = 5.9, 3.6 Hz, C2-H), 5.89 (1H, s, C2-H), 6.76 (1H, s, C6-H).

Minor diastereoisomer δ_H 1.28 (3H, t, *J* = 7.1 Hz, C2-$OCH_2\underline{CH_3}$), 1.36 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2\underline{CH_3}$), 2.19 (3H, s, Ar-Me), 2.73 (1H, d, *J* = 17.3 Hz, C5-H), around 2.76 (1H, C2-$\underline{CH_2}$, overlapped), 2.77 (3H, s, *N*-CH_3), 3.15 (1H, dd, *J* = 13.7, 5.9 Hz, C2-$\underline{CH_2}$), 3.43 (1H, d, *J* = 17.3 Hz, C5-H), 3.7-3.9 (2H, m, C2-$O\underline{CH_2}CH_3$), 3.63, 3.79, 3.80 (each 3H, s, Ar-OCH_3), 4.2-4.3 (1H, m, C2-H), 4.3-4.4 (2H, m, -$CO_2\underline{CH_2}CH_3$), 5.95 (1H, s, C2-H), 6.70 (1H, s, C6-H)

Cyclization of compound **8** using acid (General procedure)

BF_3OEt_2 or *p*-toluenesulfonic acid was added to a solution of **8** in TFA, CH_2Cl_2 or $ClCH_2CH_2Cl$ and the reaction mixture was heated under reflux. The reaction mixture was diluted with water, made alkaline with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (20 mL x 3). The combined extracts were washed with brine (20 mL), dried, and concentrated *in vacuo* and the residue was subjected to column chromatography using gradient elution with EtOAc-*n*-hexane to give **7c** and **9**.

Spiro compound (**9**)**:** pale yellow amorphous powder. IR ν_{max} (KBr) 3468, 2929, 1749, 1666 cm^{-1}. δ_H 1.09 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2\underline{CH_3}$), 2.01 (3H, s, C3-CH_3), 2.31 (1H, dd, *J* = 12.6, 6.4 Hz, C3'-H), 2.74 (1H, dd, *J* = 12.6, 11.2 Hz, C3'-H), 3.06 (3H, s, *N*-CH_3), 3.88 (1H, d, *J* = 16.7 Hz, C6'-H), 3.63, 3.99 (each 3H, s, Ar-OCH_3), 4.01-4.17 (2H, m, -$CO_2\underline{CH_2}CH_3$), 4.36 (1H, d, *J* = 16.7 Hz, C6'-H), 4.70 (1H, dd, *J* = 11.2, 6.4 Hz, C3a'-H), 4.82 (1H, s, C1'-H), 5.53 (1H, s, C6-H). δ_C 10.5 (q, C3-$\underline{CH_3}$), 14.1 (q, -$CO_2CH_2\underline{CH_3}$), 33.8 (q, *N*-Me), 39.9 (t, C-3'), 49.8 (s, C-1), 53.3 (t, C-6'), 55.2 (q, C5-$O\underline{CH_3}$), 58.5 (d, C-3a'), 61.7 (t, -$CO_2\underline{CH_2}CH_3$), 62.2 (q, C2-$O\underline{CH_3}$), 65.2 (d, C-1'), 108.3 (d, C-6), 121.1 (s, C-3), 150.3 (s, C-5), 162.2 (s, C-7'), 165.8 (s, C-4'), 167.2 (s, $\underline{C}O_2Et$), 168.1 (s, C-2), 182.0 (s, C-4). LRMS (FAB^+): 393 (M^+ + H). HRMS (FAB^+): calcd for $C_{19}H_{24}N_2O_7$: 393.1584 (M^+ + H); found: 393.1660 (M^+ + H).

Preparation of **7c** (One-pot procedure)

Trimethylsilyl chloride (26.9 μL, 0.21 mmol) was added to a solution of **6** (33.9 mg, 0.11 mmol) in

$ClCH_2CH_2Cl$ (1 mL) and triethylamine (29.3 μL, 0.21 mmol), and the reaction mixture was stirred at rt for 2 h. A solution of ethyl diethoxyacetate (37.7 μL, 0.21 mmol) in $ClCH_2CH_2Cl$ (1 mL), followed by TMSOTf (190.5 μL, 1.05 mmol), was added dropwise respectively over 5 min, and the reaction mixture was stirred at rt for 16 h. TLC monitoring at this stage revealed no trace of starting material **6**. Then, the reaction mixture was warmed to 100°C and heated under reflux for 4 h. The reaction mixture was diluted with water, made alkaline with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated *in vacuo* and the residue was subjected to column chromatography with EtOAc-*n*-hexane (9:1) to give **7c** (39.8 mg, 93%) as a solid, recrystallization of which from EtOAc afforded **7c** as colorless prisms.

mp 168-170°C. IRν_{max} (KBr) 2941, 1741, 1674 cm^{-1}. δ_H 1.27 (3H, t, *J* = 7.2 Hz, -O-$CH_2\underline{CH_3}$), 2.20 (3H, s, Ar-CH_3), 3.02 (3H, s, *N*-CH_3), 3.03 (1H, dd, *J* = 16.8, 9.8 Hz, C11-H), 3.32 (1H, dd, *J* = 16.8, 5.1 Hz, C11-H), 3.71, 3.78, 3.87 (each 3H, s, Ar-OCH_3), 4.02 (1H, d, *J* = 17.5 Hz, C3-H), 4.14 (1H, d, *J* = 17.5 Hz, C3-H), 4.21 (2H, q, *J* = 7.2 Hz, -O-$\underline{CH_2}CH_3$), 4.47 (1H, dd, *J* = 9.8, 5.1 Hz, C11a-H), 6.45 (1H, s, C6-H). δ_C 9.4 (q, Ar-CH_3), 14.1 (q, -$CO_2CH_2\underline{CH_3}$), 26.7 (t, C11), 33.6 (q, *N*-CH_3), 51.3 (d, C6), 51.6 (t, C3), 53.4 (d, C11a), 59.9, 60.0, 60.2 (each q, Ar-OCH_3), 62.0 (t, -$CO_2\underline{CH_2}CH_3$), 121.6 (s), 122.2 (s), 125.8 (s), 146.5 (s), 150.1 (s), 152.1 (s), 162.5 (s), 165.5 (s), 169.1 (s). EI-MS *m/z* (%): 406 (M^+, 13), 334 (19), 333 (100). Anal. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 58.98; H, 6.39; N, 6.87.

X-Ray crystallographic analysis of **7c** All measurements were performed on a Rigaku AFC7S diffractometer with graphite-monochromated CuKα radiation (λ=1.54178 Å). Crystal data: Colorless prismatic crystal, monoclinic, $C_{20}H_{26}N_2O_7$ (M_r=406.43), space group $P2_1/c$ with *a*=11.647(5) Å, *b*=9.299(7) Å, *c*=19.16(2) Å, β=102.06(4)°, *V*=2029(2) $Å^3$, *Z*=4, and D_{calcd}=1.330 g/cm^3. The structure was solved by direct methods (SHELXS-97[18]) and expanded using Fourier techniques (DIRDIF94[19]). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions but were not refined. The final cycle of full-matrix least-squares refinement was based on 3691 unique reflections (2θ<136.11°) and 262 variable parameters and converged with unweighted and weighted agreement factors of *R*=0.071, R_w=0.179, and R_1=0.043 for $I > 2.0\sigma(I)$ data. CCDC-No. 687,438 contains supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

(6*S**, 11a*R**)-6-Hydroxymethyl-7,8,10-trimethoxy-2,9-dimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione (**10**) A solution of lithium hydroxide monohydrate (45.0 mg, 1.07 mmol) in water (1 mL) was added to a solution of **7c** (363 mg, 0.89 mmol) in THF (3 mL) and MeOH (1 mL), and the reaction mixture was stirred at rt for 22 h. The reaction mixture was poured into aqueous 1 N HCl (10 mL) at 0°C and extracted with $CHCl_3$ (100 mL x 3). The combined extracts were washed with brine (100

mL), dried, and concentrated *in vacuo* to give a carboxylic acid (310.7 mg), which was used in the next step without further purification.

Ethyl chloroformate (102.5 μL, 1.07 mmol) was added to a stirred solution of the above residue and triethylamine (143.2 μL, 1.03 mmol) in THF (16 mL), and the reaction mixture was stirred at -5°C for 2 h. After filtration of the mixture, the filter cake was carefully washed with THF. A suspension of sodium borohydride (75.4 mg, 2.00 mmol) in water (0.5 mL) was added to the combined filtrates at 0°C, and the mixture was stirred at the same temperature for 2 h. Saturated aqueous ammonium chloride solution was added to the reaction mixture and the mixture was extracted with $CHCl_3$ (200 mL x 3). The combined extracts were washed with brine (200 mL), dried, and concentrated *in vacuo* to give a pale yellow solid (300.9 mg). Chromatography on silica gel column with EtOAc afforded **11** (56.7 mg, 17%) as a pale yellow syrup. Further elution with $CHCl_3$-MeOH (20:1) gave **10** (168.8 mg, 52%) as a colorless solid, recrystallization of which from Et_2O gave pure **10** as colorless prisms.

10: mp 214-216°C. IRν_{max} (KBr) 3383, 2937, 1662, 1643 cm^{-1}. δ_H 2.19 (3H, s, Ar-CH_3), 2.75 (1H, dd, *J* = 16.9, 12.1 Hz, C11-H), 3.04 (3H, s, *N*-CH_3), 3.51 (1H, dd, *J* = 16.9, 4.5 Hz, C11-H), 3.67 (3H, s, Ar-OCH_3), 3.77 (1H, dd, *J* = 11.2, 8.8 Hz, C12-H), 3.79 (3H, s, Ar-OCH_3), 3.90 (3H, s, Ar-OCH_3), 4.08 (1H, dd, *J* = 11.2, 3.9 Hz, C12-H), 4.09 (2H, s, C3-H), 4.51 (1H, dd, *J* = 12.1, 4.5 Hz, C11a-H), 5.93 (1H, dd, *J* = 8.8, 3.9 Hz, C6-H). δ_C 9.5 (q, Ar-CH_3), 28.5 (t, C11), 33.5 (q, *N*-CH_3), 51.3 (d, C11a), 51.5 (t, C3), 52.0 (d, C6), 60.1 (q×2, Ar-OCH_3), 60.5 (q, Ar-OCH_3), 63.8 (t, C12), 121.8 (s, C6a), 122.8 (s, C10a), 125.1 (s, C9), 145.9 (s, C7), 150.1 (s, C8), 152.2 (s, C10), 162.5 (s, C4), 165.2 (s, C1). EI-MS *m/z* (%): 364 (M^+, 4), 333 (100), 305 (14), 234 (13), 204 (10). HRMS (EI^+): calcd for $C_{18}H_{24}N_2O_6$: 364.1634 (M^+), found: 364.1636 $(M)^+$. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.16; H, 6.74; N, 7.67.

(6*R**, 11a*R**)-6-Hydroxymethyl-7,8,10-trimethoxy-2,9-dimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione (**11**): IRν_{max} (KBr) 3433, 2941, 1664 cm^{-1}. δ_H 2.21 (3H, s, Ar-CH_3), 2.78 (1H, dd, *J* = 15.7, 12.8 Hz, C11-H), 3.07 (3H, s, *N*-CH_3), 3.5-3.8 (2H, m, C12-H), 3.71 (3H, s, Ar-OCH_3), 3.77 (1H, dd, *J* = 15.7, 3.9 Hz, C11-H), 3.80 (3H, s, Ar-OCH_3), 3.88 (1H, dd, *J* = 12.8, 3.9 Hz, C11a-H), 3.90 (3H, s, Ar-OCH_3), 3.97 (1H, d, *J* = 16.7 Hz, C3-H), 4.14 (1H, dd, *J* = 16.7, 1.3 Hz, C3-H), 5.83 (1H, dd, *J* = 6.9, 4.4 Hz, C6-H). δ_C 9.4 (q, Ar-CH_3), 24.1 (t, C11), 33.8 (q, *N*-CH_3), 52.5 (t, C3), 52.8 (d, C6), 55.3 (d, C11a), 60.0 (q, Ar-OCH_3), 60.7 (q, Ar-OCH_3), 61.1 (q, Ar-OCH_3), 67.3 (t, C12), 122.9 (s), 124.1 (s), 125.6 (s), 146.0 (s), 150.4 (s), 151.6 (s), 166.5 (s), 167.4 (s). EI-MS *m/z* (%): 364 (M^+, 3), 347 (17), 333 (100), 305 (14), 234 (14), 204 (11). HRMS (EI^+): calcd for $C_{18}H_{24}N_2O_6$: 364.1634 (M^+), found: 364.1629 $(M)^+$.

(6*S**, 11a*R**)-6-Iodomethyl-7,8,10-trimethoxy-2,9-dimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione (**12**) Methyltriphenoxyphosphonium iodide (69.3 mg, 0.15 mmol) was added to

a solution of **10** (27.9 mg, 0.08 mmol) in dry DMF (1.5 mL) at 0°C, and the reaction mixture was stirred for 2.5 h at 0°C. The reaction mixture was diluted with Et_2O (15 mL) and H_2O (15 mL). The phases were allowed to separate, and the aqueous phase was extracted with Et_2O (15 mL x 3). The combined extracts were washed with brine (15 mL), dried, and concentrated *in vacuo* to give a residue, which was purified by column chromatography with $CHCl_3$ to give **12** (31.7 mg, 87%) as colorless amorphous powder.

IRν_{max} (KBr) 3452, 2933, 1664 cm^{-1}. δ_H 2.18 (3H, s, Ar-CH_3), 2.64 (1H, dd, *J* = 17.1, 12.4 Hz, C11-H), 3.07 (3H, s, *N*-CH_3), 3.30 (1H, t, *J* = 11.3 Hz, C12-H), 3.42 (1H, dd, *J* = 17.1, 4.5 Hz, C11-H), 3.66 (3H, s, Ar-OCH_3), 3.79 (3H, s, Ar-OCH_3), 3.82 (1H, dd, *J* = 11.3, 3.8 Hz, C12-H), 3.92 (3H, s, Ar-OCH_3), 4.06 (1H, dd, *J* = 17.8, 0.7 Hz, C3-H), 4.16 (1H, d, *J* = 17.8 Hz, C3-H), 4.31 (1H, dd, *J* = 12.4, 4.5 Hz, C11a-H), 5.99 (1H, dd, *J* = 11.3, 3.8 Hz, C6-H). δ_C 5.8 (t, C12), 9.6 (q, Ar-CH_3), 28.6 (t, C11), 33.6 (q, *N*-CH_3), 49.0 (d, C11a), 51.1 (d, C6), 51.4 (t, C3), 60.0 (q, Ar-OCH_3), 60.1 (q, Ar-OCH_3), 60.6 (q, Ar-OCH_3), 120.8 (s), 124.9 (s), 125.6 (s), 146.0 (s), 150.2 (s), 152.2 (s), 161.6 (s), 165.20 (s). EI-MS *m/z* (%): 474 (M^+, 26), 347 (78), 333 (100), 305 (15), 234 (10). HRMS (EI^+): calcd for $C_{18}H_{23}IN_2O_5$: 474.0652 (M^+), found: 474.0651 (M^+).

(6*S**, 11a*R**)-7,8,10-Trimethoxy-2,6,9-trimethyl-3,6,11,11a-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (**7b**) A solution of **12** (10.5 mg, 0.022 mmol) in MeOH (1.0 mL) was hydrogenated over 10% Pd/C (2.4 mg) in the presence of sodium acetate (3.0 mg, 0.022 mmol) for 4 h at rt. The catalyst was removed by filtration and washed with MeOH and $CHCl_3$. The combined filtrates were concentrated *in vacuo* and the crude material was purified by column chromatography with MeOH-$CHCl_3$ (1:100) to give **7b** (7.7 mg, 100%) as a colorless solid, whose spectra were identical with those of an authentic sample described above.

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