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CHEMISTRY OF RENIERAMYCINS PART 18. SYNTHESIS OF RENIERAMYCIN M AND SO-CALLED FENNEBRICIN A FROM (+/-)-JORUNNAMYCIN A

Masashi Yokoya,* Kento Monden, Mitsuhiro Sato, Natchanun Sirimangkalakitti, and Naoki Saito*

Graduate School of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan
E-mail: yokoya@my-pharm.ac.jp & naoki@my-pharm.ac.jp

This paper is dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.

Abstract – We report the syntheses of renieramycin M along with so-called fennebricin A from jorunnamycin A, which was prepared from pentacyclic lactam intermediate **4** in our previous total synthesis of renieramycin G, as well as the re-assignment of the NMR data of fennebricin A, which offered very important information for structure elucidation.

INTRODUCTION

Renieramycin marine natural products belong to biologically active 1,2,3,4-tetrahydroisoquinoline alkaloids, and are structurally similar to saframycin A and ecteinascidin 743.[1] This series of natural products show strong antitumor activity. Ecteinascidin 743, in particular, has been approved and marketed in approximately 80 countries worldwide for the treatment of human soft tissue sarcoma, and is undergoing additional clinical trials in other countries.[2] Renieramycin-type natural products are expected to be a candidate for novel anticancer drugs. Many researchers have reported the structures of new renieramycin-type compounds. We isolated renieramycin T (**1t**) and renieramycin Y (**1y**) from blue sponge *Xestospongia* sp. collected in the Philippines in 2012, and elucidated their structures.[3] In addition, 7-demethylrenieramycin O was isolated from the same sponge in 2017 (**Figure 1**).[4]

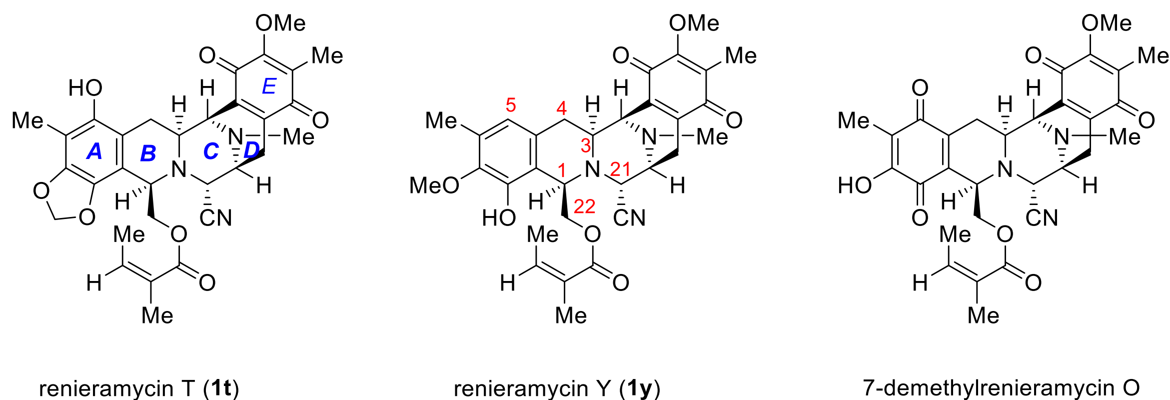


Figure 1. Structures of representative renieramycin marine natural products

In 2014, Guo and coworkers reported the isolation and structure elucidation of fennebricins A (**2a**) and B (**2b**) from the acetone extracts of nudibranch *Jorunna funebris* and blue sponge *Xestospongia* sp. collected in East China Sea.[5] As the yields of these compounds were minute, their biological activities could not be tested. Two years later, fennebricins C (**2c**) and D (**2d**) were reported by the same research group (**Figure 2**).[6]

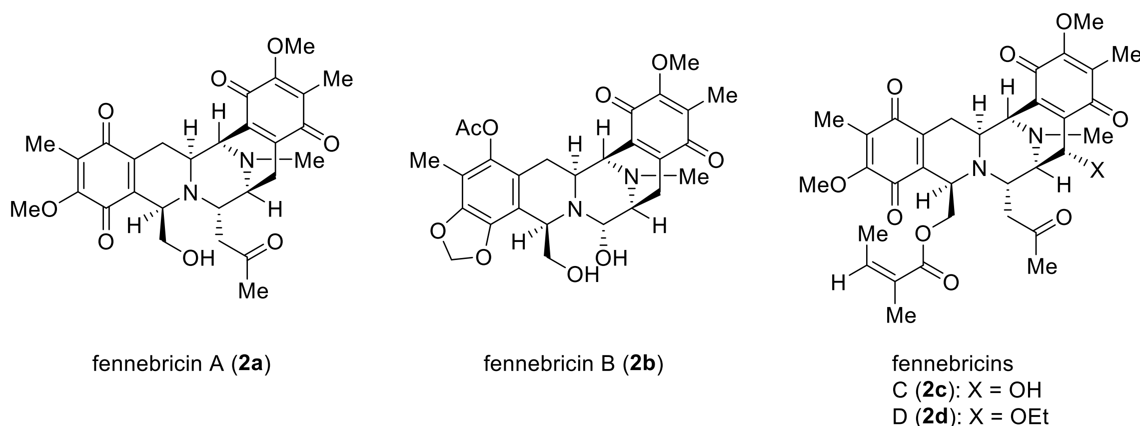
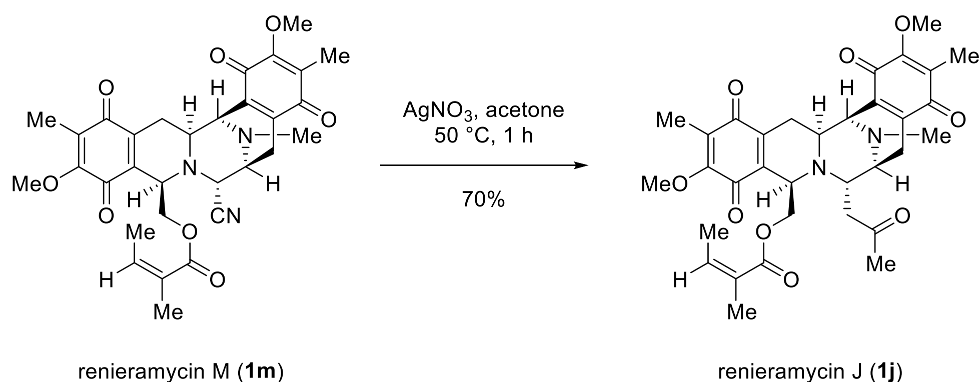


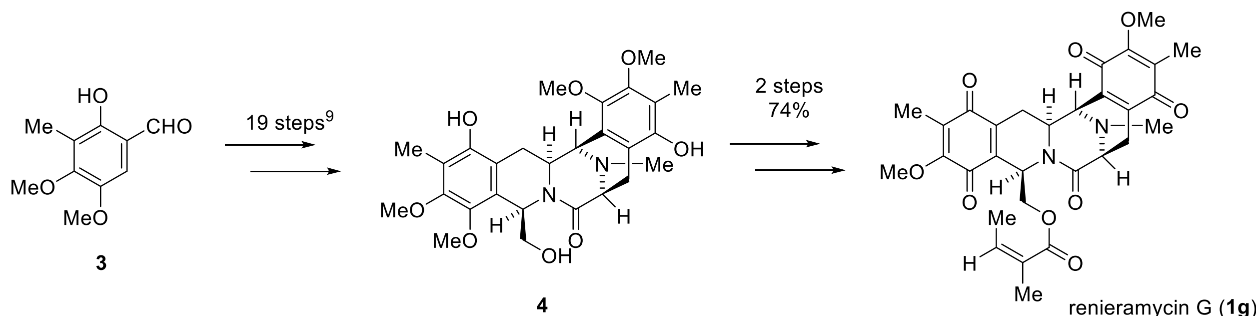
Figure 2. Structures of fennebricins A-D (**2a**-**d**)

Compounds **2a**, **2c**, and **2d** have an acetone residue at C-21, which is assumed to be derived from their corresponding precursors by acid-catalyzed aldol-type condensation during the extraction and isolation steps. On the other hand, in our search for new components in the extract of Thai blue sponge *Xestospongia* sp., we found renieramycin J (**1j**)[7] having an acetone residue at C-21. We pointed out that produced artificially. We reported that a large amount of renieramycin M (**1m**) was obtained by pretreated a pH 7 buffer suspension of blue sponge with KCN, and **1m** was easily converted into **1j** in satisfactory yield by the addition of silver nitrate (**Scheme 1**).[8]



Scheme 1. Conversion of renieramycins M into J

We report here that the treatment of jorunnamycin A (**6**) produces **2a** by replacing the CN group at C-21, in the same manner as the conversion of **1m** into **1j**. In addition, **6** could be synthesized from **4**, an intermediate in our previous total synthesis of renieramycin G (**1g**), as shown in **Scheme 2**.[9] The conversion of **6** into **1m** was also carried out.

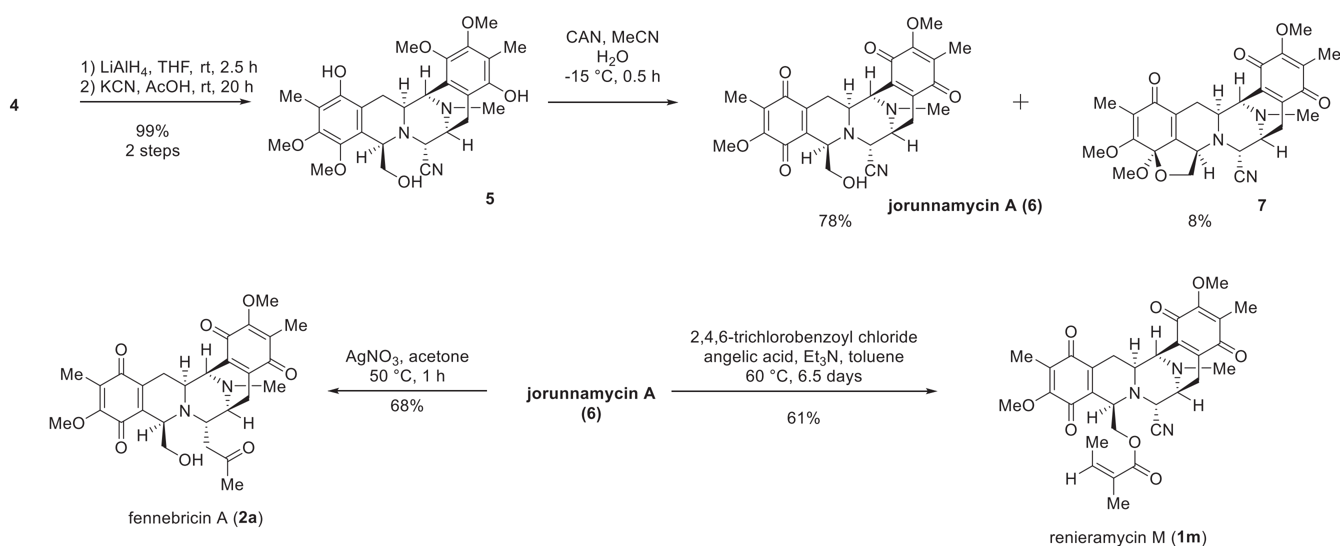


Scheme 2. Our total synthesis of (+/-)-renieramycin G

RESULTS AND DISCUSSION

Our synthesis was started from compound **4**, which was obtained from highly substituted benzaldehyde **3** in 19 steps (**Scheme 3**).[9] Partial reduction of the C-21 lactam carbonyl of **4** by $LiAlH_4$, followed by treatment with aqueous KCN in acetic acid afforded aminonitrile **5** as a single diastereomer in 99% yield. Oxidative demethylation of **5** with ceric ammonium nitrate (CAN) in aqueous acetonitrile gave **6** in 78% yield.[10] The spectral data of synthetic **6** were identical with those of natural one. In the oxidation of **5**, intramolecular cyclization product **7** was also generated in 8% yield. The formation of this type of acetal was also observed under the same conditions as those for the left-half model compound of renieramycins.[11] The primary hydroxy group in **6** was acylated with angelic acid under modified Yamaguchi conditions[12] to give **1m** in 61% yield. Direct comparison of all spectral data as well as TLC

analysis of synthetic **1m** and authentic sample[7] revealed full agreement. On the other hand, treatment of **6** with silver nitrate in acetone at 50 °C gave so-called fennebricin A (**2a**) in 68% yield as a single diastereomer (**Scheme 3**).



Scheme 3

The ^{1}H-NMR spectral data of our synthesized **2a** were similar to those of the natural product (**Table 1**), but proton signal at C-4 position was slightly shifted by approximately 0.08 ppm. In the synthetic product, in addition to geminal coupling, the methylene protons at C-23 position were coupled to the methine proton at C-21 position (8.8 Hz). In contrast, only geminal coupling was observed in the natural product. In the ^{13}C-NMR spectra, chemical shift differences of 1.5 ppm or more were observed particularly at C-4, C-9, and C-16 positions between synthetic and natural product **2a**. The stereochemistry at C-21 position of our synthesized **2a** was confirmed on the basis of the stereochemistry of the acetone residue, because differential NOE correlations were observed between C-23 methylene protons and C-1 and C-3 methine protons (**Figure 3**).

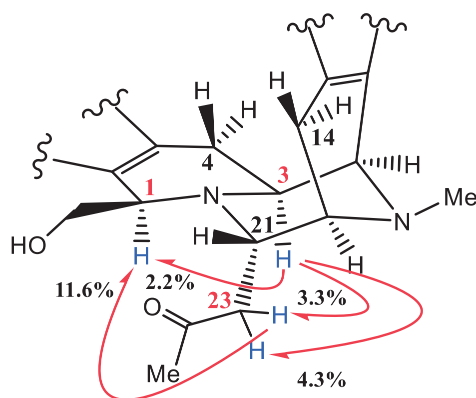


Figure 3. Selected NOE correlations of our synthesized **2a**

On the other hand, the configuration of C-21 acetone residue was estimated from the ROESY correlation between C-14 methylene proton and C-21 methine proton by Guo et al.[6] In our ^{1}H-NMR spectral data, the proton signal at C-21 (δ 3.40 ppm) was observed at a position very close to the proton signal at C-23 (δ 3.48 ppm). Thus, the correlation between C-14 proton and C-21 proton, which is the basis of the authors of the isolation report by Guo et al., might be observed between C-14 proton and C-23 proton as well. In addition, the coupling constant of the methylene hydrogen at C-23 was slightly different between our synthesized **2a** and the natural product (**Figure 4**).

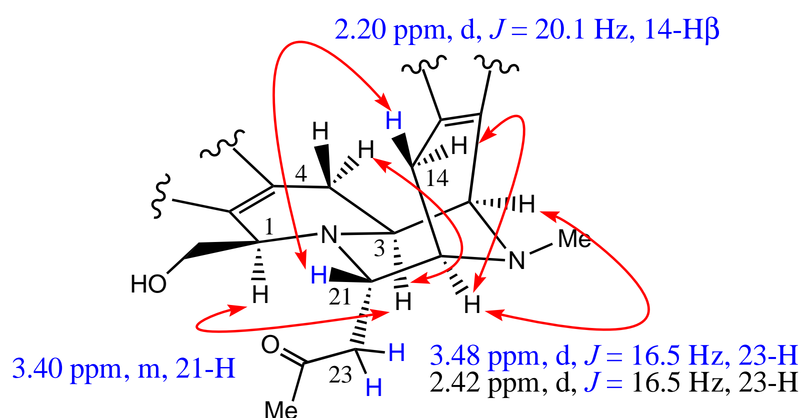


Figure 4. ROESY correlations of natural product **2a**

Table 1. ^{1}H- and ^{13}C-NMR spectral data of natural and synthesized fennebricin A (**2a**) in $CDCl_3$

	Reported natural product		Synthesized product	
Atom No.	δ_C	δ_H (mult., *J* in Hz)	δ_C ($\Delta\delta_C$)	δ_H (mult., *J* in Hz)
1	54.5	3.61, 1H, m	54.9 (0.4)	3.65, 1H, m
3	51.5	3.05, 1H, br d, 11.8	51.8 (0.3)	3.01, 1H, dt, 11.0, 2.7
4	23.7	α 2.83, 1H, dd, 16.7, 2.2 β 1.25, 1H, dd, 16.7, 11.8	25.6 (1.9)	α 2.86, 1H, dd, 17.0, 2.7 β 1.33, 1H, ddd, 17.0, 11.0, 2.0
5	185.6		185.6 (± 0)	
6	128.5		128.9 (0.4)	
7	155.0		155.5 (0.5)	
8	180.8		181.8 (1.0)	
9	135.8		137.5 (1.7)	
10	142.5		141.8 (− 0.7)	
11	54.5	3.97, 1H, overlapped	55.0 (0.5)	3.97, 1H, overlapped
13	55.3	2.92, 1H, m	55.0 (− 0.3)	2.95, 1H, br d, 7.7
14	23.4	α 2.85, 1H, dd, 20.1, 7.3 β 2.20, 1H, d, 20.1	23.3 (− 0.1)	α 2.83, 1H, dd, 21.2, 7.7 β 2.23, 1H, overlapped
15	185.5		186.3 (0.8)	

16	126.8		128.8 (2.0)	
17	155.0		155.6 (0.6)	
18	183.1		182.6 (− 0.5)	
19	135.0		135.8 (0.8)	
20	143.6		143.0 (− 0.6)	
21	58.5	3.40, 1H, m	58.3 (− 0.2)	3.38, 1H, br d, 8.8
22	63.7	α 3.67, 1H, dd, 11.0, 3.5	62.8 (− 0.9)	α 3.67, 1H, dd, 11.0, 3.7
		β 3.35, 1H, dd, 11.0, 3.7		β 3.35, 1H, m
23	38.5	α 2.42, 1H, d, 16.5	39.0 (0.5)	α 2.42, 1H, d, 17.6
		β 3.48, 1H, d, 16.5		β 3.49, 1H, dd, 17.6, 8.8
6-Me	8.5	1.92, 3H, s	8.8 (0.3)	1.93, 3H, s
16-Me	8.5	1.95, 3H, s	8.7 (0.2)	1.94, 3H, s
7-OMe	61.5	3.96, 3H, s	61.0 (− 0.5)	3.96, 3H, s
17-OMe	61.5	3.98, 3H, s	61.0 (− 0.5)	3.99, 3H, s
N-Me	41.5	2.19, 3H, s	41.8 (0.3)	2.20, 3H, s
23-CO<u>Me</u>	30.8	2.18, 3H, s	30.9 (0.1)	2.19, 3H, s
23-<u>C</u>OMe	208.0		207.8 (− 0.2)	

We evaluated our synthesized compounds and natural renieramycin M (**1m**) in terms of their inhibitory activities against two human cancer cell lines by using the CCK-8 assay (**Table 2**). The results revealed that **2a** with an acetone moiety at C-21 displayed 3- to 15-fold lower cytotoxicity than **6** with a cyano group. Compound **4** having no good leaving group was markedly less biologically active than **5**. This information is in agreement with a previous report[8b] that good leaving groups at C-21 of renieramycins were essential for the cytotoxicity. Moreover, bisphenol **5** had 5- to 25-fold lower cytotoxicity than corresponding bisquinone **6**.

Table 2. Cytotoxicities of renieramycin M (**1m**) and related compounds toward human cancer cell lines

compound	IC_{50} ± SD (μM)	
	HCT116	DU145
(−)-**1m** (natural)	0.011 ± 0.003	0.003 ± 0.000
1m (synthetic)	0.033 ± 0.007	0.006 ± 0.001
2a	0.5 ± 0.03	0.7 ± 0.1
4	> 20	> 20
5	0.7 ± 0.1	1.3 ± 0.2
6	0.03 ± 0.01	0.22 ± 0.07
7	1.2 ± 0.1	1.6 ± 0.3

HCT116: human colon carcinoma, DU145: human prostate cancer

In summary, we have succeeded in the total synthesis of renieramycin M and so-called fennebricin A. We showed that the reported structure of fennebricin A, which was determined on the basis of NMR measurement, requires further confirmation.[13] Further investigation to uncover the real structure of fennebricin A is ongoing in our laboratory.

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), respectively. All proton and carbon signals were assigned by extensive NMR data such as COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV.

(6*S**,7*R**,9*R**,14a*S**,15*R**)-4,13-Dihydroxy-9-(hydroxymethyl)-1,2,10,11-tetramethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5*H*-6,15-epiminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile (**5**)
A 1.0 M THF suspension of $LiAlH_4$ (26.8 mL, 26.8 mmol) was added to a stirred solution of **4** (552 mg, 1.07 mmol) in THF (200 mL) at 0 °C over 5 min. The reaction mixture was stirred at 25 °C for 2.5 h, then it was quenched with AcOH (1.24 mL, 21.5 mmol) in THF (5.8 mL). The addition of KCN (0.5 mol/L in H_2O, 17.0 mL, 8.5 mmol) into the above mixture, it was stirring for 20 h at 25 °C. After the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (200 mL), product was extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated in vacuo to give a residue, it was purified by SiO_2 flash chromatography (MeOH－$CHCl_3$ = 3 : 97) to give compound **5** (559 mg, 99%) as a colorless amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.93 (2H, br s, OH), 4.08-4.06 (3H, m, 7, 9, 15-H), 3.82 (3H, s, 10-OCH_3), 3.81 (3H, s, 1-OCH_3), 3.77 (3H, s, 2-OCH_3), 3.76 (3H, s, 11-OCH_3), 3.56 (1H, dd, *J* = 10.7, 4.4 Hz, 17-H), 3.43 (1H, br d, *J* = 7.8 Hz, 6-H), 3.30 (1H, dt, *J* = 12.2, 2.9 Hz, 14a-H), 3.16 (1H, dd, *J* = 10.7, 4.9 Hz, 17-H), 3.04 (1H, dd, *J* = 15.6, 2.9 Hz, 14-Hα), 2.97 (1H, dd, *J* = 18.5, 7.8 Hz, 5-Hα), 2.44 (1H, d, *J* = 18.5 Hz, 5-Hβ), 2.37 (3H, s, NCH_3), 2.13 (3H, s, 3-CH_3), 2.12 (3H, s, 12-CH_3), 1.77 (1H, dd, *J* = 15.6, 12.2 Hz, 14-Hβ); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 149.6 (s, C-11), 149.3 (s, C-2), 146.9 (s, C-4), 146.5 (s, C-13), 144.9 (s, C-1), 143.0 (s, C-10), 125.2 (s, C-9a), 123.1 (s, C-15a), 117.9 (s, CN), 117.5 (s, C-13a), 116.8 (s, C-12), 116.4 (s, C-3), 116.1 (s, C-4a), 66.2 (t, C-17), 61.2 (d, C-7), 60.8 (q, 10-OCH_3), 60.6 (q, 2-OCH_3), 60.5 (q, 1-OCH3), 60.3 (q, 11-OCH_3), 58.3 (d, C-9), 57.0 (d, C-15), 56.8 (d, C-14a), 55.0 (d, C-6), 41.7 (q, NCH_3), 25.4 (t, C-14), 21.6 (t, C-5), 8.9 (q, 12-CH_3), 8.8 (q, 3-CH_3); IR (KBr): 3447, 3421, 2936, 1460, 1070 cm^{-1}; FABMS *m/z*: 526 $[M + H]^+$; HRFABMS: calcd for $C_{28}H_{36}N_3O_7$ 526.2553; found 526.2552.

Jorunnamycin A (**6**)

A solution of CAN (913 mg, 1.66 mmol) in water (10 mL) was added to a solution of **5** (175 mg, 333 μmol) in MeCN (50 mL) at −15 °C, and resulting mixture was stirred at −15 °C for 30 min. After the reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (150 mL), it was extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash chromatography (EtOAc−*n*-Hexane = 3:7 ~ 1:1) to furnish compound **6** (128 mg, 78%) and **7** (13.9 mg, 8.0%) as a yellow amorphous powder.

6 (jorunnamycin A): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.16 (1H, d, *J* = 2.4 Hz, 21-H), 4.08 (1H, br d, *J* = 2.4 Hz, 11-H), 4.03 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 3.89 (1H, m, 1-H), 3.72 (1H, dd, *J* = 11.2, 3.4 Hz, 22-H), 3.48 (1H, br d, *J* = 11.2, 22-H), 3.42 (1H, br d, *J* = 7.8 Hz, 13-H), 3.17 (1H, dt, *J* = 11.2, 2.4 Hz, 3-H), 2.92 (1H, dd, *J* = 17.6, 2.4 Hz, 4-Hα), 2.82 (1H, dd, *J* = 21.2, 7.8 Hz, 14-Hα), 2.31 (3H, s, NCH_3), 2.27 (1H, d, *J* = 21.2 Hz, 14-Hβ), 1.94 (3H, s, Ar-CH_3), 1.94 (3H, s, Ar-CH_3), 1.42 (1H, ddd, *J* = 17.6, 11.2, 2.4 Hz, 4-Hβ); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 186.3 (s, C-15), 185.4 (s, C-5), 182.3 (s, C-18), 181.4 (s, C-8), 155.5 (s, C-7), 155.4 (s, C-17), 141.6 (s, C-20), 141.4 (s, C-10), 136.1 (s, C-9), 135.6 (s, C-19), 128.9 (s, C-6), 128.6 (s, C-16), 116.8 (s, CN), 64.0 (t, C-22), 61.1 (q, OCH_3 × 2), 59.0 (d, C-21), 58.0 (d, C-1), 54.5 (d, C-13), 54.3 (d, C-3), 54.2 (d, C-11), 41.6 (q, NCH_3), 25.4 (t, C-4), 21.5 (t, C-14), 8.8 (q, Ar-CH_3), 8.7 (q, Ar-CH3); IR (KBr): 3510, 2943, 2853, 2359, 1655, 1616, 1373, 1312, 1236, 1152 cm^{-1}; FABMS *m/z*: 494 $[M + H]^+$; HRFABMS: calcd for $C_{26}H_{28}N_3O_7$ 494.1927; found 494.1927.

(2a*R**,6a*S**,7*R**,13*S**,14*R**,15a*R**)-2a,3,9-Trimethoxy-4,10,16-trimethyl-5,8,11-trioxo-1,2a,5,6,6a,7,8,11,12,13,14,15a-dodecahydro-7,13-epiminobenzo[4,5]azocino[1,2-*b*]furo[2,3,4-*ij*]isoquinoline-14-carbonitrile (**7**)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.54 (1H, t, *J* = 7.8 Hz, 1-H), 4.17 (1H, dd, *J* = 3.9, 1.5 Hz, 7-H), 4.08 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.98 (1H, ddd, *J* = 7.8, 5.9, 2.9 Hz, 15a-H), 3.75 (1H, dd, *J* = 7.8, 5.9 Hz, 1-H), 3.66 (1H, d, *J* = 2.4 Hz, 14-H), 3.43 (1H, ddd, *J* = 7.8, 2.4, 1.5 Hz, 13-H), 3.30 (1H, ddd, *J* = 10.7, 4.4, 3.9 Hz, 6a-H), 3.13 (3H, s, 2a-OCH_3), 2.82 (1H, dd, *J* = 21.0, 7.8 Hz, 12-Hα), 2.62 (1H, ddd, *J* = 20.7, 4.4, 2.9 Hz, 6-Hα), 2.29 (3H, s, NCH_3), 2.14 (1H, d, *J* = 21.0 Hz, 12-Hβ), 1.93 (3H, s, Ar-CH_3), 1.75 (3H, s, Ar-CH_3), 1.59-1.49 (1H, m, 6-Hβ); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 186.4 (s, C-5 or C-11), 185.1 (s, C-5 or C-11), 182.6 (s, C-8), 160.2 (s, C-3 or C-9), 155.7 (s, C-3 or C-9), 143.0 (s, C-17), 141.1 (s, C-11a), 136.1 (s, C-7a), 128.4 (s, C-4 or C-10), 127.6 (s, C-5a), 117.8 (s, C-4 or C-10), 115.8 (s, CN), 98.8 (s, C-2a), 74.1 (t, C-1), 61.0 (q, 3 or 9-OCH_3), 60.4 (d, C-14), 58.9 (q, 3 or 9-OCH_3), 55.9 (d, C-15a), 55.5 (d, C-6a), 54.4 (d, C-13), 53.8 (d, C-7), 51.6 (q, 2a-OCH_3), 41.7 (q, NCH_3), 25.9 (t, C-6 or C-12), 25.8 (t, C-6 or C-12), 8.6 (q, 4 or 10-CH_3), 7.7 (q, 4 or 10-CH_3); IR (KBr): 2926, 2853, 1732, 1655, 1636,

1616, 1375, 1321, 1269, 1248, 1152, 1059, 1024 cm^{-1}; FABMS *m/z*: 508 $[M + H]^+$; HRFABMS: calcd for $C_{27}H_{30}N_3O_7$, 508.2084; found 508.2079.

Renieramycin M (**1m**)

2,4,6-Trichlorobenzoyl chloride (80.0 μL, 513 μmol) was added to a solution of angelic acid (51.4 mg, 513 μmol) and Et_3N (72.0 μL, 513 μmol) in toluene (6 mL) at 0 °C, and the reaction mixture was stirred at 25 °C for 4 h. Jorunnamycin A (25.3 mg, 51 μmol) was added to the above mixture in one portions at same temperature, and the stirring was continuing at 60 °C for 6.5 days. After the reaction mixture was quenched with H_2O (30 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (30 mL), dried, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash chromatography (EtOAc–*n*-Hexane = 2:3) to provide compound renieramycin M (**1m**) (18.0 mg, 61%) as a yellow amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.96 (1H, qq, *J* = 7.3, 1.5 Hz, 26-H), 4.54 (1H, dd, *J* = 11.7, 2.9 Hz, 22-H), 4.10 (1H, dd, *J* = 11.7, 2.9 Hz, 22-H), 4.07 (1H, d, *J* = 2.4 Hz, 21-H), 4.02 (3H, s, OCH_3), 4.01 (1H, overlapped, 11-H), 3.99 (3H, s, OCH_3), 3.99 (1H, overlapped, 1-H), 3.39 (1H, br d, *J* = 7.3 Hz, 13-H), 3.11 (1H, dt, *J* = 11.5. 2.4 Hz, 3-H), 2.89 (1H, dd, *J* = 17.1, 2.4 Hz, 4-Hα), 2.75 (1H, dd, *J* = 21.0, 7.3 Hz, 14-Hα), 2.30 (1H, d, *J* = 21.0 Hz, 14-Hβ), 2.28 (3H, s, NCH_3), 1.94 (3H, s, Ar-CH_3), 1.90 (3H, s, Ar-CH_3), 1.82 (3H, dq, *J* = 7.3, 1.5 Hz, 26-CH3), 1.58 (3H, m, 25-CH_3), 1.36 (1H, ddd, *J* = 17.1, 11.5, 2.4 Hz, 4-Hβ); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 185.9 (s, C-15), 185.4 (s, C-5), 182.5 (s, C-18), 181.0 (s, C-8), 166.5 (s, C-24), 155.8 (s, C-7), 155.2 (s, C-17), 142.0 (s, C-20), 141.3 (s, C-10), 140.6 (d, C-26), 135.7 (s, C-9), 135.0 (s, C-19), 128.6 (s, C-6), 128.4 (s, C-16), 126.3 (s, C-25), 116.9 (s, 21-CN), 61.9 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 58.5 (d, C-21), 56.3 (d, C-1), 54.6 (d, C-13), 54.2 (d, C-11), 54.1 (d, C-3), 41.5 (q, NCH_3), 25.4 (t, C-4), 21.1 (t, C-14), 20.4 (q, 25-CH_3), 15.7 (q, 26-CH_3), 8.7 (q, 6-CH_3), 8.6 (q, 16-CH_3); IR (KBr) 2932, 2230, 1717, 1655, 1620, 1452, 1373, 1234, 1150, 968 cm^{-1}; EIMS *m/z* (%): 575 (4), 356 (4), 260 (4), 245 (6), 244 (15), 243 (100), 220 (37), 219 (6), 218 (10), 204 (7); HREIMS calcd for $C_{31}H_{33}N_3O_8$ 575.2268; found 575.2260.

Fennebricin A (**2A**)

Silver nitrate (144 mg, 800 μmol) was added to a stirred solution of jorunnamycin A (19.7 mg, 40 μmol) in acetone (4 mL) at 25 °C, and the mixture was stirred at 50 °C for 1 h. After the solvent was removed in vacuo, the residue was diluted with water (20 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash chromatography (EtOAc–*n*-Hexane = 2:3 ~ 1:1) to provide fennebricn A (**2a**) (14.4 mg, 68%) as a dark yellow amorphous powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.99 (3H, s, 24-OCH_3), 3.97 (1H, m, 11-H), 3.96 (3H, s, 7-OCH_3), 3.67 (1H, dd, *J* = 11.0, 3.7 Hz, 22-H), 3.65 (1H, m,

1-H), 3.49 (1H, dd, J = 17.6, 8.8 Hz, 23-H), 3.38 (1H, br d, J = 8.8, 21-H), 3.35 (1H, m, 22-H), 3.01 (1H, dt, J = 11.0, 2.7 Hz, 3-H), 2.95 (1H, br d, J = 7.7 Hz, 13-H), 2.86 (1H, dd, J = 17.0, 2.7 Hz), 2.83 (1H, dd, J = 21.2, 7.7 Hz, 14-Hα), 2.42 (1H, d, J = 17.6, 23-H), 2.23 (1H, overlapped, 14-Hβ), 2.20 (3H, s, NCH_3), 2.19 (3H, s, 23-$COCH_3$), 1.94 (3H, s, 16-CH_3), 1.93 (3H, s, 6-CH_3), 1.33 (1H, ddd, J = 17.0, 11.0, 2.0 Hz, 4-Hβ); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 207.8 (s, $COCH_3$), 186.3 (s, C-15), 185.6 (s, C-5), 182.6 (s, C-18), 181.8 (s, C-8), 155.6 (s, C-17), 155.5 (s, C-7), 143.0 (s, C-20), 141.8 (s, C-10), 137.5 (s, C-9), 135.8 (s, C-19), 128.9 (s, C-6), 128.8 (s, C-16), 62.8 (t, C-22), 61.0 (q, 7-OCH3), 61.0 (q, 17-OMe), 58.3 (d, C-21), 55.0 (d, C-11), 55.0 (d, C-13), 54.9 (d, C-1), 51.8 (d, C-3), 41.8 (q, NCH_3), 39.0 (t, C-23), 30.9 (q, 23-$COCH_3$), 25.6 (t, C-4), 23.3 (q, C-14), 8.8 (q, 6-CH_3), 8.7 (q, 16-CH_3); IR (KBr): 3499, 3401, 3281, 2926, 2853, 2803, 2542, 1711, 1653, 1630, 1607, 1447, 1412, 1371, 1233, 802 cm^{-1}; FABMS *m/z*: 525 $[M+H]^+$; HRFABMS calcd for $C_{28}H_{33}N_2O_8$, 525.2237; found 525.2238.

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REFERENCES AND NOTES

1. J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669.
2. (a) K. L. Rinehart, *Med. Res. Rev.*, 2000, **20**, 1; (b) G. J. Aune, T. Furuta, and Y. Pommier, *Anticancer Drugs*, 2002, **13**, 545.
3. M. Tatsukawa, L. L. C. Punzalan, H. D. S. Magpantay, I. M. Villaseñor, G. P. Concepcion, K. Suwanborirux, M. Yokoya, and N. Saito, *Tetrahedron*, 2012, **68**, 7422.
4. N. Saito, K. Suwanborirux, A. Hiramatsu, H. Hirade, M. Kubota, R. Toyoshima, A. Fujino, N. Sirimangkalakitti, and G. P. Concepcion, *Heterocycles*, 2017, **95**, 748.
5. W.-F. He, Y. Li, M.-T. Feng, M. Gavagnin, E. Mollo, S.-C. Mao, and Y.-W. Guo, *Fitoterapia*, 2014, **96**, 109.
6. R.-Y. Huang, W.-T. Chen, T. Kurtán, A. Mándi, J. Ding, J. Li, X.-W. Li, and Y.-W. Guo, *Future Med. Chem.*, 2016, **8**, 17.
7. K. Suwanborirux, S. Amnuoypol, A. Plubrukarn, S. Pummangura, A. Kubo, C. Tanaka, and N. Saito, *J. Nat. Prod.*, 2003, **66**, 1441.
8. (a) Y.-i. Koizumi, A. Kubo, K. Suwanborirux, and N. Saito, *Heterocycles*, 2002, 57; (b) N. Saito, C. Tanaka, Y. Koizumi, K. Suwanborirux, S. Amnuoypol, S. Pummangura, and A. Kubo, *Tetrahedron*, 2004, **60**, 3873.
9. (a) M. Yokoya, K. Shinada-Fujino, and N. Saito, *Tetrahedron Lett.*, 2011, **52**, 2446; (b) M. Yokoya,

K. Shinada-Fujino, S. Yoshida, M. Mimura, H. Takada, and N. Saito, *Tetrahedron*, 2012, **68**, 4166.

10. K. Charupant, K. Suwanborirux, S. Amnuoypol, E. Saito, A. Kubo, and N. Saito, *Chem. Pharm. Bull.*, 2007, **55**, 81.
11. K. Nakai, K. Kubo, M. Yokoya, and N. Saito, *Tetrahedron*, 2014, **70**, 6529.
12. B. Hartmann, A. M. Kanazawa, J.-P. Deprés, and A. E. Greene, *Tetrahedron Lett.*, 1991, **32**, 5077.
13. We have made several requests to T.-W. Guo at Shanghai Institute of Materia Medica, Chinese Academy of Sciences to identify our synthesized product by comparing its spectral data with those of natural fennebricin A. However, we have not received any reply to this day.