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Asymmetric Synthesis and Cytotoxicity Evaluation of Right-Half Models of Antitumor Renieramycin Marine Natural Products

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Abstract: A general protocol for the asymmetric synthesis of 3-*N*-arylmethylated right-half model compounds of renieramycins was developed, which enabled structure–activity relationship (SAR) study of several 3-*N*-arylmethyl derivatives. The most active compound (**6a**) showed significant cytotoxic activity against human prostate cancer DU145 and colorectal cancer HCT116 cell lines (IC_{50} = 11.9, and 12.5 nM, respectively).

Keywords: renieramycin; 1,2,3,4-tetrahydroisoquinoline; cytotoxicity; asymmetric synthesis; marine natural product

1. Introduction

Natural products belonging to the *bis*-1,2,3,4-tetrahydroisoquinoline family, such as renieramycins, saframycins, and ecteinascidins, have attracted considerable attention due to their potent biological activities, structural diversity, and meager availability in nature (Figure 1) [1]. We have discovered a number of renieramycin marine natural products having extraordinary structures from blue sponges collected in Thailand and the Philippines [2–4]. For example, renieramycin M (**1m**) isolated from the Thai blue sponge *Xestospongia* sp. has *p*-quinones in both terminal rings [2]. In contrast, renieramycins T (**1t**) and U (**1u**) share a common A-ring with ecteinascidin 743 (ET-743, **2**), which has already been approved as an anticancer agent [3]. In addition, the A-ring of renieramycin Y (**1y**) has the same substituent pattern as the E-ring of **2** [4]. These renieramycins have similar structures to **2** and are expected to have similar potent antitumor activity. However, the amount obtainable from nature is scarce, and this has set back the implementation of detailed biological tests.

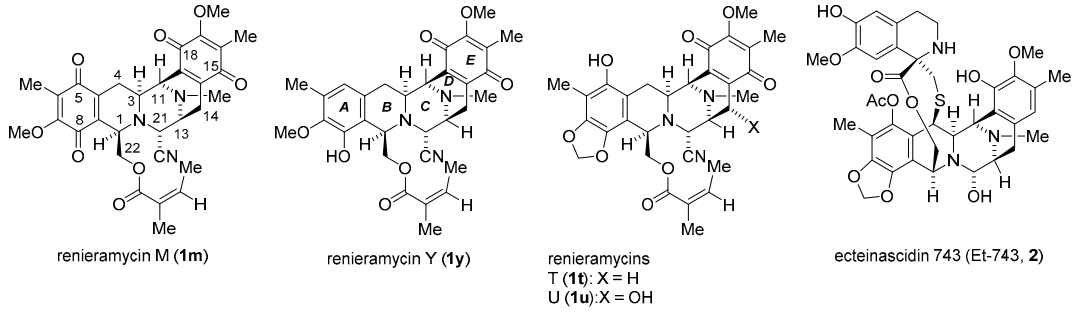


Figure 1. Antitumor tetrahydroisoquinoline marine natural products.

Under these circumstances, we have been developing a total synthesis of these fascinating marine natural products. We have succeeded in the total syntheses of renieramycins G–I, cribrostatin 4, and

renieramycin T [5–8]. However, the long and tedious procedures for the total synthesis of these natural products have impeded detailed structure–activity relationship (SAR) studies.

2. Results

We have been trying to simplify the structures of renieramycins without impairing their biological activities. Several right-hand (CDE-ring system) and left-hand (ABC-ring system) model compounds were prepared, and their in vitro cytotoxic activities against human cancer cell lines were tested [9,10]. These efforts have yielded CDE-ring model compounds (±)-**3** to (±)-**6a** (Figure 2), and the presence of amino nitriles was found to induce at nanomolar concentrations (Table 1) [9]. 3-*N*-benzyl derivative (±)-**6a** exhibited approximately five and nine times more potent cytotoxic activity against HCT116 and QG56, respectively, than 3-*N*-methylated derivative (±)-**5**, indicating the importance of the substituent at 3-nitrogen.

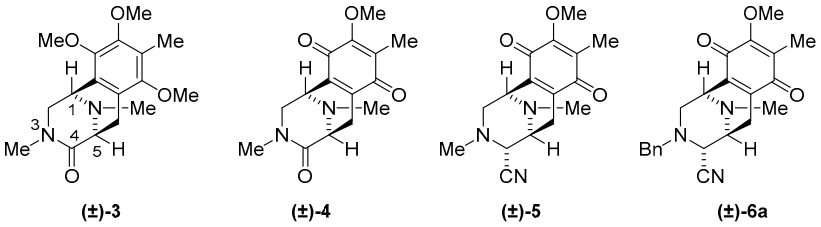


Figure 2. Structures of right-half model compounds of renieramycins.

Table 1. Cytotoxic activities of right-half model compounds against human colorectal cancer HCT116 and lung cancer QG56 cell lines.

Compound	IC_{50} (μM)	
	HCT116	QG56
(±)-**3**	>50	>50
(±)-**4**	2.4	1.9
(±)-**5**	0.084	0.24
(±)-**6a**	0.017	0.027

From the structure comparison of (±)-**6a** and **1m**, we expected that 3-*N*-Bn would correspond to the A-ring of **1m**. Thus, **6b** having an arylmethyl group whose substituent pattern was similar to the A-ring of **1m**, and **6c** having the same A-ring as **1y** were set as the new target molecules (Figure 3).

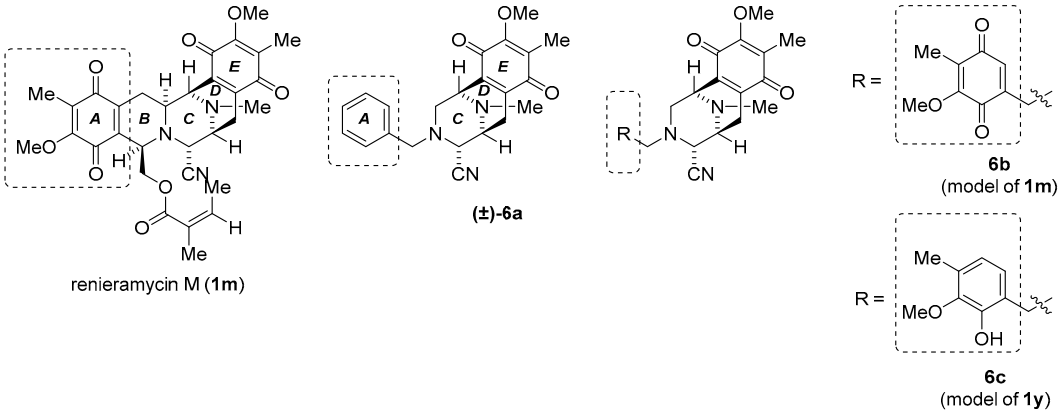
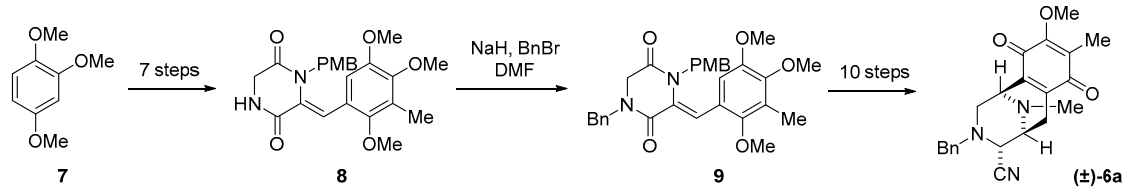


Figure 3. Structural comparison of right-half model compounds **6a**, **6b**, and **6c** with renieramycin M (**1m**).

A summary of our previously reported synthesis of racemic **6a** is shown in Scheme 1 [9,11]. Conversion of 1,2,4-Trimethoxybenzene (**7**) into piperadine-2-5-dione derivative **8** took seven steps, and treatment of **8** with NaH and BnBr gave *N*-benzyl compound **9**. Racemic compound **6a** was prepared from **9** in ten steps. As the 3-*N*-arylmethyl group was critical to generate strong antitumor activity, derivatives with different 3-*N*-arylmethyl groups were prepared in subsequent steps. In addition, it is very interesting to compare the biological activities of the racemic form and the optically active form [12]. Thus, in order to facilitate the synthesis of structural analogs, a new asymmetric synthetic route for preparing the 3-*N*-arylmethyl group in the later steps should be developed.



Scheme 1. Preparation of compound (±)-**6a** [9,11].

An outline of an alternative synthetic strategy to facilitate the asymmetric synthesis of various 3-*N*-arylmethyl derivatives is shown in Figure 4. We envisioned that the final step in the asymmetric synthesis of **6** should involve a reductive cyanation of the lactam carbonyl followed by a two-step oxidation of the phenol into *p*-quinone from **10**. An *N*-arylmethyl group, which would be important for the cytotoxic activity, should be installed on lactam **11**. The C-ring formation proceeded automatically from the lactonization of the primary amine, which was generated by the deprotection of the *N*-Cbz protecting group of **12**. The synthesis of 1,3-*cis*-1,2,3,4-tetrahydroisoquinoline **12** was accomplished via the regio- and diastereoselective Pictet–Spengler cyclization reaction of aminophenol (−)-**13** with *N*-Cbz glyoxal **14** [13]. Starting material (−)-**13** was easily prepared from L-tyrosine according to Liu's method [14].

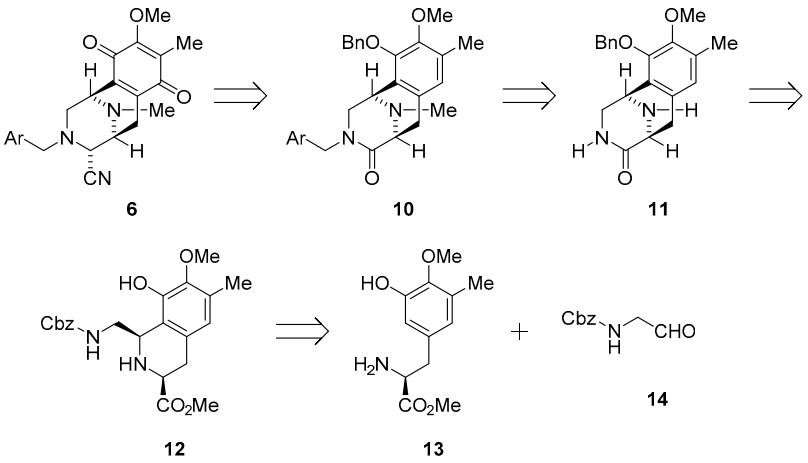
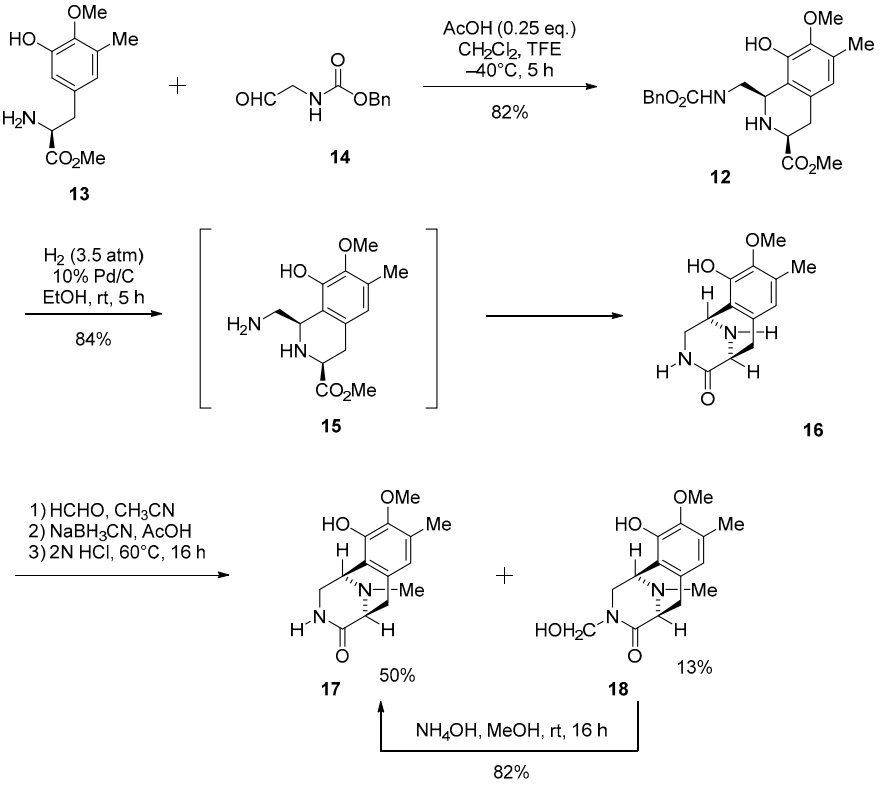


Figure 4. Retrosynthetic analysis of chiral CDE-ring model compound **6**.

Our synthesis began with the highly regio- and diastereoselective Pictet–Spengler cyclization reaction of aminophenol (−)-**13** with *N*-protected glyoxal **14**, which was prepared from commercially available 2-(Cbz-amino)-1-ethanol according to a previously reported oxidation reaction [13] (Scheme 2). This cyclization reaction of (−)-**13** with **14** in CH_2Cl_2 and 2,2,2-trifluoroethanol at −40 °C for 5 h provided (1*R*,3*S*)-1,2,3,4-tetrahydroisoqunoline (−)-**12** in 82% yield. The ^{1}H-NMR spectrum of (−)-**12** was complicated due to the presence of carbamate rotational isomers; thus, the structure determination of (−)-**12** was completed after the transformation of (−)-**12** into tricyclic compound (−)-**16**. 1,2,3,4-Tetrahydroisoquinoline (−)-**12** was de-protected by catalytic hydrogenation to afford primary amine **15**, which spontaneously intramolecularly cyclized to tricyclic compound (−)-**16** in

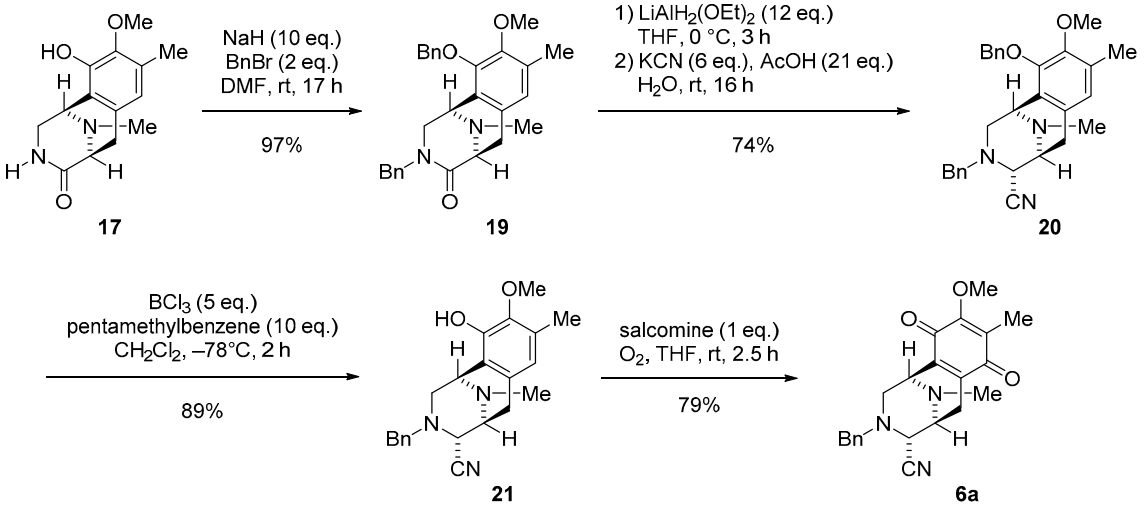
84% yield. It was confirmed that (−)-**12** obtained by the Pictet–Spengler reaction had the desired 1,3-*cis* configuration. Reductive amination of (−)-**16** followed by *N*-methylation provided (−)-**17** in 50% yield along with overreacted compound (−)-**18** in 13% yield. Obtained side product (−)-**18** was easily converted into (−)-**17** in 82% yield by treatment with ammonia in methanol.



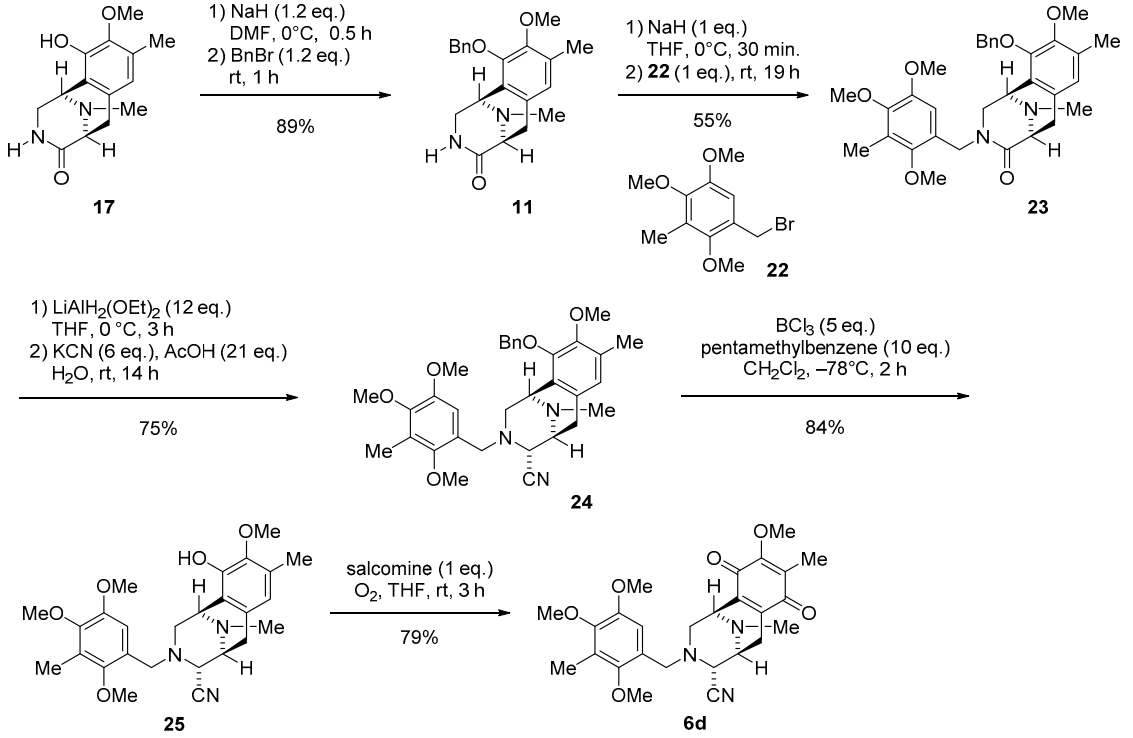
Scheme 2. Construction of tricyclic lactam **18**.

The alkylation of (−)-**17** with benzyl bromide in the presence of 10 equivalents of sodium hydride afforded dibenzylated product (−)-**19** in 97% yield (Scheme 3). The lactam carbonyl of (−)-**19** was partially reduced with $LiAlH_2(OEt)_2$ [15] in tetrahydrofuran (THF) to generate the aminal, which was treated with KCN and water to provide α-aminonitrile (−)-**20** in 74% yield as a single diastereomer. Chemoselective *O*-debenzylation was achieved with BCl_3 in the presence of pentamethylbenzene to give desired phenol (−)-**21** in 89% yield [16]. Finally, oxidation of (−)-**21** with O_2 in the presence of salcomine afforded chiral 3-*N*-benzylated CDE-ring model compound (−)-**6a**. (−)-**6a** was confirmed to have 99%ee by high performance liquid chromatography (HPLC) analysis, proving that the chiral center in L-tyrosine did not cause any racemization in this synthetic route.

With tricyclic chiral model (−)-**6a** in hand, **6d** having an arylmethyl group with more electron-rich trimethoxy substituents was prepared (Scheme 4). The phenol of (−)-**17** was selectively protected with 1.2 equivalents each of NaH and BnBr in *N*,*N*-dimethylformamide (DMF) to give (−)-**11**, which could be used to prepare several kinds of 3-*N*-alkylated compounds. The reaction of (−)-**11** with substituted benzyl bromide **22**, which was obtained by a reported method [17], produced 3-*N*-arylmethylated (−)-**23** in 55% yield. The conversion (−)-**23** into (−)-**25** was carried out using a similar three-step sequence to that shown above, and salcomine oxidation of (−)-**25** gave *p*-quinone (+)-**6d** in 79% yield.

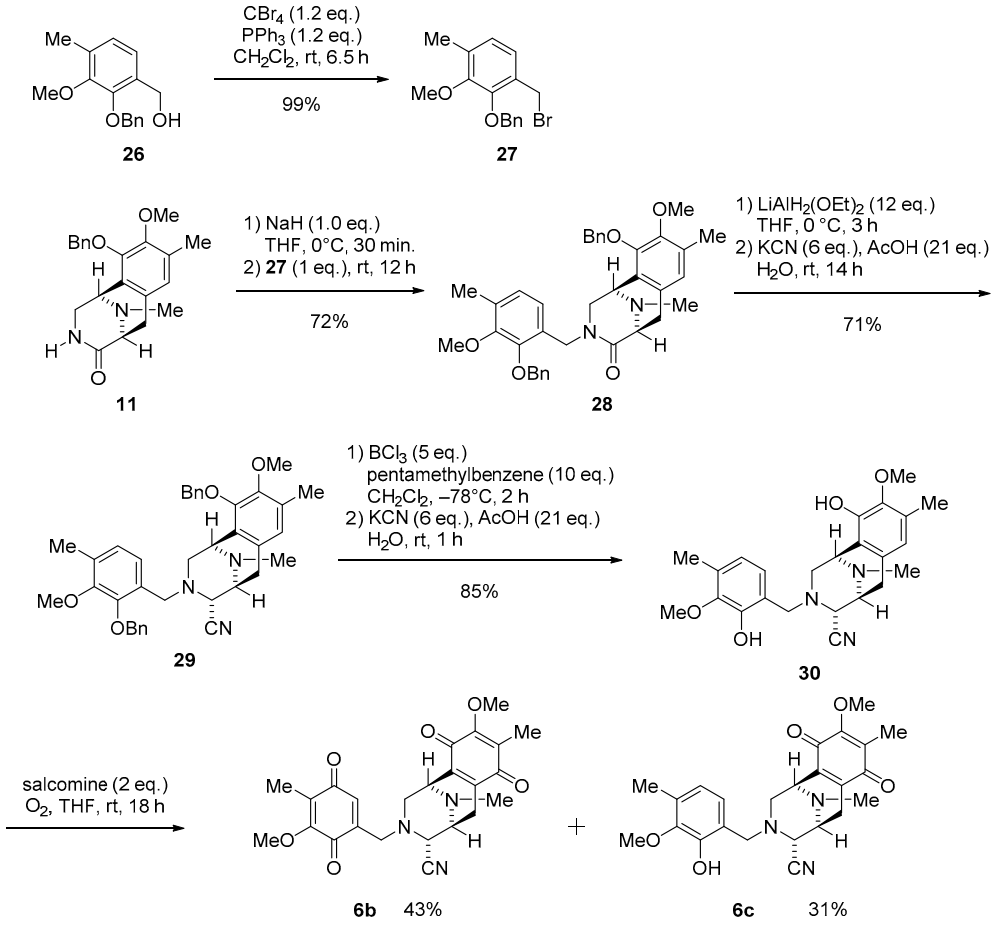


Scheme 3. Preparation of right-half model compound **6a**.



Scheme 4. Preparation of right-half model compound **6d**.

The preparation of right-half model compounds **6b** and **6c** whose A-ring substitution patterns correspond to those of **1m** and **1y**, respectively, was carried out as follows (Scheme 5). Benzyl bromide **27** was prepared by the Appel reaction of corresponding alcohol **26** [18] in 99% yield. Alkylation of the lactam nitrogen of (−)-**11** with **27** gave (−)-**28** in 72% yield. Reductive cyanation of (−)-**28** generated aminonitrile (−)-**29** in 71% yield. Debenzylation of (−)-**29** by using BCl_3 gave a crude product that was expected to contain iminium by-products produced by the cyano group elimination. Thus, the crude product without further purification was treated with KCN to furnish desired phenol (−)-**30** in 85% yield. Finally, bisphenol (−)-**30** was oxidized with two equivalents of salcomine in oxygen atmosphere to give (−)-**6b** and (+)-**6c** in 43% and 31% yields, respectively. This oxidation could be controlled by adjusting the proportion of salcomine, as shown in Table 2.



Scheme 5. Preparation of right-half model compounds **6b** and **6c**.

Table 2. Salcomine oxidation of phenol (−)-**30** gave bis-*p*-quinone (−)-**6b** and mono-*p*-quinone (+)-**6c**.

Entry	Salcomine (+ O_2) (equiv.)	Time (h)	Product (%) [1]	
			(−)-6b	(+)-6c
1	1.0	3	13	55
2	2.0	4	43	31
3	6.0	23	52	3

[1] Isolation yield.

Although the detailed molecular mechanism underlying the antitumor activities of renieramycin marine natural products were unclear, we had speculated that the cyano or hydroxyl substituent at C-21 position of renieramycin would be essential for the potent cytotoxic activity. Elimination of the functional group at C-21 produced an electrophilic iminium ion species that was implicated in the formation of covalent bonds with DNA [19]. In 2008, Avendaño and co-workers reported a series of 1,2,3,4-tetrahydroisoquinolines with antitumor activities that were attributed to both apoptosis in the G2/M checkpoint and cytostatic activity in the G1 phase [20]. In addition, we prepared a series of renieramycin left-half model compounds from phenylalanine derivatives, and re-confirmed the importance of the C-21 cyano group for favorable activity [10]. Four right-half chiral model compounds **6a**–**6d** and racemic **6a** and **6b**, including natural renieramycin M (**1m**) as positive control, were tested in vitro for cytotoxicity toward two representative human cancer cell lines (prostate cancer DU145 and colorectal cancer HCT116) using the CCK-8 assay (Table 3). Interestingly, the structure of the E-ring was found to be important for the enhanced biological activity. In order to examine the influence of the E-ring on the bioactivity, the IC_{50} values of three compounds (**6a**, **20**, **21**), in which

the 3-*N*-Bn substituent and the C-4 cyano group were fixed, were compared. *p*-Quinone **6a** was the most active, phenol **21** had comparable activity to **6a**, and benzyl ether **20** showed markedly decreased activity. Then, the importance of the cyano group at C-4 position was also confirmed in the right-half models. A significant decrease in cytotoxic activity was observed when the lactam carbonyl at C-4 position was converted into an aminonitrile (i.e., conversion of **19** into **20**, **23** into **24**, and **28** into **29**). However, it was interesting that **28** showed moderate activity even though C-4 had a lactam carbonyl.

Table 3. Cytotoxic activities of right-half model compounds against prostate cancer DU145 and colorectal cancer HCT116 cell lines: IC_{50} (μM).

Compd.	DU145	HCT116	Compd.	DU145	HCT116
1m	$(4.0 \pm 0.9) \times 10^{-3}$	$(18.1 \pm 1.4) \times 10^{-3}$	**18**	>20	>20
(±)-**6a**	$(14.0 \pm 0.6) \times 10^{-3}$	$(11.4 \pm 1.0) \times 10^{-3}$	**19**	>20	>20
(−)-**6a**	$(11.9 \pm 2.2) \times 10^{-3}$	$(12.5 \pm 0.5) \times 10^{-3}$	**20**	1.2 ± 0.1	1.3 ± 0.2
(±)-**6b**	0.7 ± 0.04	0.5 ± 0.01	**21**	$(47.7 \pm 1.0) \times 10^{-3}$	$(37.6 \pm 9.6) \times 10^{-3}$
(−)-**6b**	0.8 ± 0.02	0.6 ± 0.04	**23**	>20	>20
(+)-**6c**	1.0 ± 0.04	1.0 ± 0.1	**24**	13.1 ± 1.3	2.8 ± 0.3
(+)-**6d**	0.4 ± 0.04	0.1 ± 0.02	**25**	0.6 ± 0.1	0.4 ± 0.02
11	>20	>20	**28**	10.5 ± 0.4	11.7 ± 1.1
16	>20	>20	**29**	2.1 ± 0.3	2.0 ± 0.1
17	>20	>20	**30**	6.5 ± 0.4	2.7 ± 0.4

Next, on comparing the IC_{50} values of **21**, **25**, and **30** having characteristic 3-*N*-arylmethyl groups, **30** was found to show the least potent activity, whereas **25** with a trimethoxy arylmethyl group exhibited more potent activity. In the case of **21**, which has an unsubstituted arylmethyl group, very strong activity at nanomolar concentrations was observed. A similar tendency was also observed in the model compounds. Among compounds **6a**, **6b**, **6c**, and **6d** whose E-rings were a quinone, phenol **6c**, which has a phenol in the A-ring exhibited the weakest activity, whereas 3-*N*-benzyl **6a** showed the strongest activity.

Finally, the effect of optical activity on the biological activity was investigated. It was recently confirmed that optically active (−)-**1m** obtained from nature had approximately two to three times stronger activity than racemic (±)-**1m** [21]. Unlike **1m,** the chirality of racemic **6a** and **6b** and their chiral counterparts had no effect on their cytotoxic activities. Worth noting was that **6a** with *p*-quinone on the E-ring, a cyano group at C-4 position, and 3-*N*-benzyl was the most active compound against the two types of cancer cell lines, and had similar potency to natural **1m**.

3. Experimental Section

3.1. Chemistry

IR spectra were obtained with a Shimadzu IRAffinity-1 FT-IR spectrometer (Shimadzu Corporation, Kyoto, Japan). Optical rotations were measured with Horiba SEPA-500 polarimeters (Horiba Ltd., Kyoto, Japan). ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-AL 400 NMR spectrometer (JEOL Ltd., Tokyo, Japan) 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 tetramethylsilane (TMS) as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using correlation spectroscopy (COSY), Heteronuclear Multiple-Bond Correlation (HMBC), and Heteronuclear Multiple Quantum Correlation (HMQC) techniques. Mass spectra were recorded on a JEOL JMS 700 instrument (JEOL Ltd., Tokyo, Japan) with a direct inlet system operating at 70 eV.

3.1.1. Synthesis of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (**12**)

To a stirred solution of aldehyde **14** (2.73 g, 14.1 mmol, 1.3 eq.) and 4 Å molecular sieves (2.60 g) in CH_2Cl_2 (70 mL), a solution of amine **13** (2.60 g, 10.9 mmol), acetic acid (160 μL) and

2,2,2-trifluoroethanol (10 mL) was added slowly over 6 min at −40 °C. After being stirred at −40 °C for 5 h, the reaction mixture was neutralized with $NaHCO_3$, and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography ($CHCl_3$–EtOAc = 2:1) to afford compound **12** (3.71 g, 82%) as a pale yellow amorphous. $[\alpha]_D^{24}$ −83.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, C_5D_5N, 80 °C) δ 10.30 (1H, brs, NH or OH), 7.46–7.25 (5H, m, Bn-H), 6.54 (1H, s, 5-H), 5.35–5.25 (2H, m, 5′-H), 4.90 (1H, br t, *J* = 3.2 Hz, 1-H), 4.31–4.27 (1H, m, Bn-H), 4.00–3.94 (1H, m, Bn-H), 3.79–3.75 (1H, m 3-H), 3.73 (3H, s, 7-OCH_3), 3.70 (3H, s, 3-$COOCH_3$), 3.02 (2H, brd, *J* = 6.4 Hz, 4-H), 2.30 (3H, s, 6-CH_3); ^{13}C-NMR (400 MHz, C_5D_5N, 80 °C) δ174.0 (s, $\underline{C}OOCH_3$), 157.6 (s, C-3′), 148.2 (s, C-8), 145.9 (s, C-7), 138.3 (s, Bn), 132.2 (s, C-4a), 129.5 (s, C-6), 128.8 (d, Bn), 128.2 (d, Bn), 128.0 (d, Bn), 122.7 (s, C-8a), 121.9 (d, C-5), 66.4 (t, C-5′), 60.2 (q, 7-OCH_3), 56.0 (d, C-3), 54.2 (d, C-1), 51.8 (q, 3-$COO\underline{C}H_3$), 46.8 (t, C-1′), 33.8 (t, C-4), 15.8 (q, 6-CH_3); IR ($CHCl_3$) 3520, 3437, 3024, 3015, 2955, 2359, 2342, 1717, 1506, 1456, 1233, 1059 cm^{-1}; FABMS *m/z* 415 $[M + H]^+$; HRFABMS *m/z* 415.1867 ($[M + H]^+$, calcd for $C_{22}H_{27}N_2O_6$ 415.1869).

3.1.2. Synthesis of (1*R*,5*S*)-10-Hydroxy-9-methoxy-8-methyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**16**)

A solution of **12** (2.96 g, 7.14 mmol) in EtOH (370 mL) was hydrogenated over 10% Pd/C (55%wet, 1.52 g, 1.43 mmol) at 25 °C for 5 h under 3.5 atm hydrogen. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure and the residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 9:1) to afford compound **16** (1.49 g, 84%) as a pale brown solid. $[\alpha]_D^{24}$ −177.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.80 (1H, brs, 10-OH), 7.39 (1H, d, *J* = 4.0 Hz, 3-*N*-H), 6.37 (1H, s, 7-H), 4.19 (1H, d, *J* = 4.4 Hz, 1-H), 3.60 (3H, s, 9-OCH_3), 3.53 (1H, dd, *J* = 11.2, 4.4 Hz, 2-H), 3.49 (1H, d, *J* = 6.2 Hz, 5-H), 3.07 (1H, dd, *J* = 11.2, 4.0 Hz, 2-H), 2.86 (1H, dd, *J* = 16.5, 6.2 Hz, 6-H), 2.59 (1H, d, *J* = 16.5 Hz, 6-H), 2.13 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 171.4 (s, C-4), 145.7 (s, C-10), 143.7 (s, C-9), 129.7 (s, C-6a), 128.7 (s, C-8), 122.9 (s, C-10a), 120.6 (d, C-7), 59.9 (q, 9-O$\underline{C}H_3$), 52.4 (d, C-5), 47.5 (t, C-2), 43.7 (d, C-1), 32.0 (t, C-6), 15.5 (q, 8-CH_3); IR (KBr) 3497, 3428, 3345, 3246, 1643, 1335, 1273, 1069, 1001 cm^{-1}; EIMS *m/z* (%) 248 (M^+, 24), 191 (17), 190 (100), 175 (16); HREIMS *m/z* 248.1162 (M^+, calcd for $C_{13}H_{16}N_2O_3$ 248.1161).

3.1.3. Synthesis of (1*R*,5*S*)-10-Hydroxy-9-methoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**17**) and (1*R*,5*S*)-10-hydroxy-3-(hydroxymethyl)-9-methoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**18**)

To a stirred solution of amine **16** (248 mg, 1.00 mmol) in CH_3CN (34 mL) was added 37% HCHO (1.60 mL, 20.0 mmol, 20 eq.). The reaction mixture was stirred for 15 min, after which $NaCNBH_3$ (700 mg, 10.0 mmol, 10 eq.) was added. The reaction mixture was stirred for 15 min, after which AcOH (570 μL, 10.0 mmol, 10 eq.) was added dropwise over 3 min. The reaction mixture was stirred for 5 min, after which 2 N HCl (34 mL) was added 1 portion. The reaction was heated to 60 °C and was stirred for 16 h. The reaction was quenched with saturated $NaHCO_3$ (200 mL) and extracted with $CHCl_3$−MeOH = 9:1 (3 × 150 mL). The combined extracts were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (benzene−acetone = 1:2) to afford compound **18** (39.0 mg, 13%) as a colorless solid, and with $CHCl_3$−MeOH (6:1) to afford **17** (130 mg, 50%) as a colorless solid.

17: $[\alpha]_D^{24}$ −224.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, s, 7-H), 5.92 (1H, brs, 3-*N*-H), 4.17 (1H, d, *J* = 4.5 Hz, 1-H), 3.91 (1H, dd, *J* = 11.6, 4.5 Hz, 2-H), 3.77 (3H, s, 9-OCH_3), 3.57 (1H, d, *J* = 6.6 Hz, 5-H), 3.30 (1H, ddd, *J* = 11.6, 3.8, 0.9, 2-H), 3.17 (1H, dd, *J* = 17.0, 6.6 Hz, 6-H), 2.79 (1H, d, *J* = 17.0 Hz, 6-H), 2.52 (3H, s, *N*-CH_3), 2.25 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3 (s, C-4), 145.5 (s, C-10), 143.3 (s, C-9), 129.3 (s, C-6a), 129.0 (s, C-8), 121.9 (d, C-7), 119.2 (s, C-10a), 60.8 (q, 9-O$\underline{C}H_3$), 59.2 (d, C-5), 50.0 (d, C-1), 45.3 (t, C-2), 40.1 (q, *N*-$\underline{C}H_3$), 27.8 (t, C-6), 15.8 (q, 8-$\underline{C}H_3$); IR (KBr) 3265, 2938, 2874, 1684, 1645, 1495, 1335, 1265, 1055, 1038 cm^{-1}; EIMS *m/z* (%) 262 (M^+, 20), 205 (17), 204 (100), 189 (16); HREIMS *m/z* 262.1317 (M^+, calcd for $C_{14}H_{18}N_2O_3$ 262.1317).

18: $[\alpha]_D^{24}$ −197.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47 (1H, s, 7-H), 4.88 (1H, d, *J* = 10.4 Hz, 3-*N*-C$\underline{H}_2$OH), 4.56 (1H, d, *J* = 10.4 Hz, 3-*N*-C$\underline{H}_2$OH), 4.22 (1H, d, *J* = 4.6 Hz, 1-H), 4.08 (1H, dd, *J* = 11.5, 4.6 Hz, 2-H), 3.76 (3H, s, 9-OC$\underline{H}_3$), 3.61 (1H, d, *J* = 6.5 Hz, 5-H), 3.35 (1H, d, *J* = 11.5, 2-H), 3.15 (1H, dd, *J* = 17.0, 6.5 Hz, 6-H), 2.77 (1H, d, *J* = 17.0 Hz, 6-H), 2.49 (3H, s, 11-*N*-C$\underline{H}_3$), 2.25 (3H, s, 8-C$\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.1 (s, C-4), 145.6 (s, C-10), 143.4 (s, C-9), 129.4 (s, C-6a), 128.6 (s, C-8), 121.7 (d, C-7), 118.9 (s, C-10a), 71.6 (t, C-3), 60.7 (q, 9-O$\underline{C}$H$_3$), 59.1 (d, C-5), 50.7 (d, C-1), 50.0 (t, C-2), 39.8 (q, *N*-$\underline{C}$H$_3$), 27.1 (t, C-6), 15.7 (q, 8-$\underline{C}$H$_3$); IR (KBr) 3489, 3150, 2949, 2934, 1618, 1504, 1236, 1055, 1034 cm^{-1}; EIMS *m/z* (%) 292 (M^+, 3), 262 (17), 205 (18), 204 (100), 189 (16); HREIMS *m/z* 292.1424 (M^+, calcd for $C_{15}H_{20}N_2O_4$ 292.1423).

3.1.4. Synthesis of **17** from **18**

To a stirred solution of lactam **18** (262 mg, 0.896 mmol) in MeOH (26 mL) was added NH_4OH (10.5 mL) at room temperature (rt). The reaction mixture was stirred for 16 h. The reaction was quenched with conc. HCl at 0 °C, and then neutralized with 5% $NaHCO_3$. The reaction mixture was diluted with H_2O (200 mL) and extracted with $CHCl_3$−MeOH = 9:1 (4 × 50 mL). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 9:1) to afford compound **17** (19.3 mg, 82%) as a colorless solid.

3.1.5. Synthesis of (1*R*,5*S*)-3-Benzyl-10-(benzyloxy)-9-methoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**19**)

To a stirred solution of lactam **17** (10.0 mg, 38.0 μmol) and benzyl bromide (10.0 μL, 76.0 μmol, 2.0 eq.) in DMF (1 mL) was added NaH (60% oil dispersion, 15.2 mg, 381 μmol, 10.0 eq.) at 0 °C. The reaction mixture was stirred at 25 °C for 17 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 99:1) to afford compound **19** (16.4 mg, 97%) as a yellow oil. $[\alpha]_D^{24}$ −77.5 (*c* 1.2, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, 10-*O*-Bn-H), 7.13–7.04 (3H, m, 3-*N*-Bn-H), 6.75–6.73 (2H, m, 3-*N*-Bn-H), 6.75 (1H, s, 7-H), 4.98 (1H, d, *J* = 11.5 Hz, 10-OC$\underline{H}_2$Ph), 4.84 (1H, d, *J* = 15.1 Hz, 3-*N*-C$\underline{H}_2$Ph), 4.74 (1H, d, *J* = 11.5 Hz, 10-OC$\underline{H}_2$Ph), 4.10 (1H, d, *J* = 15.1 Hz, 3-*N*-C$\underline{H}_2$Ph), 3.89 (1H, brd, *J* = 4.4 Hz, 1-H), 3.68–3.65 (1H, m, 2-H), 3.68 (1H, d, *J* = 6.3 Hz, 5-H), 3.67 (3H, s, 9-OC$\underline{H}_3$), 3.16 (1H, dd, *J* = 17.1, 6.3 Hz, 6-H), 2.92 (1H, d, *J* = 11.7 Hz, 2-H), 2.86 (1H, d, *J* = 17.1 Hz, 6-H), 2.29 (3H, s, 11-*N*-C$\underline{H}_3$), 2.29 (3H, s, 8-C$\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2 (s, C-4), 149.3 (s, C-9), 148.3 (s, C-10), 137.3 (s, Bn), 136.3 (s, Bn), 131.2 (d, C-8), 128.4 (d×2, Bn), 128.0 (d×2, Bn), 128.2 (s, C-6a), 127.1 (d, Bn), 126.8 (d, Bn), 126.0 (d, C-7), 125.6 (s, C-10a), 74.1 (t, 10-O$\underline{C}$H$_2$Ph), 59.9 (q, 9-O$\underline{C}$H$_3$), 59.3 (d, C-5), 51.5 (d, C-1), 50.5 (t, C-2), 48.5 (t, 3-*N*-$\underline{C}$H$_2$Ar), 39.7 (q, 11-*N*-$\underline{C}$H$_3$), 27.4 (t, C-6), 15.6 (q, 8-$\underline{C}$H$_3$); IR ($CHCl_3$) 3009, 2940, 1636, 1493, 1454, 1337, 1059, 698 cm^{-1}; EIMS *m/z* (%) 442 (M^+, 30), 351 (10), 295 (23), 294 (100), 204 (30), 203 (37), 91 (11); HREIMS *m/z* 442.2254 (M^+, calcd for $C_{28}H_{30}N_2O_3$ 442.2256).

3.1.6. Synthesis of (1*R*,4*R*,5*S*)-3-Benzyl-10-(benzyloxy)-9-methoxy-8,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**20**)

To a solution of lactam **19** (45.7 mg, 103 μmol) in THF (2.5 mL) at 0 °C was slowly added $LiAlH_2(OEt)_2$ (1.0 mol/L in CH_2Cl_2, 1.20 mL, 1.20 mmol, 12 eq.) over 10 min. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with AcOH (120 μL, 2.15 mmol, 20.8 eq.), followed by the addition of KCN (40.4 mg, 620 μmol, 6.0 eq.) in H_2O (1.0 mL), and stirring was continued for 16 h at 25 °C. The reaction mixture was neutralized with 5% $NaHCO_3$ solution and diluted with saturated Rochell's salt aq., and the mixture was stirred for 1.5 h. The reaction mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 4:1) to afford compound **20** (33.2 mg, 74%) as a colorless

amorphous. $[\alpha]_D^{24}$ −48.4 (*c* 1.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (5H, m, 10-*O*-Bn-H), 7.17–7.14 (3H, m, 3-*N*-Bn-H), 6.90–6.88 (2H, m, 3-*N*-Bn-H), 6.69 (1H, s, 7-H), 5.04 (1H, d, *J* = 11.3 Hz, 10-OCH_2Ph), 4.85 (1H, d, *J* = 11.3 Hz, 10-OCH_2Ph), 3.91 (1H, brs, 1-H), 3.83 (3H, s, 9-OCH_3), 3.65 (1H, s, 4-H), 3.52 (2H, s, 3-*N*-CH_2Ph), 3.21 (1H, d, *J* = 7.6 Hz, 5-H), 3.02 (1H, dd, *J* = 17.6, 7.6 Hz, 6-H), 2.81 (1H, dd, *J* = 11.2, 3.0 Hz, 2-H), 2.51 (1H, brd, *J* = 11.2, Hz, 2-H), 2.35 (1H, d, *J* = 17.6 Hz, 6-H), 2.32 (3H, s, 8-CH_3), 2.15 (3H, s, 11-*N*-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.8 (s, C-9), 148.3 (s, C-10), 137.4 (s, Bn), 137.0 (s, Bn), 130.2 (s, C-6a), 130.0 (s, C-8), 128.4 (d×2, Bn), 128.3 (d, Bn), 128.1 (d×2, Bn), 127.2 (d, Bn), 126.5 (s, C-10a), 124.2 (d, C-7), 116.5 (s, 4-CN), 74.4 (t, 10-OCH_2Ph), 60.0 (q, 9-OCH_3), 59.1 (d, C-4), 58.9 (d, 3-*N*-CH_2Ph), 55.4 (d, C-5), 53.4 (t, C-2), 52.8 (d, C-1), 41.2 (q, 11*N*-CH_3), 25.0 (t, C-6), 15.8 (q, 8-CH_3); IR ($CHCl_3$) 3015, 2936, 2826, 2359, 2342, 2226, 1321, 1227, 1061, 1028, 700 cm^{-1}; EI-MS *m/z* (%) 453 (M^+, 2), 295 (27), 294 (100), 204 (21), 203 (20); HREIMS *m/z* 453.2416 (M^+, calcd for $C_{29}H_{31}N_3O_2$ 453.2416).

3.1.7. Synthesis of (1*R*,4*R*,5*S*)-3-Benzyl-10-hydroxy-9-methoxy-8,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**21**)

To a solution of **20** (20.0 mg, 44.1 μmol) and pentamethylbenzene (65.4 mg, 441 μmol, 10.0 eq.) in CH_2Cl_2 (6.0 mL) was added BCl_3 (1.0 mol/L in CH_2Cl_2, 220 μL, 220 μmol, 5 eq.) at −78 °C and the mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and quenched with saturated $NaHCO_3$ solution at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **21** (14.3 mg, 89%) as a colorless amorphous. $[\alpha]_D^{24}$ −127.4 (*c* 1.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (3H, m, 3-*N*-Bn-H), 6.96–6.92 (2H, m, 3-*N*-Bn-H) 6.48 (1H, s, 7-H), 5.67 (1H, brs, 10-OH), 4.09 (1H, brs, 1-H), 3.78 (3H, s, 9-OCH_3), 3.65 (1H, s, 4-H), 3.62 (1H, d, *J* = 7.8 Hz, 3-*N*-CH_2Ph), 3.54 (1H, d, *J* = 7.8 Hz, 3-*N*-CH_2Ph), 3.27 (1H, brd, *J* = 7.5 Hz, 5-H), 3.06 (1H, dd, *J* = 17.6, 7.5 Hz, 6-H), 2.96 (1H, dd, *J* = 11.2, 2.9 Hz, 2-H), 2.72 (1H, d, *J* = 11.2 Hz, 2-H), 2.38 (3H, s, 11-*N*-CH_3), 2.31 (3H, s, 8-CH_3), 2.38-2.17 (1H, m, overlapped, 6-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.4 (s, C-10), 142.8 (s, C-9), 137.1 (s, Bn), 130.8 (s, C-6a), 128.4 (d, Bn), 128.3 (d, Bn), 128.3 (s, C-8), 127.3 (s, Bn), 120.4 (d, C-7), 119.4 (s, C-10a), 116.6 (4-CN), 60.8 (q, 9-OCH_3), 59.0 (t, 3-*N*-CH_2Ph), 58.6 (d, C-4), 55.4 (d, C-5), 53.0 (t, C-2), 52.5 (d, C-1), 41.5 (q, 11-*N*-CH_3), 25.1 (t, C-6), 15.8 (q, 8-CH_3); IR ($CHCl_3$) 3534, 3019, 2928, 2359, 1454, 1418, 1227, 1059, 1026 cm^{-1}; EIMS *m/z* (%) 363 (M^+, 2), 205 (23), 204 (100), 189 (10); HREIMS *m/z* 363.1943 (M^+, calcd for $C_{22}H_{25}N_3O_2$ 363.1947).

3.1.8. Synthesis of (1*R*,4*R*,5*S*)-3-Benzyl-9-methoxy-8,11-dimethyl-7,10-dioxo-1,2,3,4,5,6,7,10-octahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**6a**)

To a solution of phenol **21** (10.0 mg, 27.5 μmol) in THF (1 mL) was added salcomine (8.90 mg, 27.5 μmol, 1.0 eq.) at 25 °C, and the reaction mixture was stirred for 2.5 h under O_2 atmosphere. The reaction mixture was filtered through a cellulose pad and washed with EtOAc. The filtrate was concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (CH_2Cl_2−MeOH = 99:1) to afford compound **6a** (8.20 mg, 79%) as a dark red amorphous. 99%ee. The ee value was determined by HPLC analysis using CHIRALPAK IC [hexane/EtOH = 80/20, flow 1.0 mL/min, t_r (minor) = 7.08 min, t_r (major) = 7.77 min]; $[\alpha]_D^{27}$ −38.0 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25–7.13 (5H, m, 3-*N*-Bn-H), 4.01 (3H, s, 9-OCH_3), 3.87 (1H, brs, 1-H), 3.66 (1H, d, *J* = 13.2 Hz, 3-*N*-CH_2Ph), 3.54 (1H, d, *J* = 13.2 Hz, 3-*N*-CH_2Ph), 3.54 (1H, d, *J* = 2.0 Hz, 4-H), 3.27 (1H, brd, *J* = 7.4 Hz, 5-H), 2.95 (1H, dd, *J* = 11.6, 3.2 Hz, 2-H), 2.70 (1H, dd, *J* = 20.5, 7.4 Hz, 6-H), 2.58 (1H, d, *J* = 11.6 Hz, 2-H), 2.32 (3H, s, 11-*N*-CH_3), 2.10 (1H, d, *J* = 20.5 Hz, 6-H), 2.01 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 186.9 (s, C-7), 182.3 (s, C-10), 155.4 (s, C-9), 141.0 (s, C-6a), 137.4 (C-10a), 136.2 (s, Bn), 128.7 (d, Bn), 128.6 (d, Bn), 128.6 (s, C-8), 127.9 (d, Bn), 115.8 (s, 4-CN), 61.0 (q, 9-OCH_3), 58.9 (t, C-12), 57.7 (d, C-4), 54.5 (d, C-5), 51.7 (t, C-2), 51.3 (d, C-1), 41.5 (q, ^{11}*N*-CH_3), 20.8 (t, C-6), 8.7 (q, 8-CH_3); IR ($CHCl_3$)

3024, 2928, 2855, 2384, 2228, 1653, 1308, 1234, 1155, 1024 cm^{-1}; EIMS *m/z* (%) 377 (M^+, 12), 220 (18), 219 (100), 218 (99), 204 (29), 176 (13), 91 (21); HREIMS *m/z* 377.1737 (M^+, calcd for $C_{22}H_{23}N_3O_3$ 377.1739).

3.1.9. Synthesis of (1*R*,5*S*)-10-(Benzyloxy)-9-methoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**11**)

To a solution of lactam **17** (3.17 g, 12.0 mmol) in DMF (250 mL) was slowly added NaH (60% oil dispersion, 580 mg, 15.0 mmol, 1.2 eq.) over 10 min at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, after which BnBr (1.70 mL, 15.0 mmol, 1.2 eq.) was added dropwise over 25 min. The reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was diluted with H_2O (300 mL) and extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 99:1) to afford compound **11** (3.81 g, 89%) as a colorless amorphous. $[\alpha]_D^{24}$ −108.2 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (5H, m, 10-O-Bn-H), 6.70 (1H, s, 7-H), 6.18 (1H, brs, 3-*N*-H), 5.18 (1H, d, *J* = 11.6 Hz, 10-OCH_2Ph), 5.08 (1H, d, *J* = 11.6 Hz, 10-OCH_2Ph), 3.92 (1H, d, *J* = 4.7 Hz, 1-H), 3.82 (3H, s, 9-OCH_3), 3.81 (1H, dd, *J* = 10.3, 4.7 Hz 2-H), 3.52 (1H, d, *J* = 6.6 Hz, 5-H), 3.17 (1H, ddd, *J* = 10.3, 3.9, 1.0 Hz, 2-H), 3.13 (1H, dd, *J* = 17.3, 6.6 Hz, 6-H), 2.76 (1H, d, *J* = 17.3 Hz, 6-H), 2.31 (3H, s, 11-*N*-CH_3), 2.25 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.2 (s, C-4), 149.4 (s, C-9), 148.3 (s, C-10), 137.6 (s, C-1′), 131.5 (s, C-8), 128.6 (d, C-3′, C-5′), 128.4 (d, C-6a), 128.1 (d, C-4′), 128.0 (d, C-2′, C-6′), 126.2 (s, C-10a), 125.8 (d, C-7), 74.2 (t, 10-OCH_2Ph), 60.1 (q, 9-OCH_3), 59.0 (d, C-5), 50.5 (d, C-1), 46.3 (t, C-2), 39.8 (q, 11-*N*-CH_3), 27.4 (t, C-6), 15.8 (q, 8-CH_3); IR (KBr) 3169, 3028, 2936, 1678, 1337, 1310, 1055, 702 cm^{-1}; EIMS *m/z* (%) 352 (M^+, 38), 295 (23), 294 (100), 261 (14), 204 (46), 203 (61), 174 (10), 91 (11); HREIMS *m/z* 352.1785 (M^+, calcd for $C_{21}H_{24}N_2O_3$ 352.1787).

3.1.10. Synthesis of (1*R*,5*S*)-10-(Benzyloxy)-9-methoxy-8,11-dimethyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**23**)

To a solution of NaH (60% oil dispersion, 80.3 mg, 2.00 mmol) in THF (10 mL) was added a solution of lactam **11** (705 mg, 2.00 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, after which a solution of bromide **22** (550 mg, 2.00 mmol) in THF (10 mL) was added at 25 °C. The reaction mixture was stirred for 19 h at 25 °C. The reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were washed with brine (150 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 49:1) to afford compound **23** (602 mg, 55%) as a yellow gummy solid and starting material **11** (139 mg, 20% recovery). $[\alpha]_D^{27}$ −55.6 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (3H, m, 10-*O*-Bn-H), 7.25–7.22 (2H, m, 10-*O*-Bn-H), 6.72 (1H, s, 7-H), 5.91 (1H, s, 6′-H), 5.06 (1H, d, *J* = 11.3 Hz, 10-OCH_2Ph), 5.00 (1H, d, *J* = 15.1 Hz, 3-*N*-CH_2Ar), 4.66 (1H, d, *J* = 11.3 Hz, 10-OCH_2Ph), 4.14 (1H, d, *J* = 15.1 Hz, 3-*N*-CH_2Ar), 3.93 (1H, brd, *J* = 4.8 Hz, 1-H), 3.71 (3H, s, 9-OCH_3), 3.69-3.65 (2H, m, 2-H, 5-H), 3.67 (3H, s, 4′-OCH_3), 3.57 (3H, s, 2′-OCH_3), 3.35 (3H, s, 5′-OCH_3), 3.18 (1H, dd, *J* = 17.2, 6.4 Hz, 6-H), 2.96 (1H, dd, *J* = 11.9 Hz, 2-H), 2.88 (1H, d, *J* = 17.2 Hz, 6-H), 2.32 (3H, s, 11-*N*-CH_3), 2.25 (3H, s, 8-CH_3), 2.13 (3H, s, 3′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6 (s, C-4), 150.6 (s, C-2′), 149.4 (s, C-9), 149.4 (s, C-5′), 148.6 (s, C-10), 146.8 (s, C-4′), 137.3 (s, Bn), 131.4 (s, C-8), 128.5 (s, C-6a), 128.5 (d, Bn), 128.4 (d, Bn), 128.1 (d, Bn), 126.4 (s, C-10a), 125.4 (d, C-7), 125.1 (s, C-3′), 124.2 (s, C-1′), 107.8 (d, C-6′), 74.1 (t, 10-OCH_2Ph), 60.9 (q, 2′-OCH_3), 60.1 (q, 4′-OCH_3), 59.9 (q, 9-OCH_3), 59.3 (d, C-5), 55.1 (q, 5′-OCH_3), 51.4 (d, C-1), 50.5 (t, C-2), 42.6 (t, 3-*N*-CH_2Ar), 39.7 (q, 11-*N*-CH_3), 27.5 (t, C-6), 15.7 (q, 8-CH_3), 9.4 (q, 3′-CH_3); IR ($CHCl_3$) 3024, 2943, 2467, 1641, 1452, 1339, 1244, 1061 cm^{-1}; EIMS *m/z* (%) 547 (11), 546 (M^+, 32), 351 (11), 295 (25), 294 (100), 204 (27), 203 (21), 195 (18); HREIMS *m/z* 546.2731 (M^+, calcd for $C_{32}H_{38}N_2O_6$ 546.2730).

3.1.11. Synthesis of (1*R*,4*R*,5*S*)-10-(Benzyloxy)-9-methoxy-8,11-dimethyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**24**)

To a solution of lactam **23** (50.0 mg, 92.0 μmol) in THF (3.0 mL) at 0 °C was slowly added $LiAlH_2(OEt)_2$ (1.0 mol/L in CH_2Cl_2, 1.10 mL, 1.10 mmol, 12 eq.) over 10 min. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with AcOH (100 μL, 1.90 mmol, 20.8 eq.), followed by the addition of KCN (35.8 mg, 549 μmol, 6.0 eq.) in H_2O (2.0 mL), and stirring was continued for 14 h at 25 °C. The reaction mixture was neutralized with 5% $NaHCO_3$ solution and diluted with saturated Rochell's salt aq., and the mixture was stirred for 1 h. The reaction mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **24** (38.2 mg, 75%) as a colorless gummy solid. $[\alpha]_D^{27}$ −23.1 (*c* 1.3, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (5H, m, 10-O-Bn-H), 6.59 (1H, s, 7-H), 6.33 (1H, s, 6′-H), 5.07 (1H, d, *J* = 11.3 Hz, 10-OC$\underline{H}_2$Ph), 4.83 (1H, d, *J* = 11.3 Hz, 10-OC$\underline{H}_2$Ph), 3.93 (1H, brs, 1-H), 3.81 (3H, s, 9-OCH_3), 3.76 (1H, brs, 4-H), 3.71 (3H, s, 4′-OCH_3), 3.58 (1H, d, *J* = 13.5 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.54 (3H, s, 5′-OCH_3), 3.46 (1H, d, *J* = 13.5 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.34 (3H, s, 2′-OCH_3), 3.26 (1H, brd, *J* = 7.7 Hz, 5-H), 3.03 (1H, dd, *J* = 17.9, 7.7 Hz, 6-H), 2.84 (1H, dd, *J* = 10.4, 3.0 Hz, 2-H), 2.56 (1H, d, *J* = 10.4 Hz, 2-H), 2.35 (1H, d, *J* = 17.9 Hz, 6-H), 2.23 (3H, s, 8-CH_3), 2.15 (3H, s, 11-*N*-CH_3), 2.13 (3H, s, 3′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.9 (s, C-2′), 148.8 (s, C-9), 148.7 (s, C-5′), 148.2 (s, C-10), 146.8 (s, C-4′), 137.2 (s, Bn), 129.9 (s, C-6a), 129.8 (s, C-8), 128.3 (d, Bn), 128.2 (d, Bn), 127.9 (d, Bn), 126.7 (s, C-10a), 125.4 (s, C-3′), 124.4 (s, C-1′), 124.0 (d, C-7), 116.5 (s, 4-CN), 109.7 (d, C-6′), 74.2 (t, 10-O$\underline{C}H_2$Ph), 60.7 (q, 2′-O$\underline{C}H_3$), 59.9 (q, 4′-O$\underline{C}H_3$), 59.8 (q, 9-O$\underline{C}H_3$), 59.0 (d, C-4), 55.2 (d, C-5), 55.1 (q, 5′-O$\underline{C}H_3$), 53.7 (t, C-2), 53.1 (t, 3-*N*-$\underline{C}H_2$Ar), 52.6 (d, C-1), 41.0 (q, 11-*N*-$\underline{C}H_3$), 24.9 (t, C-6), 15.5 (q, 8-$\underline{C}H_3$), 9.2 (q, 3′-$\underline{C}H_3$); IR ($CHCl_3$) 3015, 2938, 2226, 1485, 1321, 1227, 1088, 1011 cm^{-1}; EIMS *m/z* (%) 557 (M^+, 1), 295 (25), 294 (100), 204 (13), 203 (16); HREIMS *m/z* 557.2893 (M^+, calcd for $C_{33}H_{39}N_3O_5$ 557.2890).

3.1.12. Synthesis of (1*R*,4*R*,5*S*)-10-Hydroxy-9-methoxy-8,11-dimethyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**25**)

To a solution of **24** (115 mg, 206 μmol) and pentamethylbenzene (306 mg, 2.06 mmol, 10 eq.) in CH_2Cl_2 (30 mL) was added BCl_3 (1.0 mol/L in CH_2Cl_2, 1.00 mL, 1.00 mmol, 5 eq.) over 10 min at −78 °C and the mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated $NaHCO_3$ solution at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **25** (80.7 mg, 84%) as a colorless amorphous. $[\alpha]_D^{26}$ −35.9 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.38 (1H, s, 6′-H), 6.37 (1H, s, 7-H), 5.75 (1H, brs, 10-OH), 4.10 (1H, brs, 1-H), 3.77 (1H, brs, 4-H), 3.76 (3H, s, 9-OCH_3), 3.74 (3H, s, 4′-OCH_3), 3.61 (1H, d, *J* = 13.5 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.57 (3H, s, 5′-OCH_3), 3.55 (1H, d, *J* = 13.5 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.38 (3H, s, 2′-OCH_3), 3.32 (1H, brd, *J* = 7.8 Hz, 5-H), 3.08 (1H, dd, *J* = 18.1, 7.8 Hz, 6-H), 2.99 (1H, dd, *J* = 11.0, 3.0 Hz, 2-H), 2.80 (1H, d, *J* = 11.0 Hz, 2-H), 2.38 (3H, s, ^{11}*N* -CH_3), 2.35 (1H, d, *J* = 18.1 Hz, 6-H), 2.22 (3H, s, 8-CH_3), 2.13 (3H, s, 3′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.0 (s, C-2′), 148.9 (s, C-5′), 146.8 (s, C-4′), 145.5 (s, C-10), 142.8 (s, C-9), 130.5 (s, C-6a), 127.9 (s, C-8), 125.5 (s, C-3′), 124.5 (s, C-1′), 120.2 (d, C-7), 119.6 (s, C-10a), 116.7 (s, 4-CN), 109.7 (d, C-6′), 60.9 (q, 9-O$\underline{C}H_3$), 60.6 (q, 4′-O$\underline{C}H_3$), 60.1 (q, 2′-O$\underline{C}H_3$), 58.7 (d, C-4), 55.3 (q, 5′-O$\underline{C}H_3$), 55.3 (d, C-5), 53.4 (t, C-2), 53.3 (t, 3-*N*-$\underline{C}H_2$Ar), 52.4 (d, C-1), 41.4 (q, 11-*N*-$\underline{C}H_3$), 25.0 (t, C-6), 15.5 (q, 8-$\underline{C}H_3$), 9.3 (q, 3′-$\underline{C}H_3$); IR ($CHCl_3$) 3534, 3015, 2940, 2226, 1487, 1331, 1227, 1088, 1011 cm^{-1}; EIMS *m/z* (%) 467 (M^+, 1), 441 (13), 440 (48), 247 (16), 246 (12), 245 (57), 205 (19), 204 (100), 195 (20); HREIMS *m/z* 467.2421 (M^+, calcd for $C_{26}H_{33}N_3O_5$ 467.2420).

3.1.13. Synthesis of (1*R*,4*R*,5*S*)-9-Methoxy-8,11-dimethyl-7,10-dioxo-3-(2,4,5-trimethoxy-3-methylbenzyl)-1,2,3,4,5,6,7,10-octahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**6d**)

To a solution of phenol **25** (16.6 mg, 35.5 μmol) in THF (1 mL) was added salcomine (11.5 mg, 35.5 μmol, 1.0 eq.) at 25 °C, and the reaction mixture was stirred 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 to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 1:1) to afford compound **6d** (13.5 mg, 79%) as a yellow amorphous. $[\alpha]_D^{27}$ +104.7 (*c* 0.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$); δ 6.52 (1H, s, 6′-H), 4.01 (3H, s, 9-OCH_3), 3.88 (1H, brs, 1-H), 3.76 (3H, s, 4′-OCH_3), 3.69 (1H, brs, 4-H), 3.66 (3H, s, 5′-OCH_3), 3.61 (2H, s, 3-*N*-$C\underline{H}_2Ar$), 3.56 (3H, s, 2′-OCH_3), 3.31 (1H, brd, *J* = 7.3 Hz, 5-H), 3.00 (1H, dd, *J* = 11.3, 3.2 Hz, 2-H), 2.69 (1H, dd, *J* = 20.7, 7.3 Hz, 6-H), 2.62 (1H, d, *J* = 11.3 Hz, 2-H), 2.35 (3H, s, 11-*N*-CH_3), 2.16 (1H, d, *J* = 20.7 Hz, 6-H), 2.15 (3H, s, 3′-CH_3), 1.94 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 186.8 (s, C-7), 182.2 (s, C-10), 155.4 (s, C-9), 151.4 (s, C-2′), 149.2 (s, C-5′), 147.5 (s, C-4′), 140.9 (s, C-6a), 137.6 (s, C-10a), 128.3 (s, C-8), 126.0 (s, C-3′), 123.8 (s, C-1′), 116.1 (s, 4-CN), 109.9 (d, C-6′), 61.1 (q, 2′-O$\underline{C}H_3$), 61.0 (q, 9-O$\underline{C}H_3$), 60.2 (q, 4′-O$\underline{C}H_3$), 57.9 (d, C-4), 55.7 (q, 5′-O$\underline{C}H_3$), 54.5 (d, C-5), 53.2 (t, 3-*N*-$\underline{C}H_2Ar$), 51.9 (t, C-2), 51.4 (d, C-1), 41.5 (q, 11-*N*-$\underline{C}H_3$), 20.8 (t, C-6), 9.5 (q, 3′-$\underline{C}H_3$), 8.6 (q, 8-$\underline{C}H_3$); IR ($CHCl_3$) 3015, 2941, 2228, 1653, 1308, 1236, 1088, 1009 cm^{-1}; EI-MS *m/z* (%) 481 (M^+, 9), 220 (11), 219 (15), 218 (45), 196 (14), 195 (100); HREIMS *m/z* 481.2212 (M^+, calcd for $C_{26}H_{31}N_3O_6$ 481.2213).

3.1.14. Synthesis of 2-(Benzyloxy)-1-(bromomethyl)-3-methoxy-4-methylbenzene (**27**)

To a solution of alcohol **26** (100 mg, 387 μmol) in CH_2Cl_2 (2 mL) was added PPh_3 (125 mg, 465 μmol, 1.2 eq.) and CBr_4 (162 mg, 465 μmol, 1.2 eq.) at 25 °C, and the reaction mixture was stirred for 6.5 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 4:1) to afford compound **27** (123 mg, 99%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54–7.31 (5H, m, Bn-H), 7.03 (1H, d, *J* = 7.8 Hz, 6-H), 6.93 (1H, d, *J* = 7.8 Hz, 5-H), 5.12 (2H, s, 2-O$\underline{C}H_2$Ph), 4.56 (2H, s, 1-$\underline{C}H_2$Br), 3.86 (3H, s, 3-OCH_3), 2.30 (3H, s, 4-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.7 (s, C-3), 150.1 (s, C-2), 137.4 (s, Bn), 133.6 (s, C-4), 129.9 (s, C-1), 128.5 (d, Bn), 128.4 (d, Bn), 128.2 (d, Bn), 126.1 (d, C-5), 125.2 (d, C-6), 75.2 (t, 2-O$\underline{C}H_2$Ph), 60.2 (q, 3-OCH_3), 41.4 (t, 1-$\underline{C}H_2$Br), 15.9 (q, 4-CH_3); IR ($CHCl_3$) 3034, 3012, 2936, 1462, 1414, 1278, 1227, 1069 cm^{-1}; EIMS *m/z* (%) : 322 (1), 320 (M^+, 1), 241 (10), 151 (11), 150 (100), 149 (19), 91 (50); HREIMS *m/z* 320.0413 (M^+, calcd for $C_{16}H_{17}BrO_2$ 320.0412).

3.1.15. Synthesis of (1*R*,5*S*)-10-(Benzyloxy)-3-(2-(benzyloxy)-3-methoxy-4-methylbenzyl)-9-methoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[d]azocin-4(1H)-one (**28**)

To a solution of NaH (60% oil dispersion, 5.70 mg, 142 μmol, 1.0 eq.) in THF (10 mL) was added a solution of lactam **11** (50.0 mg, 142 μmol) in THF (0.7 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, after which a solution of bromide **27** (45.6 mg, 142 μmol, 1.0 eq.) in THF (0.7 mL) was added at 25 °C. The reaction mixture was stirred for 12 h at 25 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography ($CHCl_3$−MeOH = 49:1) to afford compound **28** (60.8 mg, 72%) as a colorless oil. $[\alpha]_D^{26}$ −67.0 (*c* 2.2, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$); δ 7.37–7.25 (10H, m, 10-*O*-Bn-H, 2′-*O*-Bn-H), 6.71 (1H, s, 7-H), 6.50 (1H, d, *J* = 7.8 Hz, 5′-H), 5.96 (1H, d, *J* = 7.8 Hz, 6′-H), 4.98 (1H, d, *J* = 11.4 Hz, 10-O$\underline{C}H_2$Ph), 4.88 (2H, s, 2′-O$\underline{C}H_2$Ph), 4.84 (1H, d, *J* = 11.4 Hz, 10-O$\underline{C}H_2$Ph), 4.76 (1H, d, *J* = 15.5 Hz, 3-*N*-$C\underline{H}_2Ar$), 4.12 (1H, d, *J* = 15.5 Hz, 3-*N*-$C\underline{H}_2Ar$), 3.90 (1H, brd, *J* = 4.6 Hz, 1-H), 3.76 (3H, s, 3′-OCH_3), 3.72 (3H, s, 9-OCH_3), 3.63 (1H, d, *J* = 6.2 Hz, 5-H), 3.59 (1H, dd, *J* = 11.8, 4.6 Hz, 2-H), 3.14 (1H, dd, *J* = 16.9, 6.2 Hz, 6-H), 2.87 (1H, d, *J* = 11.8 Hz, 2-H), 2.82 (1H, d, *J* = 16.9 Hz, 6-H), 2.31 (3H, s, 11-*N*-CH_3), 2.28 (3H, s, 8-CH_3), 2.17 (3H, s, 4′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3 (s, C-4), 151.2 (s, C-3′), 149.8 (s, C-2′), 149.4 (s, C-9), 148.4 (s, C-10), 137.4

(s×2, Bn), 131.2 (s, C-8), 130.9 (s, C-4′), 128.6 (d, Bn), 128.4 (d×2, Bn), 128.4 (s, C-6a), 128.2 (d, Bn), 128.0 (d, Bn), 127.9 (d, Bn), 126.3 (s, C-10a), 125.7 (d, C-7), 125.7 (d, C-5′), 121.9 (d, C-6′), 74.6 (t, 2′-O$\underline{C}H_2$Ph), 74.1 (t, 10-O$\underline{C}H_2$Ph), 60.0 (q, 3′-O$\underline{C}H_3$), 59.9 (q, 9-O$\underline{C}H_3$), 59.4 (d, C-5), 51.5 (d, C-1), 50.7 (t, C-2), 43.2 (t, 3-*N*-$\underline{C}H_2$Ar), 39.7 (q, 11-*N*-$\underline{C}H_3$), 27.4 (t, C-6), 15.7 (q, 8-$\underline{C}H_3$), 15.6 (q, 4′-$\underline{C}H_3$); IR ($CHCl_3$) 3013, 2938, 2467, 1641, 1449, 1337, 1273, 1061 cm^{-1}; EIMS *m/z* (%) 593 (17), 592 (M^+, 40), 295 (26), 294 (100), 204 (29), 203 (20), 91 (10); HREIMS *m/z* 592.2934 (M^+, calcd for $C_{37}H_{40}N_2O_5$ 592.2937).

3.1.16. Synthesis of (1*R*,4*R*,5*S*)-10-(Benzyloxy)-3-(2-(benzyloxy)-3-methoxy-4-methylbenzyl)-9-methoxy-8,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**29**)

To a solution of lactam **28** (85.6 mg, 144 μmol) in THF (4.5 mL) at 0 °C was slowly added $LiAlH_2(OEt)_2$ (1.0 mol/L in CH_2Cl_2, 1.70 mL, 1.70 mmol, 12 eq.) over 10 min. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with AcOH (170 μL, 3.00 mmol, 20.8 eq.), followed by the addition of KCN (57.8 mg, 866 μmol, 6.0 eq.) in H_2O (2.0 mL), and stirring was continued for 14 h at 25 °C. The reaction mixture was neutralized with 5% $NaHCO_3$ solution and diluted with saturated Rochell's salt aq., and the mixture was stirred for 1 h. The reaction mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **29** (61.5 mg, 71%) as a colorless gummy solid. $[\alpha]_D^{27}$ −31.2 (*c* 0.8, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43–7.25 (10H, m, 10-*O*-Bn-H, 2′-*O*-Bn-H), 6.70 (1H, d, *J* = 7.8 Hz, 5′-H), 6.53 (1H, d, *J* = 7.8 Hz, 6′-H), 6.46 (1H, s, 7-H), 5.03 (1H, d, *J* = 11.2 Hz, 10-OC$\underline{H}_2$Ph), 4.72 (1H, d, *J* = 11.2 Hz, 10-OC$\underline{H}_2$Ph), 4.59 (1H, d, *J* = 10.6 Hz 2′-OC$\underline{H}_2$Ph), 4.54 (1H, d, *J* = 10.6 Hz 2′-OC$\underline{H}_2$Ph), 3.95 (1H, brs, 1-H), 3.71 (3H, s, 9-OCH_3), 3.70 (1H, s, 4-H), 3.68 (3H, s, 3′-OCH_3), 3.58 (1H, d, *J* = 13.1 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.45 (1H, d, *J* = 13.1 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.23 (1H, brd, *J* = 7.8 Hz, 5-H), 2.95 (1H, dd, *J* = 16.7, 7.8 Hz, 6-H), 2.79 (1H, dd, *J* = 11.0, 3.0 Hz, 2-H), 2.56 (1H, d, *J* = 11.0 Hz, 2-H), 2.27 (1H, d, *J* = 16.7 Hz, 6-H), 2.20 (3H, s, 4′-CH_3), 2.14 (3H, s, 11-*N*-CH_3), 2.12 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.8 (s, C-3′), 150.6 (s, C-2′), 148.9 (s, C-9), 148.4 (s, C-10), 137.9 (s, Bn), 137.5 (s, Bn), 131.8 (s, C-4′), 130.1 (s, C-8), 129.9 (s, C-6a), 128.7 (s, C-1′), 128.5 (d, Bn), 128.3 (d, Bn), 128.2 (d, Bn), 128.1 (d, Bn), 127.9 (d, Bn), 127.7 (d, Bn), 126.5 (s, C-10a), 125.5 (d, C-5′), 124.9 (d, C-6′), 124.4 (d, C-7), 116.7 (s, 4-CN), 75.0 (t, 2′-O$\underline{C}H_2$Ph), 74.3 (t, 10-O$\underline{C}H_2$Ph), 60.1 (q, 3′-O$\underline{C}H_3$), 60.0 (q, 9-O$\underline{C}H_3$), 59.4 (d, C-4), 55.4 (d, C-5), 53.8 (t, 3-*N*-$\underline{C}H_2$Ar), 53.7 (t, C-2), 52.7 (d, C-1), 41.2 (q, 11-*N*-$\underline{C}H_3$), 25.0 (t, C-6), 15.7 (q, 8-$\underline{C}H_3$), 15.7 (q, 4′-$\underline{C}H_3$); IR ($CHCl_3$) 3015, 2930, 2226, 1454, 1321, 1076, 1028, 700 cm^{-1}; EI-MS *m/z* (%) 603 (M^+, 1), 337 (11), 295 (24), 294 (100), 204 (13), 203 (18), 91 (14); HREIMS *m/z* 603.3099 (M^+, calcd for $C_{38}H_{41}N_3O_4$ 603.3097).

3.1.17. Synthesis of (1*R*,4*R*,5*S*)-10-Hydroxy-3-(2-hydroxy-3-methoxy-4-methylbenzyl)-9-methoxy-8,11-dimethyl-1,2,3,4,5,6-hexahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**30**)

To a solution of **29** (47.8 mg, 79.2 μmol) and pentamethylbenzene (117 mg, 792 μmol, 10 eq.) in CH_2Cl_2 (13 mL) was added BCl_3 (1.0 mol/L in CH_2Cl_2, 400 μL, 400 μmol, 5.0 eq.) over 17 min at −78 °C and the mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$ solution (20 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a residue. To a solution of the obtained residue (168 mg) in THF (5 mL), AcOH (100 μL, 1.66 mmol, 21 eq.) was added. The reaction mixture was stirred for 5 min, after which KCN (31.0 mg, 475 μmol, 6 eq.) in H_2O (5.0 mL) was added. The reaction mixture was stirred for 1 h at 25 °C. The reaction mixture was neutralized with 5% $NaHCO_3$ and diluted with saturated Rochell's salt aq., and the mixture was stirred for 1 h. The reaction mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **30** (28.5 mg, 85%) as a colorless gummy solid. $[\alpha]_D^{27}$ −46.5 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, brs, 2′-OH), 6.67 (1H, d, *J* = 7.8 Hz, 6′-H), 6.58 (1H, d, *J* = 7.8 Hz, 5′-H), 6.52 (1H, s, 7-H), 5.63

(1H, s, 10-OH), 4.16 (1H, brs, 1-H), 3.80 (1H, brs, 4-H), 3.78 (3H, s, 9-OCH_3), 3.74 (1H, d, *J* = 13.7 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.68 (1H, d, *J* = 13.7 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.67 (3H, s, 3′-OCH_3), 3.37 (1H, brd, *J* = 7.0 Hz, 5-H), 3.14 (1H, dd, *J* = 19.2, 7.0 Hz, 6-H), 3.01 (1H, dd, *J* = 10.8, 2.7 Hz, 2-H), 2.84 (1H, d, *J* = 10.8 Hz, 2-H), 2.44 (1H, d, *J* = 19.2 Hz, 6-H), 2.41 (3H, s, 11-*N*-CH_3), 2.29 (3H, s, 8-CH_3), 2.19 (3H, s, 4′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.3 (s, C-2′), 146.2 (s, C-3′), 145.4 (s, C-10), 143.3 (s, C-9), 132.0 (s, C-4′), 129.1 (s, C-8), 129.1 (s, C-6a), 123.9 (s, C-6′), 121.4 (d, C-7), 121.3 (d, C-5′), 118.8 (s, C-1′), 118.0 (s, C-10a), 115.3 (s, 4-CN), 60.8 (q, 9-O$\underline{C}H_3$), 59.6 (q, 3′-O$\underline{C}H_3$), 57.9 (d, C-4), 57.8 (t, 3-*N*-$\underline{C}H_2$Ar), 55.1 (d, C-5), 53.3 (t, C-2), 52.2 (d, C-1), 41.5 (q, 11-*N*-$\underline{C}H_3$), 24.7 (t, C-6), 15.9 (q, 8-$\underline{C}H_3$), 15.9 (q, 4′-$\underline{C}H_3$); IR ($CHCl_3$) 3532, 3007, 2928, 2232, 1464, 1418, 1242, 1227, 1074 cm^{-1}; FABMS *m/z* 424 $[M + H]^+$; HRFABMS *m/z* 424.2234 ($[M + H]^+$, calcd for $C_{24}H_{30}N_3O_4$ 424.2236).

3.1.18. Synthesis of (1*R*,4*R*,5*S*)-9-Methoxy-3-((5-methoxy-4-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)methyl)-8,11-dimethyl-7,10-dioxo-1,2,3,4,5,6,7,10-octahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**6b**) and (1*R*,4*R*,5*S*)-3-(2-hydroxy-3-methoxy-4-methylbenzyl)-9-methoxy-8,11-dimethyl-7,10-dioxo-1,2,3,4,5,6,7,10-octahydro-1,5-epiminobenzo[d]azocine-4-carbonitrile (**6c**)

To a solution of phenol **30** (17.3 mg, 40.8 μmol) in THF (1.5 mL) was added salcomine (27.6 mg, 81.6 μmol, 2.0 eq.) at rt, and the reaction mixture was stirred for 18 h under O_2 atmosphere. The reaction mixture was filtered through a cellulose pad and washed with EtOAc. The filtrate was concentrated in vacuo to give a residue. The residue was purified by SiO_2 flash column chromatography (n-Hex.−EtOAc = 2:1) to afford compound **6b** (8.0 mg, 43%) as a yellow oil, and **6c** (5.6 mg, 31%) as a yellow oil.

6b: $[\alpha]_D^{27}$ −70.3 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.27 (1H, t, *J* = 1.8 Hz, 2′-H), 4.00 (3H, s, 9-OCH_3), 3.90 (3H, s, 5′-OCH_3), 3.86 (1H, brs, 1-H), 3.74 (1H, brd, *J* = 1.8 Hz, 4-H), 3.49 (1H, d, *J* = 16.5, 1.8 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.39 (1H, d, *J* = 16.5, 1.8 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.34 (1H, brd, *J* = 7.3 Hz, 5-H), 2.98 (1H, dd, *J* = 11.1, 3.0 Hz, 2-H), 2.75 (1H, dd, *J* = 20.7, 7.3 Hz, 6-H), 2.54 (1H, d, *J* = 11.1 Hz, 2-H), 2.34 (3H, s, 11-*N*-CH_3), 2.20 (1H, d, *J* = 20.7 Hz, 6-H), 1.98 (3H, s, 8-CH_3), 1.89 (3H, s, 4′-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 187.4 (s, C-3′), 186.7 (s, C-7), 182.5 (s, C-6′), 182.2 (s, C-10), 155.9 (s, C-5′), 155.5 (s, C-9), 141.3 (s, C-1′), 140.9 (s, C-6a), 136.9 (s, C-10a), 132.9 (d, C-2′), 129.1 (s, C-8), 129.0 (s, C-4′), 116.0 (s, 4-CN), 61.1 (q, 9-OCH_3), 60.7 (q, 5′-OCH_3), 59.3 (d, 4-C), 54.7 (d, 5-C), 52.3 (t, 3-*N*-$\underline{C}H_2$Ar), 51.2 (d, 1-C), 50.8 (t, 2-C), 41.4 (q, 11-*N*-$\underline{C}H_3$), 20.8 (t, 6-C), 8.7 (q, 8-CH_3), 8.5 (q, 4′-CH_3); IR ($CHCl_3$) 3017, 2945, 2359, 2230, 1655, 1612, 1308, 1234, 1153 cm^{-1}; EIMS *m/z* (%) 451 (M^+, 6), 261 (18), 260 (37), 233 (11), 232 (25), 220 (12), 219 (43), 218 (100), 204 (26), 190 (11), 176 (13), 166 (19), 83 (10); HREIMS *m/z* 451.1740 (M^+, calcd for $C_{24}H_{25}N_3O_6$ 451.1743).

6c: $[\alpha]_D^{27}$ +95.3 (*c* 0.2, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, brs, 2′-OH), 6.68 (1H, d, *J* = 7.8 Hz, 6′-H), 6.60 (1H, d, *J* = 7.8 Hz, 5′-H), 4.00 (3H, s, 9-OCH_3), 3.92 (1H, brs, 1-H), 3.78 (1H, d, *J* = 14.0 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.75 (1H, brs, 4-H), 3.73 (1H, d, *J* = 14.0 Hz, 3-*N*-C$\underline{H}_2$Ar), 3.70 (3H, s, 3′-OCH_3), 3.38 (1H, brd, *J* = 7.4 Hz, 5-H), 2.99 (1H, dd, *J* = 11.7, 3.2 Hz, 2-H), 2.79 (1H, dd, *J* = 20.8, 7.4 Hz, 6-H), 2.70 (1H, d, *J* = 11.7 Hz, 2-H), 2.36 (3H, s, 11-*N*-CH_3), 2.23 (1H, d, *J* = 20.8 Hz, 6-H), 2.20 (3H, s, 4′-CH_3), 2.00 (3H, s, 8-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 186.2 (s, C-7), 182.1 (s, C-10), 155.4 (s, C-9), 149.0 (s, C-2′), 146.1 (s, C-3′), 140.8 (s, C-6a), 136.9 (s, C-10a), 132.2 (s, C-4′), 129.2 (s, C-8), 124.0 (d, C-6′), 121.6 (d, C-5′), 118.2 (s, C-1′), 114.9 (s, 4-CN), 61.0 (q, 9-O$\underline{C}H_3$), 59.8 (q, 3′-O$\underline{C}H_3$), 57.5 (d, C-4), 57.2 (t, 3-*N*-$\underline{C}H_2$Ar), 54.3 (d, C-5), 51.3 (t, C-2), 51.1 (d, C-1), 41.5 (q, 11-*N*-$\underline{C}H_3$), 20.7 (t, C-6), 15.9 (q, 4′-$\underline{C}H_3$), 8.8 (q, 8-$\underline{C}H_3$); IR ($CHCl_3$) 3524, 3022, 2945, 2853, 2359, 2234, 1653, 1614, 1308, 1236, 1152 cm^{-1}; EIMS *m/z* (%) : 437 (M^+, 5), 411 (24), 410 (100), 261 (19), 260 (80), 259 (12), 245 (12), 234 (24), 233 (20), 232 (43), 231 (14), 220 (21), 219 (49), 218 (98), 217 (12), 204 (26), 203 (13), 202 (15), 192 (19), 190 (12), 176 (13), 151 (14), 150 (33), 149 (17), 91 (13), 77 (12). HREIMS *m/z* 437.1956 (M^+, calcd for $C_{24}H_{27}N_3O_5$ 437.1951).

3.2. Biological Evaluation

A single-cell suspension of each cell line (2×10^3 cells/well) was added to the serially diluted test compounds in a 96-well microplate and cultured for 4 days. Cell viability was measured with Cell Counting Kit-8 (Dojindo Laboratories, Kumamoto, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with the untreated control.

4. Conclusions

We presented a short and efficient methodology for the preparation of the chiral right-half model compounds of renieramycins. The synthesized model compounds were screened for their cytotoxic activity against DU145 and HCT116. Compounds **6a** and **21** bearing benzyl group at 3-nitrogen showed very strong activity with IC_{50} at nanomolar concentrations. It was also found that chirality had no effect on the cytotoxic activities of the model compounds.

Author Contributions: T.M. synthesized the compounds, N.S. (Natchanun Sirimangkalakitti) performed the cytotoxicity assays, M.Y. and N.S. (Naoki Saito) analyzed the data and wrote the manuscript.

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