HETEROCYCLES, Vol. 74, 2007, pp. 411 - 420. © The Japan Institute of Heterocyclic Chemistry
Received, 1st August, 2007, Accepted, 30th August, 2007, Published online, 4th September, 2007. COM-07-S(W)20

CHEMISTRY OF TETRAHYDROISOQUINOLINE ANTITUMOR NATURAL PRODUCTS: PREPARATION AND ANTITUMOR ACTIVITY OF ANALOGUES OF CRIBROSTATIN 4

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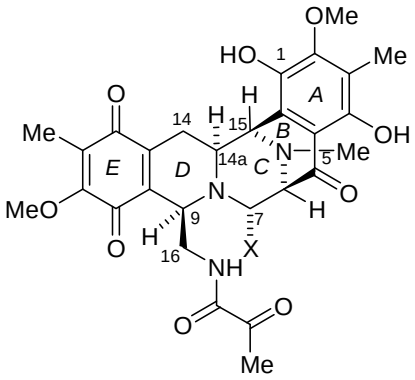
Abstract – The two-step transformation of saframycin G（**9**）into saframycin F (**1b**) and renieramycin O (**11**) into renieramycin Q (**2**) is described, along with the results of cytotoxicity studies.

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt (The University of Hanover) on the occasion of his 75th birthday.

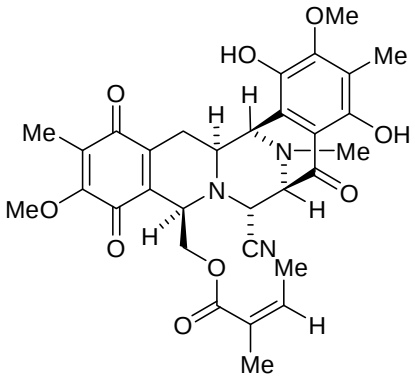
INTRODUCTION

Renieramycins are isoquinoline marine natural products that are related structurally to other isoquinoline natural products including saframycins, naphthyridinomycin, and ecteinascidins.[1] The ring system of renieramycins, along with their relative stereochemistry, is identical with that of saframycins that exhibit strong cytotoxicity against cultured cells and antitumor activity against several experimental tumors. Our research group has long been involved in the chemistry of these natural products.[2] We are very interested in monoquinone-type natural products, such as saframycins D (**1a**)[3a] and F (**1b**)[3b] from *Streptomyces lavendulae*, renieramycin Q (**2**)[4] from the Thai blue sponge *Xestospongia* sp., jorunnamycin B (**3**)[5] from the Thai nudibranch *Jorunna funebris*, and cribrostatin 4 (**4**)[6,7] from *Cribrochalina* sp. found in reef passages in the Republic of Maldives (Figure 1), because we speculate that the biosynthetic pathway may involve the initial oxidation of type I phenol to form type II *p*-quinone, into which a hydroxyl group could be introduced at the C-5 position to give type III α-hydroxyquinone, which in turn would be oxidized and reduced (redox process) to form type IV α-carbonylhydroquinone (Scheme 1).[8] Following our hypothesis,

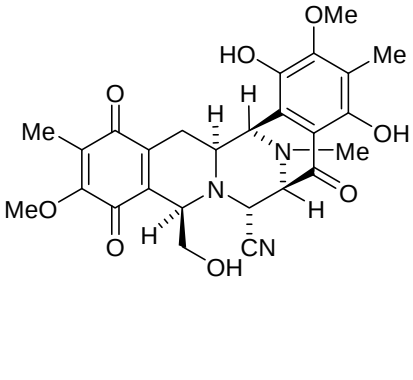
we have succeeded in the model conversion of **5** into **8** *via* **6** and **7,** as shown in Scheme 2.[9,10] However, one problem remains, namely, the yield of the transformation of **7** into **8** with selenium dioxide in *p*-xylene is low.



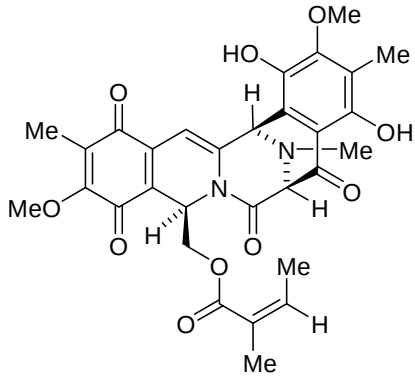
safraymycins
D (**1a**): X = H
F (**1b**): X = CN



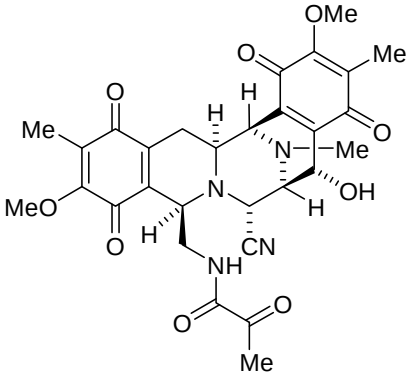
renieramycin Q (**2**)



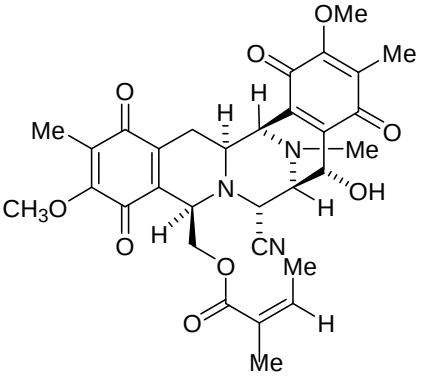
jorunnamycin B (**3**)



cribrostatin 4 (**4**)

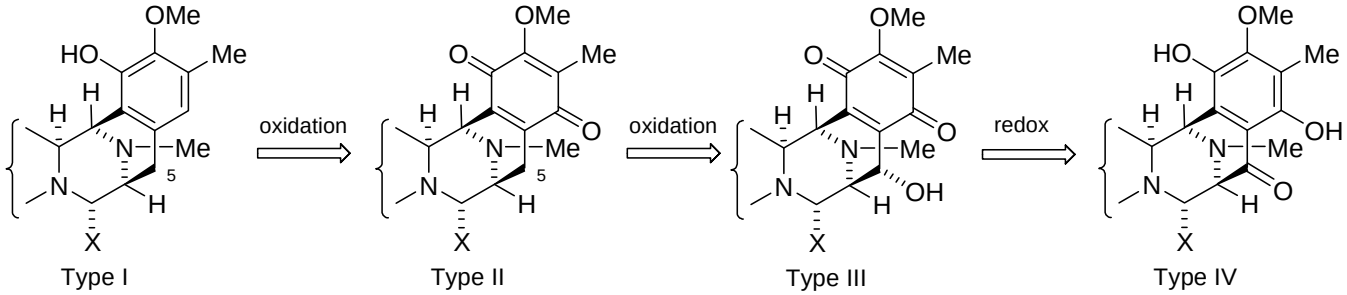


saframycin G (**9**)



renieramycin O (**11**)

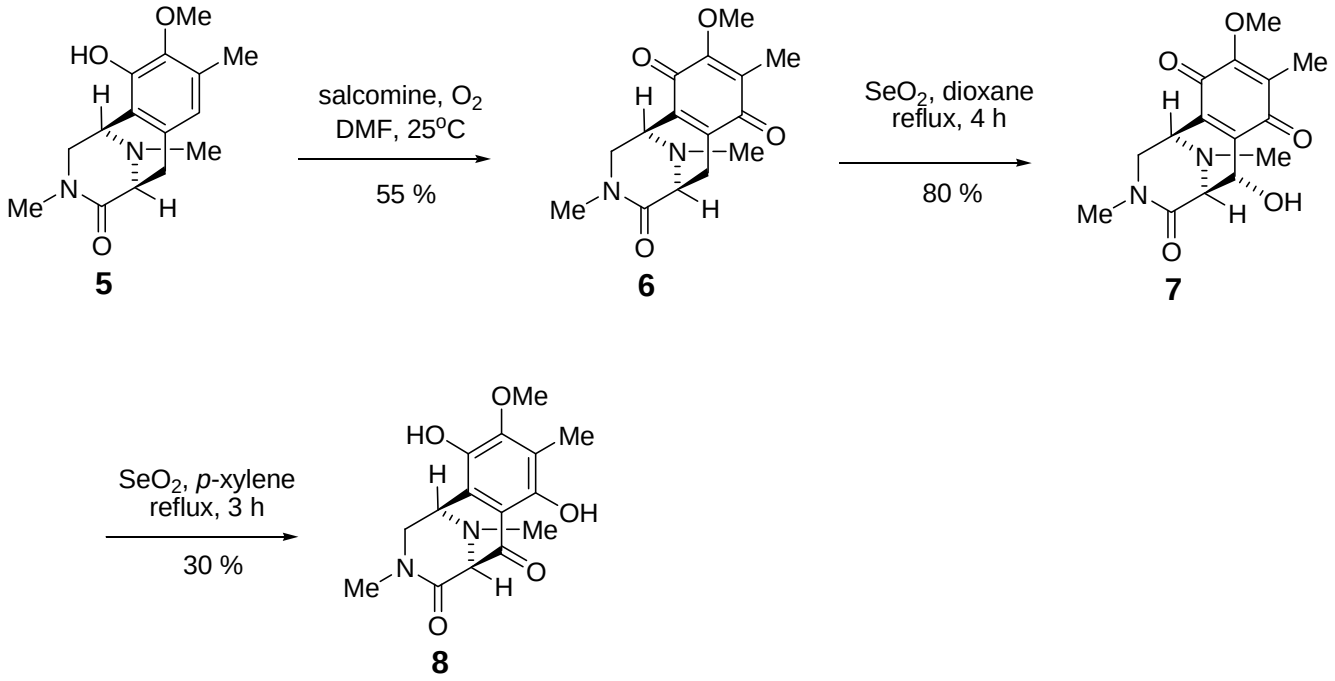
Figure 1



Scheme 1

In this paper, we report an efficient model conversion of **7** into **8** *via* α-carbonylquinone **13** by a stepwise process that includes Dess Martin periodinane (DMP)[11] oxidation and catalytic hydrogenation, and its

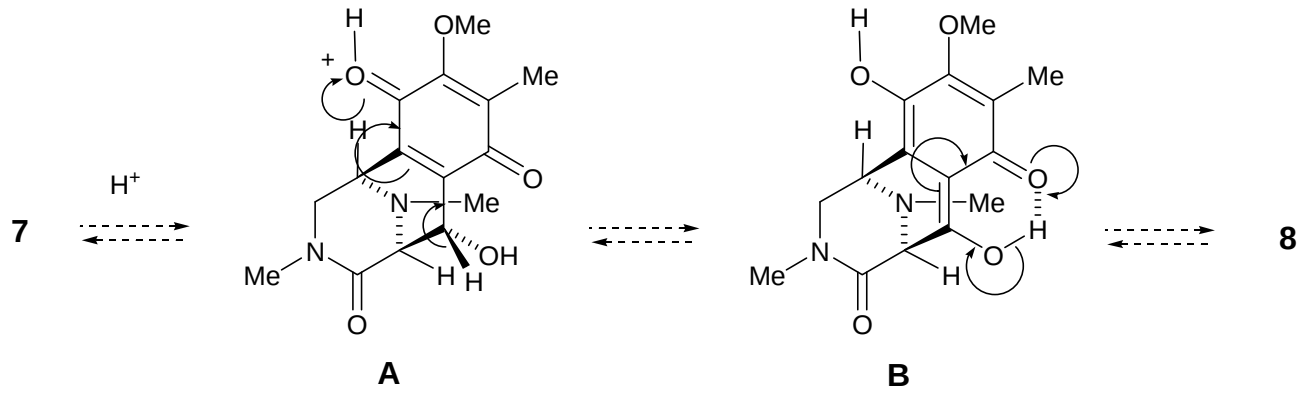
application to the successful transformation of saframycin G (**9**) into saframycin F (**1b**), and renieramycin O (**11**) into renieramycin Q (**2**), respectively.



Scheme 2

RESULTS AND DISCUSSION

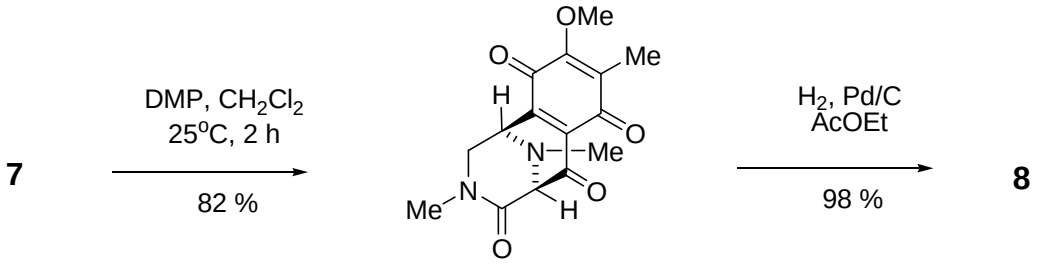
A preliminary experiment for the conversion of α-hydroxyquinone into α-carbonylhydroquinone was carried out using readily available model compound **7**.[9] We are very interested in the possibility that both isomers **7** and **8** are tautomers; however, treatment of **7** with H_2SO_4 in methanol gave no detectable products, and only the starting material was recovered (Scheme 3).



Scheme 3

Accordingly, the sequence of reactions was re-examined. Oxidation of alcohol **7** with DMP in dichloromethane afforded α-carbonylquinone **13** as dark green prisms in 82% yield. Hydrogenation of **13**

with 10% palladium on carbon in AcOEt gave **8** in 98% yield (Scheme 4).



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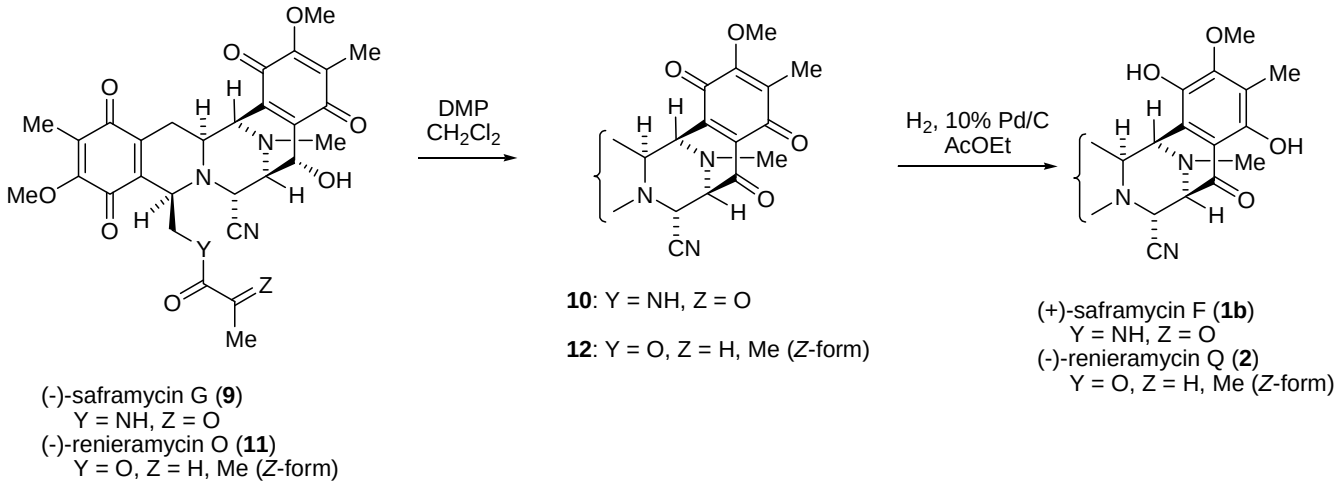
Scheme 4

Encouraged by the results of model studies, we successfully applied the above procedure to the transformation of natural products. Oxidation of (-)-saframycin G (**9**)[3b] with DMP in dichloromethane at 25°C for 7 h afforded compound **10** in 75% yield. When **10** was hydrogenated with 10% palladium on carbon in AcOEt for 10 h, the dark yellow reaction solution became colorless, indicating that the bishydroquinone was formed. During workup, however, selective air oxidation occurred at the E ring to afford (+)-saframycin F (**1b**) in 73% yield. This two-step transformation of (-)-renieramycin O (**11**)[4] into (-)-renieramycin Q (**2**) *via* compound (**12**) was also accomplished in high yield (Scheme 5).



(-)-saframycin G (**9**)
Y = NH, Z = O
(-)-renieramycin O (**11**)
Y = O, Z = H, Me (*Z*-form)

10: Y = NH, Z = O

12: Y = O, Z = H, Me (*Z*-form)

(+)-saframycin F (**1b**)
Y = NH, Z = O
(-)-renieramycin Q (**2**)
Y = O, Z = H, Me (*Z*-form)

Scheme 5

(-)-Cribrostatin 4 (**4**) possesses a characteristic chemical structure that includes the C^{14}=C^{14a} benzylic olefin, in the context of the E-ring quinone, which serves as a central connecting element in a formal vinylogous imidic network. The scarcity of natural availability of **4** in conjunction with its potent antiproliferative activity has made it an attractive synthetic target. The first total synthesis of **4** was accomplished by Danishefsky and co-workers,[12] and two total syntheses were recently accomplished by

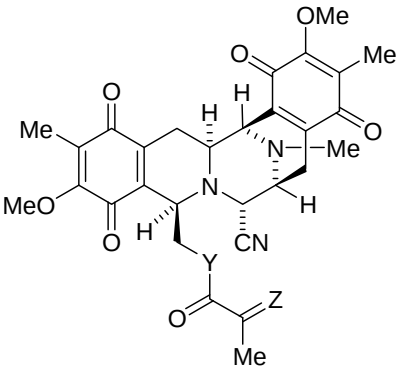
Vincent and Williams[13] and Chen and Zhu,[14] respectively. However, the structure-activity relationships of **4** are still unexplored as most of the synthetic work carried out so far focused on the total synthesis. It is very interesting that **4** displays cytotoxic and antimicrobial activities at micromolar concentrations, despite the lack of hemiaminal or α-aminonitrile function of the other members at C-7. Thus, the antiproliferative activity of the studied compounds was evaluated using three human cell lines, and the results are shown in the Table. The cytotoxicities of compounds **8**, **1b**, and **2** were similar to those of parent compounds **7**, **9**, and **11**, respectively. The activity of **10** was surprisingly low, and no cytotoxicity was detected in α-carbonylquinones **12** and **13**.

In conclusion, we succeeded in the two-step conversion of saframycin G (**9**) and renieramycin O (**11**) into saframycin F (**1b**) and renieramycin Q (**2**) *via* corresponding α-carbonylquinones **10** and **12**, respectively. The two cribrostatin 4 analogues, **1b** and **2,** in addition to corresponding α-hydroxyquinone derivatives, **9** and **11**, respectively, were examined side by side for their antiproliferative activities against three human cell lines. Both α-hydroxyquinones **9** and **11** displayed cytotoxicity at micromolar concentrations, similar to α-carbonylhydroquinones **1b** and **2**. In contrast, **10** and **12** showed little or no activity. Further studies are required to understand the results, including the fact that the introduction of a hydroxyl group at C-5 resulted in an approximately 10-fold lower activity than the parent compound.

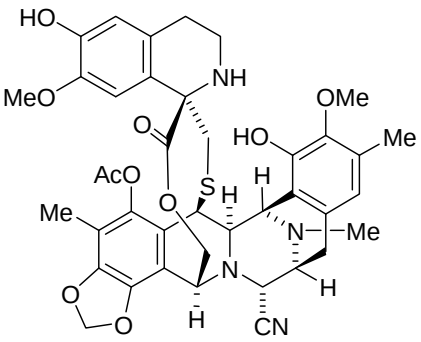
Table. *In vitro* cytotoxicity (IC_{50}, μM) of tetrahydroisoquinoline derivatives against human cancer cell lines[a)]

Compound		HCT116	QG56	DU145
	7	7.7	6.2	22.0
	13	> 1000	> 1000	> 1000
	8	6.0	32.0	20.0
saframycin G	**9**	0.021	0.038	NT
	10	550	> 1000	202
saframycin F	**1b**	0.035	0.058	NT
renieramycin O	**11**	0.028	0.040	NT
	12	> 1000	> 1000	> 1000
renieramycin Q	**2**	0.059	0.071	NT
saframycin A	**14** [15]	0.0004	0.0055	0.00063
renieramycin M	**15** [16]	0.0079	0.019	0.0096
ecteinascidin 770	**16** [17]	0.0012	0.0039	0.0024
	17 [18]	0.084	0.24	NT

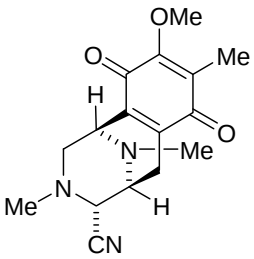
a) HCT116 = human colon carcinoma; QG56 = human lung carcinoma; DU-145 = human prostate cancer



safranycin A (**14**)
Y = NH, Z = O
renieramycin M (**15**)
Y = O, Z = H, Me (*Z*-form)



ecteinascidin 770 (**16**)



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EXPERIMENTAL

Isomerization of **7** to **8** under acidic conditions. H_2SO_4 (0.02 mL) was added to a stirred solution of **7** (10.0 mg, 0.02 mmol) in dry MeOH (1 mL), and the reaction mixture was stirred for 5 days at 25°C while monitoring by TLC. However, only the starting material was recovered after usual work up.

2,3-Dihydro-9-methoxy-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,6,7,10(1*H*, 5*H*)-tetrone (**13**). DMP (190.9 mg, 0.45 mmol) was added to a stirred solution of **7** (91.8 mg, 0.30 mmol) in CH_2Cl_2 (40 mL), and the reaction mixture was stirred for 2 h at 25°C. Then, the reaction mixture was quenched with 10% $Na_2S_2O_3$ aqueous solution (40 mL) and extracted with CH_2Cl_2 (40 mL x 2). The combined extracts were washed with water (40 mL), dried, and concentrated *in vacuo* to give a solid (92.4 mg), recrystallization of which from AcOEt gave **13** (75.0 mg, 82.2%) as dark green prisms, mp 231-232°C, whose spectra were identical with those of an authentic sample.[9b]

2,3-Dihydro-7,10-dihydroxy-9-methoxy-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,6-dione (**8**). A solution of **13** (52.3 mg, 0.172 mmol) in AcOEt (8 mL) was hydrogenated over 10% palladium on carbon (20 mg) at 1 atm for 20 min. The catalyst was removed by filtration and washed with AcOEt (100 mL). The combined filtrates were concentrated *in vacuo* to give a solid, recrystallization of which from acetone gave **8** (51.6 mg, 98%) as pale yellow needles, mp 233-234°C, whose spectra were also identical with those of an authentic sample.[9b]

2,3-Dihydro-7,10-dihydroxy-9-methoxy-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,6-dione (**8**) (2 steps). The same procedure as that described above but using **7** (61.2 mg, 0.2 mmol) and DMP (127.2 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) afforded crude **13** (129.0 mg), which was subsequently dissolved in AcOEt (9 mL) with stirring. The reaction mixture was hydrogenated over 10% palladium on carbon (25 mg) for 71 h at 25°C. The catalyst was removed by filtration and washing with AcOEt (50 mL). The combined filtrates were concentrated *in vacuo* to give a solid, recrystallization of which from acetone gave **8** (45.6 mg, 75% overall yield).

Oxidation of saframycin G (**9**)

DMP (12.7 mg, 0.03 mmol) was added to a stirred solution of **9** (11.6 mg, 0.02 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was stirred for 7 h at 25°C. The reaction mixture was quenched with 10% $Na_2S_2O_3$ aqueous solution (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were washed with water (30 mL), dried, and concentrated *in vacuo* to give a residue (17.2 mg). Chromatography on a silica gel (2 g) column with CH_2Cl_2-MeOH (200:1) gave **10** (8.6 mg, 74.8%) as dark yellow amorphous powder. $[\alpha]_D^{24}$ — 409 (*c* 0.09, $CHCl_3$); IR ($CHCl_3$): 3400, 1656, 1440, 1224 cm^{-1}; ^1H NMR δ: 1.24 (1H, ddd, *J* = 17.1, 11.6, 2.1 Hz, 14-Hβ), 1.91 (3H, s, 3-CH_3), 2.06 (3H, s, 12-CH_3), 2.25 (3H, s, $COCH_3$), 2.52 (3H, s, NCH_3), 2.94 (1H, ddd, *J* = 14.0, 4.0, 3.7 Hz, 9-CH), 2.98 (1H, dd, *J* = 17.1, 2.7 Hz, 14-Hα), 3.35 (1H, ddd, *J* = 11.6, 3.4, 2.7 Hz, 14a-H), 3.47 (1H, dd, *J* = 3.4, 1.5 Hz, 6-H), 3.74 (1H, ddd, *J* = 14.0, 10.1, 2.7 Hz, 9-CH), 3.95 (1H, br s, 9-H), 4.03 (3H, s, 11-OCH_3), 4.05 (3H, s, 2-OCH_3), 4.22 (1H, d, *J* = 3.4 Hz, 7-H), 4.42 (1H, dd, *J* = 3.4, 1.5 Hz, 15-H), 6.51 (1H, dd, *J* = 10.1, 2.7 Hz, NH); ^{13}C NMR δ: 8.7 (q, 3-CH_3), 8.9 (q, 12-CH_3), 24.2 (q, CO*C*H_3), 24.6 (t, 14C), 40.5 (t, 9-CH_2), 42.3 (q, NCH_3), 52.2 (d, 14aC), 55.3 (d, 15C), 55.5 (d, 7C), 56.5 (d, 9C), 60.8 (q, 11-OCH_3), 61.1 (q, 2-OCH_3), 66.9 (d, 6C), 115.1 (s, CN), 127.6 (s, 4aC), 127.9 (s, 12C), 131.0 (s, 3C), 136.0 (s, 9aC), 139.8 (s, 13aC), 141.8 (s, 15aC), 155.3 (s, 11C), 156.1 (s, 2C), 160.3 (s, NHCO), 180.4 (s, 10C), 183.7 (s, 13C), 184.5 (s, 1C), 185.1 (s, 4C), 193.1 (s, 5C), 196.9 (s, *C*OCH_3); EIMS *m/z* (%): no M^+, 480 (M^+ - 96, 6), 260 (13), 259 (57), 248 (100), 236 (31), 234 (49). HRMS (FAB: *m*-nitrobenzyl alcohol) Calcd for $C_{29}H_{31}N_4O_9$ [M + 3H]: 579.2091; found 579.2095; Calcd for $C_{29}H_{29}N_4O_9$ [M + H]: 577.1934; found 577.1931

N-[(6*R*, 7*R*, 9*R*, 14a*S*, 15*R*)-7-cyano-6,7,9,10,13,14,14a,15-octahydro-1,4-dihydroxy-2,11-dimethoxy-3,12,16-trimethyl-5,10,13-trioxo-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocin-9-yl]methyl-2-oxo-propanamide (saframycin F) (**1b**) A solution of **10** (17.3 mg, 0.03 mmol) in AcOEt (3 mL) was hydrogenated over 10% palladium on carbon (3 mg) at 1 atm for 10 h. The catalyst was removed by filtration and washing with AcOEt (50 mL). The combined filtrates were concentrated *in vacuo* to give a residue (19.9 mg). Chromatography on a silica gel (2 g) column with hexane-AcOEt (4:1) afforded saframycin F (**1b**: 12.6 mg, 73%) as pale yellow amorphous powder. $[\alpha]_D^{24}$ +176 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$): 3400, 1725, 1680, 1655, 1620 cm^{-1}; ^1H NMR δ: 1.54 (1H, ddd, *J* = 18.0, 11.3, 2.7 Hz, 14-Hβ), 1.91 (3H, s, 12-CH_3), 2.17 (3H, s, $COCH_3$), 2.25 (3H, s, 12-CH_3), 2.48 (3H, s, NCH_3), 3.06 (1H, ddd, *J* = 14.0, 3.9, 3.6 Hz, 9-CH), 3.07 (1H, dd, *J* = 18.0, 3.4 Hz, 14-Hα), 3.33 (1H, ddd, *J* = 11.3, 3.1, 2.7 Hz, 14a-H), 3.47 (1H, dd, *J* = 2.4, 1.2 Hz, 6-H), 3.71 (1H, ddd, *J* = 14.0, 9.5, 1.5 Hz, 9-CH), 3.94 (3H, s, 2-OCH_3), 3.99 (1H, br s, 9-H), 4.04 (3H, s, 11-OCH_3), 4.26 (1H, d, *J* = 2.7 Hz, 7-H), 4.37 (1H, dd, *J* = 2.7, 0.9 Hz, 15-H), 5.63 (1H, s, 1-OH), 6.12 (1H, dd, *J* = 9.5, 3.6 Hz, NH), 11.53 (1H, s, 4-OH); ^{13}C NMR δ: 8.6 (q, 3-CH_3), 9.0 (q, 12-CH_3), 23.8 (t, 14C), 24.2 (q, CO*C*H_3), 40.8 (t, 9-CH_2), 42.5 (q, NCH_3), 53.4 (d, 14aC), 54.3 (d, 7C),

56.2 (d, 9C), 56.5 (d, 15C), 61.1 (q, 2-OCH_3), 61.3 (q, 11-OCH_3), 66.2 (d, 6C), 111.7 (s, 4aC), 115.7 (s, CN), 116.9 (s, 15aC), 119.3 (s, 3C), 127.8 (s, 12C), 135.5 (s, 9aC), 139.8 (s, 1C), 141.1 (s, 13aC), 154.0 (s, 2C), 155.3 (s, 4C), 156.1 (s, 11C), 160.2 (s, NHCO), 180.6 (s, 10C), 185.7 (s, 13C), 195.9 (s, *C*OCH_3); 198.8 (s, 5C), EIMS *m/z* (%): no M^+, 480 (M+ - 98, 7), 259 (18), 236 (58), 235 (100), 234 (14), 219 (10), 203 (10). HRMS (FAB: dithiothreitol:thioglycerol = 1:1) Calcd for $C_{29}H_{31}N_4O_9$ [M + H]: 579.2091; found 579.2080.

Oxidation of renieramycin O (**11**)

DMP (31.8 mg, 0.075 mmol) was added to a stirred solution of **11** (29.7 mg, 0.05 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred for 3.5 h at 25°C. Then, the reaction mixture was quenched with 10% $Na_2S_2O_3$ aqueous solution (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were washed with water (30 mL), dried, and concentrated *in vacuo* to give a residue (42.3 mg). Chromatography on a silica gel (2 g) column with CH_2Cl_2-MeOH (200:1) gave **12** (8.6 mg, 74.8%) as dark yellow amorphous powder. $[\alpha]_D^{24}$ −264.5 (*c* 0.12, $CHCl_3$); IR ($CHCl_3$): 2920, 1715, 1648 cm^{-1}; ^1H NMR δ: 1.30 (1H, ddd, *J* = 17.1, 11.9, 2.4 Hz, 14-Hβ), 1.58 (3H, dd, *J* = 1.5, 1.2 Hz, COC(C*H*$_3$)=C), 1.77 (3H, dq, *J* = 7.0, 1.5 Hz, C=CHC*H*$_3$), 1.92 (3H, s, 12-CH_3), 1.96 (3H, s, 3-CH_3), 2.50 (3H, s, NCH_3), 2.97 (1H, dd, *J* = 17.1, 2.7 Hz, 14-Hα), 3.32 (1H, ddd, *J* = 11.9, 3.1, 2.7 Hz, 14a-H), 3.43 (1H, dd, *J* =2.7, 1.5 Hz, 6-H), 3.89 (1H, dd, *J* = 11.6, 2.7 Hz, 9-CH), 4.02 (3H, s, 11-OCH_3), 4.04 (3H, s, 2-OCH_3), 4.05 (1H, dd, *J* = 3.1, 2.7 Hz, 9-H), 4.30 (1H, d, *J* = 2.7 Hz, 7-H), 4.34 (1H, dd, *J* = 11.6, 3.1 Hz, 9-CH), 4.38 (1H, dd, *J* = 3.1, 1.5 Hz, 15-H), 5.95 (1H, qq, *J* = 7.0, 1.2 Hz, C=C*H*CH_3); ^{13}C NMR δ: 8.6 (q, 12-CH_3), 8.7 (q, 3-CH_3), 15.5 (q, COC(*C*H_3)=C), 20.2 (q, C=CH*C*H_3), 24.9 (t, 14C), 42.2 (q, NCH_3), 52.5 (d, 14aC), 55.6 (d, 15C), 55.6 (d, 7C), 56.3 (d, 9C), 60.9 (q, 2-OCH_3), 61.0 (q, 11-OCH_3), 63.3 (t, 9-CH_2), 66.9 (d, 6C), 115.1 (s, CN), 126.4 (s, CO*C*(CH_3)=C), 127.0 (s, 4aC), 127.9 (s, 12C), 129.8 (s, 12C), 135.9 (s, 9aC), 140.0 (d, C=*C*HCH_3), 140.1 (s, 13aC), 141.4 (s, 15aC), 155.1 (s, 2C), 156.1 (s, 11C), 166.7 (s, 9-CH_2*C*O), 180.3 (s, 10C), 183.4 (s, 13C), 184.6 (s, 1C), 185.1 (s, 4C), 192.0 (s, 5C); EIMS *m/z* (%): no M^+, 476 (M^+ - 115, 5), 315 (18). 243 (10), 236 (55), 235 (100), 234 (11), 220 (11), 204 (11), 83 (17), 82 (14), 55 (10). HRMS (FAB: *m*-nitrobenzyl alcohol) Calcd for $C_{31}H_{34}N_3O_9$ [M + 3H]: 592.2295; found 592.2996; Calcd for $C_{31}H_{32}N_3O_9$ [M + H]: 590.2138; found 590.2141.

2-Butenoic acid 2-methyl-[(6*R*, 7*R*, 9*R*, 14a*S*, 15*R*)-7-cyano-6,7,9,10,13,14,14a,15-octahydro-1,4-dihydroxy-2,11-dimethoxy-3,12,16-trimethyl-5,10,13-trioxo-6,15imino-5*H*-isoquino[3,2-*b*][3] benzazocin-9-yl]methyl ester (renieramycin Q) (**2**) A solution of **12** (9.2 mg, 0.0156 mmol) in AcOEt (2 mL) was hydrogenated over 10% palladium on carbon (2 mg) at 1 atm for 1.5 h. The catalyst was removed by filtration and washing with AcOEt (50 mL). The combined filtrates were concentrated *in vacuo* to give a residue (10.2 mg). Chromatography on a silica gel (2 g) column with hexane-AcOEt (5:1) afforded renieramycin Q (**2** 6.0 mg, 65%) as pale yellow amorphous powder. $[\alpha]_D^{24}$ −70.0 (*c* 0.08,

$CHCl_3$); IR ($CHCl_3$): 3536, 2940, 1710, 1680, 1660, 1640, 1620 cm^{-1}; ^1H NMR δ: 1.54 (1H, ddd, *J* = 18.0, 11.3, 2.7 Hz, 14-Hβ), 1.91 (3H, s, 12-CH_3), 2.17 (3H, s, $COCH_3$), 2.25 (3H, s, 12-CH_3), 2.48 (3H, s, NCH_3), 3.06 (1H, ddd, *J* = 14.0, 3.9, 3.6 Hz, 9-CH), 3.07 (1H, dd, *J* = 18.0, 3.4 Hz, 14-Hα), 3.33 (1H, ddd, *J* = 11.3, 3.1, 2.7 Hz, 14a-H), 3.47 (1H, dd, *J* = 2.4, 1.2 Hz, 6-H), 3.71 (1H, ddd, *J* = 14.0, 9.5, 1.5 Hz, 9-CH), 3.94 (3H, s, 2-OCH_3), 3.99 (1H, br s, 9-H), 4.04 (3H, s, 11-OCH_3), 4.26 (1H, d, *J* = 2.7 Hz, 7-H), 4.37 (1H, dd, *J* = 2.7, 0.9 Hz, 15-H), 5.63 (1H, s, 1-OH), 6.12 (1H, dd, *J* = 9.5, 3.6 Hz, NH), 11.53 (1H, s, 4-OH); ^{13}C NMR δ: 8.6 (q, 3-CH_3), 9.0 (q, 12-CH_3), 23.8 (t, 14C), 24.2 (q, CO*C*H_3), 40.8 (t, 9-CH_2), 42.5 (q, NCH_3), 53.4 (d, 14aC), 54.3 (d, 7C), 56.2 (d, 9C), 56.5 (d, 15C), 61.1 (q, 2-OCH_3), 61.3 (q, 11-OCH_3), 66.2 (d, 6C), 111.7 (s, 4aC), 115.7 (s, CN), 116.9 (s, 15aC), 119.3 (s, 3C), 127.8 (s, 12C), 135.5 (s, 9aC), 139.8 (s, 1C), 141.1 (s, 13aC), 154.0 (s, 2C), 155.3 (s, 4C), 156.1 (s, 11C), 160.2 (s, NHCO), 180.6 (s, 10C), 185.7 (s, 13C), 195.9 (s, *C*OCH_3), 198.8 (s, 5C); EIMS *m/z* (%): no M^+, 480 (M+ - 98, 2), 315 (6), 259 (5), 243 (11), 236 (70), 235 (100), 234 (14), 220 (11), 204 (17). HRMS (FAB: dithiothreitol:thioglycerol = 1:1) Calcd for $C_{31}H_{34}N_4O_9$ [M + H]: 592.2295; found 592.2300.

ACKNOWLEDGEMENTS

This research was partially supported by the Japan Society for the Promotion of Science (JSPS) AA Scientific Platform Program. We are grateful to Dr. Nobuo Shimma (Chugai Pharmaceutical Company Research Center) for conducting the cytotoxicity assay.

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