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SELENIUM OXIDE OXIDATION OF HEXAHYDRO-1,5-IMINO-3-BENZAZOCINE-7,10-DIONE IN ALIPHATIC ALCOHOL FOR CONVERSION OF RENIERAMYCIN MARINE NATURAL PRODUCTS

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Abstract – A selenium oxide oxidation of hexahydro-1,5-imino-3-benzazocine-7,10-dione derivatives in several aliphatic alcohols to generate C-6 ether derivatives stereoselectively is described. This procedure shows promise for the construction of several renieramycins, such as renieramycins B, D, and V. The results of cytotoxicity studies are also presented.

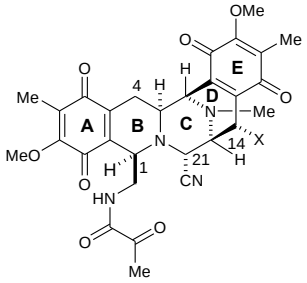
This paper is dedicated to Professor Dr. Ei-ichi Negishi (Purdue University) on the occasion of his 77th birthday and his being awarded the 2010 Nobel Prize in Chemistry.

INTRODUCTION

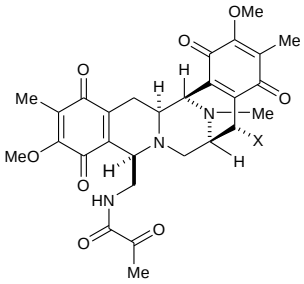
Natural products belonging to the tetrahydroisoquinolinequinone family and their reduced forms, such as saframycin antibiotics and renieramycin marine natural products, together with jorumycin and jorunnamycin, have attracted considerable interest over the past 30 years for their unique structures and meager availability in nature, and for their potent antitumor activity.[1] Monoquinone-type natural products, such as saframycins D-F (**1d-f**),[2] saframycins Mx 1 (**2a**) and Mx 2 (**2b**),[3] renieramycins N (**3n**),[4] P (**3p**),[5] and Q (**3q**),[5] cribrostatin 4 (**4**),[6] and jorunnamycin B (**6b**),[7] have a *p*-quinone moiety at ring A, a hydroquinone moiety at ring E, and a variety of oxygenated functional groups at C-14 position (Figures 1 and 2).

In regard to the chemical transformation of these natural products, we have reported the introduction of a hydroxyl group at C-6 position[8] of right-hand half model compound **7**[9] stereoselectively.[10] This method was used for the transformation of natural products, such as saframycins B (**1b**) to C (**1c**)[10b] and

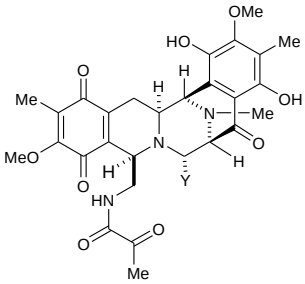
saframycins A (**1g**) to F (**1f**) via G (**1g**).[11,12] It was also utilized as one of the crucial steps for the first total synthesis of cribrostatin 4 (**4**) by Danishefsky and co-workers,[12] and adapted for the following synthesis (Figure 3: **I** → **II**).[14-16]



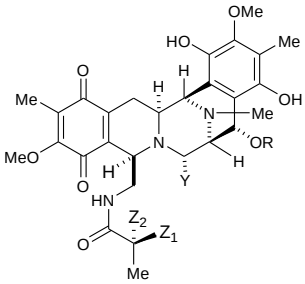
saframycins
A (**1a**): X = H
G (**1g**): X = OH



saframycins
B (**1b**): X = H
C (**1c**): X = OMe

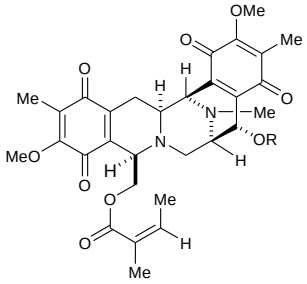


saframycins
D (**1d**): Y = H
F (**1f**): Y = CN

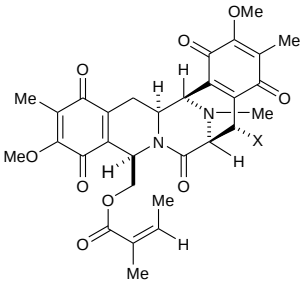


saframycin E (**1e**):
R = Y = H, Z_1, Z_2 = O
saframycins
Mx 1 (**2a**):
R = Me, Y = OH, Z_1 = NH_2, Z_2 = H
Mx 2 (**2b**)
R = Me, Y = Z_2 = H, Z_1 = NH_2

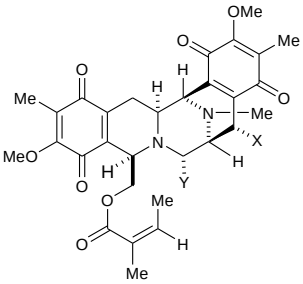
Figure 1. Structures of saframycin antibiotics



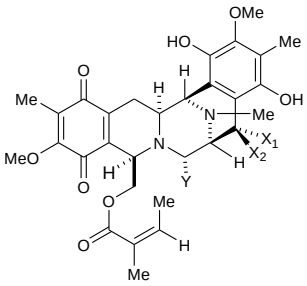
renieramycins
A (**3a**): R = H
B (**3b**): R = Et



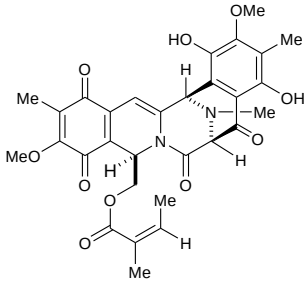
renieramycins
C (**3c**): X = OH
D (**3d**): X = OEt
G (**3g**): X = H



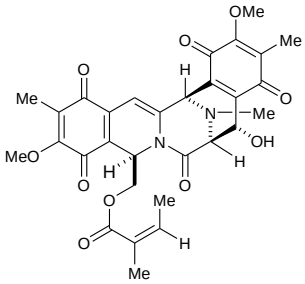
renieramycins
E (**3e**): X = H, Y = OH
F (**3f**): X = OMe, Y = OH
M (**3m**): X = H, Y = CN
O (**3o**): X = OH, Y = CN
R (**3r**): X = OMe, Y = CN



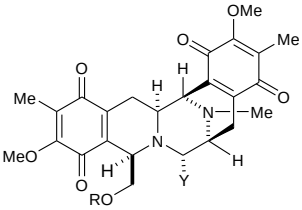
renieramycins
N (**3n**): X_1 = OH, X_2 = H, Y = CN
P (**3p**): X_1 = Y = OH, X_2 = H
Q (**3q**): X_1, X_2 = O, Y = CN



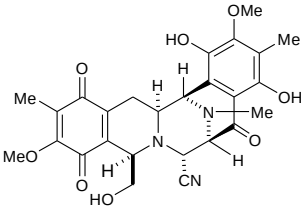
cribrostatin 4 (**4**)
(= renieramycin H)



renieramycin I (**3i**)



jorumycin (**5**):
Y = OH, R = COMe
jorunnamycins
A (**6a**): Y = CN, R = H
C (**6c**); Y = CN, R = COEt



jorunnamycin B (**6b**)

Figure 2. Structures of renieramycin marine natural products and related compounds

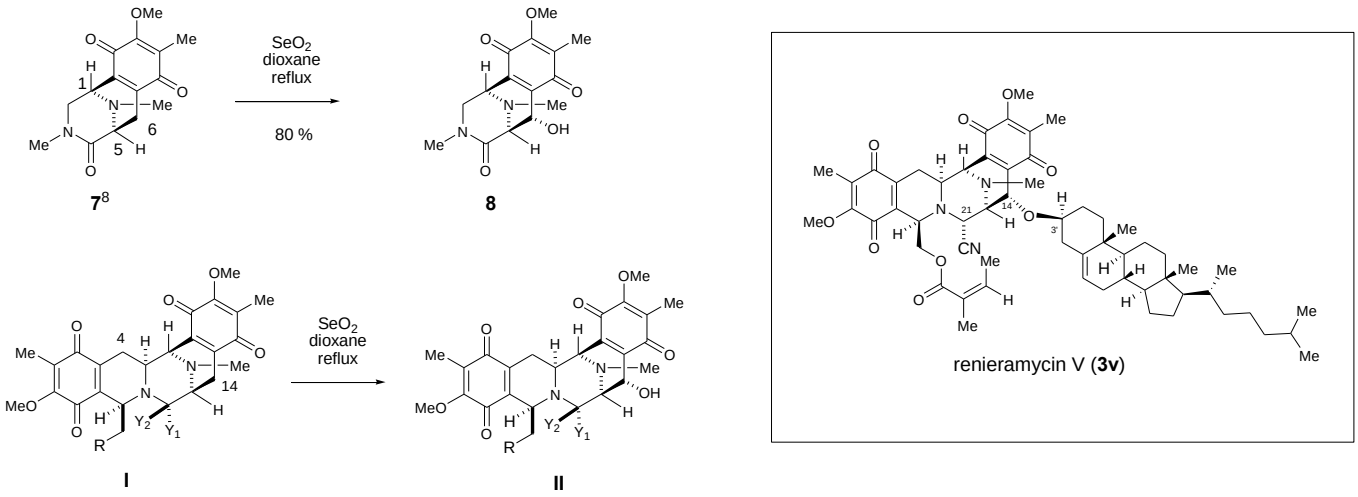


Figure 3. Regio- and stereoselective introduction of a hydroxyl group at C-14 position

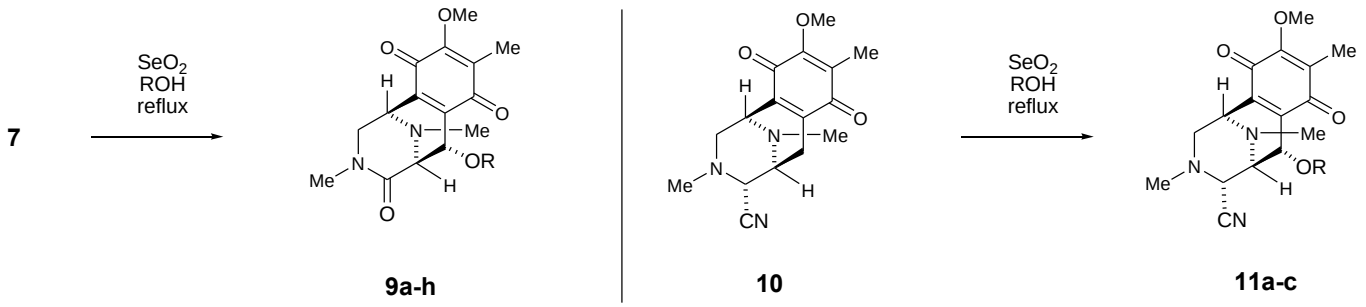
As part of our search for new metabolites via the isolation and characterization of biologically active compounds from Thai marine animals, we have isolated and elucidated the structure of renieramycin M (**3m**)[4] in gram scale from the Thai blue sponge *Xestospongia* sp. along with many minor renieramycin-type derivatives after stabilization of the sponge homogenized in phosphate buffer solution by the addition of KCN.[5,17] Recently, we succeeded in isolating renieramycin V (**3v**), the first example of renieramycin connected to a sterol moiety.[18] Renieramycin V did not show any cytotoxicity; nevertheless, we were very interested in its structure because we had hypothesized that the sterol moiety at the C-14 position of **3m** would play a role in protecting marine organism from predators. In order to devise new ways for the preparation of **3b**, **3d**, **3i**, and **3v**, we re-investigated the construction of an ether bond at C-6 position[18] of right-hand half model compounds using a selenium oxide (SeO_2) oxidation.

RESULTS AND DISCUSSION

We have reported that the reaction of **7** with SeO_2 (1.1 equiv.) in dioxane under reflux for 4 h gave **8** in 80% yield (Figure 3).[9] Our next challenge was to introduce an alkoxy group to the C-6 position of hexahydro-1,5-imino-3-benzazocine derivative **7**.[19] Treatment of **7** with SeO_2 (1.1 equiv.) in ethanol/dioxane (1:1) under reflux for 30 h gave **9a** and **8** in 25.6% and 41.8% yields, respectively. As this reaction proceeded slowly, water was added to accelerate the reaction. The reaction time of **7** with SeO_2 (1.1 equiv.) in ethanol/H_2O (1:1) under reflux was considerably reduced (10 h); however, the yields of **9a** (16.0%) and **8** (63.4%) were still unsatisfactory. After several attempts, heating a solution of **7** in EtOH under reflux in the presence of 1.1 equiv. of SeO_2 for 32 h was found to be best choice in terms of yield (**9a**: 86.0% and **8**: 9.3%). All protons and carbons of **9a** were assigned after extensive NMR

measurements using COSY, NOESY, HMQC, and HMBC techniques. The stereochemistry of C-6 in **9a** was readily identified on the basis of the chemical shifts of H-6 (δ 4.38) and H-5 (δ 3.58), along with the small coupling between H-6 and H-5 (J = 1.7 Hz), which revealed an H-6 proton orthogonal to the H-5 proton (Table 1). Heating **7** with SeO_2 oxidation in the presence of primary alcohols gave corresponding ethers **9b-e** in 69-97% yields (Table 1, entries 2-5). The usefulness of this procedure was further demonstrated by using several secondary alcohols; ethers **9f-h** were obtained in 63-89% yields. These results indicate that the present method offers a facile entry to a general procedure for the stereoselective preparation of C-6 ethers.

Table 1. Preparation of ethers **9a-h** by selenium oxide oxidation of **7** in aliphatic alcohol



Entry	Conditions			Product			
	Temp. (°C)	Time (h)	ROH		Yield (%)	δ_H (H6)	δ_C (C6)
1	100	32	ethanol	**9a**	86	4.38 (1H, d, J = 1.7Hz)	71.1
2	120	26	propanol	**9b**	97	4.35 (1H, d, J = 1.5 Hz)	71.4
3	120	27	butanol	**9c**	88	4.34 (1H, d, J = 1.5 Hz)	71.4
4	120	32	hexanol	**9d**	73	4.34 (1H, d, J = 1.5 Hz)	71.5
5	120	26	cyclohexanemethanol	**9e**	69	4.34 (1H, d, J = 1.5 Hz)	71.5
6	120	31	cyclohexanol	**9f**	89	4.53 (1H, d, J = 1.5 Hz)	69.3
7	120	31	*trans*-4-methylcyclohexanol	**9g**	63	4.53 (1H, d, J = 2.0 Hz)	69.4
8	120	37	2-butanol	**9h***	70	4.47 and 4.48 (each 1H, s)	69.5 and 69.9

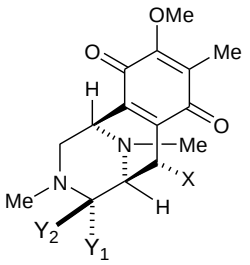
* a mixture of 2'-epimers.

In order to examine the scope of this procedure, we explored the reaction of quinone **10**,[12,20] an aminonitrile model, with SeO_2. Subjecting **10** to SeO_2 oxidation in EtOH, BuOH, and cyclohexanol under reflux led to the production of ethers [**11a** (11.1%), **11b** (5.0%), and **11c** (25.1%)] along with the recovery of a large amount of the starting material.

Finally, all synthetic compounds were tested in vitro for cytotoxicity using three representative human solid tumor cell lines (HCT116 human colon carcinoma, QG56 human lung carcinoma, and DU145 prostate carcinoma) following the standard MTT method (Table 2). Several compounds displayed micromolar inhibitory effects, but the data revealed that the introduction of the ether bond at C-6 almost did not change the in vitro activity of the model compounds.

Table 2. Cytotoxicity of model compounds to various human cancer cell lines (IC_{50} μM)[a].

Compound		HCT116	QG56	DU145
7	X = H, Y_1, Y_2 = O	> 2	1.4	> 2
8	X = OH, Y_1, Y_2 = O	> 2	> 2	> 2
9a	X = OEt, Y_1, Y_2 = O	1.2	1.1	> 2
9b	X = OPr, Y_1, Y_2 = O	1.2	0.95	> 2
9c	X = OBu, Y_1, Y_2 = O	> 2	1.1	> 2
9d	X = OHex, Y_1, Y_2 = O	> 2	1.3	> 2
9e	X = OCH_2Hex- *c*, Y_1, Y_2 = O	> 2	1.3	> 2
9f	X = OHex-*c*, Y_1, Y_2 = O	1.4	1.0	> 2
9g	X = O(4-MeHex-*c*), Y_1, Y_2 = O	1.1	0.73	> 2
9h	X = OBu-*sec*, Y_1, Y_2 = O	> 2	1.3	> 2
10	X = Y_2 = H, Y_1 = CN	0.33	0.63	0.40
11a	X = OEt, Y_1 = CN, Y_2 = H	> 2	> 2	> 2
11b	X = OBu, Y_1 = CN, Y_2 = H	> 2	1.6	> 2
11c	X = OCH_2Hex-*c*, Y_1 = CN, Y_2 = H	> 2	1.5	> 2
3m (renieramycin M)		0.0046	0.0072	0.0015



a) HCT116 = human colon carcinoma; QG56 = human lung carcinoma; DU145 = human prostate carcinoma.

In summary, the selenium oxide oxidation of **7** offers a facile entry to the preparation of C-6 ethers in a stereoselective manner. The application of this method to the transformation of renieramycins G to D along with the preparation of renieramycin V is under study in our laboratory.[21]

EXPERIMENTAL

All melting points were determined with a Yanagimoto micromelting point apparatus and uncorrected. IR spectra were obtained with a Shimadzu Prestige 21/RA Affinity-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR

spectra were recorded on a JEOL JNM-ECA 500 FT NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C (ppm, *J* in Hz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on a YANACO MT-6 CHN CORDER elemental analyzer.

Oxidation of lactam **7** with selenium oxide and ethanol

Method A: A suspension of **7** (58.0 mg, 0.20 mmol) and SeO_2 (24.4 mg, 0.22 mmol) in dioxane (2.0 mL) and EtOH (2.0 mL) was heated at reflux for 30 h. The reaction mixture was filtered and washed with $CHCl_3$ (100 mL). The combined filtrates were concentrated in vacuo and the residue was diluted with water (30 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (138 mg), which was subjected to chromatography on silica gel with CH_2Cl_2-MeOH (80:1) to furnish **9a** (17.1 mg, 25.6%) as a dark yellow solid. Further elution with CH_2Cl_2-MeOH (50:1) afforded **8** (25.6 mg, 41.8%) as pale yellow prisms.

Method B: Using the same procedure as that described above but with EtOH (2.0 mL) and water (2.0 mL) as solvent (11 h) gave a residue (67.1 mg), which was subjected to chromatography on silica gel with CH_2Cl_2-MeOH (80:1) to give **9a** (10.7 mg, 16.0%) as a dark yellow solid. Further elution with CH_2Cl_2-MeOH (50:1) afforded **8** (38.8 mg, 63.4%) as pale yellow prisms.

Method C (General Procedure): A suspension of **7** (58.0 mg, 0.20 mmol) and SeO_2 (24.4 mg, 0.22 mmol) in EtOH (10.0 mL) was heated at reflux for 32 h. The reaction mixture was filtered and washed with $CHCl_3$ (100 mL). The combined filtrates were concentrated in vacuo and the residue was diluted with water (30 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (92.4 mg), which was subjected to chromatography on silica gel with CH_2Cl_2-MeOH (100:1) to furnish **9a** (58.1 mg, 86.0%) as a dark yellow solid. Further elution with CH_2Cl_2-MeOH (80:1) afforded **8** (5.7 mg, 9.3%) as pale yellow prisms.

(1*R**,5*S**,6*S**)-6-Ethoxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9a**): Recrystallized from EtOAc-ether, mp 157-159 ^{o}C. IR ν_{max} (KBr) 1655, 1610, 1312, 1236, 1094 cm^{-1}. δ_H (500 MHz) 1.24 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.98 (3H, s, 8-CH_3), 2.65 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 13.0 Hz, 2-Hβ), 3.58 (1H, br s, 5-H), 3.85 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.97 (3H, s, 9-OCH_3), 3.98 (1H, dd, *J* = 13.0, 5.1 Hz, 2-Hα), 4.08 (1H, d, *J* = 5.1 Hz, 1-H), 4.38 (1H, d, *J* = 1.7Hz, 6-H). δ_C (125 MHz) 8.8 (8-CH_3), 15.4 (OCH_2CH_3), 34.1 (3-CH_3), 41.0

(11-CH_3), 47.7 (C2), 49.6 (C1), 60.9 (9-OCH_3), 63.9 (C5), 67.2 (O*C*H_2CH_3), 71.1 (C6), 130.2 (C8), 138.2 (C6a), 139.2 (C10a), 155.3 (C9), 166.6 (C4), 182.3 (C10), 185.9 (C7). EIMS *m/z* (%): 334 (M^+, 55), 305 (11), 290 (32), 289 (21), 234 (13), 219 (18), 218 (100), 205 (11). HREIMS *m/z* 334.1531 (M^+, calcd for $C_{17}H_{22}N_2O_5$, 334.1529). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 61.11; H, 6.58; N, 8.31.

(1*R**,5*S**,6*S**)-2,3,5,6-Tetrahydro-9-methoxyl-3,8,11-trimethyl-6-propoxy-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9b**): Yield 97%, pale yellow prisms (reflux, 26 h, recrystallization from EtOAc-ether), mp 97-100 °C. IR ν_{max} (KBr) 1647, 1622, 1308, 1236, 1152, 1088 cm^{-1}. δ_H (400 MHz) 0.92 (3H, t, *J* = 7.3 Hz, $O(CH_2)_2CH_3$), 1.62 (2H, ddq, *J* = 7.3, 6.8, 6.3 Hz, $OCH_2CH_2CH_3$), 1.98 (3H, s, 8-CH_3), 2.64 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 13.2 Hz, 2-Hβ), 3.55 (1H, br s, 5-H), 3.73 (1H, dt, *J* = 13.2, 6.8 Hz, OCH), 3.76 (1H, dt, *J* = 13.2, 6.3 Hz, OCH), 3.94 (1H, dd, *J* = 13.2, 5.4 Hz, 2-Hα), 3.97 (3H, s, 9-OCH_3), 4.06 (1H, d, *J* = 5.4 Hz, 1-H), 4.35 (1H, d, *J* = 1.5 Hz, 6-H). δ_C (100 MHz) 8.8 (8-CH_3), 10.5 ($O(CH_2)_2CH_3$), 23.0 ($OCH_2CH_2CH_3$), 34.1 (3-CH_3), 41.0 (11-CH_3), 47.8 (C2), 49.7 (C1), 60.9 (9-OCH_3), 63.9 (C5), 71.4 (C6), 73.6 (O*C*H_2), 130.2 (C8), 138.3 (C6a), 139.4 (C10a), 155.4 (C9), 166.8 (C4), 182.5 (C10), 185.9 (C7). EIMS *m/z* (%): 348 (M^+, 45), 290 (49), 289 (24), 234 (12), 219 (20), 218 (100), 205 (11). HREIMS *m/z* 348.1683 (M^+, calcd for $C_{18}H_{24}N_2O_5$, 348.1685). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.33; H, 6.88; N, 7.91.

(1*R**,5*S**,6*S**)-6-Butoxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9c**): Yield 88%, dark brown amorphous powder (120 °C, 27 h). IR ν_{max} ($CHCl_3$) 1659, 1209, 1153 cm^{-1}. δ_H (400 MHz) 0.88 (3H, t, *J* = 6.8 Hz, $O(CH_2)_5CH_3$), 1.34 (2H, m, CH_2CH_3), 1.58 (2H, quintet, *J* = 7.1 Hz, OCH_2CH_2), 1.98 (3H, s, 8-CH_3), 2.64 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 12.7 Hz, 2-Hβ), 3.55 (1H, br s, 5-H), 3.76 (1H, dt, *J* = 13.7, 6.3 Hz, OCH), 3.81 (1H, dt, *J* = 13.7, 6.3 Hz, OCH), 3.94 (1H, dd, *J* = 12.7, 5.4 Hz, 2-Hα), 3.97 (3H, s, 9-OCH_3), 4.06 (1H, d, *J* = 5.4 Hz, 1-H), 4.34 (1H, d, *J* = 1.5 Hz, 6-H). δ_C (100 MHz) 8.8 (8-CH_3), 13.8 ($O(CH_2)_3CH_3$), 19.3 (CH_2CH_3), 31.9 (OCH_2CH_2), 34.0 (3-CH_3), 41.0 (11-CH_3), 47.8 (C2), 49.7 (C1), 60.9 (9-OCH_3), 63.9 (C5), 71.4 (C6), 71.7 (O*C*H_2), 130.2 (C8), 138.3 (C6a), 139.4 (C10a), 155.4 (C9), 166.8 (C4), 182.5 (C10), 185.9 (C7). EIMS *m/z* (%): 362 (M^+, 41), 291 (14), 290 (67), 289 (26), 234 (14), 219 (20), 218 (100), 206 (12). HREIMS *m/z* 362.1840 (M^+, calcd for $C_{19}H_{26}N_2O_5$, 362.1842).

(1*R**,5*S**,6*S**)-6-Hexyloxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9d**): Yield 73%, dark brown amorphous powder (120 °C, 32 h). IR ν_{max} ($CHCl_3$) 1659,

1309, 1225, 1088 cm^{-1}. δ_H (400 MHz) 0.91 (3H, t, *J* = 6.8 Hz, $O(CH_2)_3CH_3$), 1.29 (6H, br, CH_2 x 3), 1.34 (2H, m, CH_2CH_3), 1.59 (2H, quintet, *J* = 6.8 Hz, OCH_2CH_2), 1.98 (3H, s, 8-CH_3), 2.64 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 13.2 Hz, 2-Hβ), 3.55 (1H, br s, 5-H), 3.75 (1H, dt, *J* = 13.7, 6.3 Hz, OCH), 3.80 (1H, dt, *J* = 13.7, 6.3 Hz, OCH), 3.94 (1H, dd, *J* = 12.7, 5.4 Hz, 2-Hα), 3.97 (3H, s, 9-OCH_3), 4.06 (1H, d, *J* = 5.4 Hz, 1-H), 4.34 (1H, d, *J* = 1.5 Hz, 6-H). δ_C (100 MHz) 8.8 (8-CH_3), 14.0 ($O(CH_2)_5CH_3$), 22.6 (C5'), 25.7 (C4'), 29.8 (C3'), 31.6 (C2'), 34.1 (3-CH_3), 41.0 (11-CH_3), 47.8 (C2), 49.7 (C1), 60.9 (9-OCH_3), 64.0 (C5), 71.4 (C6), 72.0 (OCH_2), 130.2 (C8), 138.3 (C6a), 139.4 (C10a), 155.4 (C9), 166.8 (C4), 182.5 (C10), 186.0 (C7). EIMS *m/z* (%): 390 (M^+, 48), 375 (11), 305 (12), 291 (17), 290 (91), 289 (33), 234 (14), 219 (20), 218 (100), 206 (13). HREIMS *m/z* 390.2156 (M^+, calcd for $C_{21}H_{30}N_2O_5$, 390.2155).

(1*R**,5*S**,6*S**)-6-Cyclohexylmethoxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9e**): Yield 69%, pale yellow prisms (120 °C, 26 h, recrystallized from EtOAc-ether), mp 112-114 °C. IR ν_{max} (KBr) 1657, 1614, 1310, 1233, 1153, 1096 cm^{-1}. δ_H (400 MHz) 0.89 (1H, dd, *J* = 12.2, 3.4 Hz, CH), 0.95 (1H, dd, *J* = 12.2, 3.4 Hz, CH), 1.10-1.26 (3H, m), 1.65-1.72 (6H, m), 1.98 (3H, s, 8-CH_3), 2.53 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 13.2 Hz, 2-Hβ), 3.54 (1H, br s, 5-H), 3.54 (1H, dd, *J* = 9.3, 6.3 Hz, OCH), 3.63 (1H, dd, *J* = 8.8, 6.3 Hz, OCH), 3.94 (1H, dd, *J* = 13.2, 5.4 Hz, 2-Hα), 3.96 (3H, s, 9-OCH_3), 4.06 (1H, d, *J* = 5.4 Hz, 1-H), 4.34 (1H, d, *J* = 1.5 Hz, 6-H). δ_C (100 MHz) 8.9 (8-CH_3), 25.8 (2 x CH_2), 26.6 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 34.1 (3-CH_3), 37.9 (C2'), 41.1 (11-CH_3), 47.9 (C2), 49.7 (C1), 60.9 (9-OCH_3), 63.8 (C5), 71.5 (C6), 77.6 (OCH_2), 130.2 (C8), 138.3 (C6a), 139.4 (C10a), 155.4 (C9), 165.8 (C4), 182.5 (C10), 185.9 (C7). EIMS *m/z* (%): 402 (M^+, 48), 375 (11), 305 (12), 291 (17), 290 (91), 289 (33), 234 (14), 219 (20), 218 (100), 206 (13). HREIMS *m/z* 402.2155 (M^+, calcd for $C_{22}H_{30}N_2O_5$, 402.2155). Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.72; H, 7.66; N, 6.84.

(1*R**,5*S**,6*S**)-6-Cyclohexyloxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9f**): Yield 89%, pale yellow prisms (120 °C, 31 h, recrystallized from EtOAc-ether), mp 138-140 °C, dark brown amorphous powder (reflux, 30 h). IR ν_{max} (KBr) 2936, 1661, 1622, 1504, 1445, 1371, 1335, 1312, 1234, 1148, 1078 cm^{-1}. δ_H (500 MHz) 1.15-1.22 (1H, m), 1.26-1.41 (4H, m), 1.55 (1H, dt, *J* = 12.2, 3.5 Hz), 1.65 (1H, br s), 1.72-1.76 (1H, m), 1.97 (3H, s, 8-CH_3), 2.05 (2H, br s), 2.63 (3H, s, 11-CH_3), 2.87 (3H, s, 3-CH_3), 2.95 (1H, d, *J* = 13.2 Hz, 2-Hβ), 3.53 (1H, dd, *J* = 1.5, 0.5 Hz, 5-H), 3.76 (1H, m, 1'-H), 3.94 (1H, dd, *J* = 13.2, 5.4 Hz, 2-Hα), 3.96 (3H, s, 9-OCH_3), 4.06 (1H, dd, *J* = 5.4, 0.5 Hz, 1-H), 4.53 (1H, d, *J* = 1.5 Hz, 6-H). δ_C (125 MHz) 8.9 (8-CH_3), 24.3 (CH_2), 24.4

(CH_2), 25.6 (CH_2), 32.4 (CH_2), 33.3 (CH_2), 34.0 (3-CH_3), 41.1 (11-CH_3), 47.8 (C2), 49.7 (C1), 60.9 (9-OCH_3), 65.4 (C5), 69.3 (C6), 79.6 (C1'), 130.2 (C8), 138.7 (C6a), 139.6 (C10a), 155.3 (C9), 167.0 (C4), 182.5 (C10), 186.0 (C7). EIMS *m/z* (%): 388 (M^+, 96), 306 (58), 305 (54), 291 (27), 290 (86), 277 (14), 275 (16), 263 (14), 247 (14), 236 (20), 235 (18), 234 (34), 232 (12), 220 (14), 219 (29), 218 (100), 206 (33), 205 (14), 131 (13). HREIMS *m/z* 388.2000 (M^+, calcd for $C_{21}H_{28}N_2O_5$, 388.1998). Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.83; H, 7.48; N, 7.05.

(1*R**,5*S**,6*S**)-6-(Trans-4'-methylcyclohexyloxy-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9g**): Yield 63%, pale yellow prisms (120 ^oC, 31 h, recrystallized from EtOAc-ether), mp 148-150 ^oC. IR ν_{max} (KBr) 2926, 1651, 1617, 1449, 1312, 1238, 1152, 1092 cm^{-1}. δ_H (400 MHz) 0.88 (3H, d, *J* = 6.3 Hz, 4'-CH_3), 0.92-1.06 (1H, m, CH_2), 1.19-1.37 (3H, m, CH_2 + 4'CH), 1.69-1.75 (2H, m, CH_2), 1.97 (3H, s, 8-CH_3), 2.11-2.04 (2H, m, CH_2), 2.63 (3H, s, 11-CH_3), 2.86 (3H, s, 3-CH_3), 2.93 (1H, dd, *J* = 13.2, 0.7 Hz, 2-Hβ), 3.51 (1H, dd, *J* = 1.5, 0.5 Hz, 5-H), 3.71 (1H, m, 1'-H), 3.93 (1H, dd, *J* = 13.2, 5.4 Hz, 2-Hα), 3.96 (3H, s, 9-OCH_3), 4.05 (1H, dd, *J* = 5.4, 0.7 Hz, 1-H), 4.53 (1H, d, *J* = 2.0 Hz, 6-H). δ_C (100 MHz) 8.9 (8-CH_3), 22.0 (4'-CH_3), 32.0 (C4'), 32.4 (CH_2), 33.3 (CH_2), 33.4 (CH_2), 33.5 (CH_2), 34.0 (3-CH_3), 41.1 (11-CH_3), 47.7 (C2), 49.6 (C1), 60.9 (9-OCH_3), 65.4 (C5), 69.4 (C6), 80.2 (C1'), 130.2 (C8), 138.7 (C6a), 139.6 (C10a), 155.3 (C9), 167.0 (C4), 182.5 (C10), 186.0 (C7). EIMS *m/z* (%): 402 (M^+, 100), 307 (15), 306 (63), 305 (49), 291 (28), 290 (82), 289 (31), 277 (14), 275 (17), 263 (15), 247 (15), 236 (18), 235 (19), 234 (34), 232 (12), 220 (14), 219 (29), 218 (97), 206 (32), 205 (13), 204 (12), 131 (15). HREIMS *m/z* 402.2156 (M^+, calcd for $C_{22}H_{30}N_2O_5$, 402.2155). Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.49; H, 7.67; N, 6.79.

(1*R**,5*S**,6*S**)-2,3,5,6-Tetrahydro-9-methoxyl-6-(2'-butoxy)-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**9h**: a mixture of 2'-epimers): Yield 70%, dark brown amorphous powder (120 ^oC, 37 h). IR ν_{max} ($CHCl_3$) 1660, 1310, 1236, 1075 cm^{-1}. δ_H (500 MHz) 0.85 and 0.94 (each 3H, t, *J* = 7.4 Hz, C4'H_3), 1.24 (2 x 3H, d, *J* = 6.2 Hz, C1'H_3), 1.42-1.54 and 1.57-1.72 (each 2H, m, C3'H_2), 1.97 (2 x 3H, s, 8-CH_3), 2.63 and 2.64 (each 3H, s, 11-CH_3), 2.86 and 2.87 (each 3H, s, 3-CH_3), 2.94 and 2.95 (each 1H, dd, *J* = 13.2, 0.8 Hz, 2-Hβ), 3.49 and 3.51 (each 1H, br s, 5-H), 3.79 and 3.90 (each 1H, sextet, *J* = 6.2 Hz, C2'H), 3.94, 3.98 (each 1H, dd, *J* = 13.2, 5.2 Hz, 2-Hα), 3.95 and 3.97 (each 3H, s, 9-OCH_3), 4.06 and 4.07 (each 1H, d, *J* = 5.2, Hz, C1H), 4.47 and 4.48 (each 1H, s, 6-H). δ_C (125 MHz) 8.9 (2 x 8-CH_3), 9.8 and 10.1 (each C4'), 19.5 and 20.1 (each C1'), 29.1 and 29.7 (each C3'), 34.0 (2 x 3-CH_3), 40.9 and 41.1 (each 11-CH_3), 47.4 and 47.7 (each C2), 49.6 and 49.8 (each C1), 60.9 (2 x 9-OCH_3), 64.7 and 65.5 (each C5), 69.5 and 69.9 (each C6), 78.5 and 78.9 (each C2'), 130.2 and 130.3 (each C8), 138.4 and 138.7 (each

C6a), 139.4 and 140.1 (each C10a), 155.3 (2 x C9), 166.9 (2 x C4), 182.4 and 182.5 (each C10), 185.9 and 186.0 (each C7). EIMS *m/z* (%): 362 (M^+, 86), 306 (32), 305 (63), 291 (17), 290 (52), 289 (32), 277 (11), 275 (12), 247 (13), 236 (17), 235 (14), 234 (32), 232 (11), 220 (13), 219 (27), 218 (100), 206 (30), 205 (15), 131 (13). HREIMS *m/z* 348.1838 (M^+, calcd for $C_{19}H_{26}N_2O_5$, 362.1842).

(1*R**,4S*,5*S**,6*S**)-6-Ethoxy-1,2,3,4,5,6,7,10-octahydro-9-methoxyl-3,8,11-trimethyl-7,10-dioxo-1,5-imino-3-benzazocine-4-carbonitrile (**11a**). A suspension of **10** (60.2 mg, 0.20 mmol) and SeO_2 (24.4 mg, 0.22 mmol) in EtOH (10.0 mL) was heated at 120 ^oC for 86 h. The reaction mixture was filtered and washed with $CHCl_3$ (100 mL). The combined filtrates were concentrated in vacuo and the residue was diluted with water (30 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (71.1 mg), which was subjected to chromatography on silica gel with hexane-EtOAc (8:1) to furnish **11a** (7.7 mg, 11.1%) as a dark yellow amorphous powder. Further elution with hexane-EtOAc (3:2) afforded **10** (24.8 mg, 41.2% recovered) as a pale yellow amorphous powder.

IR ν_{max} ($CHCl_3$) 2361, 1655, 1639, 1610, 1452, 1309, 1229, 1157, 1078 cm^{-1}. δ_H (400 MHz) 1.20 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.99 (3H, s, 8-CH_3), 2.25 (3H, s, 3-CH_3), 2.34 (1H, d, *J* = 11.7 Hz, 2-Hβ), 2.55 (3H, s, 11-CH_3), 2.75 (1H, dd, *J* = 11.7, 3.5 Hz, 2-Hα), 3.39 (1H, d, *J* = 1.4 Hz, 5-H), 3.69 (1H, d, *J* = 2.0 Hz, 4-H), 3.72 and 3.78 (each 1H, q, *J* = 7.0 Hz, OCH), 3.90 (1H, br s, 6-H), 3.91 (1H, d, *J* = 3.5 Hz, 1-H), 3.99 (3H, s, 9-OCH_3). δ_C (100 MHz) 8.9 (8-CH_3), 15.6 (OCH_2CH_3), 42.8 (11-CH_3), 43.2 (3-CH_3), 51.5 (C1), 51.6 (C2), 57.9 (C4), 60.3 (C5), 60.8 (9-OCH_3), 67.4 (C6), 68.5 (OCH_2), 115.2 (CN), 129.8 (C8), 137.4 (C10a), 139.9 (C6a), 155.1 (C9), 182.7 (C10), 186.2 (C7). EIMS *m/z* (%): 345 (M^+, 21), 219 (14), 218 (100). HREIMS *m/z* 345.1692 (M^+, calcd for $C_{18}H_{23}N_3O_4$, 345.1689).

(1*R**,4S*,5*S**,6*S**)-6-Butoxy-1,2,3,4,5,6,7,10-octahydro-9-methoxyl-3,8,11-trimethyl-7,10-dioxo-1,5-imino-3-benzazocine-4-carbonitrile (**11b**). A suspension of **10** (60.2 mg, 0.20 mmol) and SeO_2 (24.4 mg, 0.22 mmol) in BuOH (10.0 mL) was heated at 120 ^oC for 41 h. The reaction mixture was filtered and washed with $CHCl_3$ (100 mL). The combined filtrates were concentrated in vacuo and the residue was diluted with water (30 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (140.9 mg), which was subjected to chromatography on silica gel with hexane-EtOAc (5:1) to furnish **11b** (3.7 mg, 5.0%) as a dark yellow amorphous powder. Further elution with hexane-EtOAc (3:2) afforded **10** (39.6 mg, 65.8% recovered) as a pale yellow amorphous powder.

IR ν_{max} ($CHCl_3$) 2359, 1655, 1617, 1449, 1310, 1229, 1150, 1094 cm^{-1}. δ_H (500 MHz) 0.91 and 0.92 (3H,

t, J = 7.3 Hz, O(CH_2)$_3$CH_3), 1.28-1.38 (2H, m, C3'H_2), 1.48-1.56 (2H, m, C2'H_2), 1.99 (3H, s, 8-CH_3), 2.24 (3H, s, 3-CH_3), 2.33 (1H, dd, J = 11.6, 2.0 Hz, 2-Hβ), 2.53 (3H, s, 11-CH_3), 2.73 (1H, dd, J = 11.6, 3.4 Hz, 2-Hα), 3.36 (1H, d, J = 1.4 Hz, 5-H), 3.60 (1H, dt, J = 9.6, 6.8 Hz, OCH), 3.67 (1H, d, J = 2.2 Hz, 4-H), 3.75 (1H, dt, J = 9.6, 6.2 Hz, OCH), 3.86 (1H, br s, 6-H), 3.89 (1H, m, 1-H), 3.99 (3H, s, 9-OCH_3). δ_C (125 MHz) 8.9 (8-CH_3), 13.8 (4'-H_3), 19.4 (C3'), 32.1 (C2'), 42.8 (11-CH_3), 43.2 (3-CH_3), 51.5 (C1), 51.7 (C2), 58.1 (C4), 60.1 (C5), 60.9 (9-OCH_3), 68.6 (C6), 71.8 (OCH_2), 115.4 (CN), 129.8 (C8), 137.4 (C10a), 139.9 (C6a), 155.2 (C9), 182.8 (C10), 186.2 (C7). EIMS *m/z* (%): 373 (M^+, 20), 219 (15), 218 (100). HREIMS *m/z* 373.2000 (M^+, calcd for $C_{20}H_{27}N_3O_4$, 373.2002).

(1*R**,4S*,5*S**,6*S**)-6-Cyclohexyloxy-1,2,3,4,5,6,7,10-octahydro-9-methoxyl-3,8,11-trimethyl-7,10-dioxo-1,5-imino-3-benzazocine-4-carbonitrile (**11c**). A suspension of **10** (60.2 mg, 0.20 mmol) and SeO_2 (24.4 mg, 0.22 mmol) in cyclohexanol (10.0 mL) was heated at 120 ^oC for 83 h. The reaction mixture was filtered and washed with $CHCl_3$ (100 mL). The combined filtrates were concentrated in vacuo and the residue was diluted with water (30 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue (103.7 mg), which was subjected to chromatography on silica gel with hexane-EtOAc (5:1) to furnish **11c** (20.0 mg, 25.1%) as a dark yellow amorphous powder. Further elution with hexane-EtOAc (3:2) afforded **10** (24.8 mg, 41.2% recovered) as a pale yellow amorphous powder.
IR ν_{max} ($CHCl_3$) 2359 (weak), 1655, 1616, 1449, 1308, 1229, 1150, 1067 cm^{-1}. δ_H (400 MHz) 1.21-1.38 (5H, m), 1.55 (1H, m), 1.74 (2H, br s), 1.81-1.84 (1H, m), 1.97 (3H, s, 8-CH_3), 1.96-2.00 (1H, m), 2.05 (2H, br s), 2.25 (3H, s, 3-CH_3), 2.33 (1H, dd, J = 11.7, 1.0 Hz, 2-Hβ), 2.56 (3H, s, 11-CH_3), 2.75 (1H, dd, J = 11.7, 3.4 Hz, 2-Hα), 3.36 (1H, s, 5-H), 3.62 (1H, m, 1'-H), 3.72 (1H, d, J = 2.0 Hz, 4-H), 3.91 (1H, br s, 1-H), 3.99 (3H, s, 9-OCH_3), 4.06 (1H, br s, 6-H). δ_C (100 MHz) 8.9 (8-CH_3), 24.1 (CH_2), 24.3 (CH_2), 25.6 (CH_2), 32.2 (CH_2), 42.9 (11-CH_3), 43.2 (3-CH_3), 51.5 (C1), 51.7 (C2), 57.7 (C4), 60.8 (9-OCH_3), 61.6 (C5), 66.5 (C6), 79.6 (O*C*H), 115.3 (CN), 129.9 (C8), 137.4 (C10a), 140.3 (C6a), 155.1 (C9), 182.8 (C10), 186.2 (C7). EIMS *m/z* (%): 399 (M^+, 15), 219 (17), 218 (100). HREIMS *m/z* 399.2153 (M^+, calcd for $C_{22}H_{29}N_3O_4$, 399.2158).

Preparation of mesylate **12**: Methanesulfonyl chloride (MsCl, 39.1 μL, 0.5 mmol) was added dropwise to a stirred solution of **8** (30.6 mg, 0.1 mmol), TEA (70 μL, 0.5 mmol), and DMAP (6.0 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) at 0 ^oC for 5 min, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue (38.1 m),

which was subjected to chromatography on silica gel with hexane-EtOAc (1:1) to furnish **13** (11.0 mg, 33.9%) as a dark yellow amorphous powder. Further elution with hexane-EtOAc (1:2) afforded **12** (3.0 mg, 7.8%) as a pale yellow amorphous powder.

(1*R**,5*S**,6*S**)-2,3,5,6-Tetrahydro-6-methanesulfoxy-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**12**): IR ν_{max} ($CHCl_3$) 1661, 1616, 1449, 1364, 1261, 1177, 1096, 1022 cm^{-1}. δ_H (400 MHz) 1.92 (3H, s, 8-CH_3), 2.60 (3H, s, 11-CH_3), 2.81 (3H, s, 3-CH_3), 2.90 (1H, d, *J* = 12.7 Hz, 2-Hβ), 3.18 (3H, s, SO_2CH_3), 3.93 (1H, dd, *J* = 12.7, 4.6 Hz, 2-Hα), 3.95 (1H, br s, 5-H), 3.97 (3H, s, 9-OCH_3), 4.03 (1H, d, *J* = 4.6 Hz, 1-H), 5.41 (1H, s, 6-H). δ_C (100 MHz) 9.0 (8-CH_3), 34.3 (3-CH_3), 38.5 (SO_2CH_3), 40.8 (11-CH_3), 48.1 (C2), 49.8 (C1), 61.2 (9-OCH_3), 64.8 (C5), 71.4 (C6), 129.6 (C8), 134.1 (C6a), 142.5 (C10a), 155.5 (C9), 164.4 (C4), 181.5 (C10), 184.3 (C7). EIMS *m/z* (%): 384 (M^+, 18), 305 (18), 290 (29), 289 (36), 259 (14), 219 (18), 218 (100), 204 (13). HREIMS *m/z* 384.0992 (M^+, calcd for $C_{16}H_{20}N_2O_7S$, 384.0991).

(1*R**,5*S**,6*S**)-6-Chloro-2,3,5,6-tetrahydro-9-methoxyl-3,8,11-trimethyl-1,5-imino-3-benzazocine-4,7,10(1*H*)-trione (**13**): IR ν_{max} ($CHCl_3$) 1659, 1310, 1234, 1152, 1074 cm^{-1}. δ_H (400 MHz) 1.92 (3H, s, 8-CH_3), 2.63 (3H, s, 11-CH_3), 2.82 (3H, s, 3-CH_3), 2.90 (1H, d, *J* = 13.3 Hz, 2-Hβ), 3.58 (1H, br s, 5-H), 3.93 (3H, s, 9-OCH_3), 3.94 (1H, dd, *J* = 13.3, 5.1 Hz, 2-Hα), 4.06 (1H, d, *J* = 5.1 Hz, 1-H), 5.04 (1H, s, 6-H). δ_C (100 MHz) 9.1 (8-CH_3), 34.3 (3-CH_3), 40.8 (11-CH_3), 47.6 (C2), 49.7 (C1), 50.5 (C6), 61.1 (9-OCH_3), 66.4 (C5), 130.0 (C8), 138.2 (C6a), 139.1 (C10a), 155.3 (C9), 165.4 (C4), 181.5 (C10), 184.1 (C7). EIMS *m/z* (%): 326 (M^+ + 2, 12), 324 (M^+, 35), 290 (12), 289 (34), 219 (14), 218 (100). HREIMS *m/z* 324.0876 (M^+, calcd for $C_{15}H_{17}N_2O_4{}^{35}Cl$, 324.0877).

Cell growth inhibition assay: A single-cell suspension (2 x 10^3 cells/well) was added to serially diluted test compounds in a microplate. The cells were then cultured for 4 days. Cells were enumerated with a cell counting kit (DOJINDO, Osaka, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with the untreated control.

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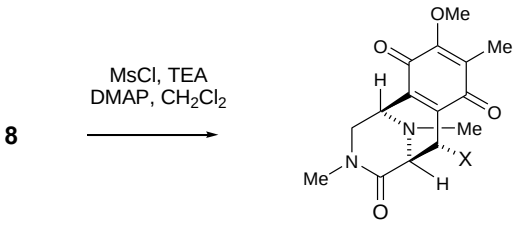
21. Another approach to prepare 6-ethoxyquinone **9a** from 6-hydroxy-*p*-quinone **8** via 6-mesylated compound **12** as a model transformation of renieramycins G to D was available, but treatment of **8** with MsCl and base at room temperature for 1 h gave **12** (7.8%) along with chloride **13** (33.9%).



12: X = OMs
13: X = Cl