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Chemistry of renieramycins. Part 11: Total synthesis of (±)-cribrostatin 4

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ABSTRACT

A 19-step synthesis of (±)-cribrostatin 4 (**1**) from readily available piperazine-2,5-dione derivative **6** is described. The synthesis features the concise construction of a pentacyclic framework, followed by the base-catalyzed epimerization of the C-1 stereo center of aldehyde (**11**). The results of cytotoxicity studies are also presented.

1. Introduction

Natural products belonging to the tetrahydroisoquinolinequinone family and their reduced forms, including saframycins,[1] renieramycins, and the most notable example, ecteinascidin 743 (Yondelis™, trabectedin),[2,3] have generated wide chemical and biological interest because of their unique structures and meager availability in nature, and for their potent antitumor activity.[4] Following the discovery of renieramycins A–D (**2a**–**d**) from the Mexican blue sponge *Reniera* sp. in 1982,[5] more than ten renieramycin marine natural products,[6–12] along with cribrostatin 4 (**1**),[13] jorumycin (**4**),[14] and jorunnamycin C (**5**),[15] were isolated from several kinds of marine organisms (Fig. 1). Because of their novel structures and remarkable biological activities, renieramycins are expected to be one of the candidates for new anticancer drugs. However, most renieramycins are isolable in only trace amounts and relatively unstable, decomposing during extraction and isolation.

As part of our search for new metabolites through the isolation and characterization of biologically active compounds from Thai marine animals, specifically the Thai blue sponge, *Xestospongia* sp., we were able to solve the above problem by converting original natural products having a very unstable amino alcohol functionality at C-21[16] into stable α-aminonitrile compounds via pretreatment with KCN.[9] We have shown that this procedure yields renieramycin M (**2m**) in gram scale and reported some structure–activity relationships (SARs) of renieramycins.[17,18]

In 1988, Parameswaran et al. reported the discovery of renieramycin H (**2h**), which was isolated from the methanol extract of the bright blue sponge *Haliclona cribricutis* collected from the intertidal region of Okha, Gujarat (India), along with renieramycin I (**2i**).[8] The structure of **2h** sparked much interest because it is the first example of renieramycins having a hydroxyl group at bridgehead position C-13. We have revised the structure of renieramycin H (**2h**) to that of cribrostatin 4 (**1**), which was independently isolated from the blue sponge *Cribrochalina* sp. in reef passages in the Republic of Maldives,[13] based on ^{13}C NMR studies of our model compounds, such as **3a**[19] and **3b**.[20,21] We are also very interested in the structure of cribrostatin 4 (**1**) because it is one of the very few examples of renieramycins having an unsaturated carbon–carbon bond between C-3 and C-4. We have focused our attention on the synthetic studies of cribrostatin 4 (**1**) in order to acquire evidence that **1** retains its cytotoxicity despite the lack of an essential hemiaminal or aminonitrile functional group at C-21 position, and to reassign all proton and carbon signals to establish our proposed structure of renieramycin H (**2h**) as some original signals are missing. To date, three total syntheses of cribrostatin 4 (**1**)[22–24] have been reported and all of them include the construction of a bicyclic AB ring system with a cis relationship at C-1 and C-3 positions, followed by the condensation of the E ring part and the elaboration of the central CD ring. We have just completed our total synthesis of **1** via a different approach that involved the key transformations outlined in Scheme 1: (1) stereoselective cyclization of lactam nitrogen of readily available 3,6-bisarylpiperazine-2,5-dione derivative **6**[25,26] with diethoxyethyl benzoate, (2) construction of the D ring to generate the pentacyclic framework, (3) and epimerization of C-1

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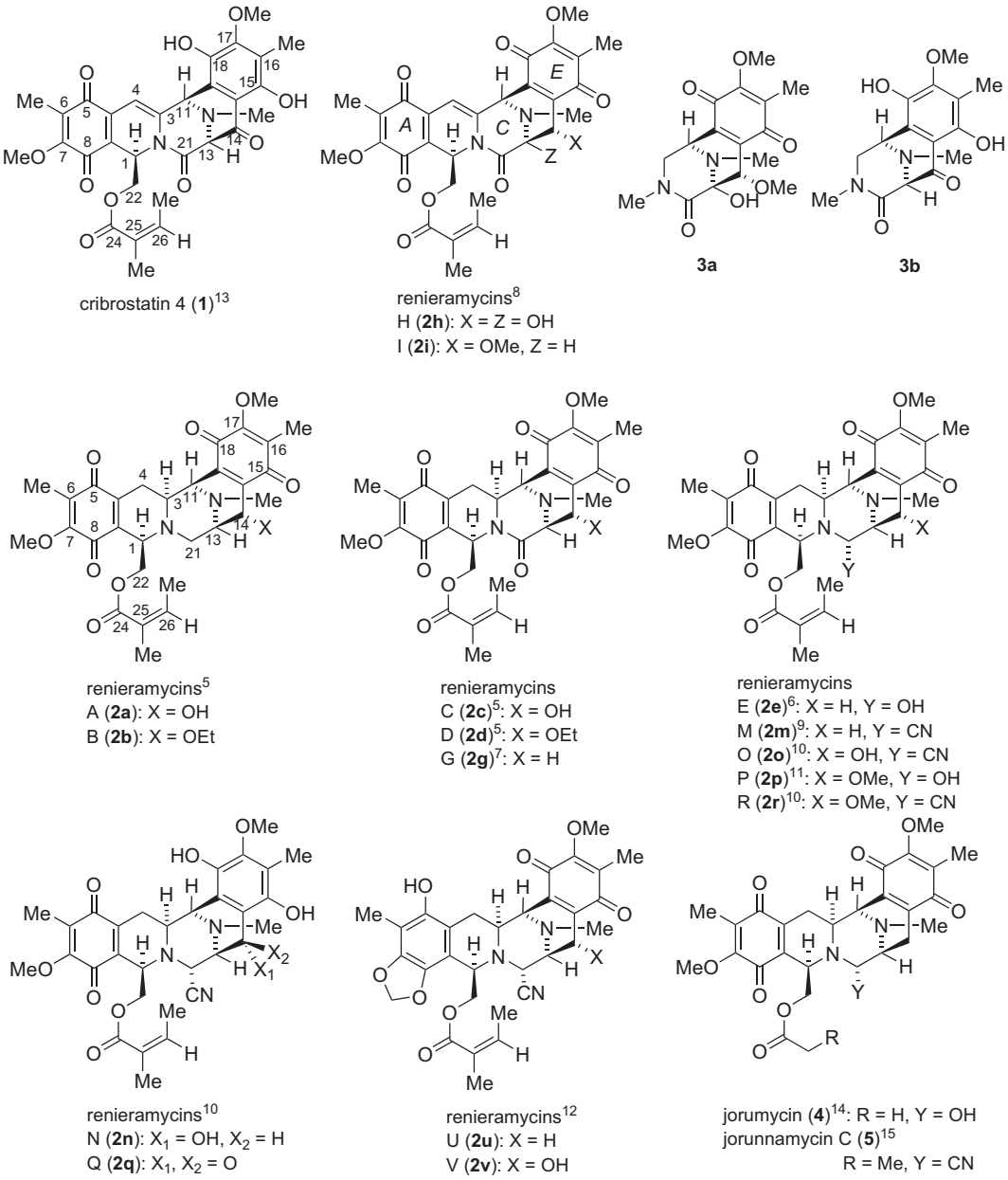


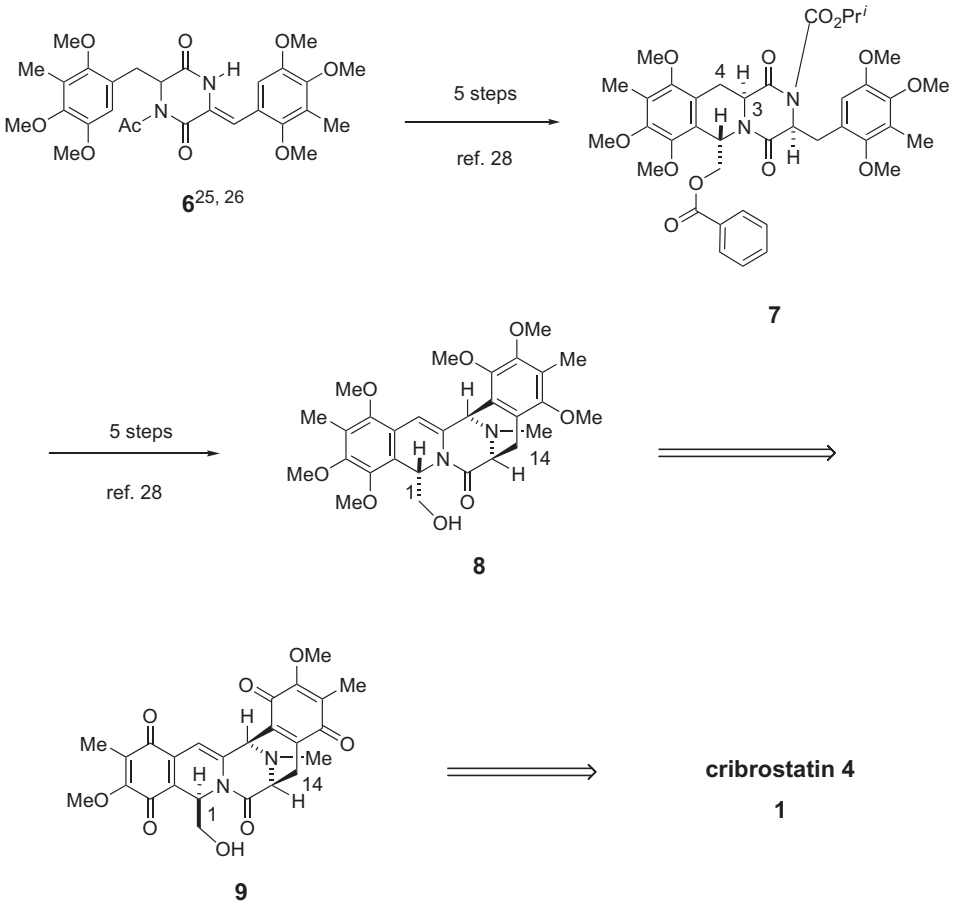
Fig. 1. Structures of renieramycin marine natural products.

center, followed by regio- and stereoselective selenium oxide (SeO_2) hydroxylation at C-14 position of bis *p*-quinones using our procedure.[20,27] This approach should provide a variety of novel analogues of cribrostatin 4 as well as a 1-*epi*-pentacyclic compound for the detailed study of SARs of these classes of antitumor marine natural products.

We have recently described an eleven-step preparation of 1-*epi*-pentacyclic alcohol **8** through the modified Pictet–Spengler cyclization of lactam nitrogen with diethoxyethyl benzoate, followed by the stereoselective hydrogenation of **7** to generate **8**.[28] In this paper, we describe the total synthesis of (±)-cribrostatin 4 (**1**) from **8** via Williams intermediate **9**.[23] The results of cytotoxicity measurements are also presented.

2. Results and discussion

Substrate **6**[25] was easily prepared from 1,4-diacetylpiperazine-2,5-dione and 2,4,5-trimethoxy-3-methylbenzaldehyde in four steps based on the procedure of Gallina and Liberatori in 80–90% overall yield.[29,30] Hydrolysis of **6** with a base gave deacetylated compound **10a** (Fig. 2), which was subsequently treated with 2,2-diethoxyethyl benzoate via *O*-trimethylsilyllactim intermediate to afford **10b** stereoselectively in 83% overall yield. X-ray crystallographic analysis was used to determine its structure and the stereochemistry between the two methine protons was found to be trans. Reduction of the double bond of **10b** occurred from the α face, and this was followed by acylation to afford **7** in 76% overall yield. Partial reduction of **7** with lithium-tri-*tert*-butoxyaluminum hydride in tetrahydrofuran (THF) gave a diastereomeric mixture of aminal that was converted into cyclization product **10c** by treatment with formic acid at 60 °C for 14 h in 80% overall yield. Deprotection of **10c** with trifluoroacetic acid (TFA) and H_2SO_4 gave secondary amine **10d** in 96% yield. Reductive methylation of **10d**, followed by hydrolysis gave pentacyclic alcohol **8** in 97% overall yield. We have succeeded in the 11-step transformation of **8** from **6** in 47% overall yield.[28]



Scheme 1. Strategy for total synthesis of cribrostatin 4 (**1**).

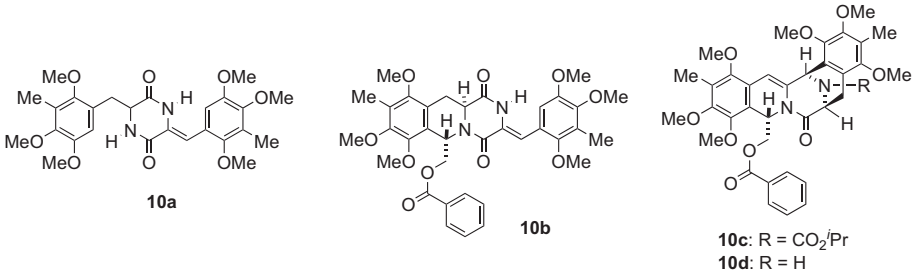
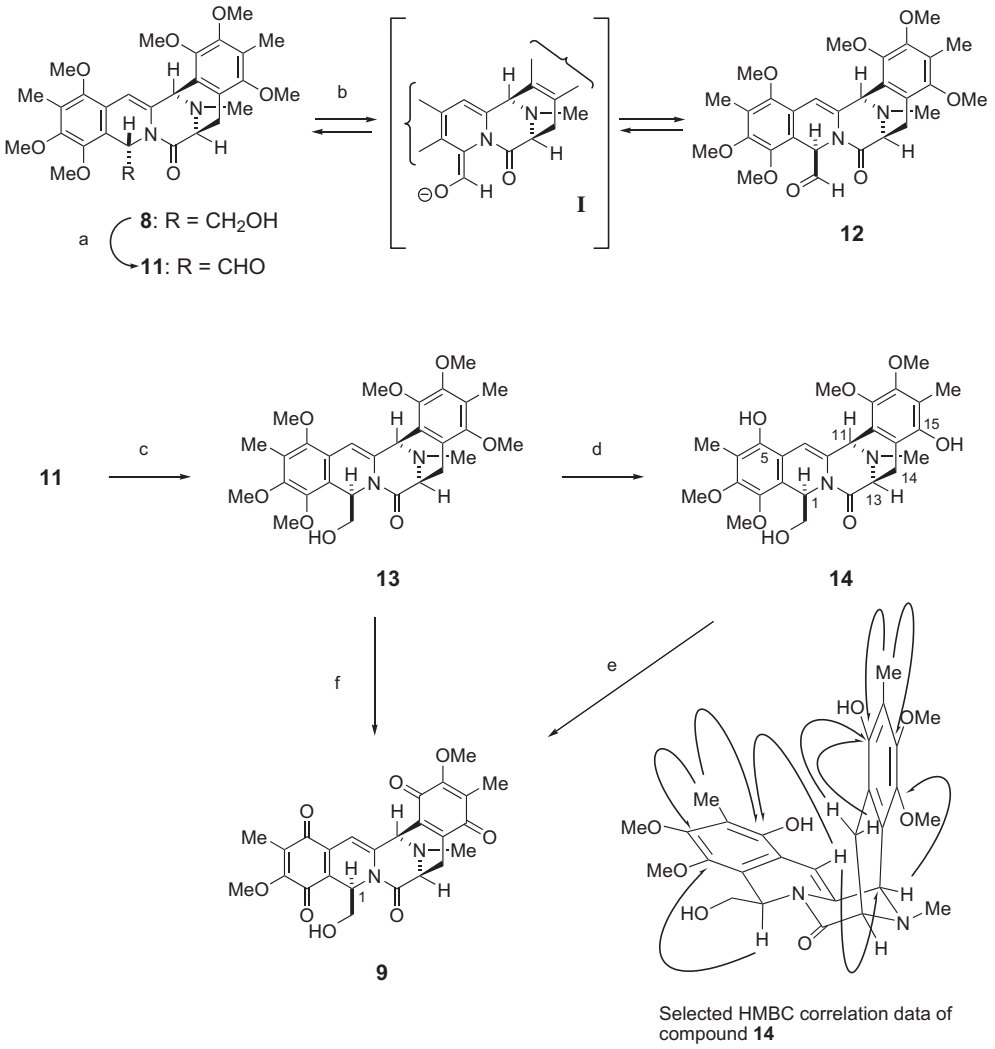


Fig. 2. Structures of compounds **10a**–**d**.

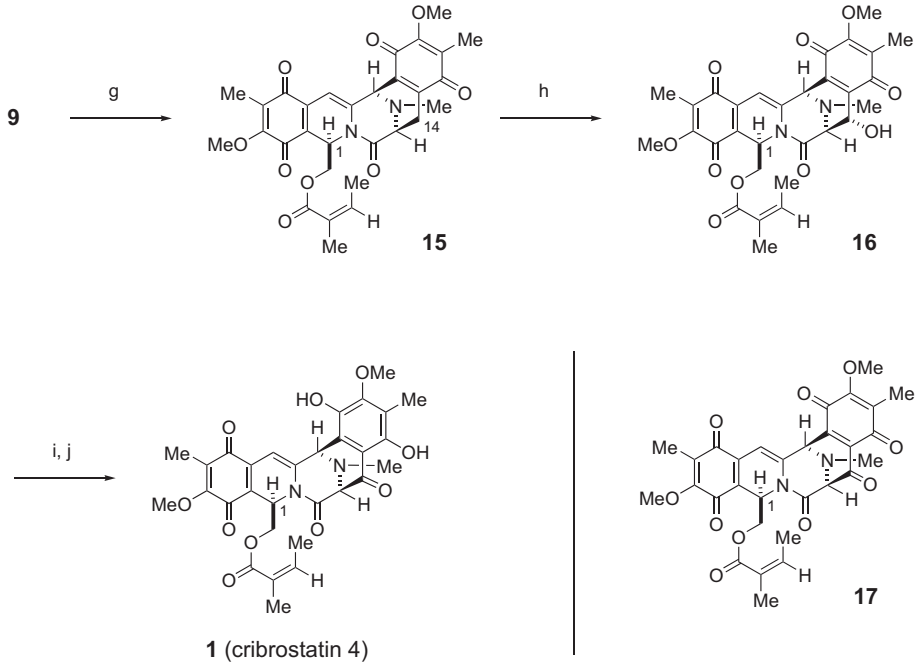
Having established the pentacyclic framework of **1**, the next hurdle was the isomerization at C-1 position of **8**. The Swern oxidation of alcohol **8** gave **11** in 92% yield (Scheme 2). Treatment of **11** with 1.0 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[31–33] in THF at 25 °C for 1 h afforded **12** in 66% yield, and 26% of starting material **11** was recovered. Their ratio could not be varied by changing the reaction conditions, such as the reaction time, or the ratio of substrate to base. This reaction presumably attained equilibrium fairly rapidly via enolate **I**. Accordingly, isomerization of recovered **11** by repeating the procedure gave **12** and **11** in 81.0% and 6.0% yields, respectively. Reduction of **12** with sodium cyanoborohydride ($NaBH_3CN$) in the presence of acetic acid (AcOH) gave **13** in 73% yield.

The conversion of polymethoxyarene **13** into cribrostatin 4 intermediate **9**[23] was accomplished by partial demethylation with boron tribromide (BBr_3), followed by oxidative demethylation. Treatment of **13** with 8.0 equiv of BBr_3 in CH_2Cl_2 at −78 °C for 1 h and then at −20 °C for 39 h gave **14** in 46% yield.[34] All the protons and carbons of **14** were assigned after extensive NMR measurements using correlation spectroscopy (COSY), ^{1}H-detected heteronuclear multiple bond coherence (HMBC), and ^{1}H-detected heteronuclear multiple-quantum coherence (HMQC) techniques. The phenolic hydroxyl groups in **14** were found at C-8 and C-15 on the basis of selected HMBC correlation data (Scheme 4).[35] Oxidation of **14** with 10 N HNO_3 at 25 °C for 10 min gave Williams intermediate **9** in 90% yield. On the other hand, treatment of **13** with 6.0 equiv of BBr_3 in CH_2Cl_2 at −78 °C for 1 h afforded the crude product, which was subjected to oxidative demethylation with 10 N HNO_3 at 25 °C for 30 min to give **9** in 55% overall yield. Both ^{1}H and ^{13}C NMR spectroscopic data were identical with the authentic data of (−)-**9**.

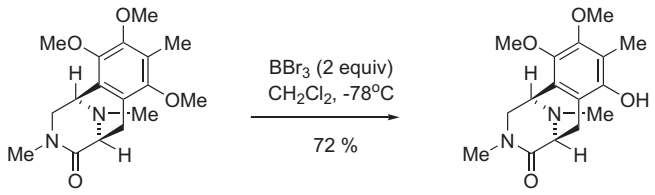
With our target in hand, we directed our efforts toward the conversion of **9** into cribrostatin 4 (**1**) according to the procedure of Vincent and Williams[23] (Scheme 3). Treatment of **9** with angeloyl



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, TEA, DMSO, −40 °C–25 °C, 92%; (b) DBU, THF, 25 °C twice, 81%; (c) $NaBH_3CN$, AcOH/MeOH, 25 °C, 73%; (d) BBr_3 (8 equiv), CH_2Cl_2, −78 °C to −20 °C, 46%; (e) 10 N HNO_3, 25 °C, 90%; (f) BBr_3 (6 equiv), CH_2Cl_2, −78 °C to −20 °C and then 10 N HNO_3, 55%.



Scheme 3. Reagents and conditions: (g) (*Z*)-MeCH=C(Me)COCl, CH_2Cl_2, 25 °C, 21 h, 84%; (h) SeO_2 (5 equiv), dioxane−H_2O, 80 °C, 6 h, 71%; (i) DMP (10.5 equiv), CH_2Cl_2, 25 °C, 3 h; (j) $Na_2S_2O_3$, THF−H_2O, 25 °C, 2 h, then work-up under air, 84% (two steps).



18 **19**

Scheme 4. Partial demethylation of model compound **18**.

We have already reported the revised structure of renieramycin H (**2h**) in which both C-1 (δ 56.2) and C-19 (δ 108.6) signals should be replaced with C-11 (δ 46.9) and C-20 (δ 119.2), respectively.[21] With synthetic **1** in hand, we present here all proton and carbon assignments of **1** by extensive NMR measurements using COSY, HMQC, and HMBC techniques (Table 1).

Natural cribrostatin 4 (**1**) has mean panel GI_{50} values of $(5.01\pm0.28)^{-3}$ μM.[13] Danishefsky and co-workers reported that the assay performed with synthetic (−)-cribrostatin 4 (**1**) corroborated the results obtained by Pettit and co-workers.[39] Thus, the compounds synthesized above, including natural renieramycin M (**2m**), 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). Compounds **9** and **16** displayed micromolar inhibitory effects, but

Table 1
^{1}H and ^{13}C NMR assignments for cribrostatin 4 (**1**) in $CDCl_3$

Atom no	Synthetic **1**				Natural **1**[13]	
	^{13}C NMR δ (125 MHz)		^{1}H NMR (500 MHz) δ (multi, integral, *J* in Hz)	HMBC correlations from C no.	^{13}C NMR (125 MHz)	^{1}H NMR (500 MHz)
1	46.9	CH	6.20 (dd, 1H, 6.2, 3.1)		56.2	6.18
3	124.2	C		1-H, 4-H	124.2	
4	100.0	CH	6.23 (s, 1H)	11-H	100.0	6.22
5	185.0	C		4-H, 6-Me	185.0	
6	127.1	C		6-Me	127.1	
7	156.4	C		6-Me, 7-OMe	156.3	
8	179.9	C			179.9	
9	134.6	C		1-H,	134.6	
10	139.8	C		1-H, 4-H	139.8	
11	56.2	CH	4.87 (d, 1H, 1.1)	4-H, 13-H, *N*-Me	46.9	4.10
13	72.5	CH	4.11 (d, 1H, 1.1)	11-H, *N*-Me	72.5	4.85
14	192.7	C=O		13-H	192.7	
15	156.3	C		15-OH, 16-Me	156.2	
16	119.1	C		16-Me, 15-OH	119.8	
17	153.2	C		16-Me, 17-OMe, 18-OH	153.3	
18	138.1	C		11-H, 18-OH	138.1	
19	119.8	C		11-H, 18-OH	108.6	
20	108.6	C		11-H, 13-H, 15-OH	119.2	
21	161.1	C		13-H	161.1	
22	62.1	CH_2	4.06 (dd, 1H, 12.0, 6.2)		62.0	4.06
			3.83 (dd, 1H, 12.0, 3.1)			3.81
24	166.8	C=O		22-H	166.8	
25	126.6	C			126.6	
26	139.3	CH	5.91 (qq, 1H, 7.1, 1.4)		139.3	5.9 (qu)
27	15.4	CH_3	1.75 (dq, 1H, 7.1, 1.4)		15.4	1.73 (d)
28	19.9	CH_3	1.47 (quint, 1H, 1.4)	26-H	19.9	1.45
6-Me	8.6	CH_3	1.95 (s, 3H)		8.6	1.93
7-OMe	61.1	CH_3	4.06 (s, 3H)		61.2	4.04
15-OH			11.35 (s, 1H)			
18-OH			5.59 (s, 1H)			
16-Me	9.0	CH_3	2.16 (s, 3H)		9.0	2.14
17-OMe	61.2	CH_3	3.86 (s, 3H)		61.1	3.84
N-Me	41.3	CH_3	2.57 (s, 3H)	11-H, 13-H	41.2	2.56

chloride in CH_2Cl_2 and dimethylformamide (DMF) afforded **15** in 84% yield. The reaction of **15** with SeO_2 (10 equiv) in dioxane at 80 °C for 8 h gave **16** in 53% yield along with recovered **15** (26%) under our original conditions.[20] The addition of water was found to accelerate the reaction; for example, the oxidation of **15** with SeO_2 in dioxane−H_2O at 80 °C for 6 h proceeded through the chemo- and diastereoselective introduction of a hydroxyl group at C-14 position to afford **16** in 71% yield. Oxidation of **16** with Dess−Martin periodinate (DMP)[36,37] in CH_2Cl_2 at 25 °C for 3 h gave ketone **17** in good yield. However, when the crude product was allowed to stand in organic solvent at 25 °C for several hours, it was converted into an 8:1 mixture of **17** and cribrostatin 4 (**1**).[38] After extensive investigation of the reaction conditions, the following procedure was found to be optimal in terms of product yield and reproducibility of the reaction: Treatment of **16** with 10.5 equiv of DMP in CH_2Cl_2 at 25 °C for 3 h, followed by sodium thiosulfate reduction and selective air oxidation of the resulting bishydroquinone afforded cribrostatin 4 (**1**) in 84% overall yield. The high stability of the hydroquinone E ring is attributable to the presence of a hydrogen bond between C-14 carbonyl (δ_C 192.7 ppm) and 15-OH (δ_H 11.35 ppm).

Table 2
Cytotoxicity of cribrostatin 4 (**1**) and related compounds to various cancer cell lines (IC_{50} μM)[a]

Compound	HCT116	QG56	DU145
8	>2	>2	>2
11	>2	>2	>2
12	>2	>2	>2
13	>2	>2	>2
14	>2	>2	>2
9	0.51	0.97	1.4
15	>2	>2	>2
16	0.30	0.90	0.39
17	>2	>2	>2
(±)-**1** (Cribrostatin 4)	>2	>2	>2
(−)-**2m** (Renieramycin M)	7.0×10^{-3}	21.0×10^{-3}	1.5×10^{-3}

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

almost all synthetic compounds, including (±)-**1**, did not show any cytotoxicity.

In summary, the stereoselective total synthesis of (±)-cribrostatin 4 (**1**) has been realized in 19 steps from readily available compound **6** in 9.5% overall yield. Efforts to refine the synthesis of **1**, including its optically active forms, and to prepare analogues for biological screening and studies of the mechanism of action are under way.

3. Experimental section

3.1. General

IR spectra were obtained with a Shimadzu Prestige 21/IRA Affinity-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL-JNM-ECA500 FT NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, on a JEOL-JNM-AL400 NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, and on a JEOL-JNM-AL300 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.

3.1.1. 1,2,4,10,11,13-Hexamethoxy-9-carboxaldehyde-3,12,16-trimethyl-7-oxo-(6S,9S*,15R*)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-b][3]-benzazocine (**11**).* A solution of oxalyl chloride (0.67 mL, 8.0 mmol) and DMSO (1.14 mL, 16.0 mmol) in CH_2Cl_2 (60 mL) was stirred for 10 min at −78 °C. A solution of **8** (540.0 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was added to the above reaction mixture over 30 min and the entire mixture was stirred at the same temperature for 2 h. Triethylamine (2.79 mL, 20 mmol) was then added dropwise and the reaction mixture was stirred for 5 min at −78 °C and an additional 70 min at 0 °C. After the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (300 mL), the resulting solution was extracted with $CHCl_3$ (300 mL×3). The combined extracts were washed with brine (300 mL), dried, and concentrated in vacuo, and the residue was subjected to silica gel chromatography with hexane–ethyl acetate=2:1 to ethyl acetate to afford **11** (496.0 mg, 92%) as a colorless amorphous powder.

IR (KBr) 3447, 2940, 2833, 1738, 1676, 1639, 1465, 1412, 1354, 1269, 1248, 1113, 1066, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.41 (1H, s, CHO), 6.48 (1H, s, 9-H), 6.19 (1H, s, 14-H), 4.84 (1H, d, *J*=1.7 Hz, 15-H), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe), 3.91 (1H, m, 6-H), 3.78 (3H, s, OMe), 3.70 (6H, s, OMe×2), 3.67 (3H, s, OMe), 3.20 (1H, dd, *J*=17.6, 7.6 Hz, 5-Hα), 3.07 (1H, dd, *J*=17.6, 1.1 Hz, 5-Hβ), 2.83 (3H, s, *N*Me), 2.15 (6H, s, ArMe×2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.3 (CHO), 168.9 (C-7), 152.1 (C-4), 149.9, 149.8 (C-2, C-11), 149.4 (C-13), 145.8 (C-1), 145.7 (C-10), 134.8 (C-14a), 127.2 (C-15a), 126.4, 124.6 (C-3, C-12), 121.0 (C-4a), 120.2 (C-9a), 114.0 (C-13a), 98.7 (C-14), 61.1 (OMe), 60.4 (OMe), 60.3 (OMe), 60.0 (OMe), 59.9 (C-6), 59.8 (OMe), 59.8 (OMe), 59.6 (C-9), 55.3 (C-15), 41.9 (*N*Me), 27.2 (C-5), 9.5 (ArMe), 9.4 (ArMe); EIMS *m*/*z* (%) 538 (M$^+$, 5), 509 (33), 481 (100), 248 (51); HRMS *m*/*z* 538.2310 (M$^+$, calcd for $C_{29}H_{34}N_2O_8$, 538.2315).

3.1.2. 1,2,4,10,11,13-Hexamethoxy-9-carboxaldehyde-3,12,16-trimethyl-7-oxo-(6S,9R*,15R*)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-b][3]-benzazocine (**12**).* DBU (156 μL, 1.04 mmol) was added over 5 min to a stirred solution of **11** (560.0 mg, 1.04 mmol) in THF (170 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 1 h. After the reaction mixture was concentrated in vacuo, the resulting residue was diluted with 5% aqueous $NaHCO_3$ solution (200 mL) and then extracted with $CHCl_3$ (200 mL×3). The combined extracts were washed with brine (200 mL), dried, and concentrated in vacuo, and the residue (607 mg) was subjected to silica gel (75 g) chromatography with hexane to hexane–ethyl acetate=2:1 to afford **11** (141.0 mg, 26% recovery). Further elution with hexane–ethyl acetate=2:1 to ethyl acetate gave **12** (374.0 mg, 66.0% yield).

Recovered **11** (141.0 mg, 0.262 mmol) was treated again with DBU (39.2 uL, 0.262 mmol) in THF (150 mL) at 25 °C for 1 h. Performing the same work-up and separation described above afforded **12** (82.0 mg) and **11** (32.2 mg). Thus, 456 mg of **12** (81.0%) could be obtained from **11** (560.0 mg) along with recovered **11** (32.3 mg, 6.0%).

IR (KBr) 3435, 2941, 1740, 1676, 1641, 1466, 1412, 1356, 1269, 1184, 1128, 1065, 1007, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.99 (1H, s, CHO), 6.43 (1H, s, 9-H), 6.18 (1H, s, 14-H), 4.71 (1H, s, 15-H), 3.91 (3H, s, OMe), 3.81 (3H, s, OMe), 3.76 (3H, s, OMe), 3.75 (3H, s, OMe), 3.74 (3H, s, OMe), 3.74 (1H, m, 6-H, signals overlapped with OMe), 3.68 (3H, s, OMe), 3.23 (1H, dd, *J*=17.1, 5.9 Hz, 5-Hα), 3.17 (1H, dd, *J*=17.1, 2.3 Hz, 5-Hβ), 2.58 (3H, s, *N*Me), 2.21 (3H, s, ArMe), 2.20 (3H, s, ArMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.8 (CHO), 167.9 (C-7), 152.3 (C-4), 150.4, 149.8 (C-2, C-11), 149.6 (C-13), 146.2 (C-1), 146.1 (C-10), 134.2 (C-14a), 126.4 (C-3 or C-12), 125.9 (C-15a), 124.6 (C-3 or C-12), 121.1 (C-4a), 119.6 (C-9a), 115.8 (C-13a), 101.8 (C-14), 61.4 (OMe), 60.6 (OMe), 60.4 (C-6), 60.1 (OMe), 60.1 (OMe), 60.1 (OMe), 59.9 (OMe), 59.5 (C-9), 56.3 (C-15), 41.6 (*N*Me), 29.0 (C-5), 9.6 (ArMe), 9.5 (ArMe); EIMS *m*/*z* (%) 538 (M$^+$, 4), 509 (34), 481 (100), 248 (48); HRMS *m*/*z* 538.2311 (M$^+$, calcd for $C_{29}H_{34}N_2O_8$, 538.2315).

3.1.3. 1,2,4,10,11,13-Hexamethoxy-9-hydroxymethyl-3,12,16-trimethyl-7-oxo-(6S,9R*,15R*)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-b][3]-benzazocine (**13**).* To a THF solution of sodium cyanoborohydride (1 M, 76.4 μL, 0.764 mmol) at 0 °C were added **12** (274.0 mg, 0.51 mmol) and AcOH (3.8 mL, 66.2 mmol) in THF (70 mL), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (300 mL) and extracted with $CHCl_3$ (300 mL×3). The combined extracts were washed with brine (300 mL), dried, and concentrated in vacuo to give a residue (295.0 mg). Chromatography on a silica gel column with $CHCl_3$ to $CHCl_3$–MeOH=50:1 gave **13** (201.0 mg, 73%) as a colorless amorphous powder.

IR (KBr) 3460, 2940, 1672, 1636, 1466, 1412, 1364, 1341, 1248, 1113, 1007, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.26 (1H, s, 14-H), 6.09 (1H, dd, *J*=7.8, 5.0 Hz, 9-H), 4.68 (1H, br s, 15-H), 3.88 (3H, s, 10-OMe), 3.86 (3H, s, 1-OMe), 3.78 (3H, s, 11-OMe), 3.76 (3H, s, 13-OMe), 3.75 (3H, s, 2-OMe), 3.70 (1H, dt, *J*=4.7, 1.2 Hz, 6-H), 3.66 (4-OMe), 3.32 (1H, ddd, *J*=11.0, 6.2, 5.0 Hz, 9-CH), 3.19 (1H, ddd, *J*=11.0, 7.8, 6.2 Hz, 9-CH), 3.18 (2H, d, *J*=4.7 Hz, 5-H_2), 2.55 (3H, s, *N*Me), 2.19 (3H, s, 12-Me), 2.18 (3H, s, 3-Me), 1.38 (1H, t, *J*=6.2 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0 (C-7), 152.4 (C-4), 150.5 (C-11), 149.9 (C-2), 149.5 (C-13), 146.1 (C-1), 145.6 (C-10), 132.7 (C-14a), 126.0 (C-15a), 125.3 (C-12), 124.9 (C-3), 121.1 (C-4a), 120.5 (C-9a), 119.4 (C-13a), 102.7 (C-14), 64.6 (9-CH_2), 61.4 (11-OMe), 60.7 (10-OMe), 60.6 (C-6), 60.2 (1-OMe), 60.2 (4-OMe), 60.1 (13-OMe), 59.9 (2-OMe), 56.6 (C-15), 49.1 (C-9), 41.7 (*N*Me), 29.5 (C-5), 9.6 (3-Me), 9.4 (12-Me); EIMS *m*/*z* (%) 540 (M$^+$, 10), 509 (28), 481 (100), 248 (41); HRMS *m*/*z* 540.2473 (M$^+$, calcd for $C_{29}H_{36}N_2O_8$, 540.2472).

3.1.4. 1,2,10,11-Tetramethoxy-9-hydroxymethyl-3,12,16-trimethyl-7-oxo-(6S,9R*,15R*)-5,6,9,15-tetrahydro-6,15-iminoisoquino[3,2-b][3]-benzazocine (**14**).* To a stirred solution of **13** (10.8 mg, 0.02 mmol) in CH_2Cl_2 (1.2 mL) at −78 °C was added a CH_2Cl_2 solution of BBr_3 (1.0 M, 160.0 μL, 0.16 mmol) over 5 min. Stirring was continued at the same temperature for 1 h, and then at −20 °C for 39 h. The reaction mixture was diluted with water (20 mL) and extracted with $CHCl_3$ (20 mL×6). The combined extracts were washed with 5% $NaHCO_3$ solution (20 mL), dried, and concentrated in vacuo and the residue (7.0 mg) was purified by silica gel column

chromatography with $CHCl_3$–MeOH=100:1 to afford **14** (4.7 mg, 46.1%) as a pale purple amorphous powder.

IR (KBr) 3421, 2938, 1636, 1464, 1423, 1354, 1251, 1117, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.23 (1H, s, 14-H), 6.05 (1H, dd, J=7.6, 4.8 Hz, 9-H), 4.68 (1H, s, 15-H), 3.85 (3H, s, 10-OMe), 3.84 (1H, m, 6-H, signals overlapped with those of OMe), 3.83 (3H, s, 1-OMe), 3.77 (3H, s, 11-OMe), 3.73 (3H, s, 2-OMe), 3.31 (1H, dd, J=11.1, 4.8 Hz, 9-CH), 3.19 (1H, dd, J=11.1, 7.6 Hz, 9-CH), 3.12 (1H, dd, J=16.8, 5.9 Hz, 5-Hα), 3.06 (1H, dd, J=16.8, 1.6 Hz, 5-Hβ), 2.57 (3H, s, *N*Me), 2.13 (3H, s, 12-Me), 2.11 (3H, s, 3-Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0 (C-7), 150.3 (C-11), 149.6 (C-2), 147.8 (C-4), 144.9 (C-13), 143.5 (C-1), 143.1 (C-10), 131.7 (C-14a), 125.3 (C-15a), 120.4 (C-9a), 117.9 (C-3), 117.8 (C-12), 114.3 (C-4a), 113.8 (C-13a), 102.7 (C-14), 64.6 (9-CH_2), 60.8 (10-OMe), 60.5 (C-6), 60.4 (1-OMe), 60.3 (11-OMe), 60.2 (2-OMe), 56.4 (C-15), 49.4 (C-9), 41.6 (*N*Me), 28.8 (C-5), 9.1 (3-Me), 9.0 (12-Me); EIMS m/z (%) 512 (M^+, 14), 481 (28), 453 (100), 234 (76); HRMS m/z 512.2160 (M^+, calcd for $C_{27}H_{32}N_2O_8$, 512.2159).

3.1.5. (6S,9R*,15R*)-5,6,9,15-Tetrahydro-9-hydroxymethyl-3,12,16-trimethyl-2,11-dimethoxy- 6,15-imino-4H-isoquino[3,2-b][3]-benzazocine-1,4,7,10,13-pentone (**9**).* A solution of **14** (7.5 mg, 14.6 μmol) in 10 N HNO_3 (0.5 mL) was stirred at 25 °C for 10 min. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL×3). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo. The residue (7.6 mg) was subjected to purification by silica gel chromatography with ethyl acetate to give **9** (6.3 mg, 90.0%) as a dark purple amorphous powder.

IR (KBr) 3343, 2926, 2855, 1683, 1653, 1616, 1568, 1558, 1456, 1373, 1308, 1234, 1227, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.26 (1H, s, 14-H), 5.96 (1H, dd, J=7.1, 4.5 Hz, 9-H), 4.55 (1H, s, 15-H), 4.02 (3H, s, OMe), 3.97 (3H, s, OMe), 3.74 (1H, dt, J=6.5, 1.5 Hz, 6-H), 3.50 (1H, dd, J=11.4, 4.5 Hz, 9-CH), 3.36 (1H, dd, J=11.4, 7.1 Hz, 9-CH), 2.96 (1H, dd, J=19.8, 6.5 Hz, 5-Hα), 2.89 (1H, dd, J=19.8, 1.5 Hz, 5-Hβ), 2.51 (3H, s, *N*Me), 1.96 (3H, s, 12-Me), 1.94 (3H, s, 3-Me), 1.62 (1H, br s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.6 (C-4), 185.0 (C-13), 180.5 (C-10), 180.5 (C-1), 168.7 (C-7), 156.0 (C-11), 155.4 (C-2), 140.7 (C-14a), 140.0 (C-4a), 136.5 (C-15a), 134.5 (C-13a), 129.1 (C-3), 127.6 (C-12), 125.0 (C-9a), 101.8 (C-14), 62.9 (9-CH_2), 61.1 (OMe), 61.0 (OMe), 59.6 (C-6), 54.4 (C-15), 48.4 (C-9), 41.2 (*N*Me), 28.7 (C-5), 8.8 (ArMe), 8.7 (ArMe); Positive FABMS m/z 481 [M^++1], HRFABMS m/z 481.1623 ([M+H]$^+$, calcd for $C_{25}H_{25}N_2O_8$, 481.1611).

3.2. Oxidative demethylation of 13 in two steps

Partial O-demethylation of **13** (21.6 mg, 0.04 mmol) in CH_2Cl_2 (2.4 mL) with a CH_2Cl_2 solution of BBr_3 (1 M, 240 mL, 0.24 mmol) as described above afforded a residue (16.6 mg). A solution of the residue in 10 N HNO_3 (0.5 mL) was stirred at 25 °C for 30 min to give **9** (10.5 mg, 55%) in two steps.

3.2.1. (6S,9R*,15R*)-(1,5,6,7,9,10,13,15-Octahydro-2,11-dimethoxy-3,12,16-trimethyl-1,4,7,10,13-pentaoxo-6,15-imino-4H-isoquino[3,2-b][3]-benzazocin-9-yl)methyl (2Z)-methyl-2-butenoate (**15**).* A solution of angelic acid (60.1 mg, 0.60 mmol) in ether (3.0 mL) was cooled with iced water and a solution of oxalyl chloride (50.6 μL, 0.59 mmol) in DMF (4.6 μL, 59.2 mmol) was added dropwise over 5 min. The resulting solution was stirred at 25 °C for 2 h and then a solution of **9** (14.2 mg, 0.030 mmol) in CH_2Cl_2 (1.5 mL) was added over 5 min. The reaction mixture was concentrated to approximately 0.3 mL with a stream of argon and CH_2Cl_2 (0.8 mL) was then added. The resulting mixture was stirred at 25 °C for 21 h. The reaction mixture was purified by silica gel chromatography with hexane–ethyl acetate=1:2 to afford **15** (13.9 mg, 84%) as a dark purple film.

IR (KBr) 2949, 1683, 1653, 1570, 1560, 1458, 1340, 1310, 1229, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.24 (1H, s, 14-H), 6.12 (1H, dd, J=5.7, 2.9 Hz, 9-H), 5.92 (1H, qq, J=7.4, 1.4 Hz, 20-H), 4.50 (1H, br s, 15-H), 4.21 (1H, dd, J=11.9, 5.7 Hz, 9-CH), 4.05 (3H, s, 11-OMe), 4.01 (3H, s, 2-OMe), 4.01 (1H, dd, J=11.9, 2.9 Hz, 9-CH), 3.72 (1H, dt, J=6.8, 1.4 Hz, 6-H), 2.95 (1H, dd, J=19.8, 6.8 Hz, 5-Hα), 2.84 (1H, dd, J=19.8, 1.4 Hz, 5-Hβ), 2.47 (3H, s, *N*Me), 1.96 (3H, s, 12-Me), 1.92 (3H, s, 3-Me), 1.75 (3H, dq, J=7.4, 1.4 Hz, 20-Me), 1.57 (1H, quint, J=1.4 Hz, 19-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.5 (C-4), 184.9 (C-13), 180.5 (C-10), 180.1 (C-1), 167.1 (C-7 and C-18), 156.2 (C-11), 155.2 (C-2), 140.6 (C-14a), 139.8 (C-4a), 139.3 (C-20), 136.2 (C-15a), 134.6 (C-13a), 128.5 (C-3), 127.3 (C-12), 126.8 (C-19), 124.2 (C-9a), 101.3 (C-14), 62.4 (C-16), 61.1 (11-OMe), 61.0 (2-OMe), 59.5 (C-6), 54.3 (C-15), 47.1 (C-9), 41.1 (*N*Me), 28.3 (C-5), 20.2 (C-22), 15.5 (C-21), 8.7 (3-Me), 8.6 (12-Me); EIMS m/z (%) 562 (M^+, 5), 449 (13), 423 (15), 423 (25), 421 (100), 218 (40); HREIMS m/z 562.1952 (M^+, calcd for $C_{30}H_{30}N_2O_9$, 562.1951).

3.2.2. (5S,6S*,9R*,15R*)-(1,5,6,7,9,10,13,15-Octahydro-5-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-1,4,7,10,13-pentaoxo-6,15-imino-4H-isoquino[3,2-b][3]-benzazocin-9-yl)methyl (2Z)-methyl-2-butenoate (**16**). Without water*: A suspension of **15** (10.6 mg, 0.019 mmol) and SeO_2 (21.0 mg, 0.186 mmol) in dioxane (2.5 mL) was stirred at 80 °C for 8 h. The reaction mixture was filtered and the filter cake was washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo to give a residue. Flash column chromatography on silica gel (4 g) with hexane–ethyl acetate=1:1 afforded **16** (5.8 mg, 53.2%) as a dark red film and starting material **15** (2.7 mg, 25.5% recovery).

With water: A suspension of **15** (7.3 mg, 0.013 mmol) and SeO_2 (7.2 mg, 0.065 mmol) in dioxane (2.0 mL) and water (0.2 mL) was stirred at 80 °C for 6 h. The reaction mixture was filtered and the filter cake was washed with ethyl acetate (20 mL). The combined filtrates were concentrated in vacuo to give a residue (10.6 mg). Flash column chromatography on silica gel (7 g) with hexane–ethyl acetate=1:1 afforded **16** (5.3 mg, 71.0%) as a dark red film and starting material **15** (1.0 mg, 14.0% recovery).

IR (KBr) 3446, 2930, 2857, 1654, 1616, 1570, 1456, 1341, 1307, 1233, 1211, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.28 (1H, s, 14-H), 6.09 (1H, dd, J=6.0, 2.9 Hz, 9-H), 5.93 (1H, qq, J=7.3, 1.5 Hz, 20-H), 4.86 (1H, dd, J=7.0, 1.7 Hz, 5-H), 4.52 (1H, d, J=1.1 Hz, 15-H), 4.19 (1H, dd, J=12.0, 5.9 Hz, 9-CH), 4.06 (3H, s, 11-OMe), 4.01 (3H, s, 2-OMe), 3.99 (1H, dd, J=12.0, 2.9 Hz, 9-CH), 3.75 (1H, dd, J=1.7, 1.1 Hz, 6-H), 2.88 (1H, d, J=7.0 Hz, OH), 2.55 (3H, s, *N*Me), 1.96 (3H, s, 12-Me), 1.93 (3H, s, 3-Me), 1.75 (3H, dq, J=7.3, 1.5 Hz, 20-Me), 1.57 (1H, quint, J=1.5 Hz, 19-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.7 (C-4), 184.7 (C-13), 181.0 (C-10), 180.0 (C-1), 167.1 (C-18), 163.9 (C-7), 156.1 (C-11), 155.4 (C-2), 139.3 (C-20), 138.4 (C-4a), 138.3 (C-13a), 136.9 (C-15a), 134.3 (C-14a), 128.8 (C-3), 127.4 (C-12), 126.7 (C-19), 124.8 (C-9a), 102.2 (C-14), 67.1 (C-6), 64.8 (C-5), 62.3 (C-16), 61.1 (11-OMe), 61.0 (2-OMe), 54.7 (C-15), 47.2 (C-9), 41.5 (*N*Me), 20.2 (C-22), 15.5 (C-21), 8.7 (3-Me), 8.7 (12-Me); EIMS m/z (%) 578 (M^+, 5), 465 (17), 438 (24), 437 (100), 422 (12), 421 (49), 234 (12), 218 (20); HREIMS m/z 578.1899 (M^+, calcd for $C_{30}H_{30}N_2O_{10}$, 578.1900).

3.2.3. (6S,9R*,15R*)-(1,6,7,9,10,13,15-Heptahydro-2,11-dimethoxy-3,12,16-trimethyl-1,4,5,7,10,13-hexaoxo-6,15-imino-4H-isoquino[3,2-b][3]-benzazocin-9-yl)methyl (2Z)-methyl-2-butenoate (**17**).* A 0.3 M dichloromethane solution of DMP (0.35 mL, 0.104 mmol) was added to a stirred solution of **16** (5.1 mg, 0.0088 mmol) in CH_2Cl_2 (1.0 mmol) at 25 °C within 1 min, and the mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ solution (10 mL) and extracted with $CHCl_3$ (10 mL×3). The combined extracts ware washed with brine (10 mL), dried, and concentrated in vacuo to give a residue in the form of a dark red oil.

IR (KBr) 2924, 2855, 1724, 1683, 1653, 1570, 1294, 1263, 1228, 1209, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.34 (1H, s, 14-H), 6.19 (1H, dd, J=6.1, 2.8 Hz, 9-H), 5.91 (1H, qq, J=7.1, 1.5 Hz, 20-H), 4.75 (1H, d, J=1.4 Hz, 15-H), 4.30 (1H, dd, J=12.2, 6.1 Hz, 9-CH), 4.07

(3H, s, 11-OMe), 4.04 (1H, d, J=1.4 Hz, 6-H), 4.03 (3H, s, 2-OMe), 3.96 (1H, dd, J=12.2, 2.8 Hz, 9-CH), 2.54 (3H, s, *N*Me), 1.97 (3H, s, 12-Me), 1.95 (3H, s, 3-Me), 1.71 (3H, dq, J=7.3, 1.5 Hz, 20-Me), 1.54 (1H, quint, J=1.5 Hz, 19-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.8 (C-5), 184.5 (C-13), 183.5 (C-4), 182.1 (C-1), 179.9 (C-10), 167.3 (C-18), 159.9 (C-7), 156.2 (C-11), 155.0 (C-2), 146.4 (C-15a), 139.2 (C-20), 136.6 (C-14a), 134.0 (C-13a), 130.0 (C-3), 127.4 (C-12), 126.7 (C-19), 125.2 (C-4a), 125.0 (C-9a), 103.0 (C-14), 73.0 (C-6), 62.3 (C-16), 61.2 (11-OMe), 60.9 (2-OMe), 55.9 (C-15), 47.9 (C-9), 41.2 (*N*Me), 20.1 (C-22), 15.4 (C-21), 8.9 (3-Me), 8.7 (12-Me); EIMS m/z 466 (M^+−100, 21), 465 (75), 438 (25), 437 (100), 234 (14); HRFABMS m/z 577.1830 (M^++1, calcd for $C_{30}H_{29}N_2O_{10}$, 577.1822), 437.1352 (calcd for $C_{23}H_{21}N_2O_7$, 437.1349), 234.0769 (calcd for $C_{12}H_{12}NO_4$, 234.0766).

3.3. Synthesis of (±)-cribrostatin 4 (1)

A 0.3 M CH_2Cl_2 solution of DMP (0.31 mL, 0.092 mmol) was added to a stirred solution of **16** (5.0 mg, 0.0087 mmol) in dichloromethane (1.0 mmol) at 25 °C within 1 min, and the mixture was stirred at 25 °C for 3 h. After the reaction mixture was diluted with THF (5 mL), saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added. The mixture was stirred vigorously at 25 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL×3). The combined extracts were washed with brine (10 mL), dried, and concentrated in vacuo. The residue (25.2 mg) was purified by silica gel (9 g) flash column chromatography with hexane–ethyl acetate=1:2 to afford cribrostatin 4 (**1**: 4.2 mg, 84.0%) as a dark red film.

IR (KBr) 3429, 2930, 2857, 2851, 1697, 1649, 1558, 1458, 1416, 1379, 1342, 1292, 1229, 1209, 1155, 1126, 1088, 845, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.35 (1H, s, 4-OH), 6.26 (1H, s, 14-H), 6.20 (1H, dd, J=6.2, 3.1 Hz, 9-H), 5.91 (1H, qq, J=7.1, 1.4 Hz, 20-H), 5.59 (1H, s, 1-OH), 4.87 (1H, d, J=1.1 Hz, 15-H), 4.11 (1H, d, J=1.1 Hz, 6-H), 4.06 (1H, dd, J=12.0, 6.2 Hz, 9-CH), 4.06 (3H, s, 11-OMe), 3.86 (3H, s, 2-OMe), 3.83 (1H, dd, J=12.0, 3.1 Hz, 9-CH), 2.57 (3H, s, *N*Me), 2.16 (3H, s, 3-Me), 1.95 (3H, s, 12-Me), 1.75 (3H, dq, J=7.1, 1.4 Hz, 20-Me), 1.47 (1H, quint, J=1.4 Hz, 19-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.7 (C-5), 185.0 (C-13), 179.9 (C-10), 166.8 (C-18), 161.1 (C-7), 156.4 (C-11), 156.3 (C-4), 153.2 (C-2), 139.8 (C-13a), 139.3 (C-20), 138.1 (C-1), 134.6 (C-9a), 127.1 (C-12), 126.6 (C-19), 124.2 (C-14a), 119.8 (C-15a), 119.1 (C-3), 108.6 (C-4a), 100.0 (C-14), 72.5 (C-6), 62.1 (C-16), 61.2 (2-OMe), 61.1 (11-OMe), 56.2 (C-15), 46.9 (C-9), 41.3 (*N*Me), 19.9 (C-22), 15.4 (C-21), 9.0 (3-Me), 8.6 (12-Me); EIMS m/z (%) 578 (M^+, 3), 465 (10), 438 (25), 437 (100), 234 (12); HREIMS m/z 578.1902 (M^+, calcd for $C_{30}H_{30}N_2O_{10}$, 578.1900).

4. Cell growth inhibition assay (IC_{50})

A single-cell suspension (2×10^3 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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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.076.

References and notes

1. Arai, T.; Kubo, A. In *Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1983; Vol. 21, pp 55–100.
2. Rinehart, K. L. *Med. Drug Rev.* **2000**, *20*, 1–27.
3. Henriquez, R.; Faircloth, G.; Cuevas, C. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G., Newman, D. J., Eds.; Taylor & Francis: New York, NY, 2005; pp 215–223.
4. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
5. Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265–269 errata: **1982**, 104, 5004.
6. He, H.-Y.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5822–5824.
7. Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721–3724.
8. Parameswaran, P. S.; Naik, C. G.; Kamat, S. Y.; Pramanik, B. N. *Indian J. Chem., Sect. B* **1998**, *37B*, 1258–1263.
9. Suwanborirux, K.; Amnuoypol, S.; Plubrukarn, A.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2003**, *66*, 1441–1446.
10. Amnuoypol, S.; Suwanborirux, K.; Pummangura, S.; Kubo, A.; Tanaka, C.; Saito, N. *J. Nat. Prod.* **2004**, *67*, 1023–1028.
11. Oku, N.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Nat. Prod.* **2003**, *66*, 1136–1139.
12. Daikuhara, N.; Tada, Y.; Yamaki, S.; Charupant, K.; Amnuoypol, S.; Suwanborirux, K.; Saito, N. *Tetrahedron Lett.* **2009**, *50*, 4276–4278.
13. Pettit, R. K.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793–798.
14. Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305–7308.
15. Charupant, K.; Suwanborirux, K.; Amnuoypol, S.; Saito, E.; Kubo, A.; Saito, N. *Chem. Pharm. Bull.* **2007**, *55*, 81–86.
16. For simplicity, natural product numbering was used in this manuscript, but IUPAC numbering was used in the Experimental.
17. Charupant, K.; Suwanborirux, K.; Daikuhara, N.; Yokoya, M.; Ushijima-Sugano, R.; Kawai, T.; Owa, T.; Saito, N. *Mar. Drugs* **2009**, *7*, 483–494.
18. Charupant, K.; Daikuhara, N.; Saito, E.; Amnuoypol, S.; Suwanborirux, K.; Owa, T.; Saito, N. *Bioorg. Med. Chem.* **2009**, *17*, 4548–4558.
19. Saito, N.; Sakai, H.; Takai, R.; Muranaka, M.; Itabashi, M.; Kubo, A.; Yazawa, K.; Mikami, Y. *Heterocycles* **1997**, *46*, 309–320.
20. Saito, N.; Ohira, N.; Wada, N.; Kubo, A. *Tetrahedron* **1990**, *46*, 7711–7728.
21. Saito, N.; Sakai, H.; Suwanborirux, K.; Pummangura, S.; Kubo, A. *Heterocycles* **2001**, *55*, 21–28.
22. Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.
23. Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517–1520; Corrigendum: Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8458.
24. Chen, X.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3962–3965.
25. Kubo, A.; Saito, N.; Yamato, H.; Kawakami, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2525–2532.
26. Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295–4310.
27. Saito, N.; Harada, S.; Inouye, I.; Yamaguchi, K.; Kubo, A. *Tetrahedron* **1995**, *51*, 8231–8246.
28. Yokoya, M.; Ito, H.; Saito, N. *Chem. Pharm. Bull.* **2011**, *59*, 787–792.
29. Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667–673.
30. González, J. F.; de la Cuesta, E.; Avendaño, C. *Synth. Commun.* **2004**, *34*, 1589–1597.
31. Epimerization of 1,3-disubstituted tetrahydroisoquinoline derivatives by DBU has been studied in the synthesis of ecteinascidin 743.[30,31]
32. Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543–546.
33. Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408.
34. Oxidative demethylation of **13** with 6.0 equiv of BBr_3 gave **14** in 35% yield and starting material **13** (4%). This transformation was unsuccessful when less than 5.0 equiv of BBr_3 was used, affording an inseparable mixture of mono demethylated products along with a large amount of the starting material.
35. The mechanism of the selective demethylation of 13 is unclear. Nevertheless, we have reported that the partial demethylation of 18 with BBr3 (2 equiv) at −78 °C afforded phenol 19 (72%), the structure of which was confirmed by X-ray crystallographic analysis (Scheme 4). See Saito, N.; Ohira, Y.; Aihara, T.; Harada, S.; Shida, Y.; Kubo, A. *Tetrahedron* **1994**, *50*, 3915–3928.
36. The DNP oxidation method was first introduced by Danishefsky and coworkers in their first synthesis of **1**,[22] and was subsequently adopted in our conversion of saframycin G into saframycin F and renieramycin Ointo renieramycin Q.[37]
37. Saito, E.; Daikuhara, N.; Saito, N. *Heterocycles* **2007**, *74*, 411–420.
38. As far as we know, there is no report of any spectroscopic data of **17** in the literature. Because **17** was difficult to isolate in its pure form, its spectroscopic data were measured after the usual work-up.
39. Wright, B. J. D.; Chan, C.; Danishefsky, S. J. *J. Nat. Prod.* **2008**, *71*, 409–414.