Antineoplastic Agents 430. Isolation and Structure of Cribrostatins 3, 4, and 5 from the Republic of Maldives *Cribrochalina* Species[1,†]

George R. Pettit,*[,‡] John C. Knight,[‡] Jeremiah C. Collins,[‡] Delbert L. Herald,[‡] Robin K. Pettit,[‡] Michael R. Boyd,[§] and Victor G. Young[⊥]

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, Arizona 85287-2404, Laboratory of Drug Discovery Research and Development, DTP, DCTD, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland 21702-1201, and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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Continued investigation of cancer-cell growth-inhibitory constituents of the blue marine sponge *Cribrochalina* sp. has led to discovery of cribrostatins 3 (**4a**), 4 (**5**), and 5 (**4b**) in 10^{-5} to 10^{-7} % of the wet weight. The structure of cribrostatin 3 (**4a**) was determined by results of high field (500 MHz) ^{1}H and ^{13}C NMR and HRMS interpretations. The same general approach to the structures of cribrostatins 4 (**5**) and 5 (**4b**) was completed by X-ray crystal structure determinations. Cribrostatins 3, 4, and 5 provided significant cancer cell line inhibitory activities. Cribrostatins 1 and 2[2] and the newly isolated cribrostatins 3−5 displayed antibacterial and/or antifungal activities.

In 1986, we began investigating the blue sponge *Cribrochalina* sp. collected in reef passages in the Republic of Maldives. Six years later, we reported the isolation of cribrostatin 1 (**1**), cribrostatin 2 (**2a**), mimosamycin (**2b**), renierone (**3a**), and its *O*-demethyl derivative (**3b**).[2] Subsequently, both cribrostatins 1 and 2 have been prepared by synthesis.[3] Although our initial summary[2] of the cribrostatins represented one of only a few known chemical investigations of the *Cribrochalina* genus (previously focused on *C. dura* and *C. vasculum*), in the interim interest has been expanding, especially with the acetylenic alcohols contained in *C. vasculum*.[4a−f] Other studies have been concerned with antifungal pyridine derivatives[5a] and marine alkaloids[5b] of *Cribrochalina* sp., the cancer-cell growth-inhibitory cyclic hexapeptide kapakahine B,[6a] other cyclic peptides,[6b−c] and a 19-norpregnane glycoside from *C. olemda*,[6d] as well as isolation of a cyclopropyl-ring containing sterol from *C. vasculum*.[7] After our initial investigation of the Maldives *Cribrochalina* sp., evidence accumulated suggesting the presence of other cancer-cell growth-inhibitory constituents. As part of that extended study, we isolated and elucidated the structures of three new biologically active components designated cribrostatins 3 (**4a**), 4 (**5**), and 5 (**4b**) (see Chart 1).

Results and Discussion

The fractions obtained from the 1988−89 recollection of *Cribrochalina* sp.,[2] beginning with the 195-g dichloromethane partition fraction, were reexamined guided by bioassay results using the murine P-388 lymphocytic leukemia. Further fractional recrystallization of constituents accompanying the original isolation of cribrostatin 1 (**1**) afforded the new isoquinoline quinone **4a** (2.8×10^{-5} % yield, P-388 ED_{50} 2.5 μg/mL). Application of high-speed countercurrent distribution procedures,[8a,b] employing an Ito Coil Planet centrifuge, to fractions accompanying the original isolation of renierone (**3a**) afforded cribrostatin 5 (**4b**, 9×10^{-7} % of wet wt, P-388 ED_{50} 0.045 μg/mL). When the fraction that originally provided mimosamycin (**2b**) was further separated by high-speed countercurrent distribution, cribrostatin 4 (**5**, 1.4×10^{-5} % of wet wt, OVCAR-3 ED_{50} 2.2 μg/mL) was isolated.

The structural assignments of cribrostatins 3, 4, and 5 were established using spectral and X-ray methods. The basic atom connectivity of cribrostatin 5 (**4b**) was established via X-ray crystal structure determination. The quinone carbonyl groups could be readily assigned from bond distances (C5−O5, 1.256 Å and C8−O8, 1.236 Å). The remaining atomic assignments of cribrostatin 5 were based upon bond distances, and the observed spectral and NMR data similarities between **4b** and the previously reported renierone[9] (**3a**), in which the ring substituent at C7 is an *O*-methyl instead of an *N*-methyl. The model used for cribrostatin 5 (**4b**) is shown in Figure 1 (X-ray numbering system). Final least-squares refinement of this structure resulted in a standard residual R1 of 0.0832 for quinone **4b**.

The close structural relationship of cribrostatin 3 (**4a**) to cribrostatin 5 (**4b**) and cribrostatin 1 (**1**) was apparent from the similarities observed in the ^{1}H and ^{13}C NMR (Table 1) and MS data exhibited by these substances. Such observations, coupled with the fact that the mass spectra showed only a 14-amu difference between cribrostatin 3 and cribrostatin 5, led to the ready solution for cribrostatin 3 as the *N*-demethylated derivative of quinone **4b**.

On the other hand, the structure of cribrostatin 4 (**5**) proved to be far more challenging and had to rely almost solely on a detailed X-ray crystal structure determination for unequivocal assignment. Crystals of this compound, which occurred as well-formed, ruby-red prisms, exhibited sufficiently intense anomalous dispersion effects with Cu radiation to allow the assignment of the absolute configuration and complete structure by X-ray diffraction methods. SHELXL[10] refinement of the enantiomer shown in Figure 2, along with the Flack absolute structure parameter,[11] resulted in a Flack parameter value of −0.1(3). But refinement of the mirror image of the model shown in Figure 2 gave a Flack parameter value of +1.1(3). In addition, a slightly larger wR2 value was observed for

* To whom correspondence should be addressed. Tel.: (480) 965-3351. Fax: (480) 965-8558.
† Dedicated to the memory of Professors Brian Green (1935−1998) and Irwin B. Douglass (1904−1998).
‡ Arizona State University.
§ DTP, DCTD, FCRDC, National Cancer Institite.
⊥ University of Minnesota.

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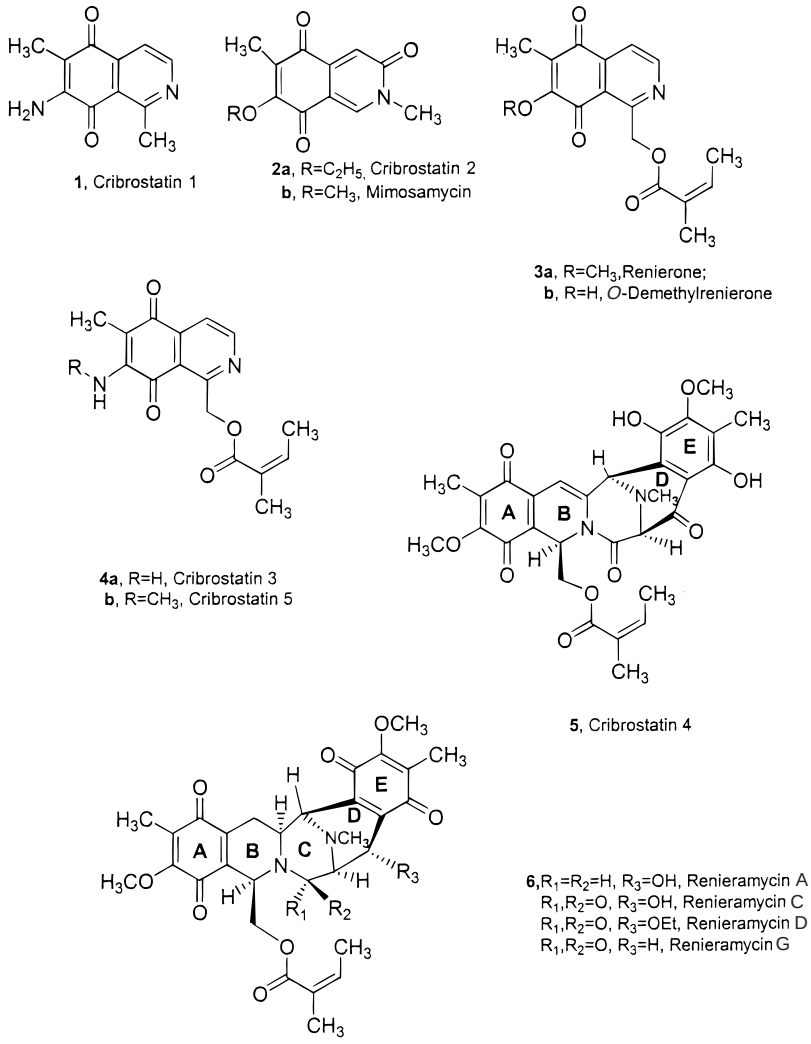
Chart 1



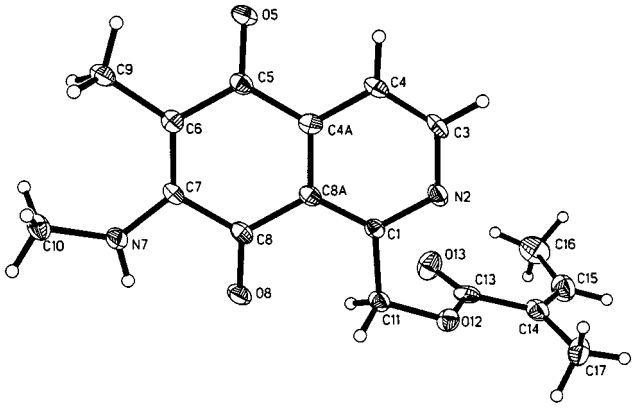


Figure 1. Crystal structure of cribrostatin 5 (**4b**).

refinement of the mirror image of the structure shown in Figure 2 (0.1932 vs 0.1930). As a consequence, the absolute stereochemistry for the three chiral centers of cribrostatin 4 (using the X-ray numbering system) were assigned as follows: 1*R*, 11*R*, 13*S*. The quinone oxygen atoms in ring A of cribrostatin 4 were readily assigned from bond distances (C6−O37, 1.225 Å; C9−O41, 1.227 Å) and were significantly shorter than the phenolic hydroxyl bond distances in ring E (C16−O32, 1.353 Å; C19−O36, 1.385 Å). As a consequence, the oxygen atoms in ring E of cribrostatin 4 (**5**) differ from those in ring E of the related renieramycin series[9c] (**6**) in that the oxygen atoms occur as a quinone in the latter.

The attractiveness of cribrostatin 4 does not seem limited to its pleasing red color and overall structure, but rather includes potential biological properties such as those already known for the related renieramycins,[9] saframycins,[12] and ecteinascidins.[13] Consequently, cribrostatin 4 (**5**) is being further pursued.

When tested against a minipanel of human cancer cell lines in our ASU−CRI laboratory, cribrostatins 3−5 showed differing levels of activity (Table 3). When tested in the NCI 60-cell in vitro panel, cribrostatin 3 (**4a**) and cribrostatin 4 (**5**) showed mean panel GI_{50} values of $(4.27 \pm 0.20) \times 10^{-6}$ M and $(5.01 \pm 0.28) \times 10^{-6}$ M, respectively (values are averages ± SEM calculated from the 40 cell lines of the NCI panel that yielded GI_{50} values for both **4a** and **5**). Individual cell-line response values are provided in the Experimental Section.

Cribrostatins 2 (**2a**)[2] and 4 (**5**) had the broadest antimicrobial spectra. Antibiotic activities of cribrostatins 1−5 were determined by disk diffusion using standard protocols.[14] Cribrostatin 2 (**2a**), the most potent antibiotic of the cribrostatin series, inhibited opportunistic fungi and a variety of bacteria, including clinical isolates of penicillin-resistant *Neisseria gonorrhoeae* and *Streptococcus pneumoniae* (Table 4). Mimosamycin, isolated from *Reniera*[9c] and *Cribrochalina*[2] sponge species and from the actinomycete *Streptomyces lavendulae*,[15] has an antimicrobial

Table 1. The ^{1}H and ^{13}C NMR Assignments (500 MHz) for Cribrostatins 3 (**4a**) and 5 (**4b**) in $CDCl_3$ Solution

position[a]	δ-^{1}H (**4a**)	δ-^{13}C (**4a**)	δ-^{1}H (**4b**)	δ-^{13}C (**4b**)
1		156.42		156.40
3	8.91 (d, J = 5 Hz)	154.63	8.87 (d, J = 5 Hz)	154.55
4	7.93 (d, J = 5 Hz)	118.88	7.91 (d, J = 5 Hz)	118.87
4a		140.50		140.88
5		181.29		182.60
6		112.81		111.46
7		145.94		147.35
8		180.85		182.60
8a		121.80		121.84
9 (CH2)	5.74 (s)	65.34	5.72 (s)	65.56
12 (angelate C−qu)		127.88		127.90
13 (angelate CH)	6.11 (qu, J = 5 Hz)	137.91	6.1 (qu, J = 5 Hz)	137.90
N−Me			3.27	32.85
6-Me	2.01 (s)	9.08	2.28 (s)	10.78
Ester C=0		167.96		167.95
14 (angelate−Me)	1.98 (d)	15.73	1.96 (d)	15.75
15 (angelate−Me)	2.02 (m)	20.60	2.00 (m)	20.65

[a] Numbering as in Pettit et al.[2]

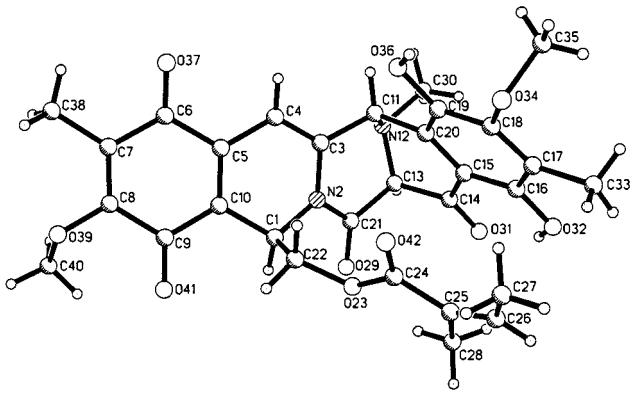


Figure 2. Solid-state conformation of cribrostatin 4 (**5**).

profile[9c] similar to that of cribrostatin 2. This finding is not surprising, given the structural similarities of cribrostatin 2 (**2a**) and mimosamycin (**2b**). The cribrostatins warrant further investigation as antibacterial and antifungal agents.

Experimental Section

General Experimental Methods. Except as now noted, the general experimental procedures employed in our original investigation of *Cribrochalina* sp. were continued here.[2] For the present experiments, melting points were measured with an electrothermal digital melting point apparatus (model 1A9200) and are uncorrected. The Ito Coil Planet centrifuge was supplied by PC, Inc., Potomac, MD. The upper phase of the system, hexane−ethyl acetate−methanol−water (700:300:150:60), was used as the mobile phase at a flow rate of 4.5 mL/min. About 66 mL of lower phase was displaced prior to equilibrium being achieved. The sample (for example, 0.133 g of the fraction leading to cribrostatin 4) was dissolved in 12 mL of the lower phase and applied using a loop injection valve. Fractions were pooled on the basis of color and TLC. The IR spectra were obtained using a Matson Instruments 2020 Galaxy series FT−IR. The EIMS data were recorded with a MAT 312 mass spectrometer, and HRFABMS were obtained with a Kratos MS-50 mass spectrometer (Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE). Optical rotation values were recorded employing the Perkin-Elmer 241 polarimeter. X-ray data collections were done with an Enraf-Nonius CAD4 diffractometer, unless noted otherwise. NMR experiments were conducted with a Varian VXR-500 instrument in $CDCl_3$, and assignments were based on comparison with known compounds and simulation using ACD software. (Advanced Chemistry Development, Inc., 133 Richmond St. West, Suite 605, Toronto, Canada M5H 2L3).

Extraction and Initial Separation of *Cribrochalina* sp. For details of the 1989 recollection (about 350 kg wet wt) of the Republic of Maldives' blue marine sponge *Cribrochalina* sp., refer to Pettit et al.[2] Fractions from the original 195-g dichloromethane-soluble fraction prepared from this recollection were further investigated.

Isolation of Cribrostatin 3 (4a). The crude methylene chloride extract (A) was chromatographed on Sephadex LH-20 successively in (a) methanol (fractions B1−B12) and (b) CH_2Cl_2−MeOH (3:2) (fractions C1−C11). The combined fractions C6 and C7 were further fractioned on Sephadex LH-20 in (c) hexane−toluene−MeOH (3:1:1) and (d) hexane−*i*PrOH−MeOH (8:1:1), providing crude cribrostatin 3 (**4a**) as a red solid (310 mg), which gave small orange-red needles (98 mg) from methylene chloride−methanol: mp 190−192 °C; P-388 ED_{50} 2.5 μg/mL; IR ν_{max} 3400, 1706, 1673, 1606, 1563, 1410, 1397, 1236 cm^{-1} ($CHCl_3$ film); ^{1}H and ^{13}C NMR, see Table 1; *anal.* calcd for $C_{16}H_{16}N_2O_4$, C 64.00%, H 5.37%, N 9.33%; found C 64.00%, H 5.36%, N 9.22%; HREIMS (*m*/*z*) 300.1102 (M^+ calcd for $C_{16}H_{16}N_2O_4$ 300.1110); LREIMS (*m*/*z*) 300, 272, 243, 217, 201, 173, 145, 117, 83, 82 (base).

Isolation of Cribrostatin 4 (5). Fractions C4 and C5 were chromatographed on Sephadex LH-20 in hexane−toluene−MeOH (3:1:1) (fractions D1−D15), followed by rechromatography of D4−D7 in hexane−*i*PrOH−MeOH (8:1:1), to give fractions E1−E10. High-speed countercurrent distribution of fraction E6 (133 mg) was performed using an Ito Coil Planet centrifuge. The upper phase of the system, hexane−EtOAc−MeOH−water (700:300:150:60) was used as the mobile phase, at a flow rate of 4.5 mL/min. About 66 mL of lower phase was displaced before equilibrium was achieved. The sample was dissolved in 12 mL of the lower phase and applied using a loop injection valve. Fractions were pooled on the basis of color and TLC (CH_2Cl_2−acetone, 9:1). An early-eluting dark wine-red fraction gave a red solid on evaporation, which crystallized from methanol to give cribrostatin 4 (**5**) as well-formed red prisms (49 mg): mp 190−192 °C (dec); P-388 ED_{50} 24 μg/mL; IR ν_{max} 3429, 1705, 1649, 1566, 1415, 1228, 1155, 754 cm^{-1} (KBr); λ_{max} (CH_3OH) 209 (40 773), 274 (13 679), 359 (8 067), 507 nm (3416); ^{1}H and ^{13}C NMR, see Table 2; HRFABMS [M + 1]$^+$ 579.1964 (calcd for $C_{30}H_{31}N_2O_{10}$, 579.1979, error 2.5 ppm); LREIMS (*m*/*z*) 580, 578, 550, 521, 467, 465, 453, 451, 439, 437 (base), 423, 409, 396, 234, 220, 206, 192, 114, 100, 83, 56.

Isolation of Cribrostatin 5 (4b). Fractions B6−B8 were combined and chromatographed twice on Sephadex LH-20 in CH_2Cl_2−MeOH (3:2), followed by hexane−toluene−MeOH (3:1:1) and hexane−*i*PrOH−MeOH (8:1:1), to give a dark red solid (69 mg). This was subjected to high-speed countercurrent distribution with an Ito Coil Planet centrifuge in hexane−EtOAc−MeOH−water (700:300:150:60) as described for cri-

Table 2. The ^{1}H and ^{13}C NMR (500 MHz) Assignments for Cribrostatin 4 (**5**) in $CDCl_3$ Solution

carbon atom[a]	δ-^{1}H	δ-^{13}C	carbon atom	δ-^{1}H	δ-^{13}C
6-Me	1.93	8.59	16		119.78
16-Me	2.14	8.96	25		126.56
27 (angelate Me)	1.73 (d)	15.42	6		127.08
28 (angelate Me)	1.45	19.86	9		134.59
N−CH3	2.55	41.21	17		153.33
11 (CH)	4.10	46.85	26 (=CH)	5.9 (qu)	139.30
1 (CH)	6.18	56.17	10		139.76
7-OMe	3.84	61.11	18		138.51
17-OMe	4.04	61.20	3		124.18
22 (CH2)	3.81, 4.06	62.02	7		156.31
13 (CH)	4.85	72.50	21 (amide C=O)		161.12
4 (CH)	6.22	100.04	24 (ester C=O)		166.76
19		108.55	8 (quinone C=O)		179.88
20		119.15	5 (quinone C=O)		184.95
15		156.22	14 (Ar. C=O)		192.67

[a] Numbering as in Cooper and Unger[12d] and Arai et al.[12f].

Table 3. GI_{50} Results (μg/mL) for Various Cancer Cell Lines

cell type	cell line	cribrostatin 3	cribrostatin 4	cribrostatin 5
pancreas-a	BXPC-3	>1	5.6	0.29
neuroblast	SK−N−SH		3.6	
ovarian	OVCAR-3	0.77	2.2	0.18
CNS	SF-295	>1	>10	0.36
thyroid ca	SW-1736		>10	
lung−NSC	NCI−H460	>1	>10	0.22
colon	KM20L2	>1	>10	0.14
pharynx-sq	FADU		0.26	
prostate	DU-145	>1	>10	0.30
mouse leukemia	P-388	2.49	24.6	0.045

Table 4. Antimicrobial Activities of Cribrostatin 1 (**1**), Cribrostatin 2 (**2a**), Cribrostatin 3 (**4a**), Cribrostatin 4 (**5**), and Cribrostatin 5 (**4b**)

	minimum inhibitory concentration (μg/disk)				
microorganism	**1**	**2a**	**4a**	**5**	**4b**
Candida albicans (ATCC 90028)	*[a]	3.12−6.25	*	*	*
Cryptococcus neoformans (ATCC 90112)	*	12.5−25	*	*	*
Micrococcus luteus (Presque Isle 456)	*	50−100	*	*	50−100
Staphylococcus aureus (ATCC 29213)	*	12.5−25	*	*	*
Enterococcus faecalis (ATCC 29212)	*	*	*	*	*
Bacillus subtilis (Presque Isle 620)	*	25−50	*	12.5−25	*
Streptococcus pneumoniae (ATCC 6303)	*	12.5−25	*	6.25−12.5	*
Penicillin-resistant *S. pneumoniae* (clinical isolate)	NT[b]	25−50	NT	50−100	NT
Invasive *S. pneumoniae* (clinical isolate)	NT	50−100	NT	*	NT
Group A *Streptococcus* (clinical isolate)	NT	*	NT	12.5−25	NT
Stenotrophomonas maltophilia (ATCC 13637)	*	*	*	*	*
Escherichia coli (ATCC 25922)	*	*	*	*	*
Enterobacter cloacae (ATCC 13047)	*	*	*	*	*
Neisseria gonorrheae (ATCC 49226)	0.39−0.78	0.39−0.78	0.0975−0.195	6.25−12.5	6.25−12.5
Penicillin-resistant *N. gonorrheae* (clinical isolate)	0.39−0.78	0.39−0.78	0.39−0.78	1.56−3.12	6.25−12.5

[a] * = No inhibition at 100 μg/disk. [b] NT = not tested.

brostatin 4. A dark orange-red solid (9.3 mg) was obtained that gave cribrostatin 5 (**4b**) as reddish-brown plates (3.0 mg) from MeOH−CH_2Cl_2; ^{1}H and ^{13}C NMR, see Table 1; HRFABMS [M + 1]$^+$ 315.1340 (calcd for $C_{17}H_{19}N_2O_4$ 315.1345, error 1.5 ppm); LREIMS (*m*/*z*) 314, 285, 256, 231, 214, 203, 187, 130, 117, 83, 56.

Crystal Structure of Cribrostatin 4 (5). Well-formed, ruby-red crystals of cribrostatin 4 (**5**) were obtained via slow evaporation of a MeOH solution. A crystal, with approximate dimensions of 0.34 × 0.18 × 0.04 mm, was mounted on the tip of a glass fiber with Super Glue. Data collection was performed at 296(2) K for an orthorhombic system, with all reflections corresponding to slightly more than a complete quadrant ($2\theta \leq 130°$) being measured using an $\omega/2\theta$ scan technique. After measurement of each reflection, Friedel reflections were also collected whenever possible. Subsequent statistical analysis of the complete reflection data set using the XPREP[10] program indicated the space group was $P2_12_12_1$. Each asymmetric unit of the cell was found to contain a single molecule of the quinone (**5**). Crystal data: $C_{30}H_{30}N_2O_{10}$, a = 8.394(2), b = 17.918(4), c = 18.992(4) Å, V = 2856.5(10) Å^3, λ (Cu Kα) = 1.54178 Å, ρ_c = 1.345 g cm^{-3} for Z = 4 and fw = 578.56, $F(000)$ = 1216. After Lorentz and polarization corrections, merging of equivalent reflections and rejection of systematic absences, 4454 unique reflections [R(int) = 0.0661] remained, of which 3951 were considered observed [$(I_o > 2\sigma(I_o)$] and were used in the subsequent structure solution and refinement. Linear and anisotropic decay corrections were applied to the intensity data as well as an empirical absorption correction (based on a series of ψ-scans).[16] Structure determination was accomplished with SHELXS.[10] All non-hydrogen atoms for **5** were located using the default settings of that program. The remaining hydrogen atom coordinates were calculated at optimal positions. The latter atoms were assigned thermal parameters equal to either 1.2 or 1.5 (depending upon chemical type) of the U_{iso} value of the atom to which they were attached, and then both coordinates and thermal values were forced to ride that atom during final cycles of refinement. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process with SHELXL.[10] The

final standard residual R1 value for the model shown in Figure 2 was 0.0744 (for observed data) and 0.0830 (for all data). The corresponding Sheldrick *R* values were wR2 of 0.1830 and 0.1930, respectively. The difference Fourier map showed insignificant residual electron density; the largest difference peak and hole being +0.444 and −0.344 e/Å^3, respectively. Final bond distances and angles were all within acceptable limits.

Crystal Structure of Cribrostatin 5 (4b). A small, red plate of this compound, obtained via slow evaporation of a MeOH−water solution, with approximate dimensions of 0.25 × 0.23 × 0.02 mm, was mounted on the tip of a glass fiber. Data collection was performed at 173(2) K on a Siemens Smart system. An initial set of cell constants was calculated from reflections harvested from three sets of 30 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed and orientation matrixes determined from 80 reflections. Final cell constants were calculated from a set of 1083 strong reflections from the actual data collection. A hemisphere data collection technique was used. A randomly oriented region of reciprocal space was surveyed to the extent of 1.3 hemispheres to a resolution of 0.84 Å. Three major swaths of frames were collected with 0.30° steps in ω. Subsequent statistical analysis of the complete reflection data set using the XPREP[10] program indicated the space group was $P\bar{1}$. Crystal data: $C_{17}H_{18}N_2O_4$, a = 7.5505(10) Å, b = 7.7383(10) Å, c = 14.321(2) Å, V = 750.5(2) Å^3, α = 103.491(2)°, β = 92.644(2)°, γ = 111.225(3)°, λ = (Mo Kα) = 0.71073 Å, ρ_c = 1.391 g cm^{-3} for Z = 2, and fw = 314.33, F(000) = 332. After Lorentz and polarization corrections, merging of equivalent reflections and rejection of systematic absences, 2407 unique reflections remained (R_{int} = 0.0358), of which 1173 were considered observed [$I_o > 2\sigma(I_o)$] and were used in the subsequent structure solution and refinement.

An absorption correction was applied to the data with SADBS.[17] Direct-methods structure determination and refinement were accomplished with SHELXTL−V5.1.[10] All non-hydrogen atoms for **4b** were located using the default settings of that program. Although the overall connectivity pattern of the non-hydrogen atoms in the structure could be readily established from the data, the observed low data-to-parameter ratio did not allow an unambiguous assignment of all the individual atomic species in **4b**. These atomic assignments were determined instead via correlation of cribrostatin 5 to closely related derivatives,[2,9c,18] taking into account the interatomic bond distances, along with NMR and MS data observed for this compound. Because the quality of data precluded the direct determination of hydrogen atom positions, the remaining hydrogen atom coordinates were calculated at optimal positions using the program SHELXL.[10] These latter atoms were assigned thermal parameters equal to either 1.2 or 1.5 (depending upon chemical type) of the U_{iso} value of the atom to which they were attached, then both coordinates and thermal values were forced to ride that atom during final cycles of refinement. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process. The final standard residual R1 value for the model shown in Figure 1 was 0.0832 (for observed data) and 0.1729 (for all data). The corresponding Sheldrick *R* values were wR2 of 0.1669 and 0.2010, respectively. The difference Fourier map showed insignificant residual electron density; the largest difference peak and hole being +0.332 and −0.399 e/Å^3 , respectively. Final bond distances and angles were all within acceptable limits.

Testing of Compounds in the NCI 60-Cell Screen. Cribrostatin 3 (**4a**) and cribrostatin 4 (**5**) were tested comparatively in the NCI 60-cell screen. Cribrostatin 5 (**4b**) was not included in this testing due to insufficient supply. Each compound was tested in quadruplicate using an upper concentration limit of 10^{-5} M and five log-spaced dilutions, otherwise using the standard NCI protocol. The 40 cell lines that gave GI_{50} values for both compounds are listed as follows, along with the averaged, corresponding negative log GI_{50} values for **4a** and **5**, respectively: CCRF−CEM (5.37, 5.77); HL-60 (TB) (5.51, 5.27); K-562 (5.13, 5.36); MOLT-4 (5.31, 5.72); RPMI-8226 (5.07, 5.21); SR (5.47, 5.42); A549/ATCC (5.46, 5.06); HOP-62 (5.27, 5.12); HOP-92 (5.02, 5.09); NCI−H226 (5.15, 5.10); NCI−H460 (5.52, 5.12); NCI−H522 (5.41, 5.38); COLO 205 (5.23, 5.09); KM 12 (5.31, 5.04); SW-620 (5.44, 5.16); SF-268 (5.20, 5.02); SF-295 (5.44, 5.05); SF-539 (5.32, 5.24); SNB-75 (5.32, 5.25); U251 (5.49, 5.19); LOX IMVI (5.39, 5.48); MALME−3M (6.21, 6.41); SK-MEL-5 (5.96, 5.09); UACC-62 (5.60, 5.01); IGROV1 (5.14, 5.07); OVCAR-3 (5.74, 5.44); OVCAR-4 (5.28, 5.74); OVCAR-8 (5.06, 5.37); 786-O (5.23, 5.21); ACHN (5.02, 5.10); RXF-393 (5.31, 5.28); SN12C (5.21, 5.15); PC-3 (5.70, 5.04); MCF7 (5.33, 5.09); MCF7/ADR−RES (5.34, 5.17); MDA-MB-231/ATCC (5.06, 5.57); HS578T (5.20, 5.06); MDA-MB-435 (5.74, 5.74); MDA-N (5.72, 5.66); T-47D (5.19, 5.68).

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Supporting Information Available: X-ray crystallographic tables of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for cribrostatin 4 (**5**) and 5 (**4b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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