SYNTHESIS OF CRIBROSTATINS 1 AND 2

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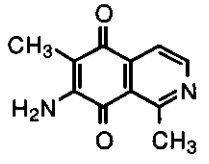
Abstract —— Synthesis of the cytotoxic isoquinolinequinone cribrostatins 1 (**1**) and 2 (**2**), which were isolated from the blue marine sponge *Cribrochalina* sp., is described.

The structures of cribrostatins 1 (**1**) and 2 (**2**), cytotoxic isoquinolinequinones isolated from the marine sponge *Cribrochalina* sp. were recently reported.[1] These pigments were found to be structurally related with mimosamycin (**3**), which was the first isoquinolinequinone antibiotic isolated from the culture filtrate of the microorganism *Streptomyces lavendulae*.[2] Mimosamycin (**3**) itself and several structurally related antibiotics, *i.e.* perfragilin A (**4**),[3,5a] B (**5**),[4,5] 2-methyl-6-methylthio-iosquinoline-3,5,8(2*H*)-trione (**6**),[4] 4-aminomimosamycin (**7**),[6] and 7-amino-7-demethoxymimosamycin (**8**),[6] have subsequently been found in marine organisms.



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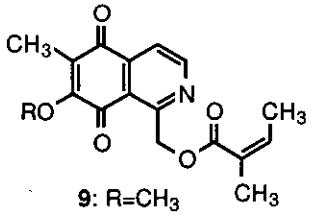
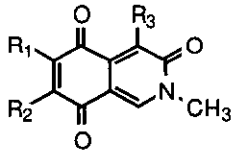


9: R=CH_3
10: R=H



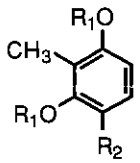
	R_1	R_2	R_3
2	CH_3	OC_2H_5	H
3	CH_3	OCH_3	H
4	SCH_3	NH_2	H
5	SCH_3	SCH_3	H
6	SCH_3	H	H
7	CH_3	OCH_3	NH_2
8	CH_3	NH_2	H

The blue marine sponge cribrostatins 1 (**1**), red-orange crystals, mp 220-235°C (decomp.) and 2 (**2**), golden-yellow solid, mp 194-195°C, were isolated along with the previously known mimosamycin (**3**), renierone (**9**), and *O*-demethylrenierone (**10**). Structures of cribrostatins were elucidated by high field nuclear magnetic resonance and mass spectral studies. Finally the structure of **1** was determined by

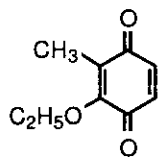
an X-ray crystallographic study. Both cribrostatins exhibited activity against the P 388 lymphocytic leukemia cell line (ED_{50} 1.58 and 2.73 μg/ml, respectively).

To obtain material for more detailed biological evaluation we have undertaken the first synthesis of cribrostatins 1 (**1**) and 2 (**2**).

As the strategy for synthesizing cribrostatins 1 (**1**) and 2 (**2**), the isoquinolinequinone skeleton was constructed using a hetero Diels-Alder reaction between a substituted 2-azabutadiene and 1,4-benzoquinone.



11: R_1=R_2=H
12: R_1=C_2H_5, R_2=H
13: R_1=C_2H_5, R_2=CHO
14: R_1=C_2H_5, R_2=OH



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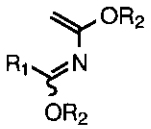
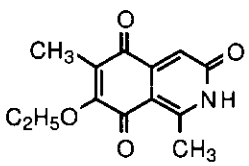


16: R_1=CH_3, R_2=TBDMS
17: R_1=H, R_2=TBDMS



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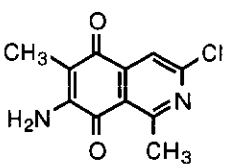

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The 1,4-benzoquinone (**15**) was prepared in four steps starting from commercial available 2-methylresorcinol (**11**). Treatment of the 1,3-diethoxytoluene (**12**), prepared from **11** in 47 % yield, with phosphorous oxychloride in *N*,*N*-dimethylformamide afforded the benzaldehyde (**13**) in 84 % yield. Reaction of **13** with *m*-chloroperoxybenzoic acid in dichloromethane at reflux for 2 h followed by treatment with 10% potassium hydroxide in methanol gave the phenol (**14**) in 72 % yield. Oxidation of **14** with cerium(IV) ammonium nitrate in aqueous acetonitrile afforded the 1,4-benzoquinone (**15**) in 79 % yield. The hetero Diels-Alder reaction of **15** with 2,4-bis(*tert*-butyldimethylsilyloxy)-3-azapenta-1,3-diene (**16**)[7] in chloroform at 85°C for 24 h gave the [4+2] cycloadduct which was treated with concentrated hydrochloric acid at room temperature for 24 h to give 3-quinolonequinone (**18**) in 50 % yield. Reaction of **18** with phosphorous oxychloride at 70°C for 2 h followed by treatment of 1 *M* ammonia in methanol at room temperature for 6 h gave the desired chloroquinolinequinone (**19**) in 59 % yield. Finally, catalytic hydrogenation of **19** on 10 % Pd-C in methanol at room temperature for 6 h afforded aminoquinolinequinone (**1**) in 87 % yield.

Next, cribrostatin-2 (**2**) was also syntheseized from 1,4-benzoquinone (**15**). The hetero Diels-Alder reaction of **15** with 1,3-bis(*tert*-butyldimethylsilyloxy)-2-azabuta-1,3-diene (**17**)[7] in chloroform at 50°C for 2 h gave the corresponding adduct after acidic workup, which was methylated with methyl iodide, potassium carbonate and tris[2-(2-methoxyethoxy)ethyl]amine in *N*,*N*-dimethylformamide at room

temperature for 2 h to provide *N*-methylquinolonequinone (**2**) in 66 % yield. The spectral data of synthetic **1** and **2** were identical to those of the natural products.[8]

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8. **1**: Ms m/z (%): 202(M^+, 100), 175(41), 145(31). Ir (KBr): 3408, 3312, 1682, 1634, 1604, 1558 cm^{-1} ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 2.01(3H, s), 2.98(3H, s), 5.16(2H, br s), 7.86(1H, d, *J*=4.9 Hz) 8.83 (1H, d, *J*= 4.9 Hz). ^{13}C-Nmr (67.8 MHz, $CDCl_3$: two drops of DMSO-d_6 were used) δ: 8.43, 24.75, 110.37, 116.69, 121.49, 139.93, 146.47, 153.10, 158.42, 179.64, 181.08. **2**: Ms m/z (%) 247(M^+,100), 232(40), 218(33), 203(48), 191(7), 175(23), 163(7). Ir (KBr): 1700, 1656, 1600, 1542cm^{-1}. ^{1}H-Nmr (270 MHz $CDCl_3$) δ: 1.40(3H, t, *J*=6.9 Hz), 2.07(3H, s), 3.66(3H, s), 4.48(2H, q, *J*=6.9 Hz), 7.10 (1H, s), 8.26(1H, s). ^{13}C-Nmr (67.8 MHz, $CDCl_3$) δ: 8.97, 25.50, 111.77, 117.54, 122.16, 140.49, 146.52, 154.00, 159.46, 180.77, 181.58.

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