A New Bisindole from Alga *Caulerpa serrulata*

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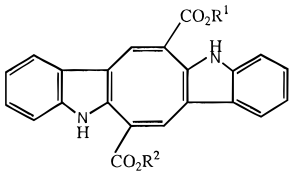
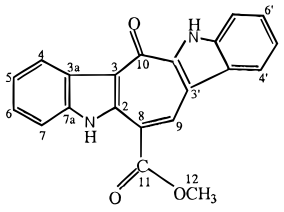
A new bis-indole, caulersin (**4**), was isolated from the alga *Caulerpa serrulata*, collected from the Xisha Islands in the South China Sea. The structure was established by spectroscopic methods.

The naturally occurring bisindole caulerpin (**1**)[1,2] and its two analogues **2** and **3**[3] have been isolated from the green alga *Caulerpa racemosa*, *C. sertularioides*, etc. Caulerpin (**1**) was found to be widely distributed in this genus,[4] and it was also shown to be a plant growth regulator in a root growth test of lettuce seeds[5] and to exhibit slight *in vitro* antitumor activity.[6]

Our earlier investigation on algae led to the isolation of caulerpin (**1**) from several species other than the genus *Caulerpa*,[7] and its crystal structure was determined by X-ray diffraction analysis.[8] Caulerpin has shown activity as a growth promoter of wheat coleoptiles and cucumber cotyledons.[9] We now report the isolation of another new bisindole, caulersin (**4**), from the alga *Caulerpa serrulata* (Forsskal) J. Agardh (Caulerpaceae). The alga *C. serrulata* was collected off the Xisha Islands and extracted with EtOH. The EtOH extract was partitioned between EtOAc and H_2O, and the organic extract was twice chromatographed on a Si gel column to yield caulersin (**4**).



	R^1	R^2
1	Me	Me
2	H	H
3	Me	H



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Caulersin (**4**) gave an M^+ peak in its HREIMS at *m/z* 342.0992, corresponding to the molecular formula $C_{21}H_{14}N_2O_3$. The ^{13}C NMR signals were similar to those of **1**. However, the ^{13}C NMR spectrum of **1** showed only 11 signals due to C_2 symmetry, while the ^{13}C NMR spectrum of **4** contained 21 signals representing all of the carbons in the molecule. The pattern of the signals in the aromatic region was characteristic of two indole rings.[10] The downfield shift of the two NH protons at δ 12.40 and 13.14 indicated that these protons formed hydrogen bonds. Its UV data showed an extensively conjugated aromatic system. Therefore, **4** would appear to be a member of the unusual structural class of bisindoles.

The IR spectrum of **4** showed absorption bands at 1690 and 1665 cm^{-1}. The ^{13}C NMR spectrum revealed a conjugated ester and a cross-conjugated ketone at δ 167.5 and 172.1.[11] Two signals at δ 146.7 (s) and 129.4 (d), suggesting a trisubstituted double bond, were also present. In the $^1H-^1H$ COSY spectrum, the partial structures CH(4)−CH(5)−CH(6)−CH(7), and CH(4′)−CH(5′)−CH(6′)−CH(7′) were revealed. The HMBC spectrum indicated the correlation C-3 to H-4, C-3a to H-5, C-7 and C-8 to H-1, C-10 to H-1′, C-11 to H-9 and H-12, C-3′ to H-4′, C-3a′ to H-5, and C-7′ to H-1′ for **4**. The spectral evidence suggested a seven-membered ring for caulersin. Two signals at δ 13.14 and 12.40 indicated that the two NH protons formed hydrogen bonds with two different kinds of carbonyl groups, which supported the structure depicted in **4**.

Table 1. ^{13}C NMR and ^1H NMR Data for Caulersin **4**[a]

position	δ_C	δ_H (*J*, Hz)	HMBC (C → H)	position	δ_C	δ_H (*J*, Hz)	HMBC (C → H)
1		13.14		1′		12.40	
2	138.3			2′	140.6		
3	112.9		4	3′	112.1		4′
3a	126.6		5	3a′	126.5		5′
4	121.7	7.79 d (8.0)		4′	123.2	7.98 m	
5	125.5	7.40 m		5′	125.8	7.52 m	
6	120.1	7.44 m		6′	121.5	7.58 m	
7	114.1	8.39 d (8.0)	1	7′	114.3	9.08 m	1′
7a	138.3			7a′	136.6		
8	129.4		1				
9	146.7	9.16 s					
10	172.1		1′				
11	167.5		9, 12				
12	52.9	4.09 s					

[a] Spectra were recorded in DMSO-d_6 using TMS as the internal standard.

Experimental Section

General Experimental Procedures. Melting point was taken on an X_4 micromelting point apparatus, and IR spectra were recorded on a Nicolet 5DX FT-IR spectrophotometer. NMR spectra were recorded on Varian XL-300 MHz, and mass spectra on Kratos MS 50 instrument.

Alga Material. The alga *Caulerpa serrulata* (#93-37) was collected off the Xisha Islands of the South China Sea. A voucher specimen is preserved in the Research Center of Organic Natural Products Chemistry, Zhongshan University, Guangzhou, China.

Extraction and Purification of 4. The chopped alga (wet wt 3.5 kg) was extracted with EtOH at room temperature. The combined extracts were concentrated *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The EtOAc soluble portion was subjected to Si gel column chromatography, eluting with petroleum ether containing increasing concentrations of Me_2CO. The fraction eluted with Me_2CO−petroleum

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ether (1:1 v/v) was further purified by flash chromatography. The fraction eluted with $CHCl_3$−Me_2CO (7:3 v/v) afforded caulersin (**4**, 7 mg).

Caulersin (**4**) was obtained as bright yellow crystals: mp 269−270 °C (MeOH); UV (EtOH) λ_{max} (log ϵ) 206 (4.51), 220 (3.62), 265 (2.02), 273 (1.10), 311 (1.36) nm; IR (KBr) ν_{max} 3380, 1690, 1675, 1258 cm^{-1}; HREIMS *m*/*z* 342.0992 [M^+], calcd for $C_{21}H_{14}N_2O_3$ 342.1004; EIMS *m*/*z* 342 (100), 310 (55), 282 (25), 254 (33), 227 (17), 141 (32), 127 (15), 84 (72), 66 (100); NMR data, see Table 1.

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