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New Prenylated Bromoquinols from the Green Alga *Cymopolia barbata*

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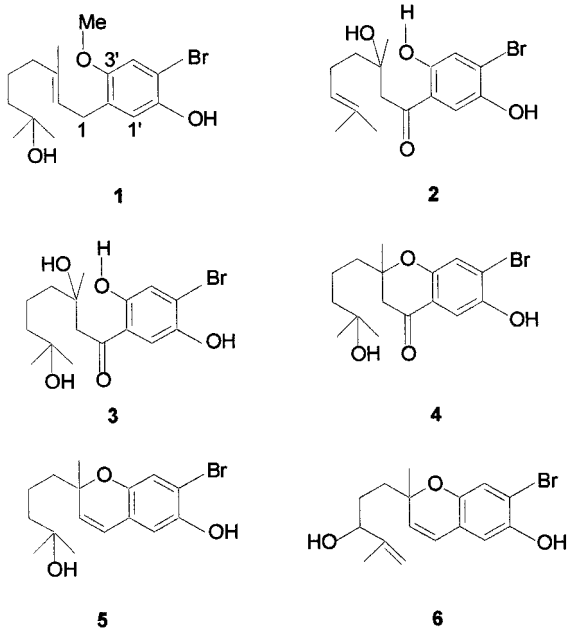
Six new prenylated bromohydroquinones, 3′-methoxy-7-hydroxycymopol (**1**), 3-hydroxycymopolone (**2**), 3,7-dihydroxycymopolone (**3**), 7-hydroxycymopochromanone (**4**), 7-hydroxycymopochromenol (**5**), and a related 6-hydroxy derivative of cymopochromenol (**6**), have been isolated from the green marine alga *Cymopolia barbata*. The structures of these cymopol-related metabolites were determined by spectral methods.

Thirty years of research into natural products from marine algae have led to the conclusion that, while red and brown algae possess physiological and biochemical mechanisms with the ability to produce a great variety of secondary metabolites with very different skeleton types and functionalities,[1] in green algae these mechanisms do not seem to be so widely diversified. Taking into account that secondary metabolites fulfill an essentially ecological role,[2,3] it is possible that green algae can adapt to the environment and survive, particularly to pressure by herbivores, without the necessity of such metabolic complexity. On the other hand, perhaps, green algae have been much less intensely researched. The genera *Caulerpa*, *Halimeda*, and *Bryopsis* from tropical and subtropical habitats have been more thoroughly investigated because of the abundant metabolites they contain, which may point to the need for chemical defense against intense feeding pressure by herbivores[1] in the aforementioned habitats.

In 1976, the "cymopols" were described[4] as the first halogenated natural products isolated from a green alga, *Cymopolia barbata* (L.) Lamouroux (Dasycladaceae). Surprisingly, after 25 years, there are only five papers on the isolation and characterization of new secondary metabolites from this same genus, despite evidence that it is a rich source of pharmacologically active compounds exhibiting antifungal,[4] antitumor,[5] antimicrobial,[6] and antimutagenic[7] properties, in addition to other biological properties of a defensive[8] and antifeedant[9−11] nature. Of these reports, four are described from *C. barbata* collected in warm waters in the Caribbean area and one is from the Atlantic (Canary Islands). It is interesting to note that all the habitats are situated at approximately the same latitude.

In this paper we report on the isolation and structure determination of six new minor metabolites **1**−**6**, together with compounds **7**−**11**, from *C. barbata* collected in Cuba. Compounds **7**−**11** were identified respectively as the previously described[4] cymopol monomethyl ether (**7**), cymopolone (**8**), cymopochromenol (**9**), isocymopolone (**10**), and a monohydrated derivative (**11**) of cymopolone[6] from spectral data that were identical with those reported in the literature. Since the reported ^{1}H and ^{13}C NMR data for these compounds are either incomplete or unassigned, they were recorded and assigned (see Tables 3 and 4).



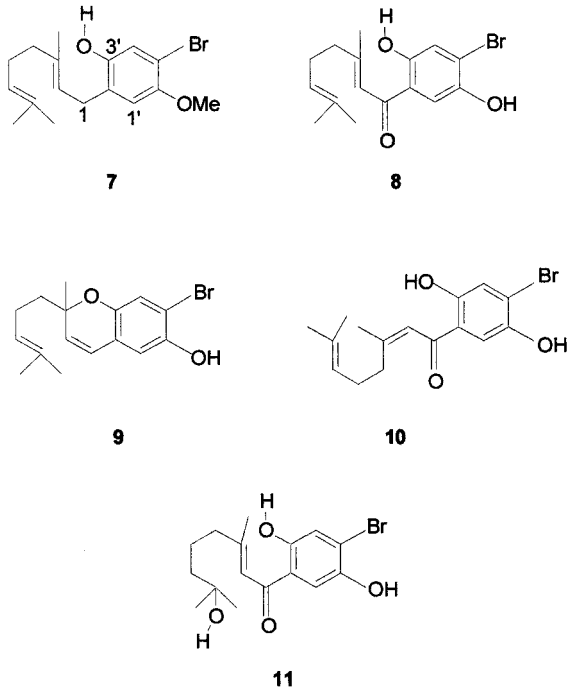


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Table 1. ^{1}H, ^{13}C, and HMBC NMR Data of Compounds **1**−**3** [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

	1			**2**			**3**		
position	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1	3.22 d (7.4)	27.6	C-2, C-3, C-1′, C-3′, C-2′		191.8			192.9	
2	5.25 t (7.4)	121.6	C-1, C-10, C-4	2.73 d (15) 2.61 d (15)	47.3	C-1, C-3, C-4, C-10	2.52 d (15) 2.70 d (15)	47.0	C-1, C-10, C-4, C-3 C-2
3		137.0			81.4			81.4	
4	2.02 t (6.5)	39.6	C-3, C-6, C-5, C-10, C-2	1.75 m 1.63 m	39.0	C-3, C-6, C-5, C-2	1.58 dd (6, 13.9) 1.66 m	39.8	C-3, C-6, C-5, C-10
5	1.47 m	43.0	C-4, C-6	2.06 m	22.1	C-4, C-6, C-7	1.43 m	18.2	C-4, C-6, C-7
6	1.45 m	22.3	C-5, C-7, C-8, C-9	5.03 t (5)	123.0	C-8, C-9	1.41 m	43.5	C-4, C-5, C-7, C-8, C-9
7		71.2			132.3			71.4	
8	1.20 s	29.1	C-6, C-7, C-9	1.56[a] s	17.5	C-6, C-7, C-9	1.19 s	29.0	C-7, C-6, C-9
9	1.20 s	29.1	C-6, C-7, C-8	1.64[a] s	25.5	C-6, C-7, C-8	1.19 s	29.0	C-7, C-6, C-8
10	1.64 s	15.8	C-2, C-3, C-4	1.37 s	23.7	C-2, C-3, C-4	1.28 s	23.4	C-2, C-3, C-4
1′	6.83 s	116.5	C-1, C-5′, C-3′, C-5′	7.42 s	111.4	C-1, C-3′, C-5′, C-6′	7.34 s	111.1	C-1, C-5′, C-3′, C-6′, C-2′
2′		131.3			120.6			119.9	
3′		152.1			153.5			153.4	
4′	6.87 s	113.7	C-5′, C-3′, C-6′, C-2′	7.12 s	121.7	C-2′, C-3′, C-6′	7.06 s	122.3	C-5′, C-3′, C-6′, C-2′
5′		105.8			118.9			119.7	
6′		146.2			146.4			147.3	
O*H*-6′	5.48 s			5.33 s		C-1′, C-5′, C-6′			
O*Me*	3.75 s	56.0	C-3′						

[a] Interchangeable signals.

Table 2. ^{1}H, ^{13}C, and HMBC NMR Data of Compounds **4**−**6** [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

	4			**5**			**6**		
position	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1		205.3		6.25 d (10)	122.1	C-3′, C-1′, C-3, C-2′	6.26 d (10)	122.3	C-3, C-1′, C-3′, C-2′
2	2.96 d (15) 2.98 d (15)	52.6	C-1, C-3, C-4, C-10	5.61 d (10)	131.3	C-1, C-3, C-2′	5.59 d (10)	131.0	C-1, C-3
3		73.7			78.5			78.4	
4	1.58 m	34.4	C-3, C-5, C-6, C-10	1.65 m 1.61 m	41.3	C-10, C-2, C-5, C-3	1.73 m 1.65 m	36.8	C-5
5	1.62 m; 1.57 m	16.2	C-4	1.44 m	18.7	C-4, C-6, C-7	1.65 m 1.71 m	29.2	C-4
6	1.44 m; 1.29 m	36.2	C-5, C-8, C-9	1.43 m	43.9	C-5, C-7	4.03 t (5.6)	75.6	
7		72.1			70.9			146.8	
8	1.03[a] s	28.0	C-6, C-7, C-9	1.18[a] s	29.5	C-6, C-7, C-9	1.68 s	17.5	C-6, C-7, C-9
9	1.17[a] s	32.1	C-6, C-7, C-8	1.17[a] s	29.2	C-6, C-7, C-8	a: 4.9 s b: 4.81 d (5.3)	111.2	C-6, C-7, C-8
10	1.33 s	26.9	C-2, C-3, C-4	1.33 s	25.9	C-2, C-3, C-4	1.33 s	25.9	C-2, C-3, C-4
1′	7.64	118.2	C-1, C-3′, C-5′, C-6′	6.62 s	112.7	C-1, C-2′, C-3′, C-5′	6.62 s	112.7	C-1, C-2′, C-3′, C-5′
2′		121.0			121.9			121.8	
3′		156.0			146.8			147.1	
4′	7.10	120.6	C-2′, C-6′, C-3′	6.87 s	118.8	C-5′, C-6′, C-2′	6.86 s	118.7	C-5′, C-6′, C-2′, C-3′
5′		118.6			108.6			108.6	
6′		144.1			146.1			146.1	
O*H*-6′	5.09		C-5′, C-6′				5.06		C-5′, C-6′, C-1′
O*H*-3′	11.97		C-4′, C-3′						

Results and Discussion

The MS and ^{1}H and ^{13}C NMR spectroscopic data of the new compounds **1**, **2**−**4**, and **5** and **6** suggested that they are closely related, respectively, to a monomethyl ether derivative of cymopol (**7**), cymopolone (**8**), and cymopochromenol (**9**), reported from the same source.

Vacuum flash chromatography of the crude dichloromethane extract of *C. barbata* gave fractions from which compounds **1**−**11** were obtained by standard chromatographic procedures involving gel filtration and recycling-HPLC (see Experimental Section). Compound **1** was isolated as a colorless oil. The EIMS showed peaks at *m*/*z* 356/358, with relative intensities suggestive of one bromine atom that corresponded to the molecular formula $C_{17}H_{25}O_3Br$ [$(M)^+$ (HRMS)]. ^{13}C and ^{1}H NMR spectral analysis and the IR data of **1** showed that a bromohydroquinone ring, which is a common component of the other compounds **2**−**11** isolated from this alga, accounted for four of its five degrees of unsaturation. The ^{1}H and ^{13}C NMR data of **1** resembled those of compound **7** (Tables 1 and 3) with the following significant differences: (a) the isopropylidene group of **7** [δ_{H-8} 1.57 (s, 3H) and δ_{H-9} 1.66 (s, 3H); δ_{C-7} 132.0] appeared as an isopropyl carbinol in **1** [$\delta_{H-8,9}$ 1.20 (s, 6H); δ_{C-7} 71.2]; (b) in a HMBC experiment, the correlation observed between the methoxyl group and the C-3′ indicated that the methoxy group of **1** was at C-3′ instead of C-6′ as in **7**. Thus, the structure of **1** could be established as 3′-methoxy-7-hydroxycymopol.

The oily compounds **2** and **3** are the mono- and dihydrated forms, respectively, of the prenyl chain of cymopolone, as can be deduced by comparison of their ^{1}H and ^{13}C NMR and MS data. Compound **2** (HRMS data *m*/*z* [$(M - H_2O)^+$] 338.047, calcd for $C_{16}H_{19}O_3Br$, 338.051) lacked the conjugated unsaturation to a carbonyl group present in cymopolone **8** [C-3: δ_C 162.2; Me-10: δ_H 2.16, s], but showed the presence of two protons of an isolated methylene at δ 2.73 (1H, d, J = 15 Hz) and 2.61 (1H, d, J = 15 Hz), between the carbonyl group and the C-3 methyl carbinol (C-3: δ_C 81.4; Me-10: δ_H 1.37, s) (Tables 1 and 3). In compound **3** (HRMS data *m*/*z* [$(M - H_2O)^+$] 356.061,

Table 3. ^{1}H, ^{13}C, and HMBC NMR Data of Compounds **7**−**9** [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

	7			**8**			**9**		
position	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1	3.29 d (7.5)	29.8	C-1′, C-2, C-3, C-2′, C-3′		195.4		6.25 d (10)	121.9	C-3, C-1′, C-2′, C-3′
2	5.26 t (7.5)	120.8	C-1, C-4, C-10	6.62 s	119.2	C-10, C-4, C-3, C-1	5.61 d (10)	131.3	C-10, C-4, C-3, C-1, C-2′
3		139.1			162.2			78.4	
4	2.06	39.5	C-2, C-3, C-5, C-10	2.25	41.5	C-10, C-5, C-2, C-3	1.67 m	40.8	C-3, C-2, C-6, C-10
5	2.09	26.3	C-3, C-4, C-6, C-7	2.23	25.9	C-4, C-6, C-7, C-3	2.06 m	22.5	C-3, C-4, C-6, C-7
6	5.04 t (6.8)	123.6	C-8, C-9	5.09 t (6.9)	122.7	C-4, C-8, C-9	5.06 t (6.6)	123.8	C-4, C-5, C-8, C-9
7		132.0			132.8			131.7	
8	1.57[a] s	17.6	C-6, C-7, C-9	1.62[a] s	17.6	C-6, C-7, C-9	1.55[a] s	17.5	C-6, C-7, C-9
9	1.66[a] s	25.5	C-6, C-7, C-8	1.70[a] s	25.6	C-6, C-7, C-8	1.65[a] s	25.5	C-6, C-7, C-8
10	1.73 s	16.1	C-2, C-3, C-4	2.16 s	20.1	C-2, C-3, C-4	1.33 s	25.9	C-2, C-3, C-4
1′	6.66 s	113.8	C-1, C-3′, C-5′	7.35 s	115.0	C-1, C-6′, C-3′, C-5′	6.62 s	112.6	C-1, C-2′, C-5′, C-3′
2′		127.1			120.5			121.9	
3′		148.5			156.7			147.0	
4′	7.00 s	120.6	C-6′, C-2′, C-5′	7.12 s	121.2	C-6′, C-3′, C-5′	6.87 s	118.7	C-2′, C-5′, C-6′
5′		109.0			118.2			108.5	
6′		150.0			144.3			146.0	
O*H*-6′				5.25		C-1′, C-6′, C-5′	5.05		C-1′, C-5′, C-6′
O*Me*	3.8 s	56.8	C-5′						
O*H*-3′	4.92		C-2′, C-3′, C-4′	12.31					

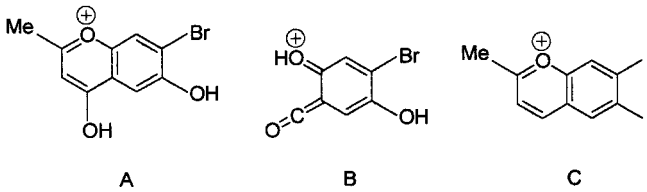
Table 4. ^{1}H, ^{13}C, and HMBC NMR Data of Compounds **10** and **11** [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

	10			**11**		
position	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC
1		194.9			195.4	
2	6.65 s	119.8	C-1, C-4, C-10	6.64 s	119.3	C-10, C-1, C-4, C-3
3		162.6			161.9	
4	2.61 t (7.7)	34.5	C-2, C-3, C-5	2.25 t (7.4)	41.7	C-10, C-6, C-2, C-3
5	2.21 q (7.6)	26.7	C-4, C-6, C-7, C-3	1.63 m	22.1	C-3, C-4, C-6
6	5.13 m	123.3	C-8, C-9	1.48 m	42.9	C-5, C-9, C-8, C-4, C-7
7		132.5			70.9	
8	1.62[a] s	17.5	C-6, C-7, C-9	1.22[a] s	29.2	C-6, C-7, C-9
9	1.64[a] s	25.5	C-6, C-7, C-8	1.22[a] s	29.2	C-6, C-7, C-8
10	2.03 s	26.1	C-2, C-3, C-4	2.15 s	19.9	C-2, C-3, C-4
1′	7.41 s	115.0		7.38 s	115.0	C-1, C-5′, C-3′, C-6′
2′		120.5			120.4	
3′		156.8			156.6	
4′	7.15 s	121.2		7.13 s	121.4	C-2′, C-3′, C-6′
5′		119.0			118.4	
6′		142.6			144.5	
O*H*-6′	5.12 s		C-1′, C-6′, C-5′			
O*H*-3′	12.3 s					

calcd for $C_{16}H_{21}O_4Br$, 356.062), the side chain was fully saturated as a methyl and an isopropyl carbinol group, respectively, at C-3 (C-3: δ_C 81.4; Me-10: δ_H 1.28, s) and C-7 (C-7: δ_C 71.4; Me-8,9: δ_H 1.19, s, 6H). Consequently, compound **3** also showed the protons of an isolated methylene at δ 2.52 (1H, d, J = 15 Hz) and δ 2.70 (1H, d, J = 15 Hz). The aromatic moiety of **2** and **3** displayed the spectroscopic features of a bromohydroquinone. Thus, **2** and **3** were in keeping with the six and five degrees of unsaturation required by the respective molecular formulas, indicating that **2** is 3-hydroxycymopolone and **3** is 3,7-dihydroxycymopolone**.** Compounds **2** and **3**, together with compound **11**, complete the series of the possible hydrated forms of the acyclic prenyl chain of cymopolone (**8**).

Compound **4** is the first bicyclic derivative of cymopolone. It was isolated as a yellow crystalline compound, and the molecular formula $C_{16}H_{21}O_4Br$, deduced by a combination of ^{13}C NMR and HRMS data ([(M)$^+$] m/z 356.060, calcd 356.062), suggested that it is a cyclization product of cymopolone. The ^{1}H NMR spectrum showed signals for the protons of an isolated methylene of a 1,3-keto carbinol at δ 2.96 (1H, d, J = 15 Hz) and δ 2.98 (1H, d, J = 15 Hz), similar to those of compounds **2** and **3**. This, along with a bromohydroquinone ring, accounted for five of its six degrees of unsaturation. Since no other unsaturation was present, the compound was concluded to be bicyclic. The spectral evidence is fully consistent with the structure of

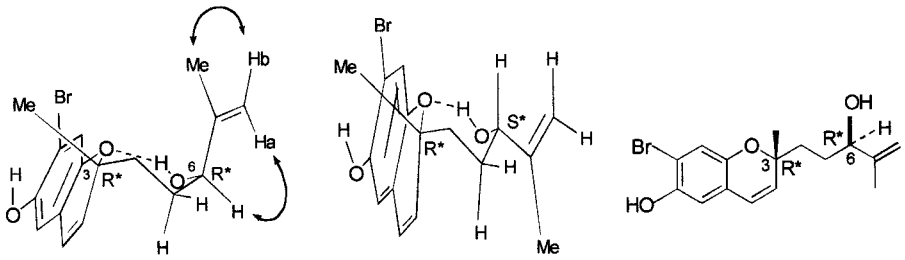
Scheme 1. Selected MS Fragments of **4** (A, B) and **5** and **6** (C)



A B C

7-hydroxycymopochromanone (**4**), which was reinforced by the MS fragments at m/z 255/257 and 215/217 corresponding to fragments[4] A and B (Scheme 1), respectively.

The ^{1}H and ^{13}C NMR data of **5** and **6** suggested the presence of a six-membered chromenol ring in both compounds, which was supported by the corresponding fragment C (Scheme 1) at m/z 239/241 (base peak) in their mass spectra. The molecular formula for **5**, $C_{16}H_{21}O_3Br$, determined by HRMS data ([(M)$^+$] m/z 340.059, calcd 340.067), differs by 18 mass units from that of cymopocromenol **9** ([(M)$^+$] m/z 322.052, calcd 322.056), suggesting that in **5** the unsaturation of the linear side chain of **9** is hydrated. Comparison of the spectroscopic data of the respective C-6−C-9 carbon atoms of both compounds (Tables 2 and 3) clearly indicated that **5** is 7-hydroxycymopochromenol. On the other hand, a difference of 16 mass units was observed between the corresponding MS of **6** ([(M)$^+$] m/z 338.049, calcd for $C_{16}H_{19}O_3Br$, 338.051) and **9** and also a difference



A B 6

Figure 1. Relative configurations of C-3 and C-6 and NOE of compound **6**.

of 2 mass units between the spectra of **6** and **5**. This information, combined with the signal observed for a terminal methylene double bond in the ^{1}H and ^{13}C NMR spectra of **6**, suggested that the compound possesses a chromenol side chain containing a 6-hydroxy isopropenyl group, which was confirmed by the correlation of C-6 with C-7/C-8/C-9 in a HMBC experiment (Table 2). Accordingly, **6** was assigned as 6-hydroxycymopochromenol.

The chemical shift assignments for the protons Ha and Hb of the olefinic methylene (Table 2) were made possible by the NOE observed between Ha and H-6 and between Hb and H_3-10 in a 2D NOESY experiment.

The relative stereochemistry of the chiral centers C-3 and C-6 was determined by a combination of molecular mechanics calculations and a study of the coupling constants. Molecular mechanics (MM2) calculations[12] were carried out on the all possible relative configurations of 6-hydroxycymopochromenol. The resulting energy-minimized structures **A** and **B**, illustrated in Figure 1, showed that the hydroxyl group at C-6 induced a H-bond interaction with the oxygen ring, forcing the side chain to adopt a chairlike seven-membered ring conformation.

The calculated ^3J coupling between the H-6 proton and the vicinal pair of methylene protons was $J = 3.0$ and 3.5 Hz in **A** and $J = 1.0$ and 10.7 Hz in **B**, while the observed coupling constant of the H-6 triplet was $J = 5.6$ Hz (Table 2), which is in good correspondence with that calculated for H-6 in **A**. Thus, the relative stereochemistry at C-3 and C-6 for 6-hydroxycymopochromenol (**6**) is **R*, **R*, respectively, as shown in Figure 1.

Since several of the new metabolites herein described could be artifacts arising during the chromatographic procedure of purification on silica gel, the dichloromethane extract of the alga was successively purified using only the gel filtration over Sephadex LH-20. All six new metabolites were again isolated and characterized by comparison of their respective ^{1}H NMR spectrum, indicating that **1**−**6** are all natural compounds.

With the exception of the samples from the Canary Islands study[6] of *C. barbata*, all the others contain carboxyclic "cymopols" such as cyclocymopol from the Bermuda collection,[4] the defensive and antifeedant debromoisocymobarbatol, the optically active diasteroisomers of cyclocymopol and cyclocymopol monomethyl ether from the Florida Keys,[8,9] and the antimutagenic cymobarbatol and 4-isocymobarbatol from Puerto Rico.[7] However, although the Cuban *C. barbata* was rich in oxacyclic and other "cymopols" with a linear prenyl side chain, it was surprising to find that none of them was carboxyclic, reflecting the same differences in the adaptative response of this species throughout the Caribbean and surrounding areas.

Experimental Section

General Experimental Procedures. IR spectra were obtained with a Perkin-Elmer 1650/FTIR spectrometer in $CHCl_3$ solution. ^{1}H NMR and ^{13}C NMR, HMQC, HMBC, and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR, using TMS as internal standard. Two-dimensional NMR spectra were obtained with the standard Bruker software. EIMS and HRMS data were taken on a Micromass Autospec spectrometer. Recycling-HPLC separations were performed with a Japan Analytical LC-908 using chloroform as eluent. The gel filtration column (Sephadex LH-20) used hexane−MeOH−CH_2Cl_2 (3:1:1) as solvent. Merck Si gels 7734 and 7729 were used in column chromatography. The spray reagent for TLC was H_2SO_4−H_2O−AcOH (1:4:20).

Plant Material. *C. barbata* was collected at the Cuban coast by scuba diving. A voucher specimen has been deposited at the Department of Marine Biology, Universidad de La Laguna, Tenerife, Canary Islands, Spain (deposit no. Dasy-cy 05-00).

Extraction and Isolation. Air-dried *C. barbata* (400 g, dry wt) was extracted with dichloromethane at room temperature. The extract was concentrated to give a dark green residue (33.7 g) and fractionated by flash chromatography on Si gel, using hexane−ethyl acetate mixtures to give fractions B and C, eluted with hexane−ethyl acetate (9:1), F (8:2), and G and J (7:3). Fraction B gave cymopolone **8** (206 mg), after gel filtration on Sephadex LH-20 eluted with hexane−methanol−dichloromethane (3:1:1), and 244 mg of a mixture of compounds **7** (24.3 mg) and **9** (152.8 mg), which were separated by chromatography on a column of Si gel eluted with hexane−ethyl acetate (9:1). Fraction C (375.3 mg) afforded compounds **10** (12 mg) and **4** (7.8 mg), and from fraction D (281.7 mg) compound **2** (9.8 mg) was isolated after purification, by recycling-HPLC (RHPLC), of the residues obtained from the respective fractions C and D after gel filtration on Sephadex LH-20. Gel filtration of fraction F (229 mg) gave a mixture of **1** (7.1 mg) and **6** (5.6 mg), which were separated and purified by RHPLC. Finally, compounds **11** (70 mg) and **5** (12.5 mg) from fraction G (461. 5 mg) and compound **3** (15 mg) from fraction J (266.2 mg) were obtained after gel filtration followed by purification by RHPLC.

3′-Methoxy-7-hydroxycymopol (1): yellow oil; IR ν_{max} (film) 3350 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 356/358 [$(M)^+$; 10, 7], 282/284 [$(M - C_5H_{12})^+$; 13, 14], 230/232 [$(M - C_9H_{18})^+$; 37, 33], 215/217 [$(M - C_9H_{17}O)^+$; 100, 98], 190 (88), 188 (23), 184 (23), 176 (43), 134 (20), 123 (39), 109 (20), 69 (24), 53 (20); HREIMS [$(M)^+$] 356.080 (calcd for $C_{17}H_{25}O_3Br$, 356.081), [$(M - C_9H_{17}O)^+$] 214.972 (calcd for $C_8H_8O_2Br$, 214.970).

3-Hydroxycymopolone (2): yellow oil; $[\alpha]^{25}_D$ −10.0 (*c*, 0.2, $CHCl_3$); IR ν_{max} (film) 3450, 1650 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 338/340 [$(M - H_2O)^+$; 16, 17], 320/322 [$(M - 2H_2O)^+$; 6, 8], 305/307 [$(M - CH_3 - H_2O)^+$; 5, 5], 277/279 [$(M - 2H_2 - C_3H_7)^+$; 7, 8], 255/257 [$(M - C_6H_{11} - H_2O)^+$; 100, 90], 239 (26), 215 (49); HREIMS [$(M - H_2O)^+$] 338.047 (calcd for $C_{16}H_{19}O_3Br$, 338.051), [$(M - 2H_2O)^+$] 322.036 (calcd for $C_{16}H_{17}O_281Br$, 322.039), [$(M - CH_3 - 2H_2O)^+$] 307.013 (calcd for $C_{15}H_{14}O_281Br$, 307.015), [$(M - C_6H_{11} - H_2O)^+$] 256.961 (calcd for $C_{10}H_8O_381Br$, 256.963).

3,7-Dihydroxycymopolone (3): yellow oil; $[\alpha]^{25}_D$ −14.6° (*c*, 0.2, $CHCl_3$); IR ν_{max} (film) 3450, 1650 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 356/358 [$(M - H_2O)^+$; 5, 6], 255/257 [$(M - C_6H_{11}O)^+$; 97, 100], 215/217 [$(M - C_9H_{13}O)^+$; 91, 80], 177 (21), 109 (28), 69 (39), 55 (22), 53 (21); HREIMS [(M −

$H_2O)^+$] 356.061 (calcd for $C_{16}H_{21}O_4Br$, 356.062), [(M − $C_6H_{11}O)^+$] 256.981 (calcd for $C_{10}H_{10}O_3Br$, 256.981).

7-Hydroxycymopochromanone (4): yellow crystalline solid; mp 123.5−124.5 °C; $[\alpha]^{25}_D$ −13.2° (*c* 0.2, $CHCl_3$); IR ν_{max} (film) 3450, 3300, 1650 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; EIMS *m/z* 356/358 [$(M)^+$; 3, 3], 305/307 [(M − $C_2H_{11}O)^+$; 3, 3], 255/257 [(M − $C_6H_{13}O)^+$; 23, 24], 230/232 [(M − $C_7H_{11}O_2)^+$; 36, 35], 215/217 [(M − $C_8H_{11}O$ − $H_2O)^+$; 100, 92], 127 (41), 109 (31), 71 (17); HREIMS [$(M)^+$] 356.060 (calcd for $C_{16}H_{21}O_4$-Br, 356.062), [(M − $C_2H_{11}O)^+$] 304.981 (calcd for $C_{14}H_{10}O_2Br$, 304.981), [(M − $C_6H_{13}O)^+$] 256.981 (calcd for $C_{10}H_{10}O_3Br$, 256.981), [(M − $C_8H_{11}O$ − $H_2O)^+$] 214.966 (calcd for $C_8H_8O_2$-Br, 214.970).

7-Hydroxycymopochromenol (5): yellow oil; $[\alpha]^{25}_D$ −9.1° (*c* 0.2, $CHCl_3$); IR ν_{max} (film) 3450, 3300, 1650 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; EIMS *m/z* 340/342 [$(M)^+$; 6, 6], 307/309 [(M − CH_3 − $H_2O)^+$; 1, 2], 251/253 [(M − $C_5H_{13}O)^+$; 5, 6], 239/241 [(M − $C_6H_{13}O)^+$; 96, 100]; HREIMS [$(M)^+$] 340.059 (calcd for $C_{16}H_{21}O_3Br$, 340.067), [(M − CH_3 − $H_2O)^+$] 309.029 (calcd for $C_{15}H_{16}O_2{}^{81}Br$, 309.031), [(M − $C_5H_{13}O)^+$] 252.965 (calcd for $C_{11}H_8O_2{}^{81}Br$, 252.968), [(M − $C_6H_{13}O)^+$] 240.966 (calcd for $C_{10}H_8O_2{}^{81}Br$, 240.968).

6-Hydroxycymopochromenol (6): yellow oil; $[\alpha]^{25}_D$ −12.8° (*c* 0.2, $CHCl_3$); IR ν_{max} (film) 3450, 3300, 1650 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; EIMS *m/z* 338/340 [$(M)^+$; 9, 9], 305/307 [(M − H_2O − $CH_3)^+$; 2, 2], 254/256 [(M − $C_5H_8O)^+$; 4, 2], 239/241 [(M − $C_7H_{13})^+$; 94, 100]; HREIMS [$(M)^+$] 338.049 (calcd for $C_{16}H_{19}O_3Br$, 338.051), [(M − H_2O − $CH_3)^+$] 307.015 (calcd for $C_{15}H_{14}O_2{}^{81}Br$, 307.015), [(M − $C_5H_8O)^+$] 253.987 (calcd for $C_{11}H_{11}O_2Br$, 253.994), [(M − $C_7H_{13})^+$] 240.954 (calcd for $C_9H_6O_3Br$, 240.950).

6′-Methoxycymopol (7): ^1H and ^{13}C NMR, see Table 3; EIMS *m/z* 338/340 [$(M)^+$; 36, 38], 270/272 [(M − $C_5H_8)^+$; 5, 4], 253/255 [(M − $C_6H_{13})^+$; 15, 15], 215/217 [(M − $C_9H_{17})^+$; 34, 34], 190 (52), 175 (48), 123 (44), 77 (44), 69 (100), 53 (20); HREIMS [$(M)^+$] 340.089 (calcd for $C_{17}H_{23}O_2{}^{81}Br$, 340.086), [(M − $C_5H_8)^+$] 272.023 (calcd for $C_{12}H_{15}O_2{}^{81}Br$, 272.023), [(M − $C_6H_{13})^+$] 254.989 (calcd for $C_{11}H_{10}O_2{}^{81}Br$, 254.984). Remaining physical and spectral properties as published.[4]

Cymopolone (8): ^1H and ^{13}C NMR, see Table 3; EIMS *m/z* 338/340 [$(M)^+$; 9, 8], 323/325 [(M − $CH_3)^+$; 5, 5], 305/307 [(M − CH_3 − $H_2O)^+$; 1, 1], 255/257 [(M − $C_6H_{11})^+$; 96, 100], 215/217 [(M − $C_9H_{15})^+$; 14, 14], 69 (42); HREIMS [$(M)^+$] 338.052 (calcd for $C_{16}H_{19}O_3Br$, 338.051), [(M − $CH_3)^+$] 323.037 (calcd for $C_{15}H_{16}O_3Br$, 323.028), [(M − CH_3 − $H_2O)^+$] 305.017 (calcd for $C_{15}H_{14}O_2Br$, 305.017), [(M − $C_6H_{11})^+$] 256.964 (calcd for $C_{10}H_8O_3{}^{81}Br$, 256.963), [(M − $C_9H_{15})^+$] 216.938 (calcd for $C_7H_4O_3{}^{81}Br$, 216.932). Remaining physical and spectral properties as published.[4]

Cymopochromenol (9): ^1H and ^{13}C NMR, see Table 3; EIMS *m/z* 322/324 [$(M)^+$; 8, 7], 307/309 [(M − $CH_3)^+$; 2, 2], 239/241 [(M − $C_6H_{11})^+$; 100, 97]; HREIMS [$(M)^+$] 322.052 (calcd for $C_{16}H_{19}O_2Br$, 322.056), [(M − $C_6H_{11})^+$] 238.966 (calcd for $C_{10}H_8O_2Br$, 238.970). Remaining physical and spectral properties as published.[4]

Isocymopolone (10): ^1H and ^{13}C NMR, see Table 4; EIMS *m/z* 338/340 [$(M)^+$; 8, 7], 320/322 [(M − $H_2O)^+$; 34, 33], 305/307 [(M − CH_3 − $H_2O)^+$; 15, 12], 255/ 257 [(M − $C_6H_{11})^+$; 93, 92], 215/217 [(M − $C_9H_{15})^+$; 38, 37], 109 (25), 81 (28), 69 (100), 57 (26), 55 (29); HREIMS [$(M)^+$] 338.046 (calcd for $C_{16}H_{19}O_3$-Br, 338.051), [(M − $H_2O)^+$] 320.036 (calcd for $C_{16}H_{17}O_2Br$, 320.041), [(M − CH_3 − $H_2O)^+$] 305.012 (calcd for $C_{15}H_{14}O_2Br$, 305.017), [(M − $C_6H_{11})^+$] 254.960 (calcd for $C_{10}H_8O_3Br$, 254.965), [(M − $C_9H_{15})^+$] 214.930 (calcd for $C_7H_4O_3Br$, 214.934). Remaining physical and spectral properties as published.[4]

7-Hydroxycymopolone (11): ^1H and ^{13}C NMR, see Table 4; EIMS *m/z* 356/358 [$(M)^+$; 1, 1], 341/343 [(M − $CH_3)^+$; 1, 1], 323/325 [(M − CH_3 − $H_2O)^+$; 7, 6], 267/269 [(M − $C_5H_{11}O)^+$; 6, 6], 255/257 [(M − $C_6H_{13}O)^+$; 100, 95], 215/217 [(M − $C_9H_{17}O)^+$; 35, 33], 109 (9), 69 (14), 59 (18); HREIMS [$(M)^+$] 356.065 (calcd for $C_{16}H_{21}O_4Br$, 356.062), [(M − $CH_3)^+$] 341.045 (calcd for $C_{15}H_{18}O_4Br$, 341.038), [(M − CH_3 − $H_2O)^+$] 323.033 (calcd for $C_{15}H_{16}O_3Br$, 323.028), [(M − $C_6H_{13}O)^+$] 254.970 (calcd for $C_{10}H_8O_3Br$, 254.965). Remaining physical and spectral properties as published.[6]

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References and Notes

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55, and references therein.
(2) Hay, M. E.; Fenical, W. *Annu. Rev. Ecol. Syst.* **1988**, *19*, 111−145.
(3) Paul, V. J., Ed. *Ecological Roles of Marine Natural Products*; Comstock Publishing Associates: Ithaca, NY, 1992.
(4) Högberg, H.-E.; Thomson, R. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1696−1701.
(5) Martínez-Nadal, N. G.; Rodríguez, L. V.; Casillas, S. *Antimicrob. Agents Chemother.* **1964**, 131.
(6) Estrada, D. M.; Martín, J. D.; Pérez, C. *J. Nat. Prod.* **1987**, *50*, 735−737.
(7) Wall, E. M.; Wani, M. C.; Manikumar, G.; Taylor, H.; Hughes, T. J.; Gerwick, W. H.; McPhail, A. T.; McPhail, D. R. *J. Nat. Prod.* **1989**, *52*, 1092−1099.
(8) McConnell, O. J.; Hughes, P. A.; Targett, N. M. *Phytochemistry* **1982**, *21*, 2139−2141.
(9) Park, M.; Fenical, W.; Hay, M. *Phytochemistry* **1992**, *31*, 4115−4118.
(10) Targett, N. M.; McConnell, O. J. *J. Chem. Ecol.* **1982**, *8*, 115.
(11) McConnell, O. J.; Hughes, P. A.; Targett, N. M.; Daley, J. *J. Chem. Ecol.* **1982**, *8*, 1427.
(12) *PCModel* (v. 4.0); Serena Software: Bloomington, IN, 47402-3076.

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