New Lamellarin Alkaloids from the Australian Ascidian, *Didemnum chartaceum*

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Five novel lamellarin-class alkaloids have been isolated from a Great Barrier Reef ascidian, *Didemnum chartaceum*. The structures of the 20-sulfated derivatives of lamellarins B, C, and L (**1**−**3**); the 8-sulfated derivative of lamellarin G (**4**), plus a nonsulfated compound, lamellarin Z (**5**), were identified by interpretation of spectroscopic data. Lamellarin G 8-sulfate (**4**) is the first example of this class of compounds sulfated at the C-8 position, while lamellarin Z (**5**) is the first example of a dimethoxylated lamellarin. The known lamellarins A, B, C, E, G, and L (**6**−**11**), plus the triacetate derivatives of lamellarins D (**12**) and N (**13**), were also isolated. An aberration in the integration of signals in the ^{1}H NMR spectra of the 20-sulfated derivatives of lamellarins B, C, and L (**1**−**3**) led to NMR relaxation studies. T_1 values were calculated for all protons in the sulfated lamellarins (**1**−**4**) and their corresponding nonsulfated derivatives (**7**, **8**, **10**, **11**). Interestingly, the protons *ortho* to the sulfate group in compounds (**1**−**4**) had T_1 values up to five times larger than the corresponding protons in their nonsulfated derivatives (**7**, **8**, **10**, **11**).

Ascidians, which are prominent producers of metabolites derived from amino acids, have been the source of many polyaromatic alkaloids. Examples include the lukianols,[1] polycitrins,[2] and, more recently, the ningalins.[3] In all these examples, the amino acid DOPA appears to be the putative precursor in the biogenesis of these interesting bioactive metabolites. The lamellarins are also believed to be DOPA-derived. This class of secondary metabolite was first reported in 1985 from a marine mollusk, *Lamellaria* sp.[4] Since that time, a total of 30 lamellarins has been isolated. Marine sources include a Seychelles ascidian, *Didemnum chartaceum*;[5] a Great Barrier Reef ascidian, *Didemnum* sp.;[6] a southern Australian sponge *Dendrilla cactos*;[7,8] and a southern Australian ascidian, *Didemnum* sp.[9] More recently, the first examples of sulfated lamellarins were isolated from an unidentified ascidian collected from the Arabian Sea.[10]

In our continuing investigation of Great Barrier Reef ascidians, we report here the isolation of the 20-sulfated derivatives of lamellarins B (**1**), C (**2**), and L (**3**) and the 8-sulfated derivative of lamellarin G (**4**), plus a nonsulfated compound, lamellarin Z (**5**), from *Didemnum chartaceum* Sluiter (Didemnidae).

Results and Discussion

A freeze-dried sample of *D. chartaceum* was exhaustively extracted with MeOH, then partitioned between hexane and 10% aqueous MeOH. The polar phase was then partitioned between 30% aqueous MeOH and $CHCl_3$. The $CHCl_3$-soluble material was chromatographed on Sephadex LH-20 (MeOH) and afforded pure lamellarin C 20-sulfate (**2**, 6.5 mg, 0.072% dry wt), lamellarins A (**6**, 7.5 mg, 0.083% dry wt) and C (**8**, 5.2 mg, 0.058% dry wt), and mixtures of other nonsulfated lamellarins. This mixture was further purified using reversed-phase C_{18} HPLC to yield lamellarins B (**7**, 3.1 mg, 0.034% dry wt), E (**9**, 5.9 mg, 0.066% dry wt), G (**10**, 13.3 mg, 0.148% dry wt), L (**11**, 19.3 mg, 0.214% dry wt), and Z (**5**, 2.8 mg, 0.031% dry wt) and a mixture of lamellarins N and D. This mixture was acetylated, then separated, using normal-phase DIOL HPLC to yield the triacetate derivatives of lamellarins D (**12**, 1.5 mg, 0.017% dry wt) and N (**13**, 1.1 mg, 0.012% dry wt). The 30% aqueous MeOH-soluble material was also chromatographed on Sephadex LH-20 (MeOH) followed by further purification on reversed-phase C_{18} HPLC to yield lamellarin G 8-sulfate (**4**, 9.5 mg, 0.106% dry wt), lamellarin L 20-sulfate (**3**, 14.6 mg, 0.162% dry wt), and lamellarin B 20-sulfate (**1**, 3.5 mg, 0.039% dry wt).

Lamellarin B 20-sulfate (**1**) was isolated as an optically inactive white solid. The molecular formula $C_{30}H_{24}NO_{12}S$ was determined by interpretation of the M^- ion (*m*/*z* 622.1029) in the high-resolution negative ion electrospray mass spectrum [(−)-HRESMS] in conjunction with the 1D and 2D NMR data. The molecular formula indicated a high level of unsaturation in the molecule, and this was supported by the UV spectrum [λ_{max} 202 (ϵ 31 000), 224 (sh, ϵ 18 000), 283 (ϵ 27 000), 301 (sh, ϵ 21 000), 321(sh, ϵ 11 000), 365 (ϵ 8000), and 386 nm (ϵ 10 000)], which showed the presence of extended conjugation. The IR spectrum contained bands at 3439 (phenol) and 1690 cm^{-1}(aromatic ester). The presence of a phenol group was supported by the UV spectrum, which underwent a bathochromic shift on addition of base.

The ^{1}H NMR spectrum of **1** (see Table 1) contained five methoxy signals at δ 3.35, 3.39, 3.76, 3.83, and 3.94; a broad exchangeable singlet at δ 9.42; three signals at δ 7.01 (1H, dd, J = 7.8, 1.8 Hz), 7.13 (1H, d, J = 7.8 Hz), and 7.15 (1H, d, J = 1.8 Hz) assigned to a 1,3,4-trisubstituted benzene ring; three aromatic methine singlets at δ 6.74 (1H, s), 7.05 (1H, s), and 7.57 (1H, s); plus two mutually coupled aromatic methine protons at δ 9.09 (1H, d, J = 7.8 Hz) and 7.43 (1H, d, J = 7.8 Hz), indicative of the α and β protons of an isoquinoline system. The ^{13}C NMR spectrum contained an aromatic ester carbonyl signal [154.2 ppm], five methoxy signals [55.1, 54.8, 56.0, 60.7, and 61.7 ppm], and 24 signals in the aromatic region [all $>$101 ppm], which required the compound be hexacyclic. All spectroscopic data indicated a typical lamellarin alkaloid with unsaturation between the C-5/C-6 positions and an oxygenated substituent at the C-7 position.[4−10]

However, one discrepancy between compound **1** and other typical lamellarins was noted in the ^{1}H NMR spectrum. Lamellarin B 20-sulfate (**1**) had an aromatic

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Table 1. NMR Data for Lamellarin B 20-Sulfate (**1**)[a]

position	^{13}C (δ)	^{1}H (δ, mult., *J* in Hz)	COSY	HMBC	ROESY
1	112.8				
2	128.3				
3	107.4				
4					
5	122.1	9.09 (d, 7.8)	6	3, 6a, 10b	6
6	107.4	7.43 (d, 7.8)	5	5, 7, 10a	5, OCH_3-7
6a	118.4				
7	148.0				
8	141.9				
9	153.1				
10	101.5	7.05 (s)		6a, 8, 9,10b	OCH_3-9, 12, 16
10a	120.7				
10b	133.0				
11	124.9				
12	114.8	7.15 (d, 1.8)	16	1, 14, 16	10, OCH_3-13, 22
13	148.8				
14	147.0				
15	116.5	7.13 (d, 7.8)	16	11, 13	16
16	123.5	7.01 (dd, 7.8, 1.8)	12, 15	1, 12, 14	10, 15, 22
17	111.5				
18	145.2[b]				
19	108.8	7.57 (s)		17, 18, 20, 21	
20	143.4[b]				
21	146.8				
22	105.8	6.74 (s)		2, 18, 20, 21	12, 16, OCH_3-21
23	154.2				
OCH_3-7	61.6	3.94 (s)		7	6
OCH_3-8	60.7	3.83 (s)		8	
OCH_3-9	54.8	3.39 (s)		9	10
OCH_3-13	56.0	3.76 (s)		13	12
OH-14		9.42 (br s)			
OSO_3^--20					
OCH_3-21	55.1	3.35 (s)		21	22

[a] Spectra were recorded in DMSO-d_6 at 30 °C. [b] Signals are interchangeable.

singlet at δ 7.57, which has never been reported for the previously isolated nonsulfated lamellarins. Aromatic singlets in typical nonsulfated lamellarins resonate upfield of δ 7.00. Analysis of the low-resolution negative ion electrospray mass spectrum [(−)-LRESMS] at a cone voltage of 80 V showed two intense ions at *m*/*z* 622 $[M]^-$ and 542 $[M - 80]^-$, with the latter ion attributed to the loss of a sulfate group. These data agreed well with the observed downfield ^{1}H NMR chemical shift, which, from previously documented studies, required the sulfate group to be positioned *ortho* to the proton at δ 7.57.[10,11] The positioning of the five methoxy groups, the phenol, and the sulfate were determined by analysis of HSQC, HMBC, and ROESY experiments. The aromatic proton singlets at δ 6.74 and 7.57 showed $^{1}J_{CH}$ correlations to the carbon signals at 105.8 (C-22) and 108.8 ppm (C-19), respectively. The resonance at δ 6.74 showed $^{2}J_{CH}$/$^{3}J_{CH}$ correlations to C-2, C-18, C-20, and C-21, plus strong ROESY correlations (ROE) to the methoxyl signal at δ 3.35 and the two mutually *meta*-coupled protons (H-12 and H-16) of the trisubstituted aromatic ring. The methoxyl signal at δ 3.35 showed a $^{3}J_{CH}$ correlation to C-21. The aromatic signal at δ 7.57, which was known to be *ortho* to the sulfate group, showed $^{2}J_{CH}$/$^{3}J_{CH}$ correlations to C-17, C-18, C-20, and C-21 and no ROE correlation, and hence the protons at δ 6.74 and 7.57 were positioned *para* to one another on a 1,2,4,5-tetrasubstituted benzene ring. The trisubstituted aromatic ring contained one methoxy and one phenol group substituted at C-13 (148.8 ppm) and C-14 (147.0 ppm), respectively. A methoxyl group was attached to C-13 because a $^{3}J_{CH}$ correlation to C-13 and a ROE correlation to the *meta*-coupled doublet at δ 7.15 [H-12] were observed from the methyl protons at δ 3.76. The remaining ^{13}C NMR data, which included seven quaternary carbons, three aromatic methines, and three methoxy carbons, indicated a trimethoxylated isoquinoline system identical to that found in lamellarin W (**14**).[10]

Table 2. NMR Data for Lamellarin C 20-Sulfate (**2**)[a]

position	^{13}C (δ)	^{1}H (δ, mult., *J* in Hz)	COSY	HMBC	ROESY
1	116.0				
2	127.0				
3	113.2				
4					
5α	41.7	4.68 (dm, 13.2)	5β, 6	6, 6a, 10b	5β, 6
5β		4.61 (dm, 13.2)	5α, 6	6, 6a, 10b	5α, 6
6	21.3	3.08 (br t, 7.2)	5α, 5β, 10	6a, 7, 10a	5α, 5β, OCH_3-7
6a	120.0				
7	150.2				
8	141.9				
9	151.3				
10	105.2	6.64 (s)	6, OCH_3-9	6a, 8, 9, 10a, 10b	OCH_3-9, 12, 16
10a	122.3				
10b	134.8				
11	125.1				
12	114.5	7.04 (d, 1.8)	OCH_3-13, 16	1, 14, 16	10, OCH_3-13
13	148.6				
14	146.7				
15	116.4	7.02 (d, 7.8)	16	11, 13, 14	16
16	123.2	6.89 (dd, 7.8, 1.8)	12, 15	12, 14, 15	10, 15
17	112.0				
18	144.6[b]				
19	108.6	7.48 (s)		17, 18, 20, 21	
20	142.4[b]				
21	146.7				
22	105.2	6.60 (s)	OCH_3-21	2, 18, 20, 21	OCH_3-21
23	154.1				
OCH_3-7	60.7	3.79 (s)		7	6
OCH_3-8	60.4	3.74 (s)		8	
OCH_3-9	54.8	3.28 (s)	10	9	10
OCH_3-13	56.0	3.75 (s)	12	13	12
OH-14		9.27 (br s)			
OSO_3^--20					
OCH_3-21	55.0	3.33 (s)	22	21	22

[a] Spectra were recorded in DMSO-d_6 at 30 °C. [b] Signals are interchangeable.

Hence, lamellarin B 20-sulfate was assigned structure **1**. The NMR assignments in Table 1 agreed well with the cited literature values for the previously isolated 20-sulfated lamellarins.[10]

Lamellarin C 20-sulfate (**2**) was isolated as an optically inactive white solid. The molecular formula $C_{30}H_{26}NO_{12}S$ was determined by (−)-HRESMS in conjunction with the 1D and 2D NMR data. The UV spectrum [λ_{max} 205 (ϵ 45 000), 225 (sh, ϵ 31 000), 265 (sh, ϵ 21 000), 276 (ϵ 25 000), 310 (ϵ 22 000), and 337 nm (sh, ϵ 17 000)] did not show absorption bands at 365 and 386 nm as in compound **1**, which meant **2** had lost some conjugation. The IR spectrum contained bands at 3445 (phenol) and 1711 cm^{-1}(aromatic ester). The ^{1}H NMR spectrum of **2** contained five methoxy signals at δ 3.28, 3.33, 3.74, 3.75, and 3.79; a broad exchangeable singlet at δ 9.27; three signals at δ 6.89 (1H, dd, $J = 7.8$, 1.8 Hz), 7.02 (1H, d, $J = 7.8$ Hz), and 7.04 (1H, d, $J = 1.8$ Hz) assigned to a 1,3,4-trisubstituted benzene ring; three aromatic methine singlets at 6.64 (1H, s), 6.60 (1H, s), and 7.48 (1H, s); plus two mutually coupled methylene protons at δ 4.61 (1H, dm, $J = 13.2$ Hz)/4.68 (1H, dm, $J = 13.2$ Hz) and 3.08 (2H, br t, $J = 7.2$ Hz), which appeared to be part of an isolated ethylene unit. The ^{13}C NMR spectrum (see Table 2) contained an aromatic ester carbonyl signal (154.1 ppm), five methoxy signals (55.0, 56.0, 54.8, 60.4, 60.7 ppm), and 22 signals in the aromatic region (all >105 ppm), and two methylene carbons at 41.7 and 21.3 ppm, with the former carbon attached to a nitrogen substituent. These two methylene carbons represented the only major difference between compounds **1** and **2**. In a manner similar to compound **1**, lamellarin C 20-sulfate also had one downfield aromatic proton at δ 7.48,

Table 3. NMR Data for Lamellarin L 20-Sulfate (**3**)[a]

position	^{13}C (δ)	^{1}H (δ, mult., *J* in Hz)	COSY	HMBC	ROESY
1	114.2				
2	126.6				
3	112.7				
4					
5α	42.0	4.64 (dm, 13.2)	5β, 6	6, 6a, 10b	5β, 6
5β		4.58 (dm, 13.2)	5α, 6	6, 6a, 10b	5α, 6
6	27.4	3.01 (m)	5α, 5β, 7, 10	5, 6a, 7, 10a	5α, 5β, 7
6a	127.1[b]				
7	115.2	6.79 (s)	6	6, 8, 9, 10a	6
8	147.0				
9	145.8				
10	109.2	6.69 (s)	6, OCH$_3$-9	6a, 8, 9, 10a, 10b	OCH$_3$-9, 12, 16
10a	117.7				
10b	135.7				
11	127.0[b]				
12	117.7	6.94 (d, 1.8)	16	1, 14, 16	10, 22
13	147.5				
14	147.5				
15	113.5	7.15 (d, 8.1)	OCH$_3$-14, 16	11, 13	OCH$_3$-14, 16
16	121.3	6.89 (dd, 8.1, 1.8)	12, 15	1, 12, 14	10, 15, 22
17	112.0				
18	144.4[c]				
19	108.7	7.47 (s)		17, 18, 20, 21	
20	142.1[c]				
21	146.5				
22	105.1	6.70 (s)	OCH$_3$-21	2, 18, 20, 21	12, 16, OCH$_3$-21
23	153.9				
OH-8		9.53 (br s)			
OCH$_3$-9	54.7	3.28 (s)	10	9	10
OH-13		9.40 (br s)		13, 14	
OCH$_3$-14	56.0	3.82 (s)	15	14	15
OSO_3^--20					
OCH$_3$-21	55.1	3.35 (s)	22	21	22

[a] Spectra were recorded in DMSO-d_6 at 30 °C. [b,c] Signals are interchangeable.

Table 4. NMR Data for Lamellarin G 8-Sulfate (**4**)[a]

position	^{13}C (δ)	^{1}H (δ, mult., *J* in Hz)	COSY	HMBC	ROESY
1	115.1				
2	126.6				
3	112.8				
4					
5α	42.0	4.68 (dm, 13.2)	5β, 6	6, 6a, 10b	5β, 6
5β		4.57 (dm, 13.2)	5α, 6	6, 6a, 10b	5α, 6
6	27.7	3.02 (m)	5α, 5β, 7, 10	5, 6a, 7, 10a	5α, 5β, 7
6a	125.8				
7	120.2	7.40 (s)	6	6, 8, 9, 10a	6
8	142.2				
9	148.5				
10	109.2	6.52 (s)	6, OCH$_3$-9	6a, 8, 9, 10a, 10b	OCH$_3$-9, 12, 16
10a	121.6				
10b	135.3				
11	126.9				
12	117.4	6.85 (d, 2.0)	16	1, 14, 16	10, 22
13	147.4				
14	147.6				
15	113.3	7.12 (d, 8.4)	OCH$_3$-14, 16	11, 13	OCH$_3$-14, 16
16	121.1	6.83 (dd, 8.4, 2.0)	12, 15	1, 12, 14	10, 15, 22
17	109.9				
18	144.4[b]				
19	100.6	7.00 (s)	OCH$_3$-20	17, 18, 20, 21	OCH$_3$-20
20	147.8				
21	142.7[b]				
22	108.2	6.67 (s)		2, 18, 20, 21	12, 16
23	154.2				
OSO_3^--8					
OCH$_3$-9	54.6	3.23 (s)	10	9	10
OH-13					
OCH$_3$-14	55.8	3.85 (s)	15	14	15
OCH$_3$-20	55.8	3.80 (s)	19	20	19
OH-21					

[a] Spectra were recorded in DMSO-d_6 at 30 °C. [b] Signals are interchangeable.

and analysis of the (−)-LRESMS showed two intense ions at *m*/*z* 624 [M]$^-$ and 544 [M − 80]$^-$, which proved compound **2** also contained a sulfate group. The difference of 2 amu between **2** and **1** suggested that lamellarin C 20-sulfate was a dihydro derivative of compound **1**. The absence of the two mutually coupled isoquinoline protons and the presence of an isolated ethylene unit gave credence to compound **2** containing a tetrahydroisoquinoline system. Confirmation by HMBC correlations and comparison with literature values [4–10] proved this partial structure. Analysis of the ROESY, HSQC, and HMBC data revealed that the substitution pattern of the phenol, sulfate, and methoxy substituents in **2** was identical to that in lamellarin B 20-sulfate (**1**). Hence, lamellarin C 20-sulfate was assigned structure **2**.

The major metabolite, lamellarin L 20-sulfate (**3**), was isolated as an optically inactive white solid. The UV and IR data was similar to compound **2**. The molecular formula $C_{28}H_{22}NO_{11}S$ was determined by (−)-HRESMS in conjunction with NMR data. The difference in molecular weight of 44 amu between compounds **3** and **2** suggested that two of the methoxy groups in lamellarin C 20-sulfate (**2**) had been replaced by an aromatic proton and a phenol substituent. This was supported by the ^{1}H NMR spectrum (see Table 3), which contained three methoxy signals at δ 3.28, 3.82, and 3.35 (two fewer signals compared to **2**); two broad exchangeable singlets at δ 9.40 and 9.53 (one extra signal than **2**); three signals at δ 6.89 (1H, dd, *J* = 8.1, 1.8 Hz), 7.15 (1H, d, *J* = 8.1 Hz), and 6.94 (1H, d, *J* = 1.8 Hz) assigned to a 1,3,4-trisubstituted benzene ring; four aromatic methine singlets at δ 6.79 (1H, s), 6.69 (1H, s), 6.70 (1H, s), and 7.47 (1H, s) (one extra signal compared with **2**); plus two mutually coupled methylene protons at δ 4.64 (1H, dm, *J* = 13.2 Hz)/4.58 (1H, dm, *J* = 13.2 Hz) and 3.01 (2H, br t, *J* = 7.2 Hz), which were known to be part of the tetrahydroisoquinoline system. The presence of a sulfate group in **3** was supported by the downfield aromatic singlet at δ 7.47 as well as the (−)-LRESMS, which showed two intense ions at *m*/*z* 580 [M]$^-$ and 500 [M − 80]$^-$. The additional aromatic singlet (δ 6.79) was positioned at C-7 due to HMBC correlations (C-6, C-8, C-9, and C-10a) and a strong ROE correlation to the methylene unit at δ 3.01. The three methoxy signals were all positioned around the hexacyclic system by means of HMBC and ROESY correlations. Hence, lamellarin L 20-sulfate was assigned structure **3**.

Lamellarin G 8-sulfate (**4**) was isolated as a white powder that was optically inactive. (−)-HRESMS and 1D and 2D NMR data were used to establish the molecular formula, $C_{28}H_{22}NO_{11}S$, which had a molecular weight identical to that of lamellarin L 20-sulfate (**3**). Analysis of the ^{1}H NMR data (see Table 4) revealed the same number of methoxy signals and aromatic methine protons and the presence of a tetrahydroisoquinoline system. The proton at δ 7.40, known to be *ortho* to the sulfate group, showed HMBC correlations to C-6, C-8, C-9, and C-10a and a strong ROE correlation to the methylene unit at δ 3.02, which enabled this proton to be positioned at C-7 with the sulfate group at C-8. The remaining methoxy and phenol substituents were positioned by means of HSQC, HMBC, and ROESY analysis, and hence lamellarin G 20-sulfate was assigned structure **4**.

A minor metabolite, and the only new nonsulfated lamellarin isolated, was lamellarin Z (**5**), $[\alpha]_D$ 0 °(*c* 0.047,

Table 5. NMR Data for Lamellarin Z (**5**)[a]

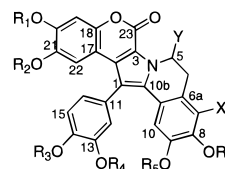
position	^{13}C (δ)	^{1}H (δ, mult., J in Hz)	COSY	HMBC	ROESY
1	114.7				
2	126.9				
3	112.4				
4					
5α	41.9	4.66 (dm, 13.2)	5β, 6	6a	5β, 6
5β		4.52 (dm, 13.2)	5α, 6	6a	5α, 6
6	27.5	2.98 (m)	5α, 5β, 7, 10	6a	5α, 5β, 7
6a	127.1				
7	115.2	6.71 (s)	6	6, 9, 10a	6
8	147.0				
9	145.9				
10	109.3	6.54 (s)	OCH$_3$-9	6a, 8, 10b	OCH$_3$-9, 12, 16
10a	118.0				
10b	136.0				
11	125.3				
12	117.8	6.74 (d, 2.4)	16	1, 14, 16	10, 22
13	146.2				
14	145.4				
15	116.7	6.92 (d, 7.8)	16	11, 13	16
16	121.4	6.67 (dd, 7.8, 2.4)	12, 15	1, 12, 14	10, 15, 22
17	110.2				
18	144.6[b]				
19	100.7	6.99 (s)	OCH$_3$-20	17, 18, 20, 21	OCH$_3$-20
20	147.8				
21	142.8[b]				
22	108.4	6.70 (s)		2, 20	12, 16
23	154.3				
OH-8					
OCH$_3$-9	54.7	3.29 (s)	10	9	10
OH-13				13, 14	
OH-14					
OCH$_3$-20	55.8	3.79 (s)	19	20	19
OH-21					

[a] Spectra were recorded in DMSO-d_6 at 30 °C. [b] Signals are interchangeable.

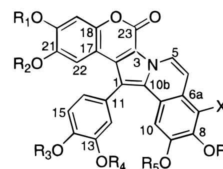
MeOH). The molecular formula, $C_{27}H_{22}NO_8$, was determined by (+)-HRESMS and NMR data. UV and IR data were similar to previously isolated lamellarins containing C-5/C-6 saturation.[4–10] The ^{1}H NMR spectrum (see Table 5) contained two methoxy signals at δ 3.29 and 3.79; many broad overlapping exchangeable signals between δ 9.0 and 9.5; three signals at δ 6.67 (1H, dd, J = 7.8, 2.4 Hz), 6.92 (1H, d, J = 7.8 Hz), and 6.74 (1H, d, J = 2.4 Hz) assigned to a 1,3,4-trisubstituted benzene ring; four aromatic methine singlets at δ 6.71 (1H, s), 6.54 (1H, s), 6.99 (1H, s), and 6.70 (1H, s); and two mutually coupled methylene protons at δ 4.66 (1H, dm, J = 13.2 Hz)/4.52 (1H, dm, J = 13.2 Hz) and 2.98 (2H, m), which were part of a tetrahydroisoquinoline system. Interpretation of ROESY and HMBC correlations was used to position the two methoxy substituents at C-20 (δ 3.79) and C-9 (δ 3.29). Four quaternary oxygenated carbons at C-8, C-13, C-14, and C-21 (147.0, 146.2, 145.4, and 142.8 ppm) were deemed to be substituted by phenols. Hence, the first dimethoxylated lamellarin, lamellarin Z, was assigned structure **5**.

Although the new lamellarins (**1**–**5**) are clearly chiral, the fact that no optical activity was recorded indicates that these molecules have been isolated as racemic mixtures. With the exception of lamellarin S (**15**),[9] all other previously isolated lamellarins [4–8,10] have been reported as displaying no optical activity. Lamellarin S (**15**) initially displayed a positive $[\alpha]_D$, indicating it to be, at the very least, enantiomerically enriched. Repeated optical rotation measurements over several months revealed slow racemization, with a half-life calculated to be ca. 90 days.[9]

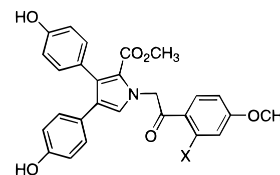
On close inspection of the ^{1}H NMR integrals for the 20-sulfated lamellarins (**1**–**3**), the aromatic methine protons



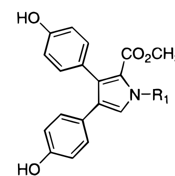
	lamellarin	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	R$_6$	X	Y
(**6**)	A	H	CH$_3$	H	H	CH$_3$	CH$_3$	OCH$_3$	OH
(**8**)	C	H	CH$_3$	H	CH$_3$	CH$_3$	CH$_3$	OCH$_3$	H
(**2**)	C 20-sulfate	SO$_3^-$	CH$_3$	H	CH$_3$	CH$_3$	CH$_3$	OCH$_3$	H
(**9**)	E	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OH	H
	F	H	CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	OH	H
(**10**)	G	CH$_3$	H	CH$_3$	H	CH$_3$	H	H	H
(**4**)	G 8-sulfate	CH$_3$	H	CH$_3$	H	CH$_3$	SO$_3^-$	H	H
	I	H	CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	OCH$_3$	H
	J	H	CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	H	H
	K	H	CH$_3$	H	CH$_3$	CH$_3$	H	OH	H
(**11**)	L	H	CH$_3$	CH$_3$	H	CH$_3$	H	H	H
(**3**)	L 20-sulfate	SO$_3^-$	CH$_3$	CH$_3$	H	CH$_3$	H	H	H
(**15**)	S	H	H	H	H	CH$_3$	H	H	H
	T	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OCH$_3$	H
	T 20-sulfate	SO$_3$Na	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OCH$_3$	H
	U	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	H	H
	U 20-sulfate	SO$_3$Na	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	H	H
	V	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OCH$_3$	OH
	V 20-sulfate	SO$_3$Na	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OCH$_3$	OH
	Y 20-sulfate	SO$_3$Na	CH$_3$	CH$_3$	H	H	CH$_3$	H	H
(**5**)	Z	CH$_3$	H	H	H	CH$_3$	H	H	H



	lamellarin	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	R$_6$	X
(**7**)	B	H	CH$_3$	H	CH$_3$	CH$_3$	CH$_3$	OCH$_3$
(**1**)	B 20-sulfate	SO$_3^-$	CH$_3$	H	CH$_3$	CH$_3$	CH$_3$	OCH$_3$
	D	H	CH$_3$	H	CH$_3$	CH$_3$	H	H
(**12**)	D triacetate	Ac	CH$_3$	Ac	CH$_3$	CH$_3$	Ac	H
	H	H	H	H	H	H	H	H
	M	H	CH$_3$	H	CH$_3$	CH$_3$	CH$_3$	OH
	N	H	CH$_3$	CH$_3$	H	CH$_3$	H	H
(**13**)	N triacetate	Ac	CH$_3$	CH$_3$	Ac	CH$_3$	Ac	H
(**14**)	W	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	OCH$_3$
	X	H	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	H



lamellarin	X
O	H
P	OH



lamellarin	R$_1$
Q	H
R	p-(C$_6$H$_5$)-OH

downfield of δ 7.40 (H-19) integrated for approximately half a proton relative to the neighboring aromatic protons. This observation suggested that these downfield protons (H-19) had a restricted relaxation pathway, which we postulated to be due to the *ortho* sulfate moiety. Relaxation NMR

Table 6. T_1 Values for Sulfated Lamellarins B, C, L, and G (**1**−**4**) and Non-sulfated Lamellarins B, C, L, and G (**7**, **8**, **11**, **10**)[a]

protonated position	B 20-sulfate (**1**)	B (**7**)	C 20-sulfate (**2**)	C (**8**)	L 20-sulfate (**3**)	L (**11**)	G 8-sulfate (**4**)	G (**10**)
5	3.11 ± 0.15	3.06 ± 0.40	*	*	*	*	*	*
5α	*[b]	*	0.68 ± 0.05	0.57 ± 0.05	0.57 ± 0.13	0.54 ± 0.04	0.62 ± 0.04	0.70 ± 0.08
5β	*	*	0.63 ± 0.03	0.59 ± 0.04	0.55 ± 0.14	0.57 ± 0.06	0.64 ± 0.04	0.71 ± 0.09
6	2.77 ± 0.14	2.40 ± 0.34	0.53 ± 0.02	0.48 ± 0.03	0.31 ± 0.09	0.50 ± 0.03	0.59 ± 0.04	0.60 ± 0.06
7	*	*	*	*	1.66 ± 0.13	1.60 ± 0.05	2.66 ± 0.08	1.74 ± 0.05
10	1.76 ± 0.05	1.64 ± 0.14	1.94 ± 0.04	1.77 ± 0.07	1.87 ± 0.13	1.92 ± 0.04	1.96 ± 0.05	1.88 ± 0.07
12	2.02 ± 0.06	1.76 ± 0.18	2.22 ± 0.06	1.94 ± 0.06	2.00 ± 0.42	1.97 ± 0.11	2.35 ± 0.09	2.29 ± 0.07
15	2.02 ± 0.09	1.75 ± 0.21	2.20 ± 0.07	1.99 ± 0.06	1.53 ± 0.17	1.60 ± 0.07	1.70 ± 0.05	1.78 ± 0.08
16	2.19 ± 0.12	1.97 ± 0.30	2.69 ± 0.09	2.28 ± 0.09	2.11 ± 0.19	2.15 ± 0.04	2.27 ± 0.06	2.31 ± 0.12
19	8.21 ± 0.27	2.64 ± 0.25	15.75 ± 0.43	3.05 ± 0.08	7.82 ± 0.30	2.84 ± 0.10	2.59 ± 0.05	2.50 ± 0.06
22	1.92 ± 0.06	1.74 ± 0.15	1.98 ± 0.08	1.88 ± 0.07	1.80 ± 0.12	1.87 ± 0.04	2.77 ± 0.06	2.83 ± 0.08
OCH_3-7	2.01 ± 0.08	2.03 ± 0.11	2.04 ± 0.10	1.74 ± 0.10	*	*	*	*
OH-8	*	*	*	*	N.O.	1.18 ± 0.27	*	2.07 ± 0.38
OCH_3-8	1.84 ± 0.09	1.88 ± 0.15	2.17 ± 0.18	1.71 ± 0.17	*	*	*	*
OCH_3-9	1.04 ± 0.04	0.98 ± 0.06	N.O.	N.O.	N.O.	1.19 ± 0.04	1.20 ± 0.04	1.14 ± 0.04
OH-13	*	*	*	*	N.O.	1.25 ± 0.17	N.O.[c]	1.87 ± 0.18
OCH_3-13	1.30 ± 0.03	1.17 ± 0.05	1.34 ± 0.06	1.21 ± 0.07	*	*	*	*
OH-14	1.82 ± 0.09	N.O.[c]	1.65 ± 0.05	N.O.	*	*	*	*
OCH_3-14	*	*	*	*	1.25 ± 0.06	1.35 ± 0.02	1.26 ± 0.03	1.24 ± 0.05
OH-20	*	*	*	N.O.	*	1.20 ± 0.34	*	*
OCH_3-20	*	*	*	*	*	*	1.23 ± 0.03	1.20 ± 0.04
OH-21	*	*	*	*	*	*	N.O.	1.86 ± 0.17
OCH_3-21	1.16 ± 0.06	1.10 ± 0.06	1.22 ± 0.13	1.20 ± 0.13	1.32 ± 0.12	1.22 ± 0.04	*	1.86 ± 0.17

[a] T_1 value units are, s ± error (errors were calculated by Varian T_1 analysis macro). [b] * = Substituent not present in molecule. [c] N.O.= Not observed due to exchange processes or signal being located under residual water signal.

studies were performed using the standard inversion−recovery method, and T_1 values were calculated (see Table 6) for all four sulfated compounds (**1**−**4**) and their corresponding nonsulfated derivatives (**7**, **8**, **10**, **11**). T_1 values for the H-19 in all four nonsulfated compounds (**7**, **8**, **10**, **11**) were found in the range, 2.8 ± 0.3 s. Comparison of these values with the corresponding 20-sulfated derivatives (**1**−**3**) showed the T_1 values increase by approximately three times for both compound **1** (8.21 ± 0.27 s) and **3** (7.82 ± 0.30 s) and approximately five times for compound **2** (15.75 ± 0.43 s). These long T_1 relaxation times for the *ortho* proton in the 20-sulfated compounds are due to the isolation of these protons (H-19), which have minimal relaxation pathways. Comparison of T_1 values of H-7 in lamellarin G (**10**) with its 8-sulfated derivative **4** showed only a 1-s increase on replacement at C-8 of the hydroxyl group with a sulfate substituent. This minor increase in T_1 for the proton *ortho* to the sulfate group (cf. compounds **1**−**3**) could be attributed to the close proximity of the methylene protons at C-6, which still facilitate relaxation through dipole−dipole interactions. With the exception of the proton *ortho* to the sulfate group, only small discrepancies (<0.4 s) were noted when comparing T_1 values for protons at the same positions in the nonsulfated lamellarin and the corresponding sulfated derivative.

Experimental Section

General Experimental Procedures. NMR spectra were recorded at 30 °C on a Varian 600 MHz Unity INOVA NMR spectrometer at 599.926 MHz for ^1H and 149.98 MHz for ^{13}C. The ^1H and ^{13}C chemical shifts were referenced to the proto-deutero solvent peak (DMSO-d_6) at δ 2.49 and 39.51 ppm, respectively. Standard parameters were used for the 2D NMR spectra obtained, which included gradient COSY, HSQC ($^1J_{CH}$ = 150 Hz), and HMBC ($^nJ_{CH}$ = 8.3 Hz) and phase-sensitive ROESY (mixing time 600 ms). NMR relaxation studies were performed using a standard Varian inversion−recovery method with T_1 minimum set to 0.5 s and T_1 maximum varied between 15 and 20 s. Relaxation delay was automatically set to four times the maximum T_1 value. T_1 values and errors were calculated using a Varian T_1 exponential analysis macro. (±)-HRESMS were recorded on a Bruker BioAPEX 47e mass spectrometer equipped with a Bradford CT 06405 electrospray ion source. (±)-LRESMS were recorded on a Fisons VG platform mass spectrometer at cone voltages of 30 or 80 V. FTIR and UV spectra were recorded on a Perkin−Elmer 1725X spectrophotometer and a GBC UV/vis 916 spectrophotometer, respectively. Size-exclusion chromatography was performed on Pharmacia Biotech Sephadex LH-20 (40-mm i.d. × 660-mm length) connected to a Waters 486 tunable UV detector and Waters fraction collector. A Waters 600 pump equipped with a Waters 996 PDA detector, Waters 717 autosampler, and a Waters fraction collector were used for analytical and semipreparative HPLC separations. Hypersil BDS 5 μm 142 Å C_{18} columns (analytical: 4.6-mm i.d. × 250-mm length, semipreparative: 10-mm i.d. × 250-mm length) and a YMC 5 μm 120 Å DIOL column (10-mm i.d. × 150-mm length) were used for HPLC separations. Alltech Davisil 30−40 μm 60 Å C_{18} was packed into SPE cartridges used for de-salting. All solvents used for HPLC, UV, $[\alpha]_D$, and MS were Merck Omnisolv grade, and the H_2O used was Millipore Milli-Q PF filtered. Ac_2O and pyridine used for acetylation were Sigma-Aldrich analytical grade.

Animal Material. A specimen of *Didemnum chartaceum* was collected during July of 1995 by scuba diving (−32 m) near Friget Cay in the Swains Reef group, Great Barrier Reef, and kept frozen prior to freeze-drying and extraction. Voucher specimen QMG305618 has been deposited at the Queensland Museum, South Brisbane, Queensland, Australia.

Extraction and Isolation. The freeze-dried ascidian (9.0 g dry wt) was exhaustively extracted with MeOH (5 × 100 mL), then concentrated under vacuum to yield a dark brown gum (1.07 g). This gum was partitioned between 10% aqueous MeOH (100 mL) and hexane (3 × 100 mL). The 10% aqueous MeOH fraction had H_2O (28.6 mL) added, and the resulting 30% aqueous MeOH fraction was subsequently partitioned with $CHCl_3$ (2 × 100 mL). The hexane, $CHCl_3$, and 30% aqueous MeOH fractions were all concentrated under vacuum and yielded 61 mg, 259 mg, and 826

mg of gum, respectively. The hexane fraction contained fats/steroids and was not further examined.

The $CHCl_3$-soluble material was chromatographed on Sephadex LH-20 using MeOH as the eluent and a flow rate of 3.2 mL/min. Sixteen fractions resulted after (±)-LRESMS analysis of which fractions 5, 8, and 10 contained pure lamellarin C 20-sulfate (**2**, 6.5 mg, 0.072% dry wt) and lamellarins A (**6**, 7.5 mg, 0.083% dry wt) and C (**8**, 5.2 mg, 0.058% dry wt), respectively. Another three of these fractions were further purified by semipreparative C_{18} HPLC at a flow rate of 4 mL/min under isocratic conditions of 60% MeOH/40% H_2O for 15 min, followed by a linear gradient up to 100% MeOH in 5 min, then 100% MeOH for a further 2 min. This yielded lamellarins B (**7**, 3.1 mg, 0.034% dry wt), E (**9**, 5.9 mg, 0.066% dry wt), G (**10**, 13.3 mg, 0.148% dry wt), and L (**11**, 19.3 mg, 0.214% dry wt). The last eluting alkaloid fractions from the Sephadex LH-20 column were chromatographed using semipreparative C_{18} HPLC at a flow rate of 4 mL/min with isocratic conditions of 70% MeOH/30% H_2O to yield lamellarin Z (**5**, 2.8 mg, 0.031% dry wt) and a mixture of two inseparable lamellarins. This mixture (6.0 mg) was acetylated using pyridine (0.5 mL) and Ac_2O (0.5 mL) and stirred at room temperature overnight. The acetylated mixture was purified by semipreparative DIOL HPLC at a flow rate of 4 mL/min with isocratic conditions of 35% *i*-PrOH/65% hexane to yield lamellarin D triacetate (**12**, 1.5 mg, 0.017% dry wt) and lamellarin N triacetate (**13**, 1.1 mg, 0.012% dry wt).

The 30% aqueous MeOH-soluble material was also chromatographed on Sephadex LH-20 using MeOH as the eluent and a flow rate of 3.7 mL/min. Fractions were analyzed by (±)-LRESMS then appropriately combined, and this resulted in three lamellarin fractions. These fractions were purified by semipreparative C_{18} HPLC using a flow rate of 4 mL/min with isocratic conditions of 55% MeOH/45% H_2O 0.2 M NaCl for 8 min followed by a linear gradient up to 100% MeOH in 7 min then 100% MeOH for a further 5 min. After lyophilization and combining of the same UV-active peaks, fractions were de-salted using a SPE cartridge packed with C_{18}, which was flushed with 100% H_2O (salt fraction) followed by 100% MeOH (lamellarin fraction). This yielded pure lamellarin G 8-sulfate (**4**, 9.5 mg, 0.106% dry wt), lamellarin L 20-sulfate (**3**, 14.6 mg, 0.162% dry wt), and lamellarin B 20-sulfate (**1**, 3.5 mg, 0.039% dry wt).

Lamellarin B 20-sulfate (1): isolated as a stable white solid; $[\alpha]_D$ 0° (*c* 0.04, MeOH); UV (MeOH) λ_{max} 202 (ϵ 31 000), 224 (sh, ϵ 18 000), 283 (ϵ 27 000), 301 (sh, ϵ 21 000), 321(sh, ϵ 11 000), 365 (ϵ 8000), 386 nm (ϵ 10 000); UV (MeOH + NaOH) λ_{max} 202 (ϵ 93 000), 283 (ϵ 27 000), 302 (sh, ϵ 22 000), 370 (ϵ 7000), 389 nm (ϵ 10 000); IR ν_{max} (KBr) 3439, 1690, 1658, 1631, 1549, 1530, 1482, 1414, 1258, 1203, 1053, 1012 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; (−)-LRESMS *m/z* 622 (95) $[M]^-$ and 542 (100) $[M - SO_3]^-$; (−)-HRESMS *m/z* 622.1029 (calcd for $C_{30}H_{24}NO_{12}S$ $[M]^-$ 622.1025, Δ +0.6 ppm).

Lamellarin C 20-sulfate (2): isolated as a stable white solid; $[\alpha]_D$ 0° (*c* 0.107, MeOH); UV (MeOH) λ_{max} 205 (ϵ 45 000), 225 (sh, ϵ 31 000), 265 (sh, ϵ 21 000), 276 (ϵ 25 000), 310 (ϵ 22 000), 337 nm (sh, ϵ 17 000); UV (MeOH + NaOH) λ_{max} 208 (ϵ 82 000), 265 (sh, ϵ 22 000), 276 (ϵ 28 000), 308 (ϵ 25 000), 339 nm (sh, ϵ 17 000); IR ν_{max} (KBr) 3445, 1711, 1641, 1546, 1509, 1476, 1415, 1261, 1240, 1200, 1146, 1122, 1088, 1050, 1008, 955, 845 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; (−)-LRESMS *m/z* 624 (100) $[M]^-$ and 544 (90) $[M - SO_3]^-$; (−)-HRESMS *m/z* 624.1197 (calcd for $C_{30}H_{26}NO_{12}S$ $[M]^-$ 624.1181, Δ +2.6 ppm).

Lamellarin L 20-sulfate (3): isolated as a stable off-white solid; $[\alpha]_D$ 0° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 203 (ϵ 32 000), 221 (sh, ϵ 21 000), 267 (sh, ϵ 16 000), 276 (ϵ 19 000), 314 (ϵ 16 000), 338 nm (sh, ϵ 14 000); UV (MeOH + NaOH) λ_{max} 202 (ϵ 74 000), 279 (ϵ 16 000), 318 (ϵ 17 000), 379 nm (sh, ϵ 6000); IR ν_{max} (KBr) 3462, 1698, 1636, 1558, 1542, 1508, 1488, 1420, 1276, 1244, 1204, 1163, 1050, 1024, 839, 760 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 3; (−)-LRESMS *m/z* 580 (100) $[M]^-$ and 500 (80) $[M - SO_3]^-$; (−)-HRESMS *m/z* 580.0935 (calcd for $C_{28}H_{22}NO_{11}S$ $[M]^-$ 580.0919, Δ +2.8 ppm).

Lamellarin G 8-sulfate (4): isolated as a stable off-white solid; $[\alpha]_D$ 0° (*c* 0.047, MeOH); UV (MeOH) λ_{max} 205 (ϵ 46 000), 225 (sh, ϵ 35 000), 266 (sh, ϵ 24 000), 275 (ϵ 28 000), 301 (sh, ϵ 20 000), 314 (ϵ 27 000), 336 nm (ϵ 22 000); UV (MeOH + NaOH) λ_{max} 208 (ϵ 87 000), 245 (sh, ϵ 32 000), 276 (ϵ 28 000), 322 (ϵ 26 000), 339 nm (sh, ϵ 23 000); IR ν_{max} (KBr) 3550, 3470, 3415, 1692, 1638, 1618, 1618, 1513, 1484, 1442, 1427, 1276, 1247, 1208, 1159, 1042, 832, 762 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 4; (−)-LRESMS *m/z* 580 (100) $[M]^-$ and 500 (100) $[M - SO_3]^-$; (−)-HRESMS *m/z* 580.0912 (calcd for $C_{28}H_{22}NO_{11}S$ $[M]^-$ 580.0919, Δ −1.2 ppm).

Lamellarin Z (5): isolated as a stable off-white solid; $[\alpha]_D$ 0° (*c* 0.047, MeOH); UV (MeOH) λ_{max} 207 (ϵ 31 000), 265 (sh, ϵ 16 000), 276 (ϵ 18 000), 314 (ϵ 16 000), 333 (ϵ 15 000), 348 (sh, ϵ 14 000), 352 nm (sh, ϵ 11 000); UV (MeOH + NaOH) λ_{max} 207 (ϵ 56 000), 280 (ϵ 15 000), 323 (ϵ 14 000), 363 nm (ϵ 12 000); IR ν_{max} (NaCl) 3425, 1680, 1589, 1486, 1422, 1279, 1249, 1206, 1163, 1041, 1028, 871 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 5; (+)-LRESMS *m/z* 510 (100) $[M + Na]^+$ and 488 (25) $[M + H]^+$; (+)-HRESMS *m/z* 488.1370 (calcd for $C_{27}H_{22}NO_8$ $[M + H]^+$ 488.1340, Δ +6.1 ppm).

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