Polychlorinated Acetamides from the Cyanobacterium *Microcoleus lyngbyaceus*

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Several new compounds were isolated from the organic extract of the cyanobacterium *Microcoleus lyngbyaceus*, and their structures were determined by spectroscopic means. Polychlorinated acetamidoalkynes and alkanes were the major metabolites. 6-Acetamido-1,1,1-trichloroundecane, a positional isomer of the naturally occurring 5-acetamido-1,1,1-trichloroundecane, was synthesized in six steps from δ-decanolactone.

Cyanobacteria represent a prolific source of bioactive structurally diverse secondary metabolites.[1] Nitrogenous compounds, occasionally incorporating halogen, occur frequently in these organisms.[2] Among the many secondary metabolites produced by the cyanobacterium *Lyngbya majuscula*, which Paul et al.[3] equate with *Microcoleus lyngbyaceus,* are the malyngamides, N-substituted amides often containing a vinylic chloride. These authors showed that such compounds serve as feeding deterrents, in agreement with the observation that *M. lyngbyaceus* is not an attractive food source for herbivorous fishes. Herein, we describe the isolation and characterization of seven new compounds from an HIV-active extract of a Chuuk Island collection of *M. lyngbyaceus.* Five of these compounds were polychlorinated acetamides.

Results and Discussion

The dichloromethane−methanol (DCM−MeOH) extract of the organism was solvent−solvent partitioned following a modified Kupchan procedure[4] with ether−hexane (9:1) substituting for carbon tetrachloride in the scheme. The ether−hexane-soluble fraction was further separated by sequential preparative thin-layer chromatography (TLC) and high-pressure liquid chromatography (HPLC).

Compound **1**, isolated as pale yellow oil, was identified as 8-acetamido-1,1,1,15,15-pentacloropentadeca-3,12-diyne in the following manner. Its molecular formula was established as $C_{17}H_{22}Cl_5NO$ by high-resolution fast atom bombardment mass spectroscopy (HRFABMS), indicating five degrees of unsaturation. Its ^{13}C NMR spectrum (Table 1) exhibited 16 signals; a 17th, too weak to observe directly, was detected through its strong cross-peaks in the HMBC spectrum. Six quaternary carbons (δ 169.7, 96.3, 85.6, 84.2, 73.4, 72), two methines (δ 48.4, 70.7), eight methylenes, and one methyl group were identified from the attached proton test (APT) spectrum. The five degrees of unsaturation can be accounted for by two acetylenic bonds and an amide carbonyl. The IR spectrum of **1** showed a carbonyl stretch at 1663 cm^{-1} and N−H stretching and bending absorptions at 3432 and 1515 cm^{-1}, respectively. Additionally, two acetylenic absorptions were present at 2232 and 2210 cm^{-1}.

The ^1H NMR spectrum of **1** (Table 1) showed a 3H singlet at δ 1.98 assigned to the methyl protons (H-18) of an acetyl group. Analysis of the $^1H-^1H$ correlation (COSY) NMR spectrum (Table 1) identified the methine proton at δ 3.95 as H-8 by its correlation to the nitrogen proton (H-16) at δ 5.14. The δ 3.55 propargylic methylene protons (H-2) adjacent to the trichloromethyl group were coupled to the δ 2.26 propargylic methylene protons (H-5). This is a five-bond coupling and is attributed to the planar structure imposed by the acetylenic bond.[5] The δ 3.05 propargylic methylene protons (H-14) were coupled to the dichloromethine proton at δ 5.75 (H-15) and to the propargylic methylene protons at δ 2.21 (H-11), again a five-bond coupling. The remaining proton sequence from H-5 through H-11 was established in a similar manner. Thus, the propargylic hydrogen at δ 2.26 (H-5) showed coupling to a two-proton multiplet at δ 1.63 (H-6), which, in turn, was coupled to a methylene group at δ 1.54 (H-7). The latter was also coupled to the amino methine at δ 3.95 (H-8). In addition to its coupling to the NH and H-7, H-8 also displayed coupling to a pair of protons at δ 1.54. This pair was further coupled to a multiplet at δ 1.51 (H-10), which, in turn, was coupled to the propargylic protons at δ 2.21 (H-11). This established the entire proton sequence of **1**. The totally correlated spectrum (TOCSY) completely supported the assignments (see Experimental Section).

The heteronuclear correlated spectrum (HMBC) confirmed the carbon chain (Table 1). The trichloromethyl carbon at δ 96.3 (C-1) was coupled to the methylene protons at δ 3.55 (H-2) and, through five bonds, to the propargylic

Table 1. NMR Data for Compound **1**

position	$^{13}C^a$ (mult.)	$^1H^b$ (mult. J = Hz)	COSY	HMBC (H no.)
1	96.3 (s)			2, 5
2	46.9 (t)	3.55 (t, 2.0)	5	4, 5
3	85.6 (s)			2, 5
4	72[c]			2, 5
5	18.5 (t)	2.26 (m)	2, 6	2, 4, 6, 7
6	34.4 (t)	1.63 (m)	5, 7	5
7	24.9 (t)	1.54 (m)	6, 8	5, 6
8	48.4 (d)	3.95 (m)	7, 9, 16	6, 7, 9, 10
9	24.8 (t)	1.54 (m)	8, 10	8, 10, 11
10	34.4 (t)	1.51 (m)	9, 11	9, 11
11	18.5 (t)	2.21 (m)	10, 14	9, 10, 12, 13
12	73.4 (s)			11, 14
13	84.2 (s)			11, 14,15
14	34.7 (t)	3.05 (dt, 6.0, 2.4)	11, 15	11, 12, 13, 15
15	70.7 (d)	5.75 (t, 6.0)	14	14
16		5.14 (d, 9.8)	8	
17	169.7 (s)			18
18	23.5 (q)	1.98 (s)		16

[a] Recorded at 50 Mz with $CDCl_3$ as internal standard at δ 77.0. [b] Recorded at 200 Mz with $CDCl_3$ as internal standard at δ 7.26. [c] Chemical shift obtained from HMBC spectrum.

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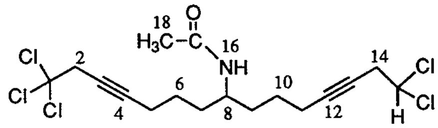
protons (H-5) at δ 2.25. The δ 85.6 carbon (C-3) was coupled to the methylene protons at 3.55 (H-2) and 2.26 (H-5). The elusive δ 72 carbon (C-4) was detected by its correlations to the δ 3.55 methylene protons (H-2) and to the δ 2.26 methylene protons (H-5), establishing the trichloromethyl carbon connection through C-2 to the two acetylenic carbons C-3 and C-4, and finally to C-5.

The δ 70.7 dichloromethyl carbon (C-15) correlated with the methylene protons at δ 3.05 (H-14), in agreement with the $^1H-^1H$ COSY NMR spectral assignments. The δ 84.2 acetylenic carbon (C-13) correlated to the methine proton at δ 5.75 (H-15) as well as to the methylene protons at δ 3.05 (H-14) and 2.21 (H-11). The acetylenic carbon at 73.4 (C-12) was coupled to the methylene protons at 3.05 (H-14) and 2.21 (H-11), establishing the dichloromethyl carbon (C-15) connection through the δ 34.7 carbon (C-14) to acetylenic carbons C-13 and C-12. The chemical shifts of C-3 through C-7 and C-9 through C-13 are consistent with those of comparable carbons in 3-heptyne.[6]

The gas chromatographic electron ionization mass spectrum (GCEIS) strongly supported the assigned structure. Prominent peaks were observed at *m*/*z* 396 (M − Cl), 234, 268, 314, and 348. Loss of $CHCl_2$ produced the 348 peak (M − 83), while loss of CCl_3 gave the 314 peak (M − 117). α-Cleavage between C-8 and C-9, with loss of $C_7H_9Cl_2$, left behind the positively charged amino fragment at *m*/*z* 268 (M − 163). Conversely, the 234 peak (M − 197) indicated α-cleavage between C-7 and C-8 with the corresponding loss of $C_7H_8Cl_3$.



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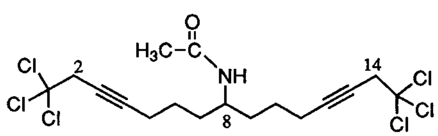

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Compound **2** (8-acetamido-1,1,1,15,15,15-hexacloropentadeca-3,12-diyne) was identified as the more highly chlorinated analogue of **1**. Its molecular formula of $C_{17}H_{21}Cl_6$ NO, established by HRFABMS, again required five degrees of unsaturation. IR analysis established the presence of a secondary amide (1663, 3434, and 1518 cm^{-1}) but only one type of acetylenic bond (2232 cm^{-1}). The symmetrical nature of the molecule was confirmed by its NMR spectra. The ^{13}C and^{13}C-APT NMR spectra of **2** (Table 2) revealed a total of only nine signals. Two signals were assigned to four quaternary carbons, two each at δ 96.1 and 85.5. Two additional equivalent quaternary carbons were assumed present at δ ~72, but, as with this analogous carbon in **1**, the signal was too weak to be observed. A seventh quaternary carbon at δ 169.7 was assigned to the amide carbonyl carbon. Further observed were one methine and one methyl carbon and four overlapping signals corresponding to eight methylene carbons. The two δ 96.1 carbons (C-1, C-15) had a chemical shift value close to that of the trichloromethyl carbon (C-1) of **1** and were assigned as such. In agreement with this is the 12.1 ppm downfield shift of C-14 in **2**, relative to its position in **1**, reflecting the deshielding effect of the additional α-chlorine atom at C-15. The remainder of the ^{13}C NMR spectrum of **2** was much the same as **1**.

Table 2. ^{13}C NMR Data for Compound **2**−**4** and **13**[a]

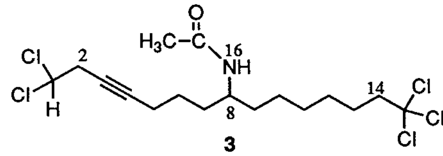
position	2	3	4	13
1	96.1 (s)	70.7 (d)	70.7 (d)	14.1 (q)
2	46.8 (t)	34.7 (t)	34.5 (t)	22.6 (t)
3	85.5 (s)	84.3 (s)	84.3 (s)	31.8 (t)
4	n.o.[b]	74.1 (s)	73.6 (s)	29.8 (t)
5	19.5 (t)	18.5 (t)	18.5 (t)	35.2 (t)
6	34.3 (t)	34.2 (t)	34.2 (t)	49.4 (d)
7	24.8 (t)	24.9 (t)	24.9 (t)	35.2 (t)
8	48.4 (d)	48.8 (d)	48.8 (d)	29.5 (t)
9	24.8 (t)	25.6[c](t)	25.8 (t)	25.8 (t)
10	34.3 (t)	23.6[c](t)	35.5 (t)	25.5 (t)
11	19.5 (t)	26.3[c](t)	25.8[c](t)	31.8 (t)
12	n.o.[b]	28.2[c](t)	28.4[c](t)	22.6 (t)
13	85.5 (s)	29.2[c](t)	29.2[c](t)	14.1 (q)
14	46.8 (t)	55.1 (t)	43.5 (t)	
15	96.1 (s)	98.7 (s)	70.7 (d)	169.9 (s)
16				23.6 (q)
17	169.7 (s)	169.7 (s)	169.7 (s)	
18	23.5 (q)	23.5 (q)	23.6 (q)	

[a] Recorded at 50 Mz with $CDCl_3$ as internal standard at δ 77.0. [b] Not observed. [c] Assignments may be interchanged.

The only significant differences in the ^1H NMR spectra of **1** (Table 1) and **2** (Table 3) were the absence in **2** of the triplet at δ 5.75 (H-15 in **1**) and the 0.50 ppm downfield shift of H-14 in **2**. The H-14 signal, a doublet of triplets in **1**, has collapsed to a simple triplet in **2**, in agreement with the replacement of a dichloromethyl group with a trichloromethyl group at C-15. Compound **2** showed the same correlations in its COSY NMR spectrum (see Experimental Section) as **1**, except for those associated with H-15, which compound **2** lacks.

Compound **3**, $C_{17}H_{26}Cl_5$ NO, was identified as 8-acetamido-1,1,15,15,15-pentachloropentadeca-3-yne. Its molecular formula was established by HRFABMS, which indicated three degrees of unsaturation, one from an amide (IR: 1663, 3434, and 1518 cm^{-1}) and the other two from an acetylenic bond (IR: 2232 cm^{-1}). The ^{13}C-APT NMR spectrum of **3** (Table 2) showed four quaternary carbons (δ 98.7, 84.3, 74.1, 169.7), two methine carbons (δ 70.7, 48.8), 10 methylene carbons, and one methyl carbon. The δ 98.7 carbon (C-15) corresponds to C-1 in **1** and was assigned to a trichloromethyl group. The downfield shift of C-14 in **3** relative to the comparable carbon (C-2) in **1** (δ 55.1 vs 46.9) resulted from the loss of the shielding effect of an adjacent triple bond. In contrast, the H-2 protons of **1** were deshielded by the triple bond and appeared at δ 3.55, while their counterpart, H-14 in **3**, were at δ 2.65 (Table 3). The chemical shifts of C-10 through C-13 were consistent with those of the corresponding carbons in *n*-octane.[6]

The $^1H-^1H$ COSY NMR spectrum of **3** (see Experimental Section) supported the proposed structure, as did the EIMS. The latter gave prominent peaks at *m*/*z* 400 (M − Cl), 352 (M − $CHCl_2$), 272 (M − 163 from α-cleavage between C-7



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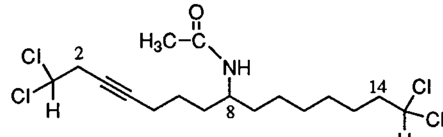

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Table 3. ^{1}H NMR Data for Compound **2**−**5** and **13**[a] (multiplicity, J = Hz)

position	2	3	4	5	13
1		5.76 (t, 6.0)	5.76 (t, 6.0)		0.87 (t, 6.6)
2	3.55 (t, 2.0)	3.05 (dt, 6.0, 2.4)	3.06 (dt, 6.0, 2.4)	2.65 (m)	1.25 (m)
3				1.62 m)	1.25 (m)
4				1.34 (m)	1.25 (m)
5	2.26 (m)	2.22 (m)	2.15 (m)	3.92 (m)	1.46 (m)
6	1.63 (m)	1.49 (m)	1.49 (m)	1.34 (m)	3.88 (m)
7	1.57 (m)	1.53 (m)	1.53 (m)	1.34 (m)	1.46 (m)
8	3.97 (m)	3.98 (m)	3.95 (m)	1.34 (m)	1.25 (m)
9	1.57 (m)	1.53 (m)	1.49 (m)	1.34 (m)	1.25 (m)
10	1.63 (m)	1.35 (m)	1.31 (m)	1.34 (m)	1.25 (m)
11	2.26 (m)	1.35 (m)	1.31 (m)	0.91 (t, 6.2)	1.25 (m)
12		1.57 (m)	1.31 (m)	5.09 (m)	1.25 (m)
13		1.76 (m)	1.31 (m)		0.87 (t, 6.6)
14	3.55 (t, 2.0)	2.65 (m)	2.13 (m)	1.98 (s)	5.14 (d, 8.6)
15			5.74 (t, 6.0)		
16	5.14 (d, 9.8)	5.10 (d, 8.4)	5.10 (d, 8.4)		1.98 (s)
17					
18	1.98 (s)	1.98 (s)	1.98 (s)		

and C-8 with loss of $C_7H_9Cl_2$), and 234 (M − 201 from α-cleavage between C-8 and C-9 with loss of $C_7H_{12}Cl_3$).

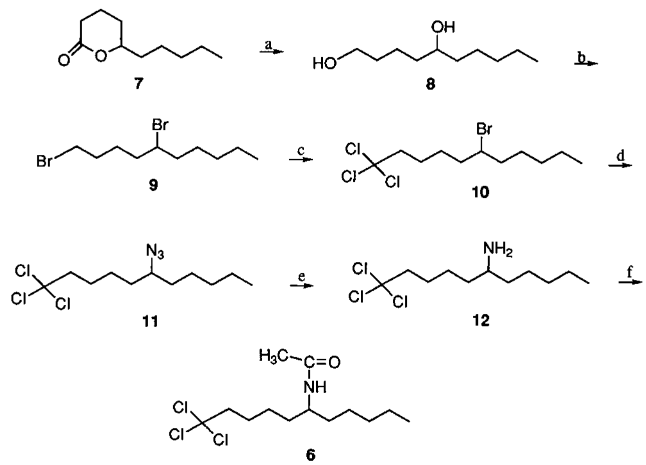
Compound **4**, $C_{17}H_{27}Cl_4NO$, also displayed secondary amide absorptions in the IR (1663, 3434, 1517 cm^{-1}) as well as an alkyne absorption (2232 cm^{-1}). Only three quaternary carbons were present (δ 169.7, 84.3, 73.6) together with three methine carbons (δ 70.7, 70.7, 48.8), 10 methylene carbons, and one methyl carbon (Table 2). The absence of a quaternary carbon at δ 98.7 and the appearance of a second methine carbon at δ 70.7 suggested that the trichloromethyl group of **3** had been replaced by a dichloromethyl group in **4**. Additionally, C-14 in **4** was shifted upfield relative to its position in **3** (δ 43.5 vs 55.1). In the ^{1}H NMR spectrum, **3** displayed one triplet at δ 5.76 (H-1), whereas **4** displayed two overlapping triplets (δ 5.76, 5.74), in agreement with two dichloromethyl protons in the latter compound.

The ^{1}H−^{1}H COSY NMR spectrum of **4** (see Experimental Section) showed all of the expected correlations and, together with the EIMS, confirmed the structure as 8-acetamido-1,1,15,15-tetrachloropentadeca-3-yne. Major peaks in the mass spectrum occurred at m/z 366 (M − Cl), 318 (M − $CHCl_2$), 238 (M − 163 from α-cleavage between C-7 and C-8 with loss of $C_7H_9Cl_2$), and 234 (M − 167 from α-cleavage between C-8 and C-9 with loss of $C_7H_{13}Cl_2$).

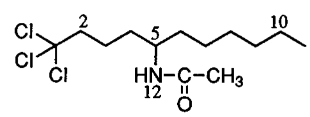
The molecular formula of compound **5** was established by HRFABMS as $C_{13}H_{24}Cl_3NO$, indicating one degree of unsaturation, which was ascribed to a secondary amide functionality (IR: 1663, 3435, and 1518 cm^{-1}). This compound was isolated in insufficient quantity for ^{13}C NMR studies. Its ^{1}H NMR spectrum displayed an acetamido methyl singlet at δ 1.98, an N−H multiplet at δ 5.09 (H-12), and a 1H multiplet at δ 3.92 assigned to the amino methine (H-5). The lack of any other significantly deshielded protons ruled out hydrogens on carbons bearing chlorine, implying the presence of a trichloromethyl group. A 2H multiplet at δ 2.65 fit well for a CH_2 adjacent to such a group. A 3H triplet at δ 0.91 required the other terminus to be a methyl group. The ^{1}H−^{1}H COSY spectrum (see Experimental Section) established the proton sequence shown.

The placement of the acetamido group at position 5, rather than on the central carbon of the chain, was suggested by the EIMS. In addition to loss of Cl (m/z 280) and C_2H_3O (m/z 272), a strong peak was evident at m/z 230 (M − 85) corresponding to α-cleavage between C-5 and C-6 with loss of C_6H_{13}. Another sizable peak at m/z 194 likely arises from loss of both HCl and C_6H_{13} from the molecular ion. This strongly supported the structure assignment as 5-acetamido-1,1,1-trichloroundecane. Unexpectedly, there was no significant peak corresponding to α-cleavage between C-4 and C-5.

Scheme 1. Synthesis of 6-Acetamido-1,1,1-trichlorodecane (**6**)[a]



[a] Reagents and conditions: (a) $LiAlH_4$, ether, reflux, 12 h, (b) PBr_3, ether, reflux, 2 h, (c) t-BuOK, $CHCl_3$ DMF, −40 °C, 2 h, (d) NaN_3, Aliquot 336, water, reflux, 16 h, (e) $LiAlH_4$, ether, 25 °C, 2 h, (f) acetic anhydride, pyridine, 25 °C, 12 h.



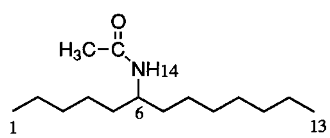
5

To provide further evidence for the acetamido group placement in **5**, its positional isomer, 6-acetamido-1,1,1-trichloroundecane (**6**) was synthesized (Scheme 1). Commercially available δ-decanolactone (**7**) was reduced with $LiAlH_4$ in 95% yield to diol **8**.[7] This diol was subjected to bromination with PBr_3[8] to give dibromide **9** in 73% yield. The dibromide was allowed to react with the trichloromethyl anion, generated from chloroform and potassium *tert*-butoxide according to the method of Russell and Roques.[9] After separation of the crude reaction product by vacuum liquid chromatography (VLC), 6-bromo-1,1,1-trichloroundecane (**10**) was isolated in 42% yield. Reaction of **10** with aqueous NaN_3[10] gave the yellow azide **11** in quantitative yield, which was directly reduced with $LiAlH_4$[11] to give amine **12** in 52% yield. Amine **12** was acylated to give 6-acetamido-1,1,1-trichloroundecane (**6**) in 79% yield. The overall yield for the six steps was 12%.

Both the IR and ^{1}H NMR spectra of **6** were very similar to those of natural product **5**. However, their mass spectra were very different. The synthetic compound (**6**) cleaved as expected with strong peaks at *m*/*z* 244 (M − C_5H_{11}) and *m*/*z* 142 (M − $C_5H_8Cl_3$) for α-directed cleavages (C-6, C-7 and C-5, C-6, respectively). Natural product **5**, on the other hand, showed neither of these peaks. It is not clear why **5** gave only the one α-cleavage (C-5, C-6), as all other compounds in this series clearly showed both posssible α-cleavages.

Compound **13** was isolated in 3.5% yield from the crude extract as a white crystalline solid. HRFABMS established its molecular formula as $C_{15}H_{31}NO$. The one degee of unsaturation implied by this formula was accounted for by the secondary amide function (IR: 1662, 3436, 1515 cm^{-1}). The ^{13}C and ^{13}C -APT NMR spectra (Table 2) showed the amide carbon at δ 169.9, one methine (δ 49.4), 10 methylene carbons, and three methyl carbons, one of which was assigned to the acetyl group and the other two to the termini of the chain. In agreement with the ^{13}C NMR data, the ^{1}H NMR spectrum (Table 3) showed two superimposed methyl triplets at δ 0.87 (H-1 and H-13) and the acetamide methyl as a singlet at δ 1.98. Only two deshielded resonances appeared, the amino methine at δ 3.88 (H-6) and the NH at δ 5.14 (H-14). These data suggested a simple acetamidotridecane structure.

The EIMS allowed placement of the acetamido group at position 6 on the chain. In addition to prominent peaks at *m*/*z* 226 (M − CH_3) and 198 (M − C_2H_3O), one at *m*/*z* 170 corresponded to α-cleavage between between C-5 and C-6 with the loss of C_5H_{11} and one at *m*/*z* 142 corresponded to α-cleavage between C-6 and C-7 with loss of C_7H_{15}.



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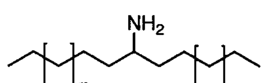

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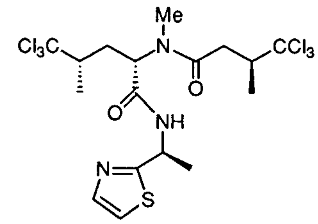
A seventh compound was obtained as part of an inseparable mixture of oils that reacted rapidly in air to form a white amorphous solid. ^{13}C and ^{1}H NMR data suggested an aminoalkane with a carbon chain 13 units long. The IR spectrum implied a primary amine with absorbances at 3620, 3435, and 1517 cm.$^{-1}$ A 1H broad multiplet centered at δ 4.02 in the ^{1}H NMR, coupled to the protons on the nitrogen (δ 3.62) and to several methylene protons, was assigned to an amino methine. A 4H multiplet centered at δ1.59 was indicative of methylene protons β to the amino group, while a 16H multiplet centered at δ 1.25 suggested eight additional sets of methylene protons. Finally, a 6H triplet at 0.93 suggested terminal methyl groups. This compound is tentatively identified as an aminotridecane, **14**, but the placement of the amino group could not be determined as the compound decomposed before mass spectral data were collected.

Compounds **1**−**5** are simple amino lipid derivatives, but their di- and trichloromethyl groups make them quite unique. Cyanobacterial metabolites with di- and trichloromethyl groups are generally amino acid derived with the polyhalogenated terminus at a methyl branch point. Examples include dysidenin, **15**,[12] and its monodechlorinated analogues,[13] herbacic acid, **16**,[14] and barbaramide, **17**.[15] Recent work has shown that chlorination, possibly by a free radical mechanism, of the pro-*S* methyl group of leucine or a leucine derivative prior to *N*-methylation gives rise to these metabolites.[16] A comparable process may be operative in the case of **1**−**5**.



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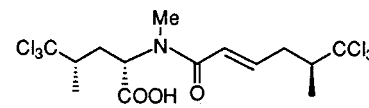

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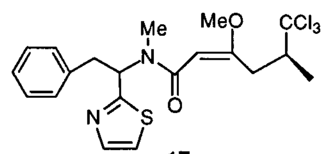

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Compounds **1** and **2** were tested in the National Cancer Institute's anti-HIV primary screen for cytopathicity.[17] Although isolated from a modestly active fraction, these compounds were essentially inactive in the assay.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer Paragon 500 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were collected on a Bruker AC 200 spectrometer, a Varian Unity 300, or a Varian Unity 500 spectrometer. All chemical shifts are reported with respect to $CDCl_3$ set at δ 7.26 for ^{1}H and 77.0 for ^{13}C. Two-dimensional experiments were performed with standard Bruker software. FABMS spectra were obtained on a JEOL SX102 mass spectrometer operated at an accelerating voltage of 10 kV. Samples were desorbed from a magic bullet matrix using 6 keV xenon atoms. Mass measurements in FAB were performed at 10 000 resolution using magnetic field scans and the matrix ions as the reference material. GCEIMS was done on a JEOL SX102 spectrometer operating in low-resolution mode. Optical rotations were measured on a Rudolph Research Autopol II polarimeter. Vacuum liquid chromatography (VLC) and TLC were performed with EM Science 60H Si gel. TLC plates were viewed under short-wave ultraviolet light or H_2SO_4/vanillin spray unless otherwise noted. HPLC separations were carried out on a Beckman instrument with detection at 254 nm on an Alltech 3m Spherisorb SiO_2 3.5 × 70 mm column.

Plant Material. The cyanobacterium was collected by scuba off Dublon Island, Chuuk Island Atoll, in 1993 and identified by Dr. Roy Tsuda as *Microcoleus lyngbyaceus* (Kuetz) Crouan. A voucher specimen was deposited at the Smithsonian Institution, voucher number OCDN0877.

Extraction and Isolation. The frozen algal mass (1.46 kg) was ground with dry ice, extracted with H_2O at 3 °C for 4 h, filtered, and freeze-dried. The dried marc (227 g) was extracted with MeOH−DCM (1:1), then MeOH, at 25 °C for 16 h; the filtered extracts were then combined and concentrated in vacuo to give 1.40 g of extract. A portion of the extract (294 mg) was solvent−solvent partitioned using a modified Kupchan partition.[4] The extract was dissolved in 45 mL of MeOH and 5 mL of H_2O. The mixture was extracted with hexane (3 × 50 mL), and the combined extracts were dried over anhydrous $MgSO_4$, then evaporated to dryness to yield 60.5 mg (21%) of hexane extract. To the aqueous−methanol phase was added 30 mL of H_2O. The resultant mixture was extracted with Et_2O−hexane (9:1) (2 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield 65.0 mg (22%) of ether−hexane extract. The remainder was concentrated, under reduced pressure, to remove MeOH and was then extracted with EtOAc (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure to yield 47.5 mg (16%) of EtOAc extract. The remainder was evaporated to dryness to yield 110 mg of water extract. The combined recovery was 98%.

The Et_2O−hexane extract (65 mg) was dissolved in a small amount of dichloromethane (DCM) and spotted on a 1000 μ SiO_2 TLC plate. Development in DCM−EtOAc (9:1) gave four fractions, which were recovered by extraction with EtOAc: 1A (11 mg, 17%), 1B (15 mg, 23%), 1C (16.5 mg, 25%), and 1D (18.5 mg, 29%). The total recovery was 94%.

Fraction 1B (15 mg) was dissolved in a small amount of DCM, spotted onto a 250 μ SiO_2 TLC plate and developed with hexane−IPA (9:1) (4×). Five fractions were recovered by extraction with EtOAc: 2A (compound **13**, 6 mg, 2%), 2B (2.5 mg, 1%), 2C (3.5 mg, 1%), 2D (2 mg, 0.6%), and 2E (1.5 mg, 0.5%). The total recovery for the separation was 100%. Fraction 2D (2 mg) was further purified by SiO_2 HPLC with hexane−IPA (95:5) into 2 fractions: 3A (1 mg, 0.3%) and 3B (compound **5**, 1 mg, 0.3%). The total recovery for the separation was 100%.

Fraction 1C (16.5 mg) was dissolved in a small amount of DCM and spotted on a 250 μ SiO_2 TLC plate. The plate was developed in hexane−IPA (9:1) (4×) to give six fractions, which were recovered by extraction with EtOAc: 4A (compound **13**, 4.5 mg, 1.5%) 4B (2.5 mg, 0.8%), 4C (3 mg, 1%), 4D (3.5 mg, 1.2%), 4E (5.5 mg, 1.8%), and 4F (compound **14**, 1.5 mg, 0.5%). The total recovery for the separation was 91%. Fraction 4B (1.5 mg) was further separated by SiO_2 HPLC with hexane−IPA (95:5) to give fractions 5A (1.0 mg, 0.3%), 5B (1.0 mg, 0.3%), 5C (unweighable), 5D (compound **3**, 1 mg, 0.3%), and 5E (unweighable). The total recovery for the separation was 85%.

Fraction 4E (5.5 mg) was dissolved in a small amount of acetonitrile and spotted on a reversed-phase (C_{18}) TLC plate. After development with acetonitrile−H_2O (9:1) five fractions were recovered by extraction with acetonitrile: 6A (**1**, 2.0 mg, 0.6%), 6B (**2**, 1 mg, 0.3%), 6C (**4**, 1 mg, 0.3%), 6D (1 mg, 0.3%), and 6E (2.5 mg, 0.8%). The total recovery for the separation was 100%.

8-Acetamido-1,1,1,15,15-pentachloropentadeca-3,12-diyne (1): oil; $[\alpha]_D$ +36.0° (*c* 0.083, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3432 (w), 2932 (s), 2864 (s), 2232 (w), 2210 (w), 1663 (s), and 1515 (s) cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; TOCSY H-2 to H-5, H-6, H-7, H-8; H-5 to H-2, H-6, H-7, H-8, H-16; H-6 to H-2, H-5, H-7, H-8, H-9, H-16; H-7 to H-2, H-5, H-6, H-8, H-10, H-11, H-14, H-15, H-16; H-8 to H-2, H-5, H-6, H-7, H-9, H-10, H-11, H-16; H-9 to H-2, H-5, H-6, H-8, H-10, H-11, H-14, H-15, H-16; H-10 to 6, H-7, H-8, H-9, H-10, H-11, H-14, H-15, H-16; H-11 to H-8, H-9, H-10, H-11, H-14; H-14 to H-9, H-10, H-11, H-15; H-15 to H-9, H-10, H-11, H-14; H-16 to H-5, H-6, H-7, H-8, H-9, H-10; HRFAB (MH^+, glyc) *m/z* 432.0213 (calcd for $C_{17}H_{23}Cl_5$ NO, 432.0219); EIMS *m/z* 398 (10), 396 (10), 350 (16), 348 (16), 316 (16), 314 (25), 272 (15), 270 (33), 268 (34), 254 (10), 236 (24), 234 (36), 229 (16), 228 (10), 227 (17), 218 (12), 195 (45), 194 (16), 193 (74), 192 (19), 190 (11), 177 (11), 175 (23), 173 (17), 164 (24), 156 (11), 154 (11), 141 (15), 139 (31), 120 (12), 113 (13), 105 (10), 103 (13), 99 (12), 96 (18), 95 (100), 93 (11), 91 (26), 79 (17), 77 (27), 67 (15), 65 (19), 60 (88), 57 (11), 56 (59), 43 (32), 42 (11).

8-Acetamido-1,1,1,15,15,15-hexachloropentadeca-3,12-diyne (2): oil; IR ($CHCl_3$) ν_{max} 3434 (w), 2232 (w), 1663 (s), and 1518 (s) cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; ^1H−^1H COSY H-2 to H-5; H-5 to H-2 and H-6; H-6 to H-5 and H-7; H-7 to H-6 and H-8; H-8 to H-7, H-9, and H-16; H-9 to H-8 and H-10; H-10 to H-9 and H-11; H-11 to H-10 and H-14; H-16 to H-8; HRFAB (MH+, glyc) *m/z* 465.9830 (calcd for $C_{17}H_{22}Cl_6NO$, 465.9830).

8-Acetamido-1,1,15,15,15-pentachloropentadeca-3-yne (3): oil; $[\alpha]_D$ +30.0° (*c* 0.067, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3434 (w), 2975 (s), 2929 (s), 2232 (w), 1663 (s), and 1518 (s) cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; ^1H−^1H COSY H-1 to H-2; H-2 to H-1 and H-5; H-5 to H-2 and H-6; H-6 to H-5 and H-7; H-7 to H-6 and H-8; H-8 to H-7, H-9, and H-16; H-9 to H-8 and H-10; H-10 to H-9 and H-11; H-11 to H-10 and H-12; H-12 to H-11 and H-13; H-13 to H-12 and H-14; H-14 to H-13; H-16 to H-8; HRFAB (MH+, glyc) *m/z* 436.0515 (calcd for $C_{17}H_{27}Cl_5NO$, 436.0531); EIMS *m/z* 404 (11), 402 (21), 400 (17), 354 (25), 352 (27), 300 (18), 298 (17), 276 (16), 274 (45), 272 (50), 270 (13), 268 (10), 241 (20), 238 (19), 236 (43), 234 (67), 232 (39), 198 (14), 197 (10), 196 (44), 195 (43), 194 (56), 193 (62), 192 (18), 170 (94), 142 (100), 139 (24), 109 (16), 105 (13), 103 (12), 99 (16), 96 (14), 95 (85), 93 (15), 91 (26), 81 (13), 79 (24), 77 (26), 75 (14), 70 (12), 67 (22), 65 (21), 60 (100), 57 (19), 56 (70), 55 (32), 53 (15), 43 (51).

8-Acetamido-1,1,15,15-tetrachloropentadeca-3-yne (4): oil; $[\alpha]_D$ +24.0° (*c* 0.083, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3434 (w), 2930 (s), 2859 (s), 2232 (w), 1663 (s), and 1517 (s) cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; ^1H−^1H COSY H-1 to H-2; H-2 to H-1 and H-5; H-5 to H-2 and H-6; H-6 to H-5 and H-7; H-7 to H-6 and H-8; H-8 to H-7, H-9, and H-16; H-9 to H-8 and H-10; H-10 to H-9 and H-11; H-11 to H-10 and H-12; H-12 to H-11 and H-13; H-13 to H-12 and H-14; H-14 to H-13 to H-15, H-15 to H-14, H-16 to H-8; HRFAB (MH+, glyc) *m/z* 402.0923 (calcd for $C_{17}H_{28}Cl_4$ NO, 402.0920); EIMS *m/z* 368 (10), 366 (11), 328 (22), 318 (35), 278 (10), 266 (19), 264 (26), 248 (40), 238 (68), 236 (42), 234 (61), 224 (13), 222 (18), 198 (56), 197 (15), 196 (89), 195 (46), 194 (22), 193 (70), 192 (21), 160 (18), 139 (25), 99 (16), 96 (15), 95 (78), 93 (16), 91 (26), 81 (17), 79 (26), 77 (27), 75 (17), 70 (13), 69 (15), 67 (27), 65 (21), 68 (100), 57 (30), 56 (69), 55 (37), 53 (18), 43 (49).

5-Acetamido-1,1,1-trichlorodecane (5): oil; $[\alpha]_D$ +60.0° (*c* 0.017, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3435 (w), 2935 (s), 2859 (s),-1663 (s), and 1518 (s) cm^{-1}; ^1H NMR, see Table 3; ^1H−^1H COSY H-2 to H-3; H-3 to H-2 and H-4; H-4 to H-3 and H-5; H-5 to H-4, H-6, and H-12; H-6 to H-5 and H-7; H-7 to H-6 and H-8, H-8 to H-7 and H-9; H-9 to H-8 and H-10; H-10 to H-9 and H-11; H-11 to H-10; H-12 to H-5; HRFAB (MH+, glyc) 316.1011 (calcd for $C_{13}H_{25}Cl_3NO$, 316.0997); EIMS *m/z* 282 (21), 281 (10), 280 (32), 279 (11), 276 (20), 274 (59), 272 (62), 238 (77), 236 (45), 234 (60), 230 (65), 223 (21), 205 (19), 196 (40), 194 (62), 177 (15), 165 (13), 163 (11), 150 (16), 149 (100), 138 (10), 137 (20), 135 (15), 133 (10), 129 (18), 127 (14), 125 (29), 124 (17), 123 (38), 121 (17), 119 (16), 115 (20), 114 (87), 113 (18), 112 (18), 111 (46), 110 (21), 109 (42), 39 (15).

6-Acetamidotridecane (13): white crystalline solid; IR ($CHCl_3$) ν_{max} 3436 (w), 2930, (s), 2858 (s), 1662 (s), and 1515 (s) cm^{-1}; ^1H and ^{13}C NMR data, see Tables 2 and 3; ^1H−^1H COSY H-1 to H-2; H-2 to H-1; H-5 to H-6; H-6 to H-5, H-7, and H-14; H-7 to H-6; H-13 to H-12; H-14 to H-6; HRFAB (MH+, glyc) *m/z* 242.2490 (calcd for $C_{15}H_{32}NO$, 242.2476); EIMS *m/z* 241 (20), 226 (30), 198 (43), 170 (95), 142 (100), 128 (95), 100 (90), 69 (10), 60 (35), 55 (19), 42 (14).

Compound 14: oil; IR ($CHCl_3$) ν_{max} 3620 (w), 3435 (w), 2962 (s), 2928 (s), and 1517, (s); ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (6H, t, J = 6.2 Hz), 1.25 (16H, m), 1.59 (4H, m), 3.62 (2H, m), 4.02 1H, bs); ^{13}C (50 MHz, $CDCl_3$) δ 51.8, 35.5, 31.8, 29.7, 29.5, 31.8, 22.7, 14.1.

1,5-Decanediol (8).[7] To a 300 mL three-neck flask equipped with a nitrogen inlet, a rubber septum, and a reflux condenser was added 1.73 g (4.55 mmol) of $LiAlH_4$ and 100 mL of dry ether. To this was added 3.10 g (1.82 mmol) of δ-decanolactone (**7**) in 10 mL of dry ether. After the addition, the mixture was heated to reflux for 12 h. The reaction was cooled and quenched by the careful addition of water (10 mL) and saturated NH_4Cl (50 mL). The residue was washed with ether (3 × 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the desired diol **8** as a colorless oil in 94% yield: IR (neat film) ν_{max} 3346 (br), 2932 (s), 2855 (s); ^1H NMR (200 MHz, $CDCl_3$) δ 3.64 (2H, t, J = 6.2 Hz), 3.61 (1H, m), 1.92 (2H, bs), 1.53 (2H, m), 1.43 (8H, m), 1.28 (4H, s), 0.88 (3H, t, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 21.8, 22.6, 25.3, 31.9, 32.6, 37.0, 37.5, 62.7, 71.9.

1,5-Dibromodecane (9). To a 300 mL three-neck flask equipped with a nitrogen inlet, a rubber septum, and a reflux condenser was added 3.20 g (1.84 mmol) of diol **8** and 100 mL of dry ether. To this was added, with vigorous stirring, 1.80 g (0.66 mmol) of PBr_3 at such a rate as to maintain reflux. The reaction was then heated to maintain reflux for another 2 h; it was cooled and then quenched by the slow addition of water (50 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL) and then dried ($MgSO_4$). The extract was concentrated in vacuo and separated on SiO_2 with hexane to give the desired dibromide **9** in 73% yield: IR (neat) ν_{max} 2929 (s), 2862 (s), 1456 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.00 (1H, pentet, J = 6.2 Hz), 3.40 (2H, t, J = 6.6 Hz), 1.80 (4H, pentet, J = 6.2 Hz), 1.25−1.65 (m), 1.29 (m), 0.88 (3H t, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 57.9, 38.9, 38.1, 33.7, 31.1, 27.9, 27.1, 26.5, 22.4, 13.9; *anal.* C 40.14%, H 6.97%, calcd for $C_{10}H_{20}Br_2$, C 40.03%, H 6.72%.

6-Bromo-1,1,1-trichloroundecane (10). To a 100 mL three-neck flask equipped with a nitrogen inlet, a rubber septum, and a 10 mL dropping funnel was added 0.75 g (0.66 mmol) of *t*-BuOK in 25 mL of dry DMF. The flask was cooled to −40 °C, and 2.0 g (0.66 mmol) of **9** was added. To this was added, dropwise, 2.35 g (2.67 mmol) of chloroform with stirring. The reaction mixture was stirred at −40 °C for an additional 2 h and then quenched by the careful addition of water (25 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give 1.84 g of crude material, which was separated by VLC on SiO_2 with hexane to give 0.95 g (42%) of **10**. An analytical sample could not be prepared because of the difficulty in separating the starting dibromide **9** from the final product: IR (neat) ν_{max} 2931 (s), 2859 (s), 1457 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.03 (1H, pentet, J = 6.6 Hz), 2.69 (2H, t, J = 8 Hz), 1.84 (4H, m), 1.61 (4H, m), 1.28 (6H, m), 0.80 (3H, t, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 99.9, 58.1, 54.9, 37.1, 36.9, 31.2, 27.3, 26.4, 25.9, 22.5, 14.0.

6-Azido-1,1,1-trichloroundecane (11). In a 50 mL round-bottom flask equipped with a reflux condenser was placed 0.85 g (0.25 mmol) of **10** and 0.06 g (0.015 mmol) of Aliquot 336. To this was added 0.66 g (1.0 mmol) of NaN_3 dissolved in 25 mL of water. The reaction mixture was heated to reflux for 16 h, cooled, and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with saturated $NaHCO_3$ (3 × 50 mL) and brine (3 × 50 mL), then dried ($MgSO_4$) to give the theoretical yield of the straw yellow azide **11**, which was used in the next step without further purification: IR (neat film) ν_{max} 2935, (s), 2860 (s), 2104 (s), 1460 (s), 1346 (w).

6-Amino-1,1,1-trichloroundecane (12). To a 50 mL three-neck flask equipped with a nitrogen inlet and a rubber septum was added 0.21 g (0.56 mmol) of $LiAlH_4$ in 10 mL of dry ether. To this was added dropwise, with vigorous stirring, 0.65 g (0.22 mmol) of the azide (**11**) dissolved in 5 mL of dry ether. The reaction mixture was stirred for 0.25 h and was quenched by the careful addition of water (5 mL) and then saturated NH_4Cl (15 mL). The organic layer was separated, and the residue was made basic with 1 M NaOH (50 mL) and extracted with ether (3 × 50 mL). The combined ethereal extracts were then washed with saturated $NaHCO_3$ (2 × 50 mL) and concentrated in vacuo. The extract was dried by azeotropic distillation with benzene (50 mL) to give the amine **12** in 52% yield, which was used without further purification: IR (neat film) ν_{max} 3368 (br), 2928 (s), 2857 (s), 1468 (m).

6-Acetamido-1,1,1-trichloroundecane (6). In a 25 mL round-bottom flask equipped with a nitrogen inlet was added 0.29 g (0.11 mmol) of the amine **12**. To this was added 0.25 g (0.32 mmol) of pyridine and 0.32 g (0.32 mmol) of acetic anhydride. The mixture was stirred at 25 °C for 12 h and then quenched by the addition of ice water (15 mL). The organic layer was separated and washed with 1 M HCl (3 × 50 mL), 1 M NaOH (3 × 50 mL), and brine (3 × 50 mL). The mixture was dried ($MgSO_4$) and concentrated in vacuo to give 0.26 g of crude product, which was separated by TLC on SiO_2 with DCM−EtOAc (95:5) (2×) to give 79% yield of the final product (**6**): IR ($CHCl_3$) ν_{max} 3435 (m), 2933 (s), 1664 (s), 1517 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.24 (1H, d, J = 9.0 Hz), 3.91 (1H, bs), 2.64 (2H, m), 1.98 (3H, s), 1.75 (2H, m), 1.53 (4H, m), 1.26 (8H, m), 0.86 (3H, t, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 99.9, 55.0, 49.2, 35.1 (2), 31.7, 26.4, 25.5, 24.8, 23.5, 22.5, 14.0; *anal.* C 49.67%; H 7.88%, calcd for $C_{13}H_{24}NOCl_3$, C 49.51%, H 7.68%; EIMS m/z 282 (30), 280 (40), 274 (73), 246 (38), 244 (41), 213 (50), 204 (39), 202 (42), 168 (14), 166 (13), 143 (44), 142 (50), 137 (25), 135 (17), 128 (12), 122 (12), 120 (34), 119 (16), 118 (36), 117 (16), 114 (27), 101 (53), 100 (100), 98 (13), 97 (11).

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