Marine Alkaloids. 18. Securamines and Securines, Halogenated Indole-Imidazole Alkaloids from the Marine Bryozoan *Securiflustra securifrons*[1]

Lisa Rahbaek, Uffe Anthoni, Carsten Christophersen,* Per H. Nielsen, and Bent O. Petersen[†]

Marine Chemistry Section, University of Copenhagen, The H. C. Ørsted Institute, Universitetsparken 5, DK-2100 Copenhagen, Denmark, and Carlsberg Laboratory, Department of Chemistry, Gamle Carlsberg Vej 10, DK-2500 Valby, Denmark

Received August 18, 1995[⊗]

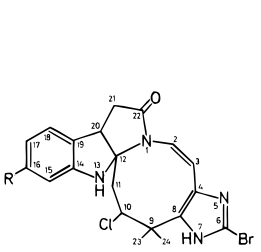
Four halogenated indole-imidazole alkaloids, securamine A−D, have been isolated from the marine bryozoan *Securiflustra securifrons* and their structures determined by NMR and mass spectrometry. Securamine A and B are in equilibrium with two macrocyclic alkaloids, securine A and B, respectively.

Introduction

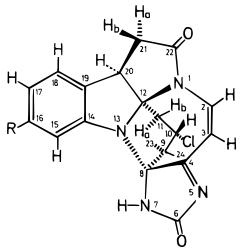
Bryozoans of the family Flustridae (*Flustra foliacea* (L.)[2,3] and *Chartella papyracea* (Ellis and Solander)[4]) have proven a rich source of unusual indole alkaloids. This report deals with the isolation and structure elucidation of unprecedented types of indole alkaloids from another member of this family, *Securiflustra securifrons* (Pallas). So far six alkaloids, securamine A (**1**), B (**2**), C (**3**), D (**4**) and securine A (**5**) and B (**6**) have been subjected to structure determination. Securamine A (**1**) and B (**2**) only differ in the presence or absence of a bromine substitution in the benzene ring as do C (**3**) and D (**4**). Securine A (**5**) and B (**6**) were obtained by dissolving securamine A (**1**) and B (**2**), respectively, in DMSO-d_6. All alkaloids, **1**−**6**, are composed of modified tryptamine, histamine, and isoprene units and **3** and **4** can formally be derived from **1** and **2** by attack of the indole nitrogen at position 8 in the imidazole ring.

Results and Discussion

The bryozoans were collected in March and July 1994 in the North Sea. Fractionation by column chromatography of the crude EtOAc extract of lyophilized material afforded pure securamine A (**1**), B (**2**), C (**3**), and D (**4**) all crystallizing (^{1}H NMR) with 1 or 2 molecules of ethyl acetate. The elemental compositions of **1** ($C_{20}H_{20}N_4OBrCl$) and **2** ($C_{20}H_{19}N_4OBr_2Cl$) were determined from the isotopic pattern of the molecular ion and HRMS on the base peaks derived by loss of HCl from the molecular ion while those of **3** ($C_{20}H_{18}N_4O_2BrCl$) and **4** ($C_{20}H_{19}N_4O_2Cl$) were determined from the isotopic pattern of the molecular ions and peak matching of the base peaks derived by loss of Cl from the molecular ion. From the ^{1}H (Table 1) and ^{13}C (Table 2) NMR spectra it was evident that **2** and **3** differ from **1** and **4**, respectively, solely by the presence of a bromine substituent in the benzene ring in the formers and only the results for **1** and **3** will be discussed in detail.



R = H: Securamine A (1)
R = Br: Securamine B (2)



R = Br: Securamine C (3)
R = H: Securamine D (4)

The presence of an amide group (β-lactam and/or vinylic) in **1** revealed itself from the carbonyl stretching frequency at 1694 cm^{-1} (KBr) in the infrared spectrum and a ^{13}C signal at δ 172.8. The proton spectra ($CDCl_3$) exhibited signals assigned (APT, COSY, extensive decoupling experiments) as originating from an ortho disubstituted benzene (H15 to H18), two CH_2CH ABX systems (H10−H11, H20−H21), a *cis* substituted double bond (H2−H3), two methyl groups at quaternary positions (H23 and H24), and two exchangeable protons (N7−H and N13−H). The carbon resonances associated with the proton signals were identified from HETCOR experiments. Most of the structure of **1** could now be assigned from HMBC experiments. The coupling from H21b to C20, C12, C19, C22 and from H21a to C20, C19, C22 interconnects the pyrroline and the pyrrolidine rings. These are further connected to the benzene ring by the coupling between H18 and C16, C14, between H17 and C15, C19, and between H16 and C18, C14. Coupling from H11b to C12, C10, C20, and C9 serves to localize the isoprene unit at C12. Coupling is observed from CH_3 (δ_H 1.38) to C23, C9, C10, C8 and from CH_3 (1.62) to C24, C9, C10, and C8, establishing the fragment C8−C9Me$_2$−C10. The attachment of the 2,3-double bond to N1 was inferred from NOE experiments (H1 to H2 and vice versa) on **5** (see below). Further support for the assignment was derived from NOESY experiments. From the molecular formula it is evident that the C2−C3 double bond and the C9−C11 isoprene fragment must be connected either through a brominated imidazole or pyrazole ring. However, the ^{13}C values found for C4, C6, and C8 are only compatible with the first alternative, thus establishing the structure of **1**.

[†] Carlsberg Laboratory.

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) For part 17 see Jensen, J.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1995**, *49*, 68.

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Table 1. ^{1}H NMR Assignments for Securamine A (1), B (2), C (3), D (4) and Securine A (5) and B (6)

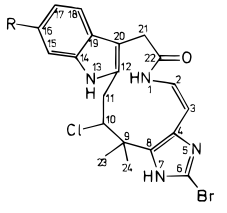
no.	1	2	3	4	5	6
1					9.15 (d, 9.6)	9.27 (d, 9.9)
2	7.04 (br d, 8)	6.98 (br d, 10)	7.49 (d, 10.5)	7.37 (d, 10.5)	6.90 (dd, 8, 9.6)	6.91 (dd, 8.1, 9.9)
3	5.52 (br d, 8)	5.51 (br d, 10)	5.93 (d, 10.5)	5.78 (d, 10.5)	5.71 (d, 8)	5.73 (d, 8.1)
7	9.20 (br)	10.1 (br s)	7.25 (br, s)	7.00 (br s)	9.21	*a*
10	5.02 (br d, 11)	4.94 (br d, 10.1)	4.74 (dd, 11.9, 5.3)	4.65 (dd, 12, 5)	4.14 (br)	4.09 (dd, 12.3, 2)
11a	2.93 (br dd, 15.6, 11.0)	2.89 (br dd, 15.7, 11.2)	2.68 (dd, 13.3, 11.9)	2.59 (dd, 13, 12)	3.33 (dd, 14.9, 2.8)	3.33 (dd, 14.7, 2)
11b	2.72 (dd, 15.6, 1.8)	2.66 (dd, 15.6, 1.7)	2.65 (dd, 13.3, 5.3)	2.55 (dd, 13, 5)	2.84 (dd, 14.9, 12.2)	2.85 (dd, 14.7, 12.3)
13	3.4 (br)	3.6 (br s)			10.75	11.0
15	6.31 (br d, 7.8)	6.40 (br d, 1.5)	6.95 (d, 1.6)	6.73 (d, 8)	7.27 (br d, 7.8)	7.45 (d, 1.83)
16	7.07 (dd, 7.8, 7.8)			7.00 (dd, 8, 8)	7.00 (dd, 7.8, 7.8)	
17	6.78 (dd, 7.8, 7.8)	6.85 (dd, 7.9, 1.5)	7.05 (dd, 1.6, 7.9)	6.85 (dd, 8, 7)	6.95 (dd, 7.8, 7.8)	7.08 (dd, 8.4, 1.83)
18	7.02 (d, 7.8)	6.82 (d 7.9)	6.98 (d, 7.9)	7.05 (d, 7)	7.48 (d, 7.8)	7.46 (d, 8.4)
20	3.59 (br d, 8.5)	3.47 (br d, 7.7)	3.70 (d, 7.1)	3.65 (d, 7)		
21a	3.07 (dd, 17.8, 8.5)	3.02 (dd, 17.8, 8.4)	3.10 (dd, 18.1, 7.1)	2.89 (d, 18.1)	3.43 (br d, 13.5)	3.43 (d, 13.4)
21b	2.88 (d, 17.8)	2.79 (d, 17.9)	2.96 (d, 18.1)	3.00 (dd, 18.1, 7)	3.77 (br d, 13.5)	3.77 (d, 13.4)
23	1.62 (s)	1.58 (s)	1.45 (s)	1.36 (s)	1.45 (s)	1.45 (s)
24	1.38 (s)	1.33 (s)	1.09 (s)	1.01 (s)	1.28 (s)	1.29 (s)

[a] Very broad signal and not discernible from the signal from traces of water in the solvent, DMSO-d_6. The spectra were recorded in the following solvents and at the following frequencies; the position of the signals are given relative to the position of the solvent signals in parentheses: **1**, 500 MHz, $CDCl_3$ (δ 7.30); **2**, 400 MHz, $CDCl_3$ (δ 7.26); **3**, 500 MHz, $CDCl_3$ (δ 7.30); **4**, 400 MHz, $CDCl_3$ (δ 7.19); **5**, 500 MHz, DMSO-d_6 (δ 2.50); **6**, 400 MHz, DMSO-d_6 (δ 2.50). In the case of 11a and 11b the assignments may be interchanged in **2** and **5** as is also the case for 21a and 21b in **5**.

Table 2. ^{13}C NMR Assignments for Securamine A (1), B (2), C (3), D (4) and Securine A (5) and B (6)[a]

no.	1	2	3	4	5	6
2	127.4 br	127.1 br	135.9	136.1	130.2	130.3
3	95.1 br	95.3	101.6	101.2	100.9	103.6
4	115.8	116.0	187.5	188.0	121.1	121.5
6	122.5	121.1	166.6	166.7	125.0	127.6
8	145.5	144.8	85.6	85.7	135.6	135.3
9	41.6 br	41.9	44.0	43.9	40.6	40.8
10	64.9	64.6	59.4	59.5	71.2	70.9
11	48.6	48.3	41.8	41.7	30.8	30.8
12	87.4	87.4	89.2	89.1	132.7	133.9
14	147.0	148.0	147.0	145.7	134.4	134.5
15	109.3	112.2	114.7	111.1	110.9	113.2
16	129.0	122.3	123.1	129.4	120.5	114.1
17	119.9	122.5	124.9	121.9	118.1	119.4
18	123.9	125.0	125.6	124.6	117.5	121.1
19	127.8	126.7	128.0	128.8	128.5	126.0
20	50.0	49.4	45.0	45.3	105.7	106.3
21	34.1	33.8	34.2	34.4	30.7	30.6
22	172.8	172.2	170.3	170.5	169.4	169.1
23	19.0	18.9	17.2	17.3	19.8	19.8
24	31.9	31.8	21.1	21.1	28.7	28.7

[a] The spectra were recorded in the following solvents and at the following frequencies; the position of the signals are given relative to the position of the solvent signals in parentheses: **1**, 125.7 MHz, $CDCl_3$ (δ 77.0); **2**, 100.6 MHz, $CDCl_3$ (δ 76.9); **3**, 125.7 MHz, $CDCl_3$ (δ 77.0); **4**, 100.6 MHz, $CDCl_3$ (δ 76.9); **5**, 125.7 MHz, DMSO-d_6 (δ 39.6); **6**, 100.6 MHz, DMSO-d_6 (δ 39.6).



R = H: Securine A (5)
R = Br: Securine B (6)

In the case of securamine C (**3**) the ^{13}C signals at δ 166.6 and 170.3 indicated the presence of two amide carbonyls. The proton spectra of **3** exhibited signals assigned (APT, COSY, HETCOR) as originating from two CH_2CH ABX systems (H10−H11, H20−H21), a *cis* substituted double bond (H2−H3), two methyl groups at quarternary positions (C23 and C24), one exchangeable proton (N7−H), and a 1,2,4-trisubstituted benzene (C15, C17, and C18) where δ_C 147.0 (C14) indicates the site of attachment of N13. The connectivity between the fragments was established from COLOC experiments. The long-range couplings from H18 to C14, C16 and C17, from H20 to C19 and C22, from H21a to C12 and C22, and from H21b to C19 interconnect the pyrrolidine ring with the indoline system. Coupling from H11a to C12 connects the CH_2 from the CH_2CH moiety (C10−C11) with C12. The presence of an isoprene unit (C9−C11, C23, and C24) was established by the couplings from H10 to C23 and C24, from H23 to C9, C10 and C24, and from H24 to C9, C10, and C23. Finally the coupling from H2 to C12 connects the double bond to N1. This leaves one carbonyl (C6), two quarternary carbons (one sp^3 (C8) and one sp^2-hybridized (C4)), one NH group, and one nitrogen atom consistent with an imidazolone or pyrazolone ring. Long-range couplings from H3 to C8, from H7 to C4 and C8, from H23 to C8, and from H24 to C8 together with NOE interaction from H7 to H15 are only consistent with an imidazolone ring. NOESY experiments confirmed the structure. NOE interactions from H2 to H10, from H7 to H15, and from H21a to H11b establish the relative stereochemistry of **3** and **4** as 8*S**,10*S**,12*R**,20*R**. None of the formulas **1**−**6** are intended to depict absolute stereochemistry.

Synthetic congeners of the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole ring system unsubstituted at the 3a position are known to be in equilibrium with the corresponding indole precursor.[5] A similar reaction was observed when securamine A and B were kept in DMSO solution. The resulting compounds, securine A (**5**) and securine B (**6**), encompass a macrocyclic lactam based on the aza-4,9,11-cyclododecatrien-2-one skeleton. The structure of **5** was inferred from HMBC and NOESY experiments and **6** by comparison with the data of **5**.

Biogenetically the securamines are composed of modified tryptamine and histamine residues linked via an isoprene unit to form the central aza-2,4-cyclononadiene ring system. It is noteworthy that the securamines combine the structural features of the flustramines from *F. foliacea* (the 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole ring system) as well as some from the chartellines

(5) See *e.g.* Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Pedersen, E. J. *Acta Chem. Scand.* **1994**, *48*, 91.

from *C. papyracea* (the modified histamine unit and an isoprene-containing macrocyclic ring system). Actually, the securines could act as precursor for the chartellines as well as for the securamines. In the former case attack of the amide nitrogen at the indole 3 position followed by loss of a proton would generate the chartelline skeleton, while in the latter case protonation at the indole 3 position followed by attack of the amide nitrogen at the indole 2 position would generate the securamine A skeleton. Except for debromoflustramine B, which was detected in trace amounts in *F. foliacea*,[3] securamine A and D are the first alkaloids from this family of bryozoans lacking bromo-substitution in the aromatic part of the indole unit.

The bryozoan material collected in March and July 1994 differs in the abundance (% of dry weight) of securamine A (March: 0.13%, July: 0.014%), whereas the remaining alkaloids are present in comparable amounts: Securamine B (March: 0.022%, July: 0.052%), C (March: 0.058%, July: 0.075%) and D (March: 0.047%, July: ca 0.02%). The variation observed is compatible with securamine A functioning as a precursor for the other alkaloids.

Experimental Section

Isolation and Purification. The bryozoans were collected twice (March and July, 1994) at a depth of 70−75 m in the North Sea near Harboøre Tange at the Danish west coast and kept frozen until lyophilization.

The lyophilized material was extracted with EtOAc, EtOH, and water successively. The EtOAc extract was subjected to purification by silica gel chromatography. The first collection (250 g wet weight, 38 g dry weight) on extraction with EtOAc (4 × 500 mL) gave 730 mg of crude extract. This was purified by liquid chromatography (Lobar LiChroprep Si 60 (40−63 μm) size B from Merck, EtOAc/heptane 1:1, UV detection at 270 nm) giving eight fractions. One of these fractions was chromatographed with 35:5:60 EtOAc/EtOH/heptane as eluent to give **1** (50 mg). A second fraction (30:5:65 EtOAc/$CHCl_3$/heptane) gave **2** (8 mg). Further separation of a third fraction from the first separation using HPLC (LiChroCART 250-10 LiChrospher Si 60 (10 μm) from Merck, EtOAc/EtOH/heptane 50:5:45, UV detection at 254 nm) gave 21 mg **3** and 17 mg **4**.

The second collection (1200 g wet weight, 185 g dry weight) on extraction with EtOAc (4 × 2400 mL) gave 3.65 g of extract. An 840 mg amount was initially separated (Lobar LiChroprep Si 60 (40−63μm) size B from Merck, EtOAc/heptane 1:1, UV detection at 270 nm) to give several fractions among which one gave 32 mg of **3** and another 8 mg of slightly impure **4**. A third fraction was further chromatographed, one fraction (30:5:65 EtOAc/$CHCl_3$/heptane) giving pure **1** (6 mg) and a fourth fraction with EtOAc/heptane 3:7, followed by 1:4 yielding **2** (22 mg).

Securamine A (**1**): colorless crystals; mp > 200 °C dec; IR (KBr) 3425, 1694; $[\alpha]^{20}_D$ −87.5° (*c* 0.064, $CHCl_3$); UV λ_{max} ($CHCl_3$) nm (log ϵ) 269 (3.97); CD, λ_{ext} (*c* 0.064, $CHCl_3$) nm ($\Delta\epsilon$) 234 (−9.42) 260 (5.09) 285 (−7.91) 310 (0.75); HREIMS $M^+ - HCl$, *m/z* 410.0737 ($C_{20}H_{19}{}^{79}BrN_4O$ Δ −1.3 ppm); ^1H and ^{13}C NMR see Tables 1 and 2.

HMBC Data for Securamine A (1) in $CDCl_3$ (600 MHz). CH_3 (δ_H 1.38) exhibits long-range couplings with δ_C 41.6, 64.9, 19.0, 145.5; CH_3 (1.62) with 41.6, 64.9, 31.9, 145.5; CH (2.88) with 172.8, 127.8, 50.0, 87.4; CH (3.07) with 172.8, 127.8, 50.0; CH (7.02) with 147.0, 129.0; CH (6.78) with 109.3, 127.8; CH (7.07) with 147.0, 123.9; CH (2.72) with 87.4, 64.9, 50.0, 41.6.

NOESY Data of 1 in $CDCl_3$ (600 MHz). Cross peaks were observed between protons of CH_3 (δ 1.38) and δ 5.02 (strong), 5.52 (weak); CH_3 (1.62) and 2.93 (s); CH (2.88) and 7.02 (s), 3.59 (w); CH (3.07) and 3.59 (s), 2.72 (medium); CH (3.59) and 2.88 (w), 3.07 (s), 7.02 (w), 2.72 (s), 2.93 (w); CH (7.02) and 2.88 (s), 3.59 (w), 6.78 (s); CH (6.78) and 7.02 (s), 7.07 (s); CH (7.07) and 6.78 (s), 6.31 (s); CH (6.31) and 7.07 (s); CH (2.72) and 3.07 (s), 3.59 (s), 1.62 (s), 3.59 (w), 5.02 (s); CH (5.02) and 1.38 (s), 2.93 (s); CH (5.52) and 1.38 (w), 7.04 (s); CH (7.04) and 5.52 (s).

Securamine B (**2**): colorless crystals; $[\alpha]^{20}_D$ −316.7° (*c* 0.030, $CHCl_3$); UV λ_{max} ($CHCl_3$) nm (log ϵ) 269 (4.23); CD, λ_{ext} (*c* 0.030, $CHCl_3$) nm ($\Delta\epsilon$) 232 (−35.09) 261 (−7.82) 280 (−24.18); HREIMS $M^+ - HCl$, *m/z* 487.9834 ($C_{20}H_{18}{}^{79}Br_2N_4O$ Δ −2.7 ppm); ^1H and ^{13}C NMR see Tables 1 and 2.

Securamine C (**3**): amorphous yellow solid; IR (KBr) 3441, 1733, 1616; $[\alpha]^{20}_D$ −433.5° (*c* 0.033, $CHCl_3$); UV λ_{max} ($CHCl_3$) (log ϵ) 249 (4.09) 299 (4.06) 327 (4.10); CD (*c* 0.033, $CHCl_3$) nm ($\Delta\epsilon$) 247 (−16.04) 272 (10.14) 289 (15.80) 316 (−23.11); EIHRMS $M^+ - Cl$, *m/z* 425.0611 ($C_{20}H_{18}O_2N_4{}^{79}Br$ Δ −0.6 ppm); ^1H and ^{13}C NMR data see Table 1 and 2.

NOESY Data of 3 in $CDCl_3$ (250 MHz). NOE effects were observed between CH (δ 7.49) and 4.74 (medium); CH (5.93) and 1.09 (m); NH (7.25) and 6.95 (m), 1.45 (strong) and 1.09 (weak); CH (4.74) and 7.49 (m) and 1.09 (s); CH (2.68) and 3.70 (s) and 1.45 (s); CH (2.65) and 3.70 (s) and 3.10 (m); CH (3.70) and 2.68 (s), 2.65 (s) and 6.98 (s); CH (3.10) and 2.65 (m); CH (2.96) and 6.98 (s); CH_3 (1.45) and 7.25 (s) and 2.68 (s); CH_3 (1.09) and 5.93 (m), 7.25 (w) and 4.74 (s).

COLOC Data of 3 in $CDCl_3$ (62.9 and 100.6 MHz, parameters were optimized for J_{CH} = 6.25, 7, and 15 Hz). Long-range couplings were observed from H2 to C3 and C12, from H3 to C2 and C8, from H7 to C4 and C8, from H10 to C11, C23 and C24, from H11a to C10 and C12, from H15 to C17, from H18 to C14, C16 and C17, from H20 to C19 and C22, from H21a to C12 and C22, from H21b to C19, from H23 to C8, C9, C10 and C24, and from H24 to C8, C9, C10 and C23.

Securamine D (**4**): amorphous green solid, $[\alpha]^{20}_D$ −320.0° (*c* 0.069, $CHCl_3$); UV λ_{max} ($CHCl_3$) (log ϵ) 293 (3.91) 327 (3.96); CD (*c* 0.069, $CHCl_3$) nm ($\Delta\epsilon$) 243 (−11.75) 271 (6.55) 286 (8.49) 322 (−10.82); HREIMS $M^+ - Cl$, *m/z* 347.1497 ($C_{20}H_{19}O_2N_4$ Δ −3.1 ppm); ^1H and ^{13}C NMR data see Tables 1 and 2.

Securine A (**5**). When securamine A was dissolved in DMSO-d_6 a pronounced change took place in the appearence of the NMR spectra signifying a conversion of **1** to another compound. On concentration followed by redissolving in $CDCl_3$ the original spectrum reappeared. For ^1H and ^{13}C NMR assignments see Tables 1 and 2.

HMBC Data for 5 in DMSO-d_6 (600 MHz). CH_3 (δ_H 1.28) exhibits long-range couplings with δ_C 40.6, 71.2, 19.8; CH_3 (1.45) with 40.6, 71.2, 28.7; CH (3.77) with 132.7, 105.7; CH (3.43) with 132.7, 105.7; CH (7.48) with 134.4, 120.5; CH (6.95) with 110.9, 128.5; CH (7.00) with 134.4, 117.5; CH (7.27) with 118.1, 128.5; NH (10.75) with 128.5, 105.7, 132.7, 134.4; CH (2.84) with 132.7, 105.7.

NOESY Data of 5 in DMSO-d_6 (600 MHz). Cross peaks were observed between protons of CH_3 (δ 1.28) and 4.14 (strong), 5.71 (s); CH_3 (1.45) and 2.84 (s); CH (3.77) and 7.48 (s), 9.15 (s); CH (7.48) and 6.95 (s), 3.77 (s); CH (6.95) and 7.00 (s), 7.48 (s); CH (7.00) and 7.27 (s), 6.95 (s), CH (7.27) and 10.75 (s), 7.00 (s); NH (10.75) and 7.27 (s); CH (2.84) and 1.45 (s); CH (3.33) and 4.14 (weak), 9.15 (w); CH (4.14) and 3.33 (w), 1.28 (s); CH (9.21) and 1.28 (medium); CH (5.71) and 6.90(s), 1.28 (s); CH (6.90) and 9.15 (m), 5.71 (s); NH (9.15) and 3.77 (s), 6.90 (w), 3.33 (w).

Securine B (**6**). Securamine B treated as described above for securamine A gave analogous findings. For ^1H and ^{13}C NMR assignments see Tables 1 and 2.

Acknowledgment. We are pleased to acknowledge the generous gift of the bryozoan material from Dr. N. Jacobsen, and Dr. M. Pereira for the taxonomic classification of the material. The project was carried out with financial support from the Danish Biotechnology Programme 1991−1995. We are indebted to Dr. S. E. Harnung for determination of CD data measured on a modifed Jasco 710 instrument financed by the Danish Natural Science Research Council, Grant No.//-0373-1.

JO951527A