Acta Chemica Scandinavica, 1995: 49: 68–71
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Marine Alkaloids. 17. Synthesis of (±)-Debromoflustramide B and E and (±)-Debromoflustramine B and E

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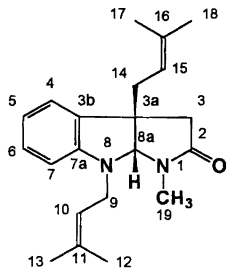
Jensen, J., Anthoni, U., Christophersen, C. and Nielsen, P. H., 1995. Marine alkaloids. 17. Synthesis of (±)-Debromoflustramide B and E and (±)-Debromoflustramine B and E. – Acta Chem. Scand. 49: 68–71 © Acta Chemica Scandinavica 1995.

(±)-Debromoflustramide B, (±)-debromoflustramine B, (±)-debromoflustramide E and (±)-debromoflustramine E have been synthesized and characterized. In addition a dimer of (±)-debromoflustramide B, 1,1′-dimethyl-3a,3a′-di(3-methylbut-2-enyl)-8,8′-(3,3,4,4-tetramethylhexa-1,5-dienylidene)bis{3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one} has been isolated and characterized. The spectroscopic properties are reported for all compounds.

Flustramide B and flustramine B and E are 6-bromoindole alkaloids isolated from the marine bryozoan *Flustra foliacea* (L).[1–3] We now wish to report a facile synthesis of the racemic debromoanalogues, (±)-1-methyl-3a,8-di-(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]-indol-2(1*H*)-one (**1**), (±)-1-methyl-3a,8-di(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**2**) and (±)-1-methyl-3a-(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**4**). In addition (±)-1-methyl-3a-(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo-[2,3-*b*]indole-2(1*H*)-one (**3**) has been synthesized.



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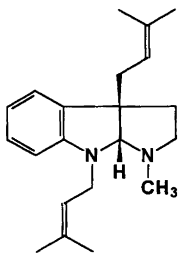

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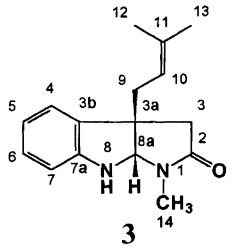

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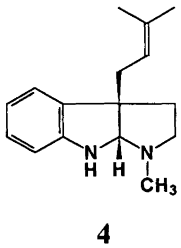

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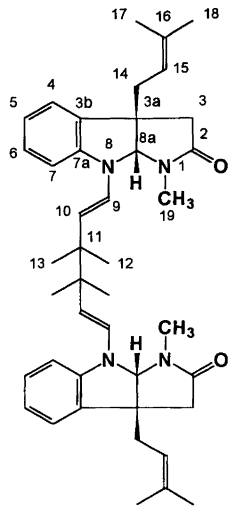
Electrophilic attack on indole derivatives occurs at the 3-position and generates an electrophilic center at the 2-position. Thus, with indole derivatives carrying a nucleophilic group located γ to the 3-position, reaction with electrophiles causes cyclisation to tricyclic derivatives with the electrophile occupying the 3a position. This reaction was the basis for an earlier synthesis of (±)-debromoflustramine B.[4]

In accordance with expectations the methylamide of indol-3-ylacetic acid on reaction with 1-bromo-3-methyl-2-butene (γ,γ-dimethylallyl bromide) gave a fair yield of debromoflustramide B (**1**) along with a dimer, 1,1′-dimethyl-3a,3a′-di(3-methyl-2-butenyl)-8,8′-(3,3,4,4-tetramethylhexa-1,5-dienylidene)bis{3,3a,8,8a-tetrahydropyrrolo-



5

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Table 1. ^{1}H and ^{13}C NMR data of debromoflustramide B and debromoflustramine B.[a]

	Debromoflustramide B			Debromoflustramine B		
Position	^{1}H δ	$J_{H/H}$/Hz	^{13}C δ	^{1}H δ	$J_{H/H}$/Hz	^{13}C δ
2			172.8	2.05 (1 H,ddd)	$J_{2,2'}=11.9$ $J_{2,3}=6.6$ $J_{2,3'}=9.1$	52.7
2′				1.90 (1 H,ddd)	$J_{2',3}=3.4$ $J_{2',3'}=5.9$	
3	2.67 (2 H,s)		41.6	2.66 (1 H,ddd)	$J_{3,3'}=9.3$	38.9
3′				2.56 (1 H,ddd)		
3a			49.7			57.0
3b			135.3*			135.3 #
4	7.01 (1 H,d)	$J_{4,5}=7.5$	122.9	6.96 (1 H,d)	$J_{4,5}=7.3$	122.7
5	6.73 (1 H,dd)	$J_{5,6}=7.5$	118.8	6.64 (1 H,dd)	$J_{5,6}=7.5$	117.3
6	7.10 (1 H,dd)		128.3	7.03 (1 H,dd)		127.4
7	6.52 (1 H,d)	$J_{6,7}=7.7$	108.7	6.41 (1 H,d)	$J_{6,7}=7.9$	107.2
7a			149.0			151.7
8a	4.71 (1 H,s)		87.2	4.25 (1 H,s)		91.4
9	3.98 (1 H,dd)	$J_{9,9'}=15.7$ $J_{9,10}=6.2$	46.9	3.92 (1 H,dd)	$J_{9,9'}=16.0$ $J_{9,10}=5.7$	46.7
9′	3.90 (1 H,dd)	$J_{9',10}=6.9$		3.80 (1 H,dd)	$J_{9',10}=7.2$	
10	5.23 (1 H,dd)		120.6	5.17 (1 H,dd)		121.4
11			135.1*			133.9 #
12	1.73 (3 H,s)		17.8	1.53 (3 H,s)		18.0
13	1.73 (3 H,s)		25.4	1.71 (3 H,s)		25.8
14	2.37 (2 H,m)		37.4	2,42 (2 H,m)		38.4
15	4.99 (1 H,dd)	$J_{14,15}=6.8$	118.3	4.79 (1 H,dd)	$J_{14,15}=7.6$	120.7
16			135.0*			133.3 #
17	1.69 (3 H,s)		17.8	1.65 (3 H,s)		17.9
18	1.56 (3 H,s)		25.7	1.70 (3 H,s)		25.6
19	2.87 (3 H,s)		27.6	2.48 (3 H,s)		37.9

[a] Spectra measured at 400 MHz (^{1}H) and 100 MHz (^{13}C) for samples in $CDCl_3$ relative to internal TMS δ=0.00. Assignments confirmed by C–H heterocorrelated spectroscopy. Those assignments marked with identical symbols may be interchanged.

[2,3-*b*]indol-2(1*H*)-one} (**5**). Reduction of **1** and **3** with excess lithium aluminum hydride gave **2** and **4**, respectively, in good yields.

The NMR (^{1}H and ^{13}C) data, for **1–4** presented in Tables 1 and 2, were assigned with the aid of C,H heterocorrelated spectroscopy. NOE difference spectroscopy served to establish the *cis* junction in **1** and **3** of the two five-membered rings (a small effect, less than 1% enhancement of the H-8a signal on saturation of the signal originating from H-14 for **1** and a 5% enhancement of the H-8a signal on saturation of the signal originating from H-9 for **3**). Since the products are racemic mixtures none of the structures **1–5** are intended to depict absolute configuration. The structure of **5** was deduced from the mass spectrum which exhibited the molecular ion at *m/z* 646 and a signal at *m/z* 323 with an isotope pattern excluding a doubly charged molecular ion. The ^{1}H NMR spectrum (Table 3) showed a singlet at 4.80 ppm originating from H-8a and an upfield shift of the aromatic protons relative to the starting material characteristic of cyclized indole derivatives. Two doublets at 5.93 and 5.42 ppm, respectively, with a mutual coupling constant of 16.2 Hz demonstrated the presence of a *trans*-disubstituted double bond indicating rearrangement and/or migration of the isoprene double bond. Considering the symmetric dimeric nature of the compound and the remaining signals in the proton NMR spectrum the only possible structure is that of **5**. Whether **5** is a racemic mixture or the *meso* form has not been determined.

Experimental

The ^{1}H (400 MHz and 250 MHz) and ^{13}C (100.6 MHz) spectra were recorded on a Varian XL-400 and a Bruker 250 AM spectrometer, respectively. The mass, UV, and IR spectra originate from JEOL JMS-HX/HX110A, Perkin Elmer Lambda 17 and Perkin Elmer FT-IR 1760x instruments, respectively.

(±)-1-Methyl-3a,8-di(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1H)-one (**1**), *(±)-1-methyl-3a-(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-2(1H)-one* (**3**) *and 1,1′-dimethyl-3a,3a′-di(3-methyl-2-butenyl)-8,8′-(3,3,4,4-tetramethylhexa-1,5-dienylidene)-bis{3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1H)-one}* (**5**). The γ,γ-dimethylallyl bromide used was prepared by suspending CuBr (6 g) in hydrobromic acid (70 ml; 47%) in a separatory funnel. Isoprene (42 ml) was added and the mixture was shaken vigorously for 10 min. The organic layer was dried over K_2CO_3 and $CaCl_2$ and successively distilled twice at 100 mmHg (b.p. 65–70°C) to yield 22 g

Table 2. ^1H and ^{13}C NMR data of debromoflustramide E and debromoflustramine E.[a]

	Debromoflustramide E			Debromoflustramine E		
Position	^1H δ	$J_{H/H}$/Hz	^{13}C δ	^1H δ	$J_{H/H}$/Hz	^{13}C δ
2			172.2	2.70 (1 H,ddd)	$J_{2,2'}=9.0$ $J_{2,3}=6.8$ $J_{2,3'}=4.0$	52.2
2′				2.60 (1 H,ddd)	$J_{2',3}=8.7$ $J_{2',3'}=6.1$	
3	2.66 (2 H,s)		41.2	2.12 (1 H,ddd)	$J_{3,3'}=12.2$	38.5
3′				1.96 (1 H,ddd)		
3a			50.5			57.8
3b			134.2*			135.2 #
4	7.04 (1 H,d)	$J_{4,5}=7.7$	122.9	7.03 (1 H,d)	$J_{4,5}=7.5$	123.1
5	6.74 (1 H,dd)	$J_{5,6}=7.5$	119.1	6.72 (1 H,dd)	$J_{5,6}=6.3$	118.7
6	7.02 (1 H,dd)		128.0	7.02 (1 H,dd)		127.4
7	6.58 (1 H,d)	$J_{6,7}=7.6$	110.0	6.58 (1 H,d)	$J_{6,7}=7.7$	108.9
7a			147.4			149.8
8a	4.90 (1 H,s)		81.5	4.44 (1 H,s)		86.6
9	2.40 (1 H,dd)	$J_{9,9'}=14.5$ $J_{9,10}=8.0$	36.3	2.46 (2 H,d)	$J_{9,10}=6.6$	37.8
9′	2.31 (1 H,dd)	$J_{9',10}=6.8$				
10	5.06 (1 H,dd)		118.0	5.04 (1 H,t)		120.1
11			135.0*			133.8 #
12	1.53 (3 H,s)		17.6	1.58 (3 H,s)		18.0
13	1.68 (3 H,s)		25.4	1.66 (3 H,s)		25.8
14	2.78 (2 H,m)		26.1	2.46 (3 H,s)		36.7

[a] Spectra measured at 400 MHz (^1H) and 100 MHz (^{13}C) for samples in $CDCl_3$ relative to internal TMS δ=0.00. Assignments confirmed by C–H heterocorrelated spectroscopy. Those assignments marked with identical symbols may be interchanged.

(35%) γ,γ-dimethylallyl bromide. γ,γ-Dimethylallyl bromide (23.9 mmol) was added dropwise to a stirred solution of the methylamide of indol-3-ylacetic acid[5] (7.98 mmol) in 47 ml acetate buffer (glacial acetic acid 50 ml, water 5 ml, sodium acetate 2 g) in a nitrogen atmosphere. The reaction was stirred for 20 h at room temperature, after which water (75 ml) was added and the mixture was extracted with diethyl ether (3 × 50 ml). Drying ($MgSO_4$) and evaporation of the ether phase left 2.908 g of crude product as a brown oil. Column chromatography (silica gel, Lobar, Merck) with ethyl acetate–heptane–methanol (15:5:1) as the eluent resulted in the isolation of pure **1** (991 mg, 38%) and **3** (486 mg, 28%) as yellow oils. A fraction eluting in between **1** and **3**, on evaporation, gave a yellow oil. Trituration of this with ethyl acetate afforded **5** (176 mg, 7%) as a white solid.

1. MS [E 70 eV; *m/z* (% rel. int.)] 324 (94, M^+), 255 (50, $M^+ - C_5H_9$), 198 (30, $M^+ - C_7H_{12}NO$), 187 (100, $M^+ - C_{10}H_{17}$), 130 (53, $M^+ - C_{12}H_{20}NO$), 69 (46, $M^+ - C_{16}H_{19}N_2O$). UV [abs. ethanol (log ε)] 204 (3.98), 246 (3.45), 285 (3.00) nm. IR (KBr): 3332 (w), 2968 (s), 2916 (s), 2859 (m), 1695 (vs) ($\nu_{C=O}$ in five-membered lactam), 1606 (s), 1489 (vs), 744 (s) (1,2-disubstituted benzene) cm^{-1}. NMR data are given in Table 1.

3. MS [E 70 eV; *m/z* (% rel. int.)] 256 (41, M^+), 187 (67, $M^+ - C_5H_9$), 130 (100, $M^+ - C_7H_{12}NO$). UV [abs. ethanol (log ε)] 203 (4.48), 243 (3.79), 295 (3.42) nm. IR (KBr): 3310 (s), 2960 (m), 2910 (s), 1670 (vs) ($\nu_{C=O}$ in five-membered lactam), 1605 (s), 1480 (vs), 740 (s) (1,2-

Table 3. ^1H and ^{13}C NMR data of 1,1′-dimethyl-3a,3a′-di(3-methyl-2-butenyl)-8,8′-(3,3,4,4-tetramethylhexa-1,5-dienylidene)bis{3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one} (**5**).

Position	^1H δ	$J_{H/H}$/Hz	^{13}C δ
2			172.7
3	2.76 (2 H,d)	$J_{3,3'}=16.5$	40.9
3′	2.51 (2 H,d)		
3a			55.2
3b			134.9*
4	7.02 (2 H,d)	$J_{4,5}=7.2$	124.6
5	6.75 (2 H,t)	$J_{5,6}=7.6$	119.5
6	7.08 (2 H,t)		128.4
7	6.66 (2 H,d)	$J_{6,7}=7.9$	109.6
7a			146.5
8a	4.80 (2 H,s)		90.3
9	5.93 (2 H,d)	$J_{9,10}=16.2$	142.4
10	5.42 (2 H,d)		124.9
11			41.3
12»	1.06 (6 H,s)		22.4
13»	1.05 (6 H,s)		23.9
14	2.19 (4 H,m)		34.5
15			118.8
16			133.3*
17	1.37 (6 H,s)		17.9
18	1.68 (6 H,s)		24.9
19	2.68 (6 H,s)		25.9

[a] Spectra measured at 400 MHz (^1H) and 100 MHz (^{13}C) for samples in $CDCl_3$ relative to internal TMS δ=0.00. Assignments confirmed by C–H heterocorrelated spectroscopy. Those assignments marked with the same symbol may be interchanged.

disubstituted benzene) cm^{-1}. NMR data are given in Table 2.

5. M.p. 262–263°C. MS [E 70 eV; *m/z* (% rel. int.)] 646 (45, M^+), 323 (30, $M^+ - C_{21}H_{27}N_2O$), 255 (100, $M^+ - C_{26}H_{35}N_2O$), 196 (39, $M^+ - C_{28}H_{40}N_3O_2$), 182 (31, $M^+ - C_{29}H_{42}N_3O_2$). UV [acetonitrile (log ε)] 204 (4.88), 244 (4.11), 294 (3.75) nm. IR (KBr): 3386 (m), 3313 (m), 2968 (m), 2912 (m), 1674 (vs) ($\nu_{C=O}$ in five-membered lactam), 1611 (m), 1485 (s), 1378 (m), 742 (m) (1,2-disubstituted benzene) cm^{-1}. NMR data are given in Table 3.

*(±)-1-Methyl-3a,8-di(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**2**).* A suspension of **1** (0.25 mmol) in 5 ml of ether, dried over sodium–lead alloy, was added to a stirred solution of $LiAlH_4$ (10.3 mmol) in 25 ml dry ether at room temperature. After 1 h TLC analysis showed complete consumption of the amide. Excess reducing agent was destroyed by careful addition of ethyl acetate. The reaction mixture was poured into a separatory funnel containing 100 ml of water and extracted with three 75 ml portions of ether. The combined ether phase was washed twice with an equal volume of water, dried over $MgSO_4$ and evaporated to dryness to leave pure **2** (60 mg, 76%). NMR data are given in Table 1. Based on C,H heterocorrelated experiments C-8a is reassigned from the previous value[4] of 87 ppm to 91.4 ppm. All other data are consistent with those previously reported.[4]

*(±)-1-Methyl-3a-(3-methyl-2-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**4**).* $LiAlH_4$ (10.26 mmol) was added in one portion to a stirred solution of debromoflustramide E (0.4 mmol) in 30 ml of ether, dried over sodium prior to use. After 24 h TLC analysis showed complete consumption of the amide. Excess reducing agent was destroyed by careful addition of ethyl acetate. The reaction mixture was transferred to a separatory funnel containing 100 ml of water and extracted with five 50 ml portions of ether. The combined ether phase was washed twice with 50 ml of water, dried over $MgSO_4$ and evaporated to dryness to leave pure **4** (92 mg, 97%). MS [E 70 eV; *m/z* (% rel. int.)] 242 (33, M^+), 173 (68, $M^+ - C_5H_9$), 130 (71, $M^+ - C_7H_{14}N$), 72 (100, $M^+ - C_{12}H_{12}N$). UV [abs. ethanol (log ε)] 206 (4.36), 246 (3.82), 296 (3.40) nm. IR (KBr): 3274 (s), 2966 (vs), 2927 (vs), 2791 (s), 2467 (m), 1705 (m), 1652 (s), 1607 (vs), 1488 (vs), 744 (vs) (1,2-disubstituted benzene) cm^{-1}. NMR data are given in Table 2.

Acknowledgments. The present study was supported by the Danish Biotechnology Programme 1991–1995.

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Received August 4, 1994.