Total Syntheses of Five Indole Alkaloids from the Marine Bryozoan *Flustra foliacea*

Martha S. Morales-Ríos, Oscar R. Suárez-Castillo, Joel J. Trujillo-Serrato, and Pedro Joseph-Nathan*

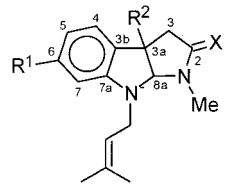
Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politéctico Nacional, Apartado 14-740, México D. F., 07000 Mexico

pjoseph@nathan.chem.cinvestav.mx

Received August 21, 2000

A general, efficient, and conceptually new approach to the total syntheses of marine-derived indole alkaloids, including (±)-flustramines A (**1**) and B (**2**), (±)-flustramides A (**3**) and B (**4**), and (±)-debromoflustramine B (**5**), is outlined. The key step in the syntheses involves the conjugated addition of an organomagnesium species derived from prenyl bromide to 2-hydroxyindolenines. Compounds **1**, **2**, and **5** have been synthesized in five steps with 23%, 17%, and 16% overall yield, respectively, whereas flustramides **3** and **4** have been synthesized in only four steps with 24% and 18% overall yield, respectively, on the basis of 2-hydroxyindolenines.

Marine invertebrates of the phylum Bryozoa, order Cheilostomata have been investigated heavily in recent years as sources of interesting secondary metabolites. Many of the novel compounds isolated from the cheilostome bryozoan, namely *Flustra foliacea*, are bromoindole alkaloids, most of which display interesting biological activity.[1] Antibacterial testing of the methylene chloride extracts from *F. foliacea* shows strong activity against *Bacillus subtilis*, while the crude petroleum ether extracts strongly inhibits plaque formation for influenza virus.[2] Flustramines A (**1**) and B (**2**) isolated from *F. foliacea*[3] were the first members of the family to be identified. These molecules exhibit muscle relaxant activity affecting both skeletal and smooth muscle.[1] A series of novel marine-derived indole alkaloids, including the flustramides A (**3**)[4] and B (**4**)[5] and the debromoflustramine B (**5**),[1b] were reported between 1982−1994. These alkaloids have in common the basic physostigmine skeleton known from the minor group of terrestrial alkaloids from Calabar bean (*Physostigma venenosum* Balf), and some of them have two prenyl or inverted prenyl units at the 8 and/or 3a positions as shown below. Other closely related substances, from very diverse biological origins, belonging to the pyrrolo[2,3-*b*]indole class of alkaloids include mollenines A and B,[6] fructigenines A and B,[7] amauromines,[8] aszonalenin,[9] ardeemin,[10] pseudophrynamine A,[11a] pseudophrynaminol,[11a,b] urochordamins,[12] calycanthidine[13] and chaetocin.[13]



1: R^1 = Br, R^2 =  , X = H, H Flustramine A

2: R^1 = Br, R^2 =  , X = H, H Flustramine B

3: R^1 = Br, R^2 =  , X = O Flustramide A

4: R^1 = Br, R^2 =  , X = O Flustramide B

5: R^1 = H, R^2 =  , X = H, H Debromoflustramine B

Because flustramines and related compounds are available from Nature in only minute amounts and may

* To whom correspondence should be addressed. Phone: (52) 5747-7112. Fax: (52) 5747−7137.

(1) (a) Christophersen, C. *Acta Chem. Scand. B* **1985**, *39*, 517−529. (b) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997−1000.

(2) Laycock, M. V.; Wright, J. L. C.; Findlay, J. A.; Patil, A. D. *Can. J. Chem.* **1986**, *64*, 1312−1316.

(3) (a) Carlé, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012−4013. (b) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586−1589.

(4) Wulff, P.; Carlé, J. S.; Christophersen, C. *Comp. Biochem. Physiol.* **1982**, *71B*, 523−524.

(5) Keil, P.; Nielsen, E. G.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand. B* **1986**, *40*, 555−558.

(6) Wang, H.-j.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1998**, *61*, 804−807.

(7) Arai, K.; Kimura, K.; Mushiroda, T.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2937−2939.

(8) (a) Takase, S.; Iwami, M.; Ando, T.; Okamoto, M.; Yoshida, K.; Horiai, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Nat. Prod.* **1984**, *37*, 1320−1323. (b) Takase, S.; Kawai, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1985**, *41*, 3037−3048. (c) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143−11144. (d) Laws, I.; Mantle, P. G. *Phytochemistry* **1985**, *24*, 1395−1397. (e) de Guzman, F. S.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1992**, *55*, 931−939.

(9) Kimura, Y.; Hamasaki, T.; Nakajima, H.; Isogai, A. *Tetrahedron Lett.* **1982**, *23*, 225−228.

(10) (a) Karwowski, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 374−379. (b) Hochlowski, J. P.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine. J. B. *J. Antibiot.* **1993**, *46*, 380−386.

(11) (a) Spande, T. F.; Edwards, M. W.; Pannell, L. K.; Daly, J. W.; Erspamer, V.; Melchiorri, P. *J. Org. Chem.* **1988**, *53*, 1222−1226. (b) Crich, D.; Pavlovic, A. B.; Samy, R. *Tetrahedron*, **1995**, *51*, 6379−6384.

(12) Tsukamoto, S.; Hirota, H.; Kato, H.; Fusetani, N. *Tetrahedron Lett.* **1993**, *34*, 4819−4822.

(13) (a) Kutney, J. P. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, 273−438. (b) Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H. *J. Org. Chem.* **1993**, *58*, 6016−6021. (c) Weber, H. P. *Acta Crystallogr. B*, **1972**, *B28*, 2945−2951.

10.1021/jo0012647 CCC: $20.00
Published on Web 01/27/2001

be of significant interest for more detailed pharmacological investigations, it was the goal of the current project to develop efficient total syntheses for these indole alkaloids. The first total synthesis of a member of this family of natural products, debromoflustramine B (**5**), via C3 alkylation of a tryptamine derivative was reported.[14] This strategy was extended to the synthesis of flustramine B (**2**),[15] as well as to the diastereoselective synthesis of **5**[16] using, in this case, the cyclic tautomer of an L-tryptophan derivative.[17] Another approach to **5**, via a Claisen rearrangement as the key reaction, involves a six-step sequence and 4.4% overall yield on the basis of 1-methoxyindole-3-carbaldehyde.[18] To date, no published syntheses for flustramine A (**1**) nor flustramides A (**3**) and B (**4**) exist.

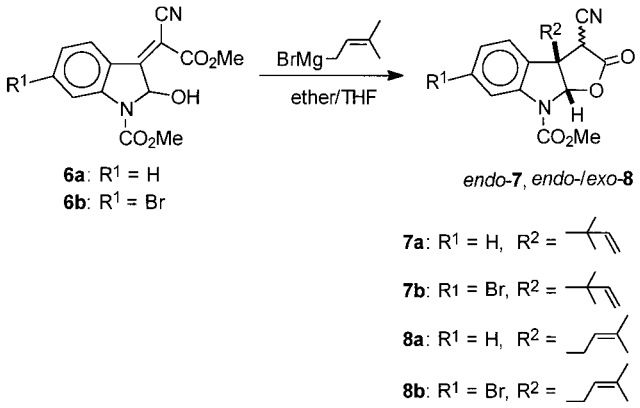
In our preliminary communication,[19] we have demonstrated the usefulness of the addition of an organomagnesium species to 2-hydroxyindolenines for introducing an alkyl group at the C3 position of the indole nucleus and, therefore, the preparation of suitable intermediates for the synthesis of debromoflustramine B (**5**). To extend the methodology developed for this compound, we now describe a total synthesis of flustramine B (**2**) and the first total syntheses of flustramine A (**1**) and flustramides A (**3**) and B (**4**), demonstrating that this protocol is a general and efficient approach for the total synthesis of marine bryozoan *Flustra foliacea* alkaloids.

Results and Discussion

Previously, we reported[20] a flexible approach to 2-hydroxyindolenines **6** bearing different substitution patterns on the benzene ring. These cyclic hemiaminals also proved to be good substrates for further carbon−carbon bond formation.[21] The first step (Scheme 1) in the synthesis of *F. foliacea* alkaloids involves the prenyl reagent addition to 2-hydroxyindolenines **6** to provide a ready access to a range of functionalized 2-oxofuro[2,3-*b*]indolines **7** and **8**. Prenyl ligand was found to add from both the α and γ sites with high levels of chemoselectivity, as no competing 1,2-adducts were detected (Scheme 1).[22]

After exploring several reaction conditions, the best yields for compounds **7** and **8** were obtained at −78 °C. THF was used as a cosolvent in the Grignard reactions

Scheme 1



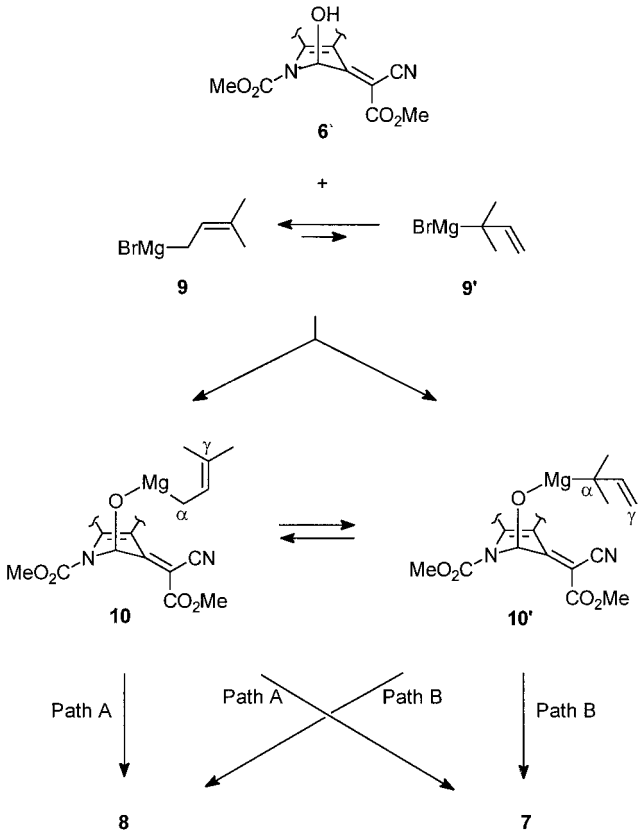
to increase the solubility of the starting materials. Typically, when the 2-hydroxyindolenine **6a** was stirred with an excess (4 equiv) of prenylmagnesium bromide (3-methyl-2-butenylmagnesium bromide) at −78 °C in anhydrous THF/ether, the products of the 1,4-addition, the prenylated 2-oxofuro[2,3-*b*]indoline **8a** (12:1 mixture of endo/exo isomers as determined by ^{1}H NMR) and the 1,1-dimethylallyl isomer **7a** (only endo isomer), were obtained in a combined yield of 77% in a ratio of 61 (**7a**):39 (**8a**). The structures of both **7a** and **8a** were established unequivocally by ^{1}H and ^{13}C NMR. On the basis of these precedents, the reaction of the brominated 2-hydroxyindolenine **6b** with prenylmagnesium bromide was carried out at −78 °C to afford the C3a-alkylated 2-oxofuroindolines **7b** (endo isomer) and **8b** (as approximately 12:1 mixture of endo/exo isomers) in a combined yield of 76% in a ratio of 53 (**7b**):47 (**8b**). The dependence of the C3/C3a endo/exo ratios on the alkyl group at C3a is in line with our previous observations.[19]

Taken together, our results seem to indicate in a first glance that the nucleophilic addition involves the initial complexation of the indolenine alkoxide of **6** and the equilibrating mixture of prenylmagnesium bromide **9** and its 1,1-dimethylallyl isomer **9′** leading to a secondary or a quaternary carbon in adducts **10** or **10′** (Scheme 2). Although it is known that the α vs γ equilibrium between **9** and **9′** lies heavily on the side of **9**,[23] our results show that **7** is preferred over **8**. By that account, it is possible that simultaneous intramolecular electrophilic assistance by the magnesium bond to the oxygen, and the prenyl delivery at either the α or γ sites leads, via **10** (path A), to the observed products **7** and **8**. It is also conceivable that an equilibrium between **10** and **10′** comes into play leading analogously, via **10′** (path B), to α- and γ-adducts **7** and **8**. Thus, formation of species **10** or **10′** is likely to be the chemocontrolling step in the overall process. Scheme 2 has to rely on a regiochemistry analysis rather than on a quantitative prediction.

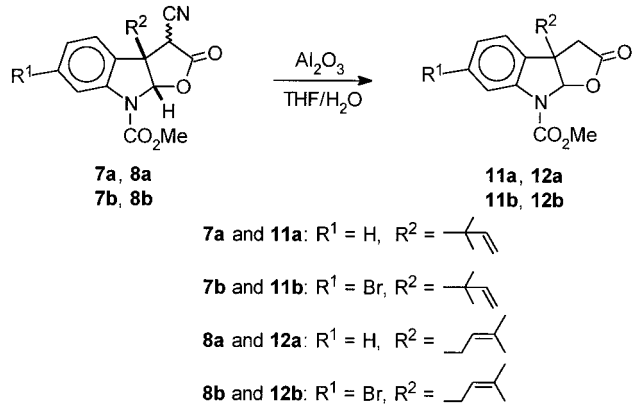
The one-pot hydrolytic decyanation of the α-cyano-γ-lactones **7a**, **7b**, **8a**, and **8b** was conducted in refluxing THF for 3−13 h, in the presence of wet alumina, to afford the corresponding γ-lactones **11a**, **11b**, **12a,** and **12b** in 95%, 89%, 86%, and 64% yield, respectively. The yield of **12b** was improved to 83% when the reaction was effected at room temperature, although the reaction was mark-

(14) Muthusubramanian, P.; Carlé, J. S.; Christophersen, C. *Acta Chem. Scand. B* **1983**, *37*, 803−807.
(15) Hino, T.; Tanaka, T.; Matsuki, K.; Nakagawa, M. *Chem. Pharm. Bull.* **1983**, *31*, 1806−1808.
(16) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543−5549.
(17) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487−1494.
(18) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327−2330.
(19) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *J. Org. Chem.* **1999**, *64*, 1086−1087.
(20) Compounds **6a** and **6b** were prepared in good overall yields by treatment of the appropriately substituted 3-acetonitrilindole with an alkyl carbonate in basic medium, followed by oxidation with either HNO_3/AcOH or CrO_3/AcOH. See: Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *J. Heterocycl. Chem.* **1993**, *30*, 953−956.
(21) (a) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron* **1996**, *52*, 5339−5348. (b) Morales-Ríos, M. S.; García-Martínez, C.; Bucio, M. A.; Joseph-Nathan, P. *Monatsh. Chem.* **1995**, *126*, 789−794. (c) Morales-Ríos, M. S.; Bucio, M. A.; García-Martínez, C.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 6087−6088. (d) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 881−882.
(22) For related 1,4-addition studies of prenyl Grignard reagent, see: Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437−7444.
(23) (a) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *Discussions Faraday Soc.*, **1962**, *34*, 185−190. (b) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 2010−2011. (c) Benkeser, R. A. *Synthesis* **1971**, 347−358.

Scheme 2



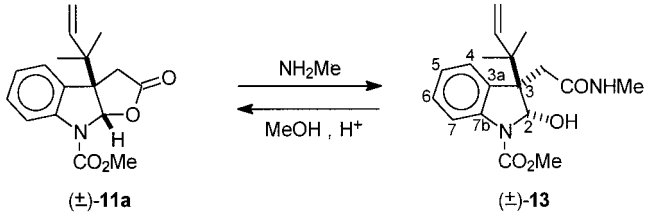
Scheme 3



edly sluggish and required 5 days for complete decyanation. No intermediates were detected during the reactions (Scheme 3) and a mechanism involving two successive pseudopericyclic [4 + 2] hydration processes has been proposed for the decyanation.[24,25]

When γ-lactone **11a** was treated with methylamine at room temperature, a single product, γ-hydroxyamide **13**, was obtained which by heating in methanol and aqueous HCl to reflux gave back γ-lactone **11a** (Scheme 4).[26] We

Scheme 4



assumed that the electron-withdrawing *N*-CO_2Me substituent deactivates the hydroxyl group at C2 toward nucleophilic substitution to give the desired lactam. The structure of **13** was established unequivocally by ^{1}H and ^{13}C NMR.

It was then of interest to investigate the possibility of introducing the N_8 prenyl group in the synthetic sequence before effecting the lactamisation. Attempts to remove the electron-withdrawing *N*-CO_2Me substituent of compound **11a** with 10% KOH in EtOH or HCO_2H[26b] resulted solely in decomposition, while heating **11a** (120−130 °C) with KOH in aqueous EtOH in a sealed tube[27] afforded the desired deprotected product **14a**, albeit in modest yield. In view of these results, we tested MeONa/MeOH at reflux as the cleavage method of the indoline ester group and, to our pleasure, product **14a** was obtained in good yield. This compound proved to decompose slowly on standing at room temperature and therefore it was immediately *N*-alkylated by reaction with K_2CO_3 and prenyl bromide in acetone at reflux to give **16a** in a combined yield of 60% for the two-step process (Scheme 5). Using this two-step sequence, compound **12a** gave the N-prenylated compound **17a**, through **15a**, in 70% overall yield. Treatment of brominated lactone **11b** or **12b** with MeONa/MeOH afforded **14b** or **15b** which was immediately N-prenylated to produce the desired lactone **16b** (68% overall yield) or **17b** (60% overall yield). The debrominated compounds **16a** and **17a** were then chosen for study to further evaluate lactamisation and reduction reactions. Stirring MeOH solutions of **16a** or **17a** with methylamine at room temperature for few hours gave the expected debromoflustramides A (**18**) or B (**19**) in high yields (98% and 92%, respectively). The larger reaction time required for the formation for **18** (5 h) as compared to that of **19** (2 h) was not surprising taking into account the greater steric hindrance of the bulky 1,1-dimethylallyl group in **16a**, which could retard formation of the open ring 2-hydroxyindoline intermediary. Further reduction of **18** or **19** with $LiAlH_4$ in refluxing THF gave debromoflustramines A (**20**) or B (**5**) in near-quantitative yields (Scheme 5). The spectral properties of **5** are identical (IR, ^{1}H and ^{13}C NMR, EIMS) to those reported for the marine natural product debromoflustramine B, except for the optical activity.[1b,16]

On the basis of these precedents, we next examined the lactamization of **16b** or **17b** required for the synthesis of the brominated natural products **3** or **4**. As shown in Scheme 6, treatment of lactones **16b** or **17b** with methylamine in MeOH at room temperature provided flustramides A (**3**) or B (**4**) in 98% isolated yields. The final reduction of **3** or **4** turned out to be somewhat delicate due to the inherent lability of the aromatic bromides

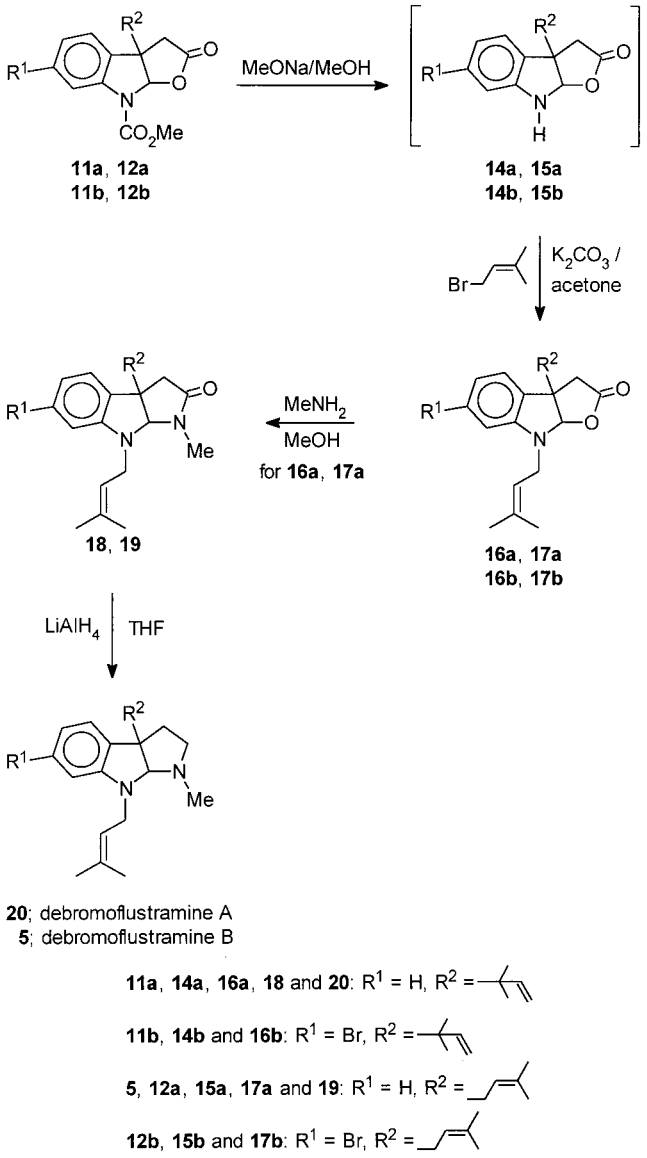
(24) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; García-Martínez, C.; Joseph-Nathan, P. *Synthesis* **1998**, 1755−1759.

(25) For earlier examples of pseudopericyclic reactions, see: (a) Ross, J. A., Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325−4327. (b) Wagenseller, P. E.; Birney, D. M.; Roy, D. *J. Org. Chem.* **1995**, *60*, 2853−2859. (c) Ham, S.; Birney, D. M. *J. Org. Chem.* **1996**, *61*, 3962−3968. (d) Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243−251.

(26) Similar observations have been reported before: (a) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2399−2404. (b) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572.

(27) Ikeda, M.; Matsugashita, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1770−1772.

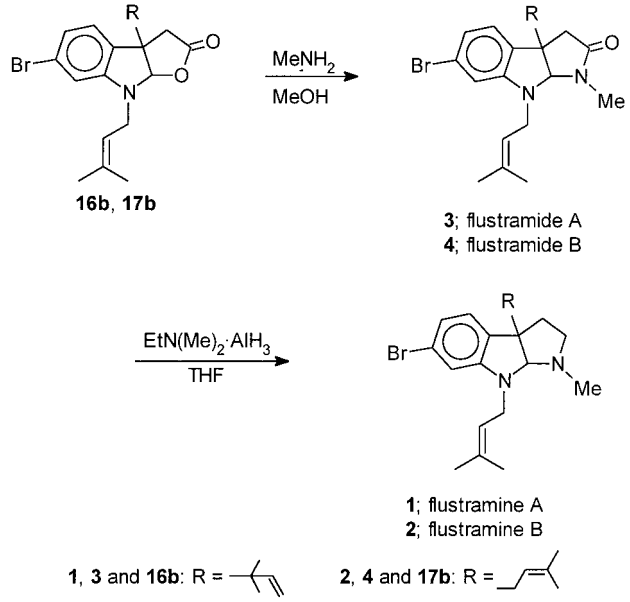
Scheme 5



toward the nonselective nature of $LiAlH_4$.[28] Convertion of brominated lactams **3** or **4** into the corresponding tetrahydropyrroles **1** or **2** was then accomplished by treatment with alane-*N*,*N*-dimethylethylamine complex at room temperature for 45 min in excellent yields (96% and 97%, respectively) (Scheme 6). This completes the total synthesis of flustramines A (**1**) and B (**2**). The spectral properties of **1**−**4** are identical (IR, ^{1}H and ^{13}C NMR) to those reported for the marine natural products flustramines A[4] and B[4] and flustramides A[5] and B,[6] respectively, except for the optical activity.

In summary, we have described a practical, efficient, and general approach to the total syntheses of five marine indole alkaloids including flustramines A (**1**) and B (**2**), flustramides A (**3**) and B (**4**), and debromoflustramine B (**5**) via the conjugated addition of an organomagnesium species derived from prenyl bromide to 2-hydroxyindolenines. This approach provides a widely potential route to a variety of marine *F. foliacea* alkaloids carrying the basic physostigmine skeleton. Further applications of this methodology toward the construction of alkaloids

Scheme 6



containing the 3a-alkylhexahydropyrrolo[2,3-*b*]indole ring system are currently in progress in our laboratory.

Experimental Section

General Methods. Dry THF and ether were obtained by distillation over sodium. All the commercial grade reagents were used without further purification. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was performed using silica gel 60 (230−400 mesh) from Aldrich. IR spectra were obtained using a Perkin-Elmer 16F PC FT spectrophotometer. NMR spectra were recorded on Varian XL-300GS and Mercury 300 spectrometers working at 300 and 75.4 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. Electron impact mass spectra (EIMS) were recorded on a Hewlett-Packard 5989A spectrometer at an ionizing voltage of 70 eV. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A spectrometer. Microanalytical determinations were performed by the Microanalytical Laboratory, Elbach, Germany.

General Procedure for Grignard Addition. To a precooled (−78 °C) stirred suspension of the Grignard reagent, prepared from prenyl bromide (30.0 mmol) and Mg turnings (3.5 g, 0.14 mol) in dry ether (50 mL) under argon at 25 °C, was added dropwise a solution of **6** (3.5 mmol) in THF/ether (25/25 mL) over a 0.5 h period. The reaction was completed in 2 h at −78 °C, quenched with saturated NH_4Cl solution (10 mL), and diluted with EtOAc (150 mL). The organic layer was separated, washed with saturated NH_4Cl solution (2 × 15 mL), and dried over Na_2SO_4. The reaction products **7** and **8** were then purified by silica gel column chromatography.

Methyl 3-Cyano-3a-(2-methyl-3-buten-1-yl)-2-oxo-2,3,-3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 7a. Prepared from methyl *Z*-1-carbomethoxy-2-hydroxy-3-indolinylidencyanoacetate **6a** as colorless crystals (537 mg, 47%): mp 168−169 °C (CH_2Cl_2−hexane); R_f 0.19 (3:2 ether/hexane); IR ($CHCl_3$) ν_{max} 2934, 2254, 1789, 1732, 1604, 1480 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.78 (1H, br s), 7.69, (1H, br d, J = 7.8 Hz), 7.50 (1H, td, J = 7.8, 1.2 Hz), 7.26 (1H, td, J = 7.7, 1.1 Hz), 6.48 (1H, s), 5.93, (1H, dd, J = 17.3, 10.8 Hz), 5.40 (1H, s, ex. D_2O), 5.20 (1H, d, J = 17.3), 5.12 (1H, d, J = 10.8), 3.89 (3H, s), 1.07 (3H, s), 1.06 (3H, s); ^{13}C NMR (DMSO-d_6) δ 166.6, 151.6, 141.3, 140.3, 130.7, 127.1, 126.6, 123.7, 116.2, 115.0, 114.9, 93.3, 59.6, 53.7, 41.1, 39.2, 22.3, 21.9; EIMS *m*/*z* (relative

(28) Brown, H. C.; Krishamurthy, S. *J. Org. Chem.* **1969**, *34*, 3918−3922.

intensity) 326 (M^+, 68); HRMS (FAB) *m/e* 326.1267 (M^+, $C_{18}H_{18}N_2O_4$ requires 326.1267). Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58; O, 19.61. Found: C, 66.19; H, 5.62; N, 8.46; O; 19.73.

Methyl 6-Bromo-3-cyano-3a-(2-methyl-3-buten-2-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 7b. Prepared from methyl *Z*-6-bromo-1-carbomethoxy-2-hydroxy-3-indolinylidencyanoacetate **6b** as colorless crystals (570 mg, 40%): mp 218−220 °C (EtOAc/hexane); R_f 0.43 (2:3 EtOAc/hexane); IR (KBr) ν_{max} 2966, 2258, 1788, 1722, 1604, 1442 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.90 (1H, br s), 7.60, (1H, d), 7.47 (1H, dd, J = 8.3, 1.9 Hz), 6.48 (1H,s), 5.90 (1H, dd, J = 17.3, 10.7 Hz), 5.40 (1H, s, ex. D_2O), 5.20 (1H, d, J = 17.3 Hz), 5.12 (1H, d, J = 10.9), 3.90 (3H, s), 1.08 (3H, s), 1.05 (3H, s); ^{13}C NMR (DMSO-d_6) δ 166.3, 151.4, 141.8, 141.0, 128.8, 126.5, 126.2, 123.6, 117.7, 116.4, 114.8, 93.3, 59.4, 54.0, 41.1, 39.9, 22.3, 21.8; EIMS *m/z* (relative intensity) 404/406 (M^+, 18/17), 292/294 (61/65); HRMS (FAB) *m/e* 404.0366 (M^+, $C_{18}H_{17}BrN_2O_4$ requires 404.0372). Anal. Calcd for $C_{18}H_{17}BrN_2O_4$: C, 53.35; H, 4.23; Br, 19.72; N, 6.91. Found: C, 53.18; H, 4.35; Br, 19.65; N, 6.73.

Methyl 3-Cyano-3a-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 8a. Prepared from **6a** as colorless crystals (335 mg, 30%): mp 108−110 °C (ether/hexane); R_f 0.23 (3:2 ether/hexane); IR ($CHCl_3$) ν_{max} 3018, 2258, 1800, 1732, 1600, 1484 cm^{-1}; ^1H NMR (DMSO-d_6), diastereomeric ca. 12:1 endo/exo ratio δ (endo isomer) 7.73 (1H, br s), 7.58, (1H, br d, J = 7.7 Hz), 7.45 (1H, td, J = 7.6, 1.3 Hz), 7.22 (1H, td, J = 7.6, 1.1 Hz), 6.42 (1H, s), 5.18 (1H, s, ex. D_2O), 4.97 (1H, br t, J = 7.5 Hz), 3.87 (3H, s), 2.68 (1H, 2d, J = 14.3, 7.1 Hz), 2.61 (1H, dd, J = 14.3, 8.4 Hz), 1.63 (3H, s), 1.47 (3H, s); ^{13}C NMR (DMSO-d_6) δ 165.4, 151.8, 140.0, 137.0, 130.2, 128.5, 125.7, 123.9, 116.4, 115.0, 114.2, 95.1, 53.9, 53.6, 41.6, 34.6, 25.5, 17.7; ^1H NMR (DMSO-d_6) δ (exo isomer) 7.73 (1H, br s), 7.50, (1H, br d, J = 7.7 Hz), 7.38 (1H, td, J = 7.7, 1.3 Hz), 7.16 (1H, td, J = 7.5, 1.1 Hz), 6.58 (1H, s), 5.12 (1H, s), 4.81 (1H, br t, J = 7.6 Hz), 3.87 (3H, s), 2.84 and 2.61 (2H, 2dd, J = 14.2, 8.4 and 14.2, 7.1 Hz), 1.55 (3H, s), 1.42 (3H, s); EIMS *m/z* (relative intensity) 326 (M^+, 72), 214 (53), 69 (100); HRMS (FAB) *m/e* 326.1269 (M^+, $C_{18}H_{18}N_2O_4$ requires 326.1267).

Methyl 6-Bromo-3-cyano-3a-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 8b. Prepared from **6b** as colorless crystals (510 mg, 36%): mp 123−125 °C (ether/hexane); R_f 0.56 (2:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2960 2258, 1802, 1736, 1598, 1444 cm^{-1}; ^1H NMR (DMSO-d_6), diastereomeric ca. 12:1 endo/exo ratio δ (endo isomer) 7.86 (1H, br s), 7.49, (1H, d, J = 8.3 Hz), 7.44 (1H, dd, J = 8.3, 1.8 Hz), 6.41 (1H, s), 5.18 (1H, s, ex. D_2O), 4.99 (1H, br t, J = 7.6 Hz), 3.89 (3H, s), 2.69 (1H, 2d, J = 14.3, 7.4 Hz), 2.61 (1H, dd, J = 14.3, 8.4 Hz), 1.64 (3H, s), 1.46 (3H, s); ^{13}C NMR (DMSO-d_6) δ 166.5, 151.7, 141.4, 137.3, 128.0, 127.5, 126.8, 123.0, 117.7, 116.1, 114.1, 95.1, 53.8, 53.7, 41.4, 34.4, 25.5, 17.4; ^1H NMR (DMSO-d_6) δ (exo isomer) 7.86 (1H, br s), 7.49, (1H, d, J = 8.3 Hz), 7.36 (1H, dd, J = 8.3, 1.8 Hz), 6.54 (1H, s), 5.12 (1H, s), 4.82 (1H, br t, J = 7.6 Hz), 3.89 (3H, s), 2.85 and 2.72 (2H, 2dd, J = 14.2, 8.4 and 14.2, 7.4 Hz), 1.57 (3H, s), 1.44 (3H, s); EIMS *m/z* (relative intensity) 404/406 (M^+, 31/31), 292/294 (49/46), 69 (100); HRMS (FAB) *m/e* 404.0377 (M^+, $C_{18}H_{17}BrN_2O_4$ requires 404.0372).

General Procedure for Hydrolytic Decyanation. A mixture of the appropriate α-cyano-γ-lactone **7** or **8** (0.72 mmol) and alumina (650 mg) in 3.0% aqueous THF (6 mL) was stirred at reflux or at rt, as described below for each case, until TLC analysis showed complete loss of starting material. After the mixture was cooled to rt, the alumina was filtered off and washed with EtOAc (5 × 20 mL). The filtrate and the eluates were combined and evaporated to afford the corresponding crude γ-lactone **11** or **12** which was purified by flash chromatography on silica gel (2:3 EtOAc/hexane).

Methyl 3a-(2-Methyl-3-buten-2-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 11a. Prepared from **7a** as a colorless oil, the reaction reached completion at reflux in 16 h (206 mg, 95%): R_f 0.53 (2:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2938, 1779, 1718, 1604, 1483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67 (1H, br s), 7.41 (1H, br d, J = 7.6 Hz), 7.35 (1H, td, J = 7.6, 1.2 Hz), 7.13 (1H, td, J = 7.5, 1.1 Hz), 6.29 (1H, s), 5.90, (1H, dd, J = 17.3, 10.8 Hz), 5.10 (1H, dd, J = 10.8, 1.1 Hz), 5.04 (1H, dd, J = 17.3, 1.1), 3.84 (3H, s), 3.27 (1H, d J = 18.2 Hz), 2.89 (1H, d, J = 18.2 Hz), 1.01 (3H, s), 0.89 (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.7, 152.0, 142.8, 140.1, 132.1, 129.5, 126.2, 123.8, 114.9, 114.6, 93.4, 57.9, 53.5, 40.2, 36.2, 22.4, 22.0; EIMS *m/z* (relative intensity) 301 (M^+, 39), 233 (33), 188 (100); HRMS (FAB) *m/e* 301.1329 (M^+, $C_{17}H_{19}NO_4$ requires 301.1314).

Methyl 6-Bromo-3a-(2-methyl-3-buten-2-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 11b. Prepared from **7b** as colorless crystals, the reaction reached completion at reflux in 9 h (245 mg, 89%): mp 138−140 °C (ether/hexane); R_f 0.52 (2:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3020, 1779, 1722, 1596 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.86 (1H, br s), 7.44 (1H, d, J = 8.1 Hz), 7.39 (1H, dd, J = 8.2, 1.8 Hz), 6.36 (1H, s), 5.95, (1H, dd, J = 17.3, 10.8 Hz), 5.17 (1H, dd, J = 10.8, 1.1 Hz), 5.10 (1H, dd, J = 17.3, 1.1), 3.93 (3H, s), 3.33 (1H, d J = 18.3 Hz), 2.97 (1H, d, J = 18.3 Hz), 1.07 (3H, s), 1.00 (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.3, 151.8, 142.4, 141.5, 131.6, 128.0, 126.4, 122.0, 117.1, 115.0, 93.4, 57.7, 53.6, 40.1, 35.8, 22.3, 21.7; EIMS *m/z* (relative intensity) 379/381 (M^+, 22/22), 282/284 (25/25), 266/268 (92/100).

Methyl 3a-(3-Methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 12a. Prepared from **8a** as a colorless oil, the reaction reached completion at reflux in 3.5 h (186 mg, 86%): R_f 0.55 (2:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2936, 1780, 1719, 1604, 1483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67 (1H, br s), 7.40 (1H, dd, J = 7.5, 0.6 Hz), 7.33 (1H, td, J = 7.5, 1.3 Hz), 7.13 (1H, td, J = 7.5, 1.1 Hz), 6.24 (1H, s), 4.95, (1H, br t, J = 7.5 Hz), 3.85 (3H, s), 3.06 (1H, d J = 17.8 Hz), 2.93 (1H, d, J = 17.8 Hz), 2.51 (2H, s), 1.60 (3H, s), 1.45 (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.9, 152.3, 139.6, 135.4, 134.0, 128.9, 124.6, 123.9, 117.6, 114.5, 114.4, 95.1, 53.2, 51.8, 38.7, 34.8, 25.5, 17.7; EIMS *m/z* (relative intensity) 301 (M^+, 85), 233 (62), 204 (42), 188 (100).

Methyl 6-Bromo-3a-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate 12b. Prepared from **8b** as a colorless oil, the reaction reached completion at reflux in 3 h (175 mg, 64%) or at rt in 5 days (228 mg, 83%): R_f 0.53 (2:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3032, 1783, 1727, 1600, 1480, 1442 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.80 (1H, br s), 7.38 (1H, d, J = 8.2 Hz), 7.32 (1H, dd, J = 8.1, 1.7 Hz), 6.25 (1H, s), 4.95, (1H, br t, J = 7.5 Hz), 3.87 (3H, s), 3.05 (1H, d J = 18.0 Hz), 2.95 (1H, d, J = 18 Hz), 2.52 (2H, d, J = 5.6 Hz), 1.61 (3H, s), 1.46 (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.8, 152.2, 141.2, 135.8, 133.7, 126.7, 126.6, 121.5, 117.5, 117.3, 95.3, 53.6, 51.8, 38.5, 34.7, 25.6, 17.8; EIMS *m/z* (relative intensity) 379/381 (M^+, 40/40), 311/313 (35/34), 266/268 (94/100).

Methyl 2-Hydroxy-3-(2-methyl-3-buten-2-yl)-3-[2-oxo-2-(methylamino)ethyl]-2,3-dihydro-1*H*-indole-1-carboxylate 13. Excess methylamine (10 mL) was condensed at −78 °C in a flask containing **11a** (0.150 g, 0.50 mmol). The cooling bath was removed, and the reaction mixture was stirred until the excess methylamine evaporated. The residue was purified by crystallization from ether to afford **13** (162 mg, 98%) as colorless crystals: mp 137−139 °C; R_f 0.13 (1:1 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2958, 1706, 1648, 1602, 1486, cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.64 (1H, q, J = 4.5 Hz), 8.48 (1H, br d, J = 11.0 Hz), 7.61 (1H, br s), 7.18 (1H, td, J = 7.6, 1.3 Hz), 7.06 (1H, dd, J = 7.5, 1.0 Hz), 6.92 (1H, td, J = 7.5, 1.1 Hz), 5.56 (1H, dd, J = 16.5, 11.5 Hz), 5.41, (1H, d, J = 11.0 Hz), 4.97 (1H, d, J = 17.3 Hz), 4.96 (1H, d, J = 8.8 Hz), 3.74 (3H, s), 2.36 (3H, d, J = 4.5 Hz), 2.91 (1H, d J = 14.8 Hz), 2.79 (1H, d, J = 14.8 Hz), 0.93 (3H, s), 0.84 (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.3, 152.8, 143.1 141.5, 130.9, 128.0, 125.5, 121.4, 113.8, 113.6, 87.3, 55.8, 52.5, 42.4, 35.4, 25.7, 22.0, 21.3; EIMS *m/z* (relative intensity) 332 (M^+, 9), 263 (70), 231 (100), 204 (44).

General Procedure for N_8-Prenylation. To a solution of **11** or **12** (0.125 g, 0.41 mmol) in MeOH (15 mL) at 0 °C was added NaH (0.83 mmol). The mixture was heated at reflux for 2 h, and the volatiles were evaporated. The residue was dissolved in EtOAc (100 mL) and saturated aqueous NH_4Cl

(5 mL). The organic phase was washed with brine (3 × 20 mL), and the combined aqueous phases were extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to give the crude product **14** or **15** which was used in the next step without purification.

The crude compound **14** or **15** was heated to reflux with added acetone (15 mL), K_2CO_3 (0.167 g, 1.2 mmol) and prenyl bromide (1.2 mmol). The insoluble part was removed by filtration and washed with acetone (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to afford the corresponding crude *N*-prenylated compund **16** or **17**, which was purified by flash chromatography on silica gel (1:3 EtOAc/hexane).

3a-(2-Methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole 16a. Prepared from **11a** as a colorless oil, the reaction reached completion in 36 h (77 mg, 60%): R_f 0.47 (1:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2920, 1760, 1606, 1488 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.20 (1H, br d, J = 7.9 Hz), 7.15 (1H, td, J = 7.7, 1.2 Hz), 6.76 (1H, td, J = 7.7, 0.9 Hz), 6.56 (1H, br d, J = 7.8 Hz), 6.00 (1H, dd, J = 17.3, 10.8 Hz), 5.90 (1H, s), 5.28 (1H, br t, J = 6.7 Hz), 5.12 (1H, dd, J = 10.8, 1.2 Hz), 5.05 (1H, dd, J = 17.3, 1.2 Hz), 4.00 (1H, dd, J = 15.1, 6.2 Hz), 3.87 (1H, dd, J = 14.4, 7.3 Hz), 3.15 (1H, d, J = 17.9 Hz), 2.75 (1H, d, J = 17.9 Hz), 1.74 (6H, s), 1.02 (3H, s), 0.91 (3H, s); ^{13}C NMR (DMSO-d_6) δ 174.6, 148.2, 143.6, 135.3, 130.8, 129.0, 125.3, 119.8, 118.4, 114.2, 107.0, 100.2, 58.0, 42.2, 40.0, 37.4, 25.5, 22.3, 22.0, 17.7; EIMS *m/z* (relative intensity) 311 (M^+, 85); HRMS (FAB) *m/e* 311.1896 (M^+, $C_{20}H_{25}NO_2$ requires 311.1885).

6-Bromo-3a-(2-methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole 16b. Prepared from **11b** as a colorless oil, the reaction reached completion in 80 h (109 mg, 68%): R_f 0.51 (1:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3018, 1766, 1598, 912 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.14 (1H, d, J = 7.9 Hz), 6.90 (1H, dd, J = 7.9, 1.7 Hz), 6.73 (1H, d, J = 1.7 Hz), 5.97 (1H, dd, J = 17.4, 10.8 Hz), 5.90 (1H, s), 5.25 (1H, br t, J = 6.2 Hz), 5.11 (1H, dd, J = 10.8, 1.3 Hz), 5.04 (1H, dd, J = 17.4, 1.3 Hz), 4.01 (1H, dd, J = 15.2, 6.2 Hz), 3.86 (1H, dd, J = 15.1, 7.4 Hz), 3.14 (1H, d, J = 18.1 Hz), 2.77 (1H, d, J = 18.1 Hz), 1.74 (6H, s), 1.00 (3H, s), 0.92 (3H, s); ^{13}C NMR (DMSO-d_6) δ 174.2, 149.7, 143.1, 135.7, 130.3, 126.8, 121.9, 120.6, 119.0, 114.3, 109.6, 99.5, 57.6, 41.9, 39.8, 36.8, 25.3, 22.2, 21.8, 17.6; EIMS *m/z* (relative intensity) 389/391 (M^+, 25/25), 320/322 (19/19), 252/254 (28/30), 224/226 (52/49), 69 (100).

3a,8-Bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole 17a. Prepared from **12a** as a colorless oil, the reaction reached completion in 36 h (90 mg, 70%): R_f 0.46 (1:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2916, 1762, 1608, 1488 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.18 (1H, dd, J = 7.3, 1.1 Hz), 7.13 (1H, td, J = 7.7, 1.3 Hz), 6.74 (1H, td, J = 7.5, 0.9 Hz), 6.58 (1H, br d, J = 7.7 Hz), 5.69 (1H, s), 5.25 (1H, ddq, J = 9.0, 6.2, 1.4 Hz), 5.07 (1H, ddq, J = 8.4, 7.1, 1.3 Hz), 3.98 (1H, dd, J = 15.0, 6.1 Hz), 3.84 (1H, dd, J = 14.9, 7.6 Hz), 2.97 (1H, d, J = 17.5 Hz), 2.80 (1H, d, J = 17.5 Hz), 2.37 (2H, d, J = 7.3 Hz), 1.73 (6H, s), 1.64 (3H, s), 1.47 (3H, s); ^{13}C NMR (DMSO-d_6) δ 174.7, 147.4, 135.5, 134.5, 132.8, 128.6, 123.7, 119.6, 118.7, 118.5, 107.1, 101.5, 52.1, 41.9, 39.3, 34.1, 25.5, 25.4, 17.7, 17.6; EIMS *m/z* (relative intensity) 311 (M^+, 50); HRMS (FAB) *m/e* 311.1895 (M^+, $C_{20}H_{25}NO_2$ requires 311.1885).

6-Bromo-3a,8-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole 17b. Prepared from **12b** as a colorless oil, the reaction reached completion in 80 h (96 mg, 60%): R_f 0.41 (1:3 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3012, 1770, 1600, 1484 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13 (1H, d, J = 7.8 Hz), 6.89 (1H, dd, J = 7.9, 1.7 Hz), 6.77 (1H, d, J = 1.7 Hz), 5.69 (1H, s), 5.23 (1H, br t, J = 7.0 Hz), 5.03 (1H, br t, J = 7.5 Hz), 4.01 (1H, dd, J = 14.9, 6.2 Hz), 3.83 (1H, dd, J = 14.9, 7.8 Hz), 2.97 (1H, d, J = 17.7 Hz), 2.82 (1H, d, J = 17.7 Hz), 2.39 (2H, d, J = 7.3 Hz), 1.74 (3H, s), 1.73 (3H, s), 1.64 (3H, s), 1.47 (3H, s); ^{13}C NMR (DMSO-d_6) δ 174.4, 149.2, 136.1, 134.8, 132.3, 125.5, 121.7, 121.0, 119.0, 118.2, 109.9, 101.0, 51.8, 41.8, 39.1, 34.0, 25.5, 25.4, 17.7 (2C); EIMS *m/z* (relative intensity) 389/391 (M^+, 14/15), 321/323 (85/85), 276/278 (179/181); HRMS (FAB) *m/e* 390.1069 (M^+ + H, $C_{20}H_{24}BrNO_2$ requires 390.1069).

General Procedure for Lactamization. To a solution of the appropriate lactone **16a** (0.32 mmol), **17a** (0.32 mmol), **16b** (0.23 mmol), or **17b** (0.23 mmol) in MeOH (10 mL) was added NH_2Me (2 mL of a 2.0 M solution in MeOH, 4 mmol). The reaction mixture was stirred for 5, 2, 24, or 15 h, respectively, at rt. The mixture was evaporated, and the resultant crude lactam **18**, **3**, **19**, or **4** was purified by silica gel flash column chromatography (1:1 EtOAc/hexane).

1-Methyl-3a-(2-methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole, Debromoflustramide A (18). Prepared from **16a** as a colorless oil (102 mg, 98% yield): R_f 0.45 (1:1 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2934, 1678, 1602, 1492 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.13 (1H, br d, J = 7.4 Hz), 7.12 (1H, br t, J = 7.6 Hz), 6.93 (1H, br t, J = 7.4 Hz), 6.51 (1H, br d, J = 7.8 Hz), 5.92 (1H, dd, J = 17.3, 10.9 Hz), 5.33 (1H, br t, J = 6.6 Hz), 5.13 (1H, dd, J = 10.9, 1.2 Hz), 5.08 (1H, dd, J = 17.3, 1.5 Hz), 5.05 (1H, s), 4.09 (1H, dd, J = 15.9, 6.7 Hz), 3.97 (1H, dd, J = 15.9, 6.7 Hz), 2.82 (1H, d, J = 17.1 Hz), 2.79 (3H, s), 2.44 (1H, d, J = 17.1 Hz), 1.78 (3H, s), 1.76 (3H, s), 1.02 (3H, s), 0.92 (3H, s); ^{13}C NMR (DMSO-d_6) δ 171.5, 149.5, 143.9, 134.0, 132.4, 128.6, 124.9, 121.5, 117.5, 114.0, 107.6, 84.7, 55.2, 45.7, 40.9, 39.1, 27.2, 25.4, 22.5, 21.5, 17.9; EIMS *m/z* (relative intensity) 324 (M^+, 22); HRMS (FAB) *m/e* 324.2199 (M^+, $C_{21}H_{28}N_2O$ requires 324.2202).

1-Methyl-3a,8-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole, Debromoflustramide B (19). Prepared from **17a** as a colorless oil (96 mg, 92% yield): R_f 0.43 (1:1 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 2930, 1678, 1604, 1488 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.08 (1H, br d, J = 8.0 Hz), 7.06 (1H, td, J = 7.9, 1.3 Hz), 6.68 (1H, td, J = 7.8, 0.8 Hz), 6.53 (1H, br d, J = 7.8 Hz), 5.20 (1H, br t, J = 6.8 Hz), 4.98 (1H, br t, J = 7.4 Hz), 4.80 (1H, s), 4.07 (1H, dd, J = 15.7, 6.7 Hz), 3.91 (1H, dd, J = 16.1, 7.1 Hz), 2.75 (3H, s), 2.68 (1H, d, J = 17.1 Hz), 2.47 (1H, d, J = 17.1 Hz), 2.38 (1H, dd, J = 14.6, 7.8 Hz), 2.30 (1H, dd, J = 14.8, 6.8 Hz), 1.72 (3H, s), 1.70 (3H, s), 1.65 (3H, s), 1.51 (3H, s); ^{13}C NMR (DMSO-d_6) δ 171.5, 149.0, 135.2, 134.4, 134.3, 128.3, 123.2, 121.0, 119.1, 118.3, 108.5, 86.2, 49.4, 45.9, 41.4, 36.9, 27.2, 25.7, 25.4, 17.8 (2C); EIMS *m/z* (relative intensity) 324 (M^+, 38), 187 (100); HRMS (FAB) *m/e* 324.2201 (M^+, $C_{21}H_{28}N_2O$ requires 324.2202).

6-Bromo-3a-(2-methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole, Flustramide A (3). Prepared from **16b** as a colorless oil (91 mg, 98% yield): R_f 0.35 (1:1 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3006, 1680, 1594, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92 (1H, d, J = 8.0 Hz), 6.81 (1H, dd, J = 8.0, 1.8 Hz), 6.57 (1H, d, J = 1.8 Hz), 5.78 (1H, dd, J = 17.3, 10.9 Hz), 5.26 (1H, br t, J = 6.7 Hz), 5.12 (1H, dd, J = 10.9, 1.1 Hz), 5.05 (1H, dd, J = 17.3, 1.1 Hz), 4.83 (1H, s), 3.93 (2H, d, J = 6.7 Hz), 2.85 (3H, s), 2.84 (1H, d, J = 17.6 Hz), 2.55 (1H, d, J = 17.6 Hz), 1.77 (3H, s), 1.75 (3H, s), 1.03 (3H, s), 0.93 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.6, 151.1, 143.3, 135.7, 131.7, 126.2, 122.5, 120.7, 120.3, 114.6, 110.9, 85.9, 55.4, 46.3, 41.2, 39.4, 27.9, 25.6, 22.6, 21.8, 18.1; EIMS *m/z* (relative intensity) 402/404 (M^+, 6/6), 333/335 (20/20), 265/267 (63/61), 208/210 (16/16), 69 (100).

6-Bromo-3a,8-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole, Flustramide B (4). Prepared from **17b** as a colorless oil (91 mg, 98% yield): R_f 0.32 (1:1 EtOAc/hexane); IR ($CHCl_3$) ν_{max} 3026, 1682, 1596, 1488 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (1H, d, J = 7.2 Hz), 6.83 (1H, dd, J = 7.2, 1.4 Hz), 6.60 (1H, d, J = 1.5 Hz), 5.18 (1H, br t, J = 6.7 Hz), 4.95 (1H, br t, J = 7.4 Hz), 4.73 (1H, s), 3.96 (1H, dd, J = 16.4, 6.6 Hz), 3.88 (1H, dd, J = 16.3, 7.4 Hz), 2.87 (3H, s), 2.64 (2H, s), 2.38 (1H, dd, J = 14.4, 7.7 Hz), 2.30 (1H, dd, J = 14.4, 6.8 Hz), 1.75 (3H, s), 1.74 (3H, s), 1.70 (3H, s), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.8, 150.6, 136.0 (2C), 134.3, 124.4, 122.2, 121.5, 120.1, 118.2, 111.7, 87.4, 49.5, 46.6, 41.7, 37.4, 28.0, 26.0, 25.7, 18.1 (2C); EIMS *m/z* (relative intensity) 402/404 (M^+, 36/35), 333/335 (24/22), 265/267 (100/97); HRMS (FAB) *m/e* 403.1398 (M^+ + H, $C_{21}H_{27}BrN_2O$ requires 403.1385).

General Procedure for Lactam Reduction. To a stirred solution of LAH (2.50 mmol in 10 mL of dry THF) was added the appropriate lactam **18** or **19** (0.100 g, 0.31 mmol) in THF (5 mL), and the mixture was heated at reflux for 3 h. After the mixture was cooled to 0 °C, the reaction was quenched by adding dropwise EtOAc (120 mL), washed with brine, dried over Na_2SO_4, and evaporated. The resultant crude tetrahydropyrrole **20** or **5** was purified by silica gel flash column chromatography (EtOAc).

1-Methyl-3a-(2-methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, Debromoflustramine A (20). Prepared from **18** as a colorless oil (94 mg, 98%): R_f 0.48 (EtOAc); IR ($CHCl_3$) ν_{max} 2934, 1600, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (1H, dd, J = 7.4, 1.3 Hz), 7.05 (1H, td, J = 7.5, 1.3 Hz), 6.60 (1H, td, J = 7.4, 1.0 Hz), 6.39 (1H, d, J = 7.8 Hz), 5.98 (1H, dd, J = 17.3, 10.9 Hz), 5.27 (1H, br t, J = 6.6 Hz), 5.06 (1H, dd, J = 10.9, 1.2 Hz), 4.99 (1H, dd, J = 17.3, 1.2 Hz), 4.33 (1H, s), 3.90 (1H, dd, J = 15.9, 6.5 Hz), 3.82 (1H, dd, J = 15.9, 7.4 Hz), 2.65 (1H, m), 2.43 (1H, m), 2.43 (3H, s), 2.25 (1H, m), 1.79 (1H, m), 1.73 (3H, s), 1.71 (3H, s), 1.03 (3H, s), 0.95 (3H, s); ^{13}C NMR ($CDCl_3$) δ 152.5, 145.4, 133.8, 133.3, 127.7, 124.7, 121.8, 116.5, 112.6, 106.5, 89.1, 63.6, 53.2, 46.4, 41.5, 37.6, 34.7, 25.6, 23.6, 22.7, 18.0; EIMS *m*/*z* (relative intensity) 310 (M^+, 45), 241 (100); HRMS (FAB) *m*/*e* 310.2401 (M^+, $C_{21}H_{30}N_2$ requires 310.2409).

1-Methyl-3a,8-bis(3-methyl-2-buten-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, Debromoflustramine B (5). Prepared from **19** as a colorless oil (94 mg, 98%): R_f 0.12 (EtOAc); IR ($CHCl_3$) ν_{max} 2930, 1678, 1602, 1488 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04 (1H, td, J = 7.5, 1.4 Hz), 6.97 (1H, dd, J = 6.9, 1.3 Hz), 6.65 (1H, td, J = 7.7, 1.3 Hz), 6.41 (1H, br d, J = 7.8 Hz), 5.17 (1H, br t, J = 7.2 Hz), 4.97 (1H, br t, J = 7.9 Hz), 4.26 (1H, s), 3.93 (1H, dd, J = 15.9, 5.8 Hz), 3.80 (1H, dd, J = 16.1, 7.2 Hz), 2.67 (1H, m), 2.56 (1H, m), 2.48 (3H, s), 2.42 (2H, d, J = 7.5 Hz), 2.05 (1H, m), 1.91 (1H, m), 1.71 (3H, s), 1.70 (3H, s), 1.65 (3H, s), 1.59 (3H, s); ^{13}C NMR ($CDCl_3$) δ 151.8, 135.7, 134.0, 133.3, 127.5, 122.8, 121.4, 120.8, 117.4, 107.2, 91.4, 57.0, 52.8, 46.8, 39.0, 38.4, 38.0, 25.9, 25.7, 18.1 18.0; EIMS *m*/*z* (relative intensity): 310 (M^+, 45), 241 (100); HRMS (FAB) *m*/*e* 311.2477 ($M^+ + H$, $C_{21}H_{30}N_2$ requires 311.2487).

General Procedure for Selective Lactam Reduction. To a stirred solution of **3** or **4** (77 mg, 0.19 mmol in 10 mL of dry THF) was added alane-*N*,*N*-dimethylethylamine complex (0.6 mL of a 0.5 M solution in toluene, 0.3 mmol) and the reaction mixture was stirred for 45 min at rt. The reaction was quenched by adding slowly a mixture of THF−H_2O (1:1, 10 mL) followed by EtOAc (70 mL). The insoluble part was removed by filtration and washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated to afford the crude flustramine A (**1**) or B(**2**), which was purified by flash chromatography on silica gel (EtOAc).

6-Bromo-1-methyl-3a-(2-methyl-3-buten-2-yl)-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole, Flustramine A (1). Prepared from **3** as a colorless oil (71 mg, 96%): R_f 0.40 (5:95 MeOH/$CHCl_3$); IR ($CHCl_3$) ν_{max} 2970, 1592, 1488, 1372 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, d, J = 7.9 Hz), 6.69 (1H, dd, J = 7.9, 1.8 Hz), 6.48 (1H, d, J = 1.8 Hz), 5.95 (1H, dd, J = 17.4, 10.9 Hz), 5.22 (1H, br t, J = 6.6 Hz), 5.06 (1H, dd, J = 10.9, 1.5 Hz), 4.99 (1H, dd, J = 17.4, 1.1 Hz), 4.34 (1H, s), 3.84 (2H, br d, J = 7.00 Hz), 2.65 (1H, m), 2.43 (1H, m), 2.42 (3H, s), 2.23 (1H, m), 1.73 (1H, m), 1.73 (6H, s), 1.00 (3H, s), 0.95 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.5, 144.9, 134.5, 132.5, 125.7, 121.7, 120.9, 119.0, 113.0, 109.2, 89.4, 63.4, 53.2, 45.8, 41.3, 37.8, 34.5, 25.6, 23.5, 22.5, 18.0; EIMS *m*/*z* (relative intensity) 388/390 (M^+, 22/23), 319/321 (96/100); HRMS (FAB) *m*/*e* 389.1607 ($M^+ + H$, $C_{21}H_{29}BrN_2$ requires 389.1592).

6-Bromo-1-methyl-3a,8-bis(3-methyl-2-buten-1-yl)-1,2,3,-3a,8,8a-hexaydropyrrolo[2,3-*b*]indole, Flustramine B (2). Prepared from **4** as a colorless oil (72 mg, 97%): R_f 0.38 (5:95 MeOH/$CHCl_3$); IR ($CHCl_3$) ν_{max} 2966, 2934, 1598, 1486, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (1H, d, J = 7.8 Hz), 6.74 (1H, dd, J = 7.8, 1.7 Hz), 6.50 (1H, d, J = 1.6 Hz), 5.13 (1H, br t, J = 6.5 Hz), 4.93 (1H, br t, J = 7.2 Hz), 4.29 (1H, s), 3.88 (1H, dd, J = 16.4, 5.5 Hz), 3.79 (1H, dd, J = 16.2, 7.2 Hz), 2.67 (1H, m), 2.55 (1H, m), 2.47 (3H, s), 2.39 (2H, d, J = 7.1 Hz), 2.04 (1H, m), 1.86 (1H, m), 1.72 (3H, s), 1.71 (3H, s), 1.65 (3H, s), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.0, 134.8, 134.7, 133.8, 123.9, 121.3, 120.6, 120.3, 119.9, 110.0, 91.6, 56.8, 52.7, 46.2, 38.9, 38.2, 38.0, 25.9, 25.7, 18.1 (2C); EIMS *m*/*z* (relative intensity) 388/390 (M^+, 38/39), 319/321 (96/100); HRMS (FAB) *m*/*e* 389.1577 ($M^+ + H$, $C_{21}H_{29}BrN_2$ requires 389.1592).

Acknowledgment. This research was partially supported by CONACYT (Mexico). O.R.S.-C. gratefully acknowledges CONACYT for a doctoral fellowship. The authors thank I. Q. Luis Velasco Ibarra (Instituto de Química, UNAM) for recording the HRMS.

Supporting Information Available: ^1H and ^{13}C NMR spectra of the natural products **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0012647