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Total Synthesis of (±)-Flustramines A and C, (±)-Flustramide A, and (−)- and (+)-Debromoflustramines A

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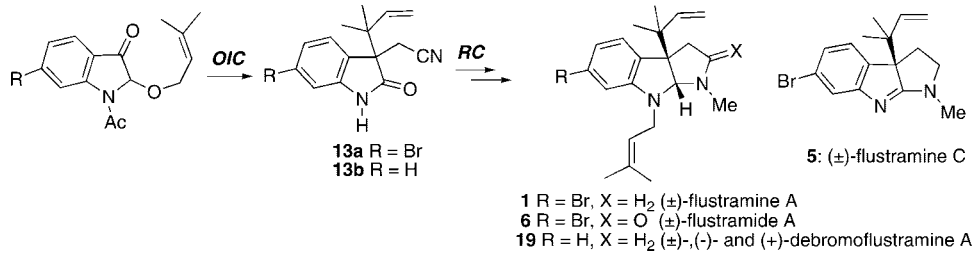

Here we describe the efficient total synthesis of the three title hexahydropyrrolo[2,3-*b*]indole alkaloids and debromo derivative from readily available indolin-3-ones using key domino reactions, olefination−isomerization−Claisen rearrangement (OIC), and reductive cyclization (RC). (±)-Flustramine C (**5**) was synthesized in five steps from 6-bromoindolin-3-one **9** via a key intermediate **13a**. (±)-Flustramine A (**1**) has been obtained by reduction of flustramide A (**6**), which has been prepared in five steps from **13a**. (±)-Debromoflustramine A (**19**) was provided in a similar manner from **13b**. The (−)- and (+)-enantiomers of **19** were synthesized through optical resolution of (±)-carboxylic acid **17b** using (*R*)-4-phenyloxazolidin-2-one.

Introduction

The flustramines and flustramides, isolated from the marine invertebrate Bryozoa *Flusta foliacea*, are a small family of brominated hexahydropyrrolo[2,3-*b*]indole alkaloids bearing isoprenyl substituents at various positions.[1–8] These alkaloids are classified into two structural categories (Figure 1): (i) pyrroloindole having a 1,1-dimethylallyl (reverse prenyl) group at the 3a-position, e.g., flustramines A (**1**), C (**5**), D (**2**), flustramide A (**6**), isoflustramine D (**3**), and dihydroflustramine C (**4**), and (ii) pyrroloindoline containing a 3a-prenyl group, e.g., flustramines B (**7**) and E (**8**). Flustramines A (**1**) and B (**7**), isolated from *F. foliacea*, were the first members of the family to be identified.[1] These compounds exhibit both skeletal and smooth muscle relaxant activities.[9] Recently, flustramine A (**1**) was demonstrated to have blocking activity on a voltage-activated potassium channel.[10] Flustramine D (**2**) and dihydroflustramine C (**3**) show antibacterial activities.[6,11] The unique structural array and the interesting biological activities displayed by these alkaloids make them and the related compounds attractive synthetic targets.[12] Recently, we have developed our synthetic methodology using the domino olefination−isomerization−Claisen rearrangement (OIC) and reductive cyclization (RC) for construction of the 3a-allylpyrrolo[2,3-*b*]-indoline architecture including the related alkaloids of flustramines.[13] In the present paper, we describe the total synthesis of (±)-flustramines A (**1**) and C (**5**), (±)-flustramide A (**6**), and (±)-debromoflustramine A (**19**) as an efficient approach to *F.*

(1) Flustramines A and B: (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.

(2) Flustramine C: Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440–3443.

(3) Flustramide A: Wulff, P.; Carlé, J. S.; Christophersen, C. *Comp. Biochem. Physiol.* **1982**, *71B*, 523–524.

(4) Dihydroflustramine C: Wright, J. L. C. *J. Nat. Prod.* **1984**, *47*, 893–895.

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

(6) Flustramine D: Laycock, M. V.; Wright, J. A.; Patil, A. D. *Can. J. Chem.* **1986**, *64*, 1312–1316.

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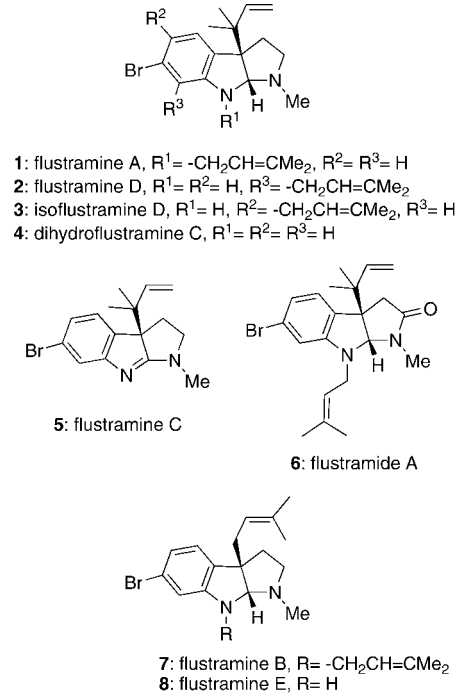
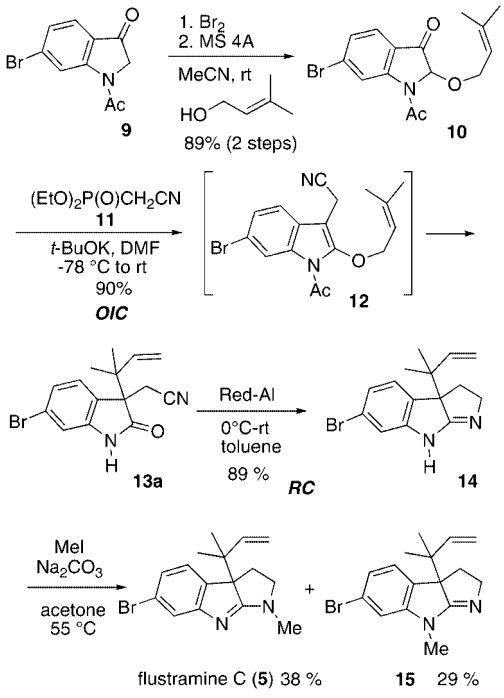


FIGURE 1. Flustramines and flustramide.

SCHEME 1. Synthesis of (±)-Flustramine C (5)



foliacea alkaloids. Furthermore, we performed synthesis of (−)-**19** and (+)-**19** through optical resolution of (±)-carboxylic acid **17b** by coupling with (*R*)-4-phenyloxazolidin-2-one.

Results and Discussion

Initially the synthesis of flustramine C (**5**) was performed as illustrated in Scheme 1. Bromination of 6-bromoindolin-3-one (**9**)[14] at the C2 site and successive substitution with prenyl alcohol in the presence of MS 4A were carried out to give 2-prenyloxyindolin-3-one **10** in 89% yield over two steps. When **10** was allowed to react with cyanomethylphosphonate **11** in the presence of *t*-BuOK at −78 °C, followed by warming to room temperature, Horner−Wadsworth−Emmons olefination of **10**, isomerization, Claisen rearrangement of **12**, and deacetylation took place continuously to produce 3-cyanomethyl-3-(2-methyl-3-buten-2-yl)indolin-2-one (**13a**) in 90% yield. On treatment of **13a** with Red-Al reduction at 0 °C, followed by warming to room temperature, selective reduction of the nitrile group with subsequent cyclization gave pyrroloindole **14** in 89% yield.[15] Methylation of **14** afforded (±)-flustramine C (**5**) in 38% yield together with its isomer **15** (29%). A comparison of the spectroscopic data of synthetic (±)-**5** with that reported for the natural[2,10] and synthetic products[12c,e] revealed that they were identical except for the optical activity.

Next, we synthesized (±)-flustramine A (**1**) and (±)-flustramide A (**6**) from the nitrile **13a** as shown in Scheme 2. *N*-Alkylation of **13a** with prenyl bromide in the presence of NaH followed by selective hydrolysis of **16a** with NaOH in boiling MeOH gave the corresponding carboxylic acid **17a** in excellent yield. Consecutive treatment of **17a** with pentafluorophenol and EDC and with methylamine facilitated condensation to yield *N*-methylamide **18a** (93%). On treatment of the amide **18a** with alane-*N*,*N*-dimethylethylamine complex at −15 °C for 5 min, chemoselective reduction of the lactam carbonyl group of **18a** proceeded smoothly without reduction of the side chain amide or debromination, and successive cyclization produced (±)-flustramide A (**6**) in 92% yield. Furthermore, according to Morales-Ríos's procedure,[12j] reduction of **6** with the alane complex at room temperature afforded (±)-flustramine A (**1**, 90%). The spectral properties of our synthetic compounds **1** and **6** are identical to those reported for the natural and synthetic products flustramine A[1,12e,j] and flustramide A,[3,12j] respectively, except for the optical activity.

Using this procedure (Scheme 2), debromoflustramine A (**19**) was prepared from **13b**,[13b] which was readily obtained by domino OIC reactions of debromo derivative of **9**. The similar three-step transformation of **13b** to **18b** was smoothly carried

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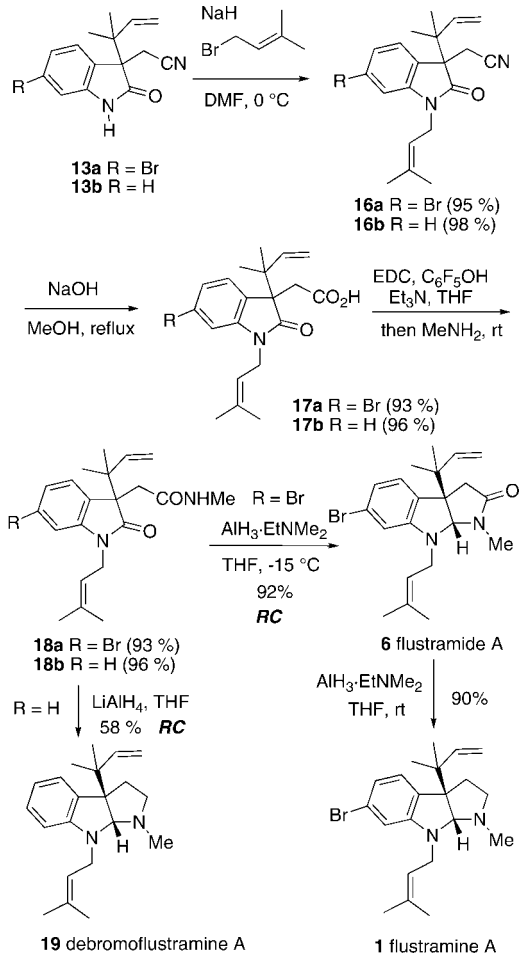
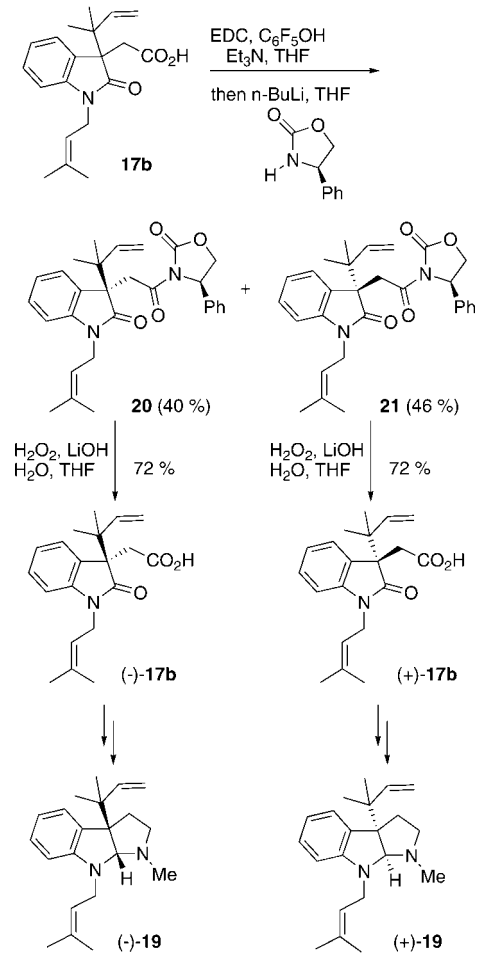
(15) The regiochemistry of **14** was confirmed by comparing its chemical shifts (δ 3.77 and 3.87) of C2-methylene proton signals with that of flustramine C (**5**) (δ 3.39 and 3.94) and its regioisomer **15** (δ 3.80 and 3.99).

SCHEME 2. Synthesis of (±)-Flustramide A (1), Flustramine A (6), and Debromo Derivative 19



SCHEME 3. Synthesis of (−)- and (+)-Debromoflustramine A (19)



out in 90% overall yield. Reductive cyclization of **18b** with $LiAlH_4$ instead of alane directly afforded debromoflustramine A (**19**)[12j] in a moderate yield.

Finally, in order to obtain optically active **19**, we performed optical resolution of (±)-carboxylic acid **17b** (Scheme 3). Thus, successive treatment of **17b** with pentafluorophenol and EDC and with the lithium salt of (*R*)-4-phenyloxazolidin-2-one furnished *N*-acyloxazolidin-2-ones **20** (40%) and **21** (46%).[16] Hydrolysis of **20** and **21** with 30% aq H_2O_2 and LiOH afforded (−)-**17b** and (+)-**17b**, each in 72% yield, respectively. Condensation of (−)-**17b** with methylamine using EDC and $LiAlH_4$ reduction of (−)-**18b** to (−)-**19** were accomplished in the same way as for the racemic version. (+)-**19** also was obtained from (+)-**17b**. The stereochemistry of (−)-**19** was elucidated by comparing with the specific rotation of the known pyrrolo[2,3-*b*]indoline compounds, e.g., (−)-flustramines[1–8] and (−)-physostigmine.[17]

In conclusion, we have accomplished the concise total synthesis of four marine indole alkaloids including (±)-flustramines A (**1**) and C (**5**), (±)-flustramide A (**6**), and (±)-debromoflustramine A **19** via domino olefination−isomerization−Claisen rearrangement (OIC) and reductive cyclization (RC) as key steps. This approach provides a potentially wide route to a variety of pyrrolo[2,3-*b*]indole alkaloids containing a reversed prenyl group at the 3a position. The optical resolution of (±)-carboxylic acid **17b** was employed in preparation of optically active debromoflustramine A **19**. Further applications of this methodology to the synthesis of other related alkaloids are now underway.

(16) The stereochemistries of **20** and **21** were tentatively assigned by their transformation to (−)-**19** and (+)-**19**, respectively.

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Experimental Section

1-Acetyl-6-bromoindolin-3-one (**9**)[14] and 3-(2-methylbut-3-en-2-yl)-3-cyanomethylindolin-2-one (**13b**)[13b] were prepared according to the reported procedures.

1-Acetyl-6-bromo-2-(3-methylbut-2-en-1-yloxy)indolin-3-one (10). To a solution of **9** (1.10 g, 4.33 mmol) in dry dichloromethane (20 mL) was added a dichloromethane solution of bromine (1.0 M, 7.36 mL, 7.36 mmol) at 0 °C. After 1.5 h at the same temperature, the reaction mixture was diluted with dichloromethane, washed with satd $NaHCO_3$ and with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue (1.39 g) as 2-bromoindolin-3-one was used without further purification in the next reaction. A suspension of the residue, 3-methylbut-2-enol (850 μL, d = 0.85, 8.34 mmol), and MS 4A (0.8 g) in dry acetonitrile (10 mL) was stirred at room temperature under nitrogen atmosphere. After 3 days, the reaction mixture was diluted with Et_2O and filtered through Celite. The filtrate was washed with 5% NH_4OH and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was chromatographed by silica gel column with AcOEt−hexane (1:2) as an eluent to give **10** (1.30 g, 89%) as a viscous oil: IR ($CHCl_3$) 1732, 1694, 1599, 1426 cm^{-1}; ^1H NMR

($CDCl_3$, 300 MHz) δ 1.59 (3H, s), 1.69 (3H, s), 2.35 (3H, s), 4.08 (1H, dd, J = 11.0, 7.4 Hz), 4.18 (1H, dd, J = 11.0, 7.4 Hz), 5.18 (1H, s), 5.29 (1H, tt, J = 7.4, 1.4 Hz), 7.33 (1H, dd, J = 8.2, 1.8 Hz), 7.54 (1H, d, J = 8.2 Hz), 8.72 (1H, d, J = 1.8 Hz); MS m/z 339 (M + 2, 1), 337 (M^+, 1), 271 (13), 269 (14), 255 (50), 253 (51), 228 (94), 226 (100), 213 (15), 211 (16), 69 (48), 43 (47); HRMS (EI) m/z calcd for $C_{15}H_{16}NO_3Br$ 337.0314, found 337.0315.

2-[6-Bromo-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile (13a). A solution of diethyl cyanomethylphosphonate (**11**) (1.55 mL, d = 1.13, 9.7 mmol) in dry DMF (8 mL) was added to a suspension of potassium *tert*-butoxide (1.03 g, 8.9 mmol) in dry DMF (12 mL) at 0 °C. After being stirred at the same temperature for 1 h, the mixture was cooled to −78 °C. A solution of **10** (0.99 g, 2.97 mmol) in dry DMF (10 mL) was gradually added to the mixture at −78 °C. After TLC showed that **10** was consumed (ca. 0.5 h), the reaction mixture was warmed slowly to room temperature, stirred at the same temperature for 0.5 h, quenched by10% aq HCl at 0 °C, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was chromatographed by silica gel column with AcOEt−hexane (1:1.5) as an eluent to give **13a** (0.84 g, 90%) as colorless crystals: mp 156−157 °C (AcOEt−hexane); IR ($CHCl_3$) 3430, 2255, 1612, 1481 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.16 (3H, s), 2.84 (1H, d, J = 16.5 Hz), 3.00 (1H, d, J = 16.5 Hz), 5.10 (1H, d, J = 17.4, 0.9 Hz), 5.23 (1H, dd, J = 10.8, 0.9 Hz), 6.02 (1H, dd, J = 17.4, 10.8 Hz), 7.10 (1H, d, J = 1.7 Hz), 7.14 (1H, d, J = 8.2 Hz), 7.22 (1H, dd, J = 8.2, 1.7 Hz), 8.21 (1H, brs); MS m/z 320 (M + 2, 2), 318 (M^+, 3), 252 (64), 250 (67), 225 (18), 223 (19), 69 (100), 41 (23); HRMS (EI) m/z calcd for $C_{15}H_{15}N_2OBr$ 318.0368, found 318.0364. Anal. Calcd for $C_{15}H_{15}N_2OBr$: C, 56.44; H, 4.74; N, 8.78. Found: C, 56.38; H, 4.72; N, 8.72.

6-Bromo-1,2,3,3a-tetrahydro-3a-(2-methylbut-3-en-2-yl)pyrrolo[2,3-*b*]indole (14). To a solution of **13a** (29 mg, 0.09 mmol) in toluene (2 mL) was added Red-Al (65% toluene solution, 136 μL, 0.45 mmol) at 0 °C. After being stirred at room temperature for 14 h, the reaction mixture was treated with 5% aq NaOH (3 mL) and extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $CHCl_3$−MeOH (30:1) as an eluent to give **14** (25 mg, 89%) as pale yellow crystals: mp 169−171 °C (C_6H_6); IR ($CHCl_3$) 1719, 1680, 1635, 1605, 1586 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (3 H, s), 1.00 (3 H, s), 2.06 (1 H, dt, J = 12.9, 9.2 Hz), 2.40 (1 H, dd, J = 12.9, 5.2 Hz), 3.31 (1 H, brs), 3.77 (1 H, dd, J = 12.2, 9.2 Hz), 3.87 (1 H, ddd, J = 12.2, 9.2, 5.6 Hz), 5.01 (1 H, d, J = 17.1 Hz), 5.04 (1 H, d, J = 10.9 Hz), 6.01 (1 H, dd, J = 17.1, 10.9 Hz), 6.93 (1 H, d, J = 7.9 Hz), 6.97 (1 H, dd, J = 7.9, 1.3 Hz), 7.04 (1 H, d, J = 1.3 Hz); MS m/z 306 (M + 2, 31), 304 (M^+, 33), 237 (99), 235 (100), 210 (8), 208 (9), 156 (34), 129 (18), 69 (7); HRMS (EI) m/z calcd for $C_{15}H_{17}N_2Br$ 304.0575, found 304.0574.

Flustramine C (5). A suspension of **14** (10 mg, 0.033 mmol), methyl iodide (1.0 M acetone solution, 266 μL, 0.266 mmol), and Na_2CO_3 in acetone (1 mL) was heated at 55 °C for 7 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with $CHCl_3$−MeOH (50:1) as an eluent to give flustramine C (**5**, 4.0 mg, 38%) and 6-bromo-2,3,3a,8-tetrahydro-8-methyl-3a-(2-methylbut-3-en-2-yl)pyrrolo[2,3-*b*]indole (**15**, 3.0 mg, 29%) as viscous oils.

5: IR ($CHCl_3$) 1636, 1586, 1565, 1426, 1416 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.89 (3 H, s), 0.99 (3 H, s), 2.06 (1 H, ddd, J = 8.9, 9.9, 12.9 Hz), 2.35 (1 H, dd, J = 6.6, 12.9 Hz), 3.02 (3 H, s,), 3.39 (1 H, t, J = 9.9 Hz), 3.94 (1 H, ddd, J = 6.6, 8.9, 9.9 Hz), 5.04 (1 H, d, J = 17.2 Hz), 5.06 (1 H, d, J = 10.9 Hz), 6.01 (1 H, dd, J = 17.2, 10.9 Hz), 6.910 (1 H, d, J = 7.9 Hz), 6.912 (1 H, d, J = 7.9 Hz), 7.21 (1 H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 21.6, 22.8, 27.9, 33.2, 42.9, 59.7, 65.7, 113.6, 119.1, 121.9, 122.0, 124.3, 137.6, 143.4, 163.5, 188.1; MS m/z 320 (M + 2, 32), 318 (M^+, 33), 251 (99), 249 (100), 210 (4), 208 (5), 170 (42), 138 (11), 129 (13), 69 (5); HRMS (EI) m/z calcd for $C_{16}H_{19}N_2Br$: 318.0732, found 318.0730.

15: IR ($CHCl_3$) 1669, 1601, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (3 H, s), 0.97 (3 H, s), 2.03 (1 H, dt, J = 12.7, 9.0 Hz), 2.41 (1 H, dd, J = 12.7, 5.4 Hz), 3.12 (3 H, s), 3.80 (1 H, dd, J = 14.0, 9.0 Hz), 3.99 (1 H, ddd, J = 14.0, 9.0, 5.4 Hz), 4.96 (1 H, d, J = 17.5 Hz), 5.00 (1 H, d, J = 10.9 Hz), 5.93 (1 H, dd, J = 17.5, 10.9 Hz), 6.79 (1 H, d, J = 1.7 Hz), 6.93 (1 H, dd, J = 7.9 Hz), 6.97 (1 H, dd, J = 7.9, 1.7 Hz); MS m/z 320 (M + 2, 15), 318 (M^+, 13), 251 (98), 249 (100), 224 (4), 222 (5), 170 (19), 143 (7), 129 (5), 69 (4); HRMS (EI) m/z calcd for $C_{16}H_{19}N_2Br$ 318.0732, found 318.0736.

2-[6-Bromo-1-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile (16a). A solution of **13a** (400 mg, 1.25 mmol) in dry DMF (8 mL) was added to a suspension of NaH (60% in mineral oil, 60 mg, 1.50 mmol) in DMF (4 mL) at 0 °C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 0.5 h, 4-bromo-2-methyl-2-butene (173 μL, d = 1.29, 1.50 mmol) was added under the same conditions. After 0.5 h, the reaction mixture was quenched with water and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt−hexane (1:3) as an eluent to give **16a** (463 mg, 95%) as a viscous oil: IR ($CHCl_3$) 2255, 1713, 1603, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, s), 1.05 (3H, s), 1.66 (3H, s), 1.76 (3H, s), 2.75 (1H, d, J = 16.3 Hz), 2.90 (1H, d, J = 16.3 Hz), 4.12 (1H, dd, J = 15.4, 6.8 Hz), 4.36 (1H, dd, J = 15.4, 6.4 Hz), 4.99 (1H, dd, J = 17.4, 0.9 Hz), 5.04 (1H, m), 5.12 (1H, dd, J = 10.6, 0.9 Hz), 5.92 (1H, dd, J = 17.4, 10.6 Hz), 6.91 (1H, d, J = 1.7 Hz), 7.07 (1H, d, J = 8.0 Hz), 7.14(1H, dd, J = 8.0, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.5, 21.97, 21.99, 25.7, 38.4, 41.8, 54.5, 112.3, 115.3, 116.3, 117.3, 122.8, 124.8, 126.4, 126.6, 137.4, 141.5, 144.9, 175.3; MS m/z 388 (M + 2, 9), 386 (M^+, 10), 320 (76), 318 (76), 264 (61), 262 (62), 251 (8), 249 (8), 225 (5), 223 (5), 69 (100), 41 (34); HRMS (EI) m/z calcd for $C_{20}H_{23}BrN_2O$ 386.0994, found 386.0993.

2-[6-Bromo-1-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetic Acid (17a). A solution of **16a** (210 mg, 0.54 mmol) and 35% aq NaOH (1.6 mL) in MeOH (10 mL) was heated under reflux for 45 h. After evaporation in vacuo, the residue was acidified with 10% HCl and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford **17a** (205 mg, 93%) as a solid: mp 123−126 °C; IR ($CHCl_3$) 3200, 1712, 1601, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3H, s), 1.05 (3H, s), 1.71 (3H, s), 1.80 (3H, s), 2.79 (1H, d, J = 16.4 Hz), 3.11 (1H, d, J = 16.4 Hz), 4.14 (1H, dd, J = 15.6, 6.4 Hz), 4.35 (1H, dd, J = 15.6, 6.4 Hz), 4.98 (1H, dd, J = 17.4, 0.9 Hz), 5.04 (1H, t, J = 6.4 Hz), 5.10 (1H, dd, J = 10.8, 0.9 Hz), 5.91 (1H, dd, J = 17.4, 10.8 Hz), 6.86 (1H, d, J = 1.7 Hz), 6.94 (1H, d, J = 8.1 Hz), 7.09 (1H, dd, J = 8.1, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 21.7, 21.8, 25.7, 36.6, 38.2, 41.8, 54.0, 111.5, 114.4, 117.7, 121.6, 123.8, 125.6, 128.2, 136.4, 142.2, 145.6, 175.3, 177.3; MS m/z 407 (M + 2, 13), 405 (M^+, 14), 339 (98), 337 (100), 293 (14), 291 (13), 283 (62), 281 (64), 238 (27), 236 (28), 69 (90), 41 (54); HRMS (EI) m/z calcd for $C_{20}H_{24}BrNO_3$ 405.0940, found 405.0932.

2-[6-Bromo-1-(3-methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]-*N*-methylacetamide (18a). A solution of **17a** (186 mg, 0.46 mmol), pentafluorophenol (253 mg, 1.37 mmol), triethylamine (127 mL, d = 0.73, 0.92 mmol), and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) HCl salt (132 mg, 0.69 mmol) in THF (6.5 mL) was kept at room temperature for 1.5 h. Gaseous methylamine was passed through the reaction mixture at room temperature. After acidification with 10% HCl, the resulted mixture was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chroma-

tography with AcOEt as an eluent to give **18a** (179 mg, 93%) as crystals: mp 78−83 °C (AcOEt−hexane); IR ($CHCl_3$) 3463, 1698, 1603, 1525, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (3H, s), 1.08 (3H, s), 1.73 (3H, s), 1.83 (3H, s), 2.50 (3H, d, J = 4.9 Hz), 2.65 (1H, d, J = 14.0 Hz), 3.00 (1H, d, J = 14.0 Hz), 4.21 (1H, dd, J = 15.8, 6.6 Hz), 4.40 (1H, dd, J = 15.8, 6.6 Hz), 4.98 (1H, dd, J = 17.4, 1.1 Hz), 5.07−5.09 (1H, m), 5.10 (1H, dd, J = 10.8, 1.1 Hz,), 5.44 (1H, br), 5.96 (1H, dd, J = 17.4, 10.8 Hz), 6.89 (1H, d, J = 1.7 Hz), 7.04 (1H, d, J = 8.1 Hz), 7.11 (1H, dd, J = 8.1, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 21.7, 22.1, 25.7, 26.1, 38.2, 38.6, 41.9, 55.4, 111.5, 114.0, 117.9, 121.5, 123.8, 126.1, 128.4, 136.4, 142.5, 145.2, 169.4, 178.0; MS *m/z* 420 (M + 2, 10), 418 (M^+, 10), 352 (99), 350 (100), 294 (29), 292 (23), 238 (52), 236 (53), 225 (21), 223 (20), 69 (39), 41 (16); HRMS (EI) *m/z* calcd for $C_{21}H_{27}BrN_2O_2$ 418.1256, found 418.1257. Anal. Calcd for $C_{21}H_{27}BrN_2O_2$: C, 60.15; H, 6.49; N, 6.68. Found: C, 60.34; H, 6.72; N, 6.41.

Flustramide A (6). To a solution of **18a** (50 mg, 0.12 mmol) in THF (5 mL) was added $AlH_3 \cdot EtMe_2N$ (0.5 M toluene solution, 1.2 mL, 0.60 mmol) at −15 °C. After 5 min, the reaction mixture was treated with THF−water (1:1, 10 mL) at the same temperature and stirred at room temperature for 15 min. The mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to give a residue, which was diluted with AcOEt. The organic solution was washed with satd aq Na_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with AcOEt−hexane (1:1) as an eluent to give flustramide A (**6**, 44.3 mg, 92%) as a viscous oil: IR ($CHCl_3$) 1682, 1593, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, s), 1.03 (3H, s), 1.75 (3H, s), 1.77 (3H, s), 2.54 (1H, d, J = 17.4 Hz), 2.84 (1H, d, J = 17.4 Hz), 2.85 (1H, s), 3.93 (2H, d, J = 6.6 Hz), 4.83 (1H, s), 5.05 (1H, dd, J = 17.4, 1.1 Hz), 5.17 (1H, dd, J = 10.8, 1.1 Hz) 5.26 (1H, t, J = 6.6, Hz), 5.78 (1H, dd, J = 17.4, 10.8 Hz), 6.56 (1H, d, J = 1.7 Hz), 6.81 (1H, dd, J = 7.9, 1.7 Hz), 6.92 (1H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 22.0, 22.7, 25.8, 28.1, 39.5, 41.3, 46.4, 55.5, 85.9, 110.9, 114.5, 120.3, 120.6, 122.4, 126.1, 131.6, 135.6, 143.1, 150.9, 172.4; MS *m/z* 404 (M + 2, 37), 402 (M^+, 37), 335 (44), 333 (45), 267 (94), 265 (97), 210 (20), 208 (20), 69 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{27}BrN_2O$ 402.1307, found 402.1301.

Flustramine A (1). To a solution of **6** (35 mg, 0.087 mmol) in THF (7 mL) was added $AlH_3 \cdot EtMe_2N$ (0.5 M toluene solution, 0.26 mL, 0.13 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 5 min, treated with THF−H_2O (1:1, 10 mL), and filtered through Celite. The filtrate was evaporated to give a residue, which was basified with satd aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt−hexane (3:2) as an eluent to give flustramine A (**1**, 30.3 mg, 90%) as a viscous oil: IR ($CHCl_3$) 2968, 2930, 2857, 1591, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (3H, s), 1.00 (3H, s), 1.72 (3H, s), 1.73 (1H, ddd, *J* 11.8, 5.3 and 2.6 Hz), 1.75 (3H, s), 2.23 (1H, ddd, *J* 11.8, 9.7 and 6.8 Hz), 2.42 (3H, s), 2.43 (1H, ddd, *J* 9.9, 9.7 and 5.3 Hz), 2.65 (1H, ddd, *J* 9.9, 6.8 and 2.6 Hz), 3.82 (1H, dd, *J* 16.7 and 6.3 Hz), 3.84 (1H, dd, *J* 16.7 and 5.8 Hz), 4.34 (1H, s), 4.98 (1H, d, *J* 17.4 Hz), 5.06 (1H, d, *J* 10.8 Hz), 5.22 (1H, dd, 6.3 and 5.8 Hz), 5.94 (1H, dd, *J* 17.4 and 10.8 Hz), 6.47 (1H, d, *J* 1.5 Hz), 6.68 (1H, dd, *J* 7.8 and 1.5 Hz), 6.90 (1H, d, *J* 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 22.5, 23.5, 25.6, 34.5, 37.8, 41.3, 45.9, 53.1, 63.4, 89.3, 109.3, 113.0, 119.1, 120.9, 121.7, 125.8, 132.5, 134.6, 144.9, 153.6; MS *m/z* 390 (M + 2, 22), 388 (M^+, 22), 321 (96), 319 (98), 290 (12), 288 (11), 278 (12), 276 (13), 253 (94), 251 (100), 210 (19), 172 (16), 171 (14), 69 (35); HRMS (EI) *m/z* calcd for $C_{21}H_{29}BrN_2$ 388.1514, found 388.1518.

2-[1-(3-Methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetonitrile (16b). A solution of **13b** (1.00 g, 4.2 mmol) in dry DMF (10 mL) was added to a suspension of NaH (60% in mineral oil, 0.20 mg, 4.99 mmol) in DMF (8 mL) at 0 °C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 0.5 h, 4-bromo-2-methyl-2-butene (575 μL, d = 1.29, 4.99 mmol) was added under the same conditions. After 1.5 h, the reaction mixture was quenched with 10% HCl and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt−hexane (1:3) as an eluent to give **16b** (1.25 g, 98%) as colorless powder: mp 109 °C (AcOEt−hexane); IR ($CHCl_3$) 2251, 1707, 1612, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H), 1.13 (s, 3H), 1.72 (s, 3H), 1.83 (s, 3H), 2.84 (d, 1H, J = 16.4 Hz), 2.97 (d, 1H, J = 16.4 Hz), 4,23 (dd, 1H, J = 15.6, 6.6 Hz), 4.46 (dd, 1H, J = 15.6, 6.6 Hz), 5.07 (dd, 1H, J = 17.4, 1.1 Hz), 5.12 (m, 1H), 5.18 (dd, 1H, J = 10.8, 1.1 Hz), 6.07 (dd, 1H, J = 17.4, 10.8 Hz), 6.84 (d, 1H, J = 7.5 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.25−7.34 (m, 2H); MS *m/z* 308 (M^+, 8), 240 (60), 184 (100), 171 (11), 145 (10), 128 (7), 69 (36), 41 (15); HRMS (EI) *m/z* calcd for $C_{20}H_{24}N_2O$ 308.1889, found 308.1893. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 78.00; H, 8.07; N, 8.83.

2-[1-(3-Methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetic Acid (17b). A solution of **16b** (6.51 g, 21.1 mmol) and 35% aq NaOH (48.2 mL) in MeOH (75 mL) was heated under reflux for 15 h. After evaporation in vacuo, the residue was acidified with 10% HCl and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford **17b** (6.60 g, 96%) as a colorless powder: mp 83−86 °C (AcOEt); IR ($CHCl_3$) 3100, 1713, 1610, 1489, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (s, 3H), 1.06 (s, 3H), 1.70 (s, 3H), 1.80 (s, 3H), 2.81 (d, 1H, J = 16.2 Hz), 3.11 (d, 1H, J = 16.2 Hz), 4.18 (dd, 1H, J = 15.6, 6.4 Hz), 4.39 (dd, 1H, J = 15.6, 6.4 Hz), 4.98 (dd, 1H, J = 17.4, 1.3 Hz), 5.08 (m, 1H), 5.08 (dd, 1H, J = 10.8, 1.3 Hz), 5.97 (dd, 1H, J = 17.4, 10.8 Hz), 6.72 (d, 1H, J = 7.5 Hz), 6.92 (t, 1H, J = 7.5 Hz), 7.07 (d, 1H, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 21.8, 21.9, 25.7, 36.8, 38.2, 41.9, 54.3, 108.2, 114.0, 118.4, 121.0, 124.6, 128.0, 129.1, 135.8, 142.7, 144.3, 174.4, 177.5; MS *m/z* 327 (M^+, 16), 259 (100), 213 (18), 203 (91), 158 (43), 145 (32), 128 (8), 117 (9), 69 (29), 41 (16); HRMS (EI) *m/z* calcd for $C_{20}H_{25}NO_3$ 327.1834, found 327.1834.

2-[1-(3-Methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]-*N*-methylacetamide (18b). A solution of **17b** (290 mg, 0.89 mmol), pentafluorophenol (325 mg, 1.77 mmol), triethylamine (238 mL, d = 0.73, 1.77 mmol), and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) HCl salt (253 mg, 1.33 mmol) in THF (10 mL) was kept at room temperature for 2 h. Gaseous methylamine was passed through the reaction mixture at room temperature. After acidification with 20% HCl, the resulted mixture was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt as an eluent to give **18b** (295 mg, 98%) as colorless crystals: mp 150−154 °C (AcOEt−hexane); IR ($CHCl_3$) 3462, 1688, 1611, 1528, 1489, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3H), 1.09 (s, 3H), 1.71 (s, 3H), 1.83 (s, 3H), 2.47 (d, 3H, J = 4.7 Hz), 2.68 (d, 1H, J = 13.9 Hz), 3.00 (d, 1H, J = 13.9 Hz), 4.27 (dd, 1H, J = 15.6, 6.9 Hz), 4.39 (dd, 1H, J = 15.6, 6.1 Hz), 4.99 (dd, 1H, J = 17.4, 1.3 Hz), 5.09 (m, 1H), 5.09 (dd, 1H, J = 10.8, 1.3 Hz), 5.37 (1H, br), 6.02 (dd, 1H, J = 17.4, 10.8 Hz), 6.76 (d, 1H, J = 7.5 Hz), 7.00 (t, 1H, J = 7.5 Hz), 7.19−7.26 (m, 2H); MS *m/z* 340 (M^+, 17), 272 (100), 213 (26), 158 (67), 145 (23), 69 (15), 41 (9); HRMS (EI) *m/z* calcd for $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2152. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.06; H, 8.43; N, 8.12. (−)-(3*R*)-**18b**: $[\alpha]^{23}_D$ = −41.3 (c = 0.77, $CHCl_3$). (+)-(3*S*)-**18b**: $[\alpha]^{23}_D$ = +41.7 (c = 0.24, $CHCl_3$).

1-Methyl-3a-(2-methylbut-3-en-2-yl)-8-(3-methylbut-2-enyl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (19, Debromoflustramine A). To a solution of **18b** (100 mg, 0.29 mmol) in THF (10 mL)

was added $LiAlH_4$ (1 M THF solution, 2.93 mL, 2.93 mmol) at room temperature. After being refluxed for 4 h, the reaction mixture was treated with THF−water (1:1, 10 mL). The resulting mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to give a residue, which was diluted with AcOEt. The organic solution was washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with AcOEt−hexane (1:1) as an eluent to give **19** (53 mg, 58%) as a viscous oil: IR ($CHCl_3$) 2934, 1599, 1489, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (s, 3H), 1.03 (s, 3H), 1.71 (s, 3H), 1.73 (s, 3H), 1.78 (ddd, 1H, J = 11.9, 5.5, 2.7 Hz), 2.24 (ddd, 1H, J = 11.9, 9.7, 6.6 Hz), 2.42 (ddd, 1H, J = 9.7, 9.0, 5.5 Hz), 2.43 (s, 3H), 2.64 (ddd, 1H, J = 9.0, 6.6, 2.7 Hz), 3.84 (dd, 1H, J = 16.0, 7.4 Hz), 3.88 (dd, 1H, J = 16.0, 6.0 Hz), 4.32 (s, 1H), 4.99 (dd, 1H, J = 17.3, 1.4 Hz), 5.06 (d, 1H, J = 10.8, 1.4 Hz), 5.26 (m, 1H), 5.98 (dd, 1H, J = 17.3, 10.8 Hz), 6.39 (d, 1H, J = 7.9 Hz), 6.59 (td, 1H, J = 7.4, 1.3 Hz), 7.04 (td, 1H, J = 7.5, 1.3 Hz), 7.07 (dd, 1H, J = 7.4, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 22.8, 23.7, 25.7, 34.8, 37.7, 41.5, 46.5, 53.3, 63.7, 89.0, 106.4, 112.5, 116.4, 121.7, 124.6, 127.5, 133.2, 133.6, 145.2, 152.2; MS m/z 310 (M^+, 28), 241 (100), 210 (12), 198 (18), 173 (88), 130 (26), 69 (12); HRMS (EI) m/z calcd for $C_{21}H_{30}N_2$ 310.2409, found 310.2415. (−)-(3a*R*)-**19**: $[\alpha]^{23}_D$ = −132.6 (c = 0.89, $CHCl_3$). (+)-(3a*S*)-**19**: $[\alpha]^{23}_D$ = +137.4 (c = 1.55, $CHCl_3$).

(3″*R*,4*R*)- and (3″*S*,4*R*)-3-{2′-[1″-(3-Methylbut-2-enyl)-3″-(2-methylbut-3-en-2-yl)-2″-oxoindolin-3″-yl]acetyl}-4-phenyloxazolidin-2-one (20 and 21). A solution of **17b** (2.00 g, 6.10 mmol), pentafluorophenol (2.24 g, 12.2 mmol), triethylamine (1.69 mL, d = 0.73, 12.2 mmol), and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) HCl salt (1.74 g, 9.15 mmol) in THF (60 mL) was kept at room temperature for 1.5 h. After concentration of the reaction mixture under reduced pressure, an AcOEt solution of the residue was washed with satd Na_2CO_3 and with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in THF (70 mL) was added a solution of lithium salt generated from (*R*)-4-phenyloxazolidin-2-one (1.99 g, 12.2 mmol) and *n*-buthyllithium (1.58 mmol/mL, 8.5 mL, 13.4 mmol) in THF (70 mL) at 0 °C. After 10 min, the resulting mixture was concentrated and extracted with diethyl ether. After neutralization with 1 N HCl, the extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt−hexane (1:3) as an eluent to give **20** (1.15 g, 40%) and **21** (1.33 g, 46%).

20: mp 143−147 °C (ACOEt−hexane); $[\alpha]^{16}_D$ = −155.8 (c = 1.23, $CHCl_3$); IR ($CHCl_3$) 1781, 1709, 1611, 1536, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (3H, s), 1.11 (3H, s), 1.65 (3H, d, J = 1.5 Hz), 1.74 (3H, d, J = 0.9 Hz), 3.44 (1H, d, J = 17.1 Hz), 4.11 (1H, dd, J = 8.8, 3.7 Hz), 4.12 (1H, dd, J = 15.6, 6.6 Hz), 4.14 (1H, d, J = 17.1 Hz), 4.36 (1H, dd, J = 15.6, 6.6 Hz), 4.45 (1H, t, J = 8.8 Hz), 5.03 (1H, dd, J = 8.8, 3.7 Hz), 5.00−5.07 (1H, m), 5.03 (1H, dd, J = 17.4, 1.1 Hz), 5.11 (1H, dd, J = 10.8, 1.1 Hz), 6.01 (1H, dd, J = 17.4, 10.8 Hz), 6.74 (1H, d, J = 7.9 Hz), 6.95 (1H, td, J = 7.9, 1.1 Hz), 7.08−7.30 (7H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 21.7, 22.3, 25.6, 37.6, 38.2, 42.1, 54.7, 57.2, 69.9, 108.1, 114.1, 118.5, 120.8, 124.1, 125.4 (2C), 127.8, 128.3, 128.9 (2C), 129.9, 135.6, 138.2, 142.6, 144.5, 153.7, 169.1, 177.6; MS m/z 472 (M^+, 7), 404 (100), 241 (30), 213 (15), 185 (25), 172 (43), 158 (15), 145 (17), 69 (16); HRMS (EI) m/z calcd for $C_{29}H_{32}N_2O_4$ 472.2362, found 472.2366.

21: viscous oil; $[\alpha]^{16}_D$ = −90.4 (c = 3.74, $CHCl_3$); IR ($CHCl_3$) 1781, 1705, 1611, 1535, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (3H, s), 1.11 (3H, s), 1.62 (3H, d, J = 1.1 Hz), 1.74 (3H, d, J = 1.1 Hz), 3.30 (1H, d, J = 16.3 Hz), 3.99 (1H, dd, J = 8.8, 3.7 Hz), 4.06 (1H, dd, J = 15.6, 6.1 Hz), 4.29 (1H, d, J = 16.3 Hz), 4.36 (1H, dd, J = 15.6, 6.1 Hz), 4.48 (1H, t, J = 8.8 Hz), 4.96−5.04 (1H, m), 5.02 (1H, dd, J = 17.4, 1.1 Hz), 5.09 (1H, dd, J = 10.8, 1.1 Hz), 5.15 (1H, dd, J = 8.8, 3.7 Hz), 6.07 (1H, dd, J = 17.4, 10.8 Hz), 6.58 (1H, d, J = 7.5 Hz), 6.63−6.69 (2H, m), 6.89 (1H, td, J = 7.5, 1.1 Hz), 7.05−7.20 (4H, m), 7.23 (1H, td, J = 7.5, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 21.7, 22.4, 25.6, 37.0, 38.1, 42.0, 54.9, 57.3, 69.8, 108.1, 114.0, 118.7, 120.8, 124.4, 124.8 (2C), 127.7, 127.8, 128.6 (2C), 129.3, 135.2, 138.1, 142.7, 144.3, 153.6, 169.1, 177.7; MS m/z 472 (M^+, 7), 404 (100), 241 (30), 213 (15), 185 (25), 172 (43), 158 (15), 145 (17), 69 (16); HRMS (EI) m/z calcd for $C_{29}H_{32}N_2O_4$ 472.2362, found 472.2361.

(−)-(3*R*)- and (+)-(3*S*)-2-[1-(3-Methylbut-2-enyl)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl]acetic Acid (17b). A solution of **20** (500 mg, 1.05 mmol), 30% H_2O_2 (424 mL, 4.23 mmol), and $LiOH \cdot H_2O$ (88 mg, 2.10 mmol) in THF−H_2O (15 mL, 2:1) was stirred at 0 °C for 12 h. After treatment with Na_2SO_3, the reaction mixture was washed with diethyl ether, acidified with 20% HCl (pH 1−2), and extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt−hexane (1:1) as eluent to give (−)-(*R*)-**17b** (251 mg, 72%). In the same way, (+)-(*S*)-**17b** (250 mg, 72%) was obtained from **21** (500 mg, 1.05 mmol). (−)-(3*R*)-**17b**: $[\alpha]^{23}_D$ −79.2 (c = 0.98, $CHCl_3$); (+)-(3*S*)-**17b**: $[\alpha]^{23}_D$ +76.0 (c = 1.82, $CHCl_3$).

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Supporting Information Available: ^1H NMR spectra of synthetic flustramines A (**1**) and C (**5**), flustramide A (**6**), debromoflustramine A (**19**), and all synthetic intermediates **10**, **13**−**18**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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