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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1805–1808

Total synthesis of (±)-debromoflustramine B and E and (±)-debromoflustramide B based on one-pot intramolecular Ullmann coupling and Claisen rearrangement

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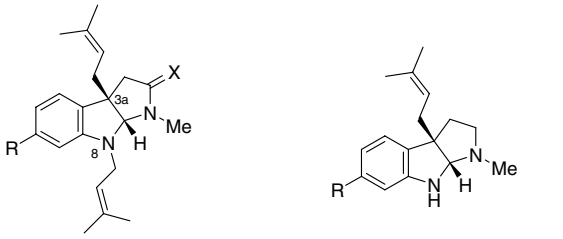
Received 14 December 2006; accepted 4 January 2007
Available online 7 January 2007

Abstract—Total syntheses of (±)-debromoflustramine B and E and (±)-debromoflustramide B were accomplished using a common and versatile intermediate spirocyclic oxindole **14**, which was concisely prepared through intramolecular Ullmann coupling and Claisen rearrangement from iodoindole **13** on a multigram scale.

Pyrrolidinoindoline natural products, which possess the C-3a substituted hexahydropyrrolo[2,3-*b*]indole ring system as a common framework, have been isolated from a wide variety of natural sources and exhibit a broad range of biological activities.[1] Flustramines are the simplest members of this family, most of which display interesting biological activities (Fig. 1).[2] For example, flustramine B (**1**)[3] bearing two prenyl substituents at C-3a and N-8 was found in the marine bryozoan *Flustra foliacea* and exhibits muscle relaxant activity affecting skeletal and smooth muscle,[4] while debromoflustramine E (**5**),[5] which was detected in the skin of the Australian frog *Pseudophyrne semimarmorata* is a known antibacterial agent active against vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus*.[6] The hexahydropyrrolo[2,3-*b*]indole nucleus, having a quaternary carbon prenylated at C-3a, is the defining structural feature of these alkaloids and therefore many efficient methods have been developed for their synthesis.[7]



flustramine B (**1**: R = Br, X = H_2)
debromoflustramine B (**2**: R = H, X = H_2)
debromoflustramide B (**3**: R = H, X = O)

flustramine E (**4**: R = Br)
debromoflustramine E (**5**: R = H)

Figure 1.

We have recently described a stereoselective synthesis of racemic spiro[cyclohex-3-ene-1,3′-indol]-2′(1′*H*)-one **8** from iodoindole **6** through a sequential intramolecular Ullmann coupling and Claisen rearrangement (Scheme 1).[8] The resulting spirocyclic derivatives are considered to be useful intermediates for the synthesis of pyrrolidinoindolines as oxidative cleavage of the cyclohexene ring would provide a C-3a substituted oxindole skeleton. In this Letter, we report the synthesis of a series of hexahydropyrrolo[2,3-*b*]indole alkaloids, (±)-debromoflustramine B (**2**), (±)-debromoflustramine E (**5**) and (±)-debromoflustramide B (**3**) through intramolecular Ullmann coupling and Claisen rearrangement.

The synthesis of the key intermediate **14** was performed as illustrated in Scheme 2. Thus, indole **9** was subjected to a regioselective halogenation using Bergman's protocol to afford 2-iodoindole **10** in high yield.[9] $InCl_3$-catalyzed conjugate addition of **10** with methyl vinyl ketone proceeded smoothly at an ambient temperature to afford **11**,[10] which was protected with a benzyl group

Keywords: Oxindoles; Claisen rearrangement; Ullmann coupling; Total synthesis; Pyrrolidinoindoline alkaloids; One-pot reaction.
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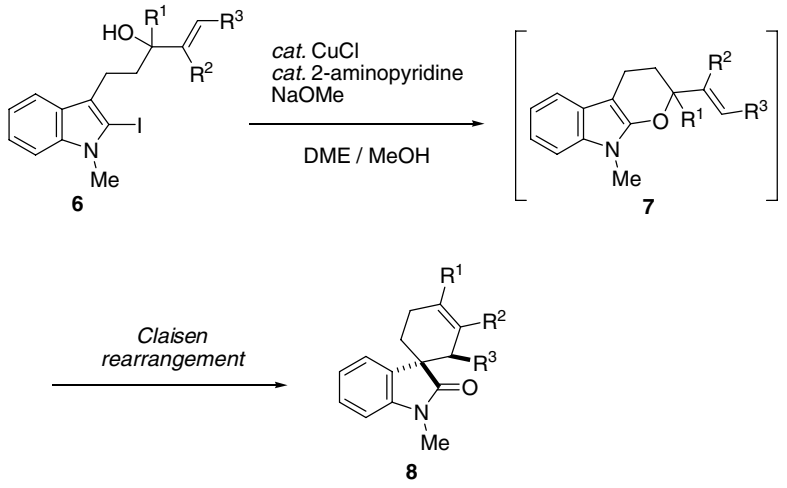
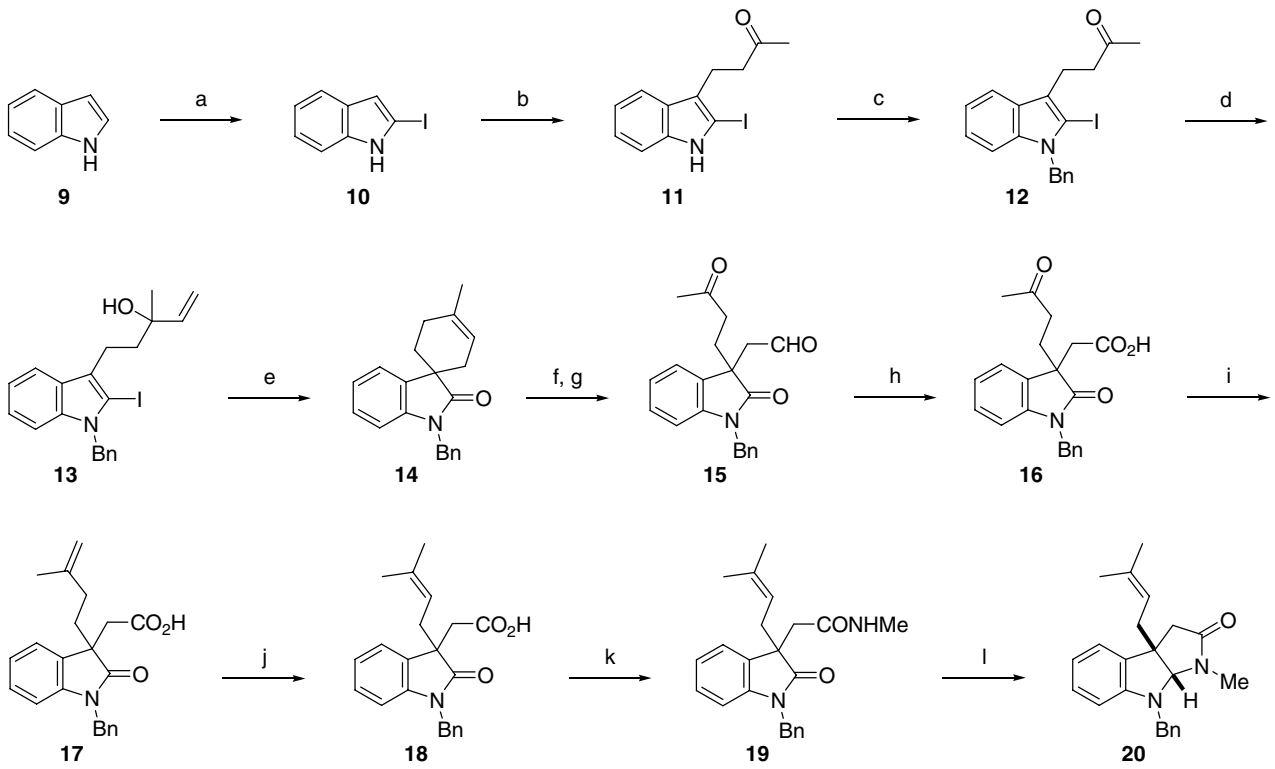
doi:10.1016/j.tetlet.2007.01.002



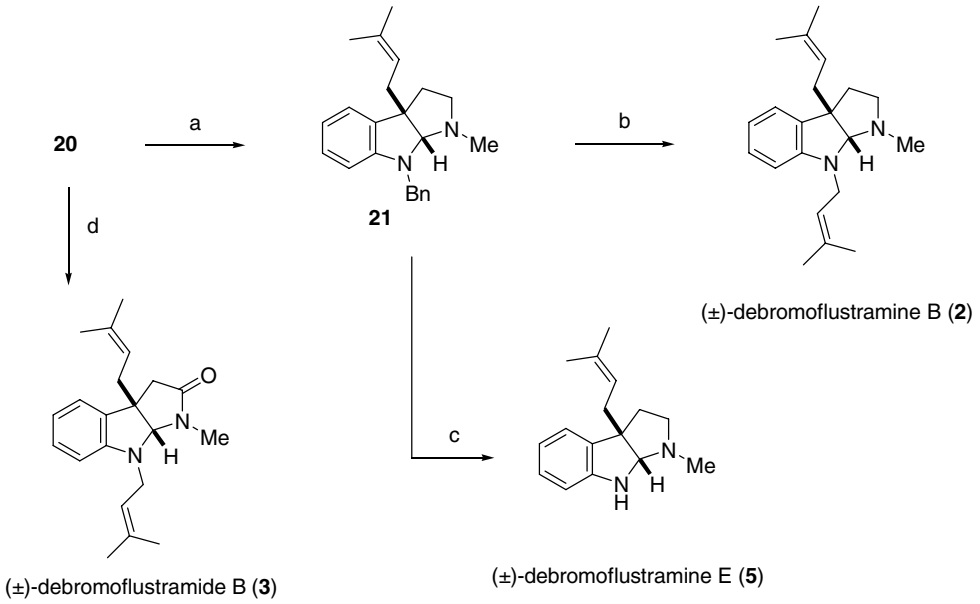
Scheme 1.



Scheme 2. Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, 30 min; then CO_2 gas, −78 °C, 10 min; (ii) *t*-BuLi, THF, −78 °C, 1 h; then 1,2-diiodoethane, −78 °C, 1 h to room temperature, 86%; (b) $InCl_3$, MVK, CH_2Cl_2, 0 °C, 1 h to room temperature, 3 h, 90%; (c) BnBr, KOH, DMF, 0 °C, 10 min, 91%; (d) vinylmagnesium bromide, THF, 0 °C, 10 min; (e) CuCl, 2-aminopyridine, NaOMe/MeOH (25 wt %), diglyme, 130 °C, 1 h, 77% from **12**; (f) OsO_4, NMO, *t*-BuOH/H_2O (4:1), room temperature, 2 h; (g) $NaIO_4$, THF/H_2O (1:1), room temperature, 15 h; (h) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, THF/*t*-BuOH/H_2O (2:2:1), room temperature, 1 h; (i) Ph_3PCH_3Br, *n*-BuLi, THF, room temperature, 2.5 h, 75% from **14**; (j) H_2SO_4, $MgSO_4$, 1,4-dioxane, 60 °C, 18 h; (k) $ClCO_2Et$, Et_3N, THF, 0 °C, 1 h; then $MeNH_2$/THF (2 M), −60 °C, 1 h, 65% from **17**; (l) $AlH_3{\cdot}EtNMe_2$, THF, −15 °C, 5 min, 89%.

to obtain indole ketone **12**. Treatment of **12** with vinylmagnesium bromide provided the required **13**, without any undesired deiodination product. Conversion of **13** to oxindole **14** was efficiently carried out on a multigram scale by a slight modification of our protocol: Crude **13** was treated with 10 mol % of each of CuCl and 2-aminopyridine and 2 equiv of NaOMe/MeOH (25 wt %) in diglyme at 130 °C for 1 h. Intramolecular Ullmann coupling and Claisen rearrangement thus proceeded successively to give **14** in 77% yield based on **12**.

Oxidative cleavage of the carbon–carbon double bond of **14** with OsO_4–$NaIO_4$ gave ketoaldehyde **15**, which was further oxidized with $NaClO_2$ to obtain a carboxylic



Scheme 3. Reagents and conditions: (a) AlH_3·$EtNMe_2$, THF, room temperature, 10 min, 87%; (b) Na, liq NH_3/THF, −78 °C, 15 min; then prenyl bromide, −78 °C, 30 min to room temperature, 92%; (c) Na, liq NH_3/THF, −78 °C, 15 min; then Ph_2O, *i*-PrOH, −78 °C to room temperature, 91%; (d) prenyl bromide, Na, liq NH_3/THF, −78 °C, 15 min; then Ph_2O, −78 °C to room temperature, 65%.

acid **16**. Ketoacid **16** was then converted into *exo*-methylene **17** by Wittig olefination with the ylide generated from methyltriphenylphosphonium bromide and *n*-BuLi in 75% yield from **14**. Treatment of *exo*-methylene **17** with concd H_2SO_4 in the presence of $MgSO_4$ resulted in the desired isomerization to an internal olefin, affording **18** as a 20:1 mixture with **17**. Carboxylic acid **18** was transformed to an amide **19**, by the mixed anhydride method using ethyl chloroformate and $MeNH_2$, in 65% yield from **17**.[7c] The lactam carbonyl group of **19** was reduced chemoselectively by an excess of AlH_3·$EtNMe_2$ complex at −15 °C for 5 min, to afford the cyclized amide **20** in 89% yield.[7a]

For the synthesis of **21**, which serves as a common precursor of (±)-debromoflustramine B and E, lactam **20** was further reduced with AlH_3·$EtNMe_2$ complex, and the desired tricyclic compound **21** was obtained in 87% yield (Scheme 3).[7a] Synthesis of (±)-debromoflustramine B from **21** was accomplished using a modification of Bruncko's protocol[7b] as follows: *N*-benzyl derivative **21** was subjected to a Birch reduction with Na in liquid NH_3, followed by the addition of prenyl bromide to the reaction mixture to obtain (±)-debromoflustramine B (**2**) in 92% yield. Synthesis of (±)-debromoflustramine E (**5**) was also carried out by Birch reduction and quenching the reaction mixture with Ph_2O and *i*-PrOH, giving **5** in 91% yield.[11] Transformation of **20** to (±)-debromoflustramide B (**3**) was best accomplished by Birch reduction in the presence of prenyl bromide, furnishing the product in 65% yield. The ^1H and ^{13}C NMR spectra of our synthetic **2**, **3** and **5** are consistent with the reported data.[7j]

In conclusion, we have completed the total synthesis of (±)-debromoflustramine B and E and (±)-debromoflustramide B based on intramolecular Ullmann coupling and Claisen rearrangement. We also demonstrated the utility of oxindole **14** as a synthetic intermediate of hexahydropyrrolo[2,3-*b*]indole alkaloids bearing a prenyl group at C-3a. Further applications of this methodology including a synthesis of optically active flustramines are in progress.

Acknowledgments

Support for this research was provided by Chugai Pharmaceutical Co., Ltd. (A.N.). We thank Professor Masanori Somei (Kanazawa University) for the helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.002.

References and notes

1. For reviews, see: Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 13, pp 163–236.
2. (a) Wright, J. L. C. *J. Nat. Prod.* **1984**, *47*, 893–895; (b) Laycock, M. V.; Wright, J. L. C.; Findlay, J. A.; Patil, A. D. *Can. J. Chem.* **1986**, *64*, 1312–1316; (c) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997–1000; (d) Peters, L.; König, G. M.; Terlau, H.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1633–1637.
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. Sjöblom, T.; Bohlin, L.; Christophersen, C. *Acta Pharm. Suec.* **1983**, *20*, 415–418.

5. Smith, B. P.; Tyler, M. J.; Kaneko, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **2002**, *65*, 439–447.
6. (a) Hodgson, J. W.; Mitchell, M. O.; Thomas, M. L.; Waters, K. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2527–2528; (b) Dix, A. V.; Meseck, C. M.; Lowe, A. J.; Mitchell, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522–2524.
7. For synthesis of enantiomerically pure pyrrolidinoindolines, see: (a) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420–422; (b) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543–5549; (c) Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493–2499; (d) Cardoso, A. S.; Srinivasan, N.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2001**, *42*, 6663–6666; For racemic synthesis, see: (e) López-Alvarado, P.; Caballero, E.; Avendaño, C.; Menéndez, J. C. *Org. Lett.* **2006**, *8*, 4303–4306; (f) Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801–1803; (g) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186–1192; (h) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Tetrahedron* **2002**, *58*, 1479–1484; (i) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327–2330; (j) Jensen, J.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1995**, *49*, 68–71; (k) Mitchell, M. O.; Dorroh, P. *Tetrahedron Lett.* **1991**, *32*, 7641–7642.
8. Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274–2277.
9. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495–2497.
10. Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165–2169.
11. Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053.