Enantioselective total synthesis of (−)-flustramines A, B and (−)-flustramides A, B *via* domino olefination/isomerization/Claisen rearrangement sequence†

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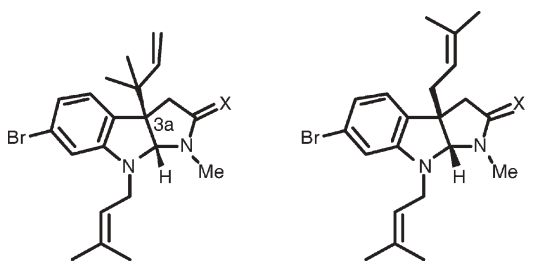
Received (in Cambridge, UK) 6th September 2005, Accepted 14th November 2005
First published as an Advance Article on the web 6th December 2005
DOI: 10.1039/b512485a

The concise total synthesis of marine alkaloids, (−)-flustramines A and B, and (−)-flustramides A and B has been achieved through the domino olefination/isomerization/Claisen rearrangement (OIC) for highly enantioselective construction of the asymmetric quaternary carbon center and the chemoselective reduction–cyclization (RC) for pyrrolidine formation as key steps.

Brominated hexahydropyrrolo[2,3-*b*]indole alkaloids containing a prenyl or reverse-prenyl group at the 3a-position, flustramines A (**1**) and B (**2**)[1] and flustramides A (**3**)[2] and B (**4**) (Fig. 1),[3] were isolated from the marine bryozoan, *Flustra foliacea*. Flustramines A (**1**) and B (**2**) have been found to exhibit both skeletal and smooth muscle relaxant activities.[4] Recently, flustramine A (**1**) has been also demonstrated to have blocking activity on a voltage-activated potassium channel.[5] In addition to the flustramines, the biologically active hexahydropyrrolo[2,3-*b*]indole alkaloids having the prenyl units at the 3a-site have recently received broad synthetic attention.[6] Some elegant routes to amauromine,[7,8] ardeemins,[8] roquefortines,[9] asozonalenin,[10] and pseudophrynaminol[11] have been reported, however, to our best knowledge, these methodologies have not been exploited for the synthesis of brominated alkaloids, flustramines. Therefore, some other tactics for an approach to (±)-flustramines[12] and their debromo-derivatives[13] have been developed, but synthetic progress toward the optically active flustramines has been limited. Only (−)-flustramine B has been synthesized more recently through a Michael addition/cyclization strategy by MacMillan's group.[14]



(-)-flustramine A (**1**, X = H_2) (-)-flustramide A (**3**, X = O)
(-)-flustramine B (**2**, X = H_2) (-)-flustramide B (**4**, X = O)

Fig. 1 Structures of the flustramine family.

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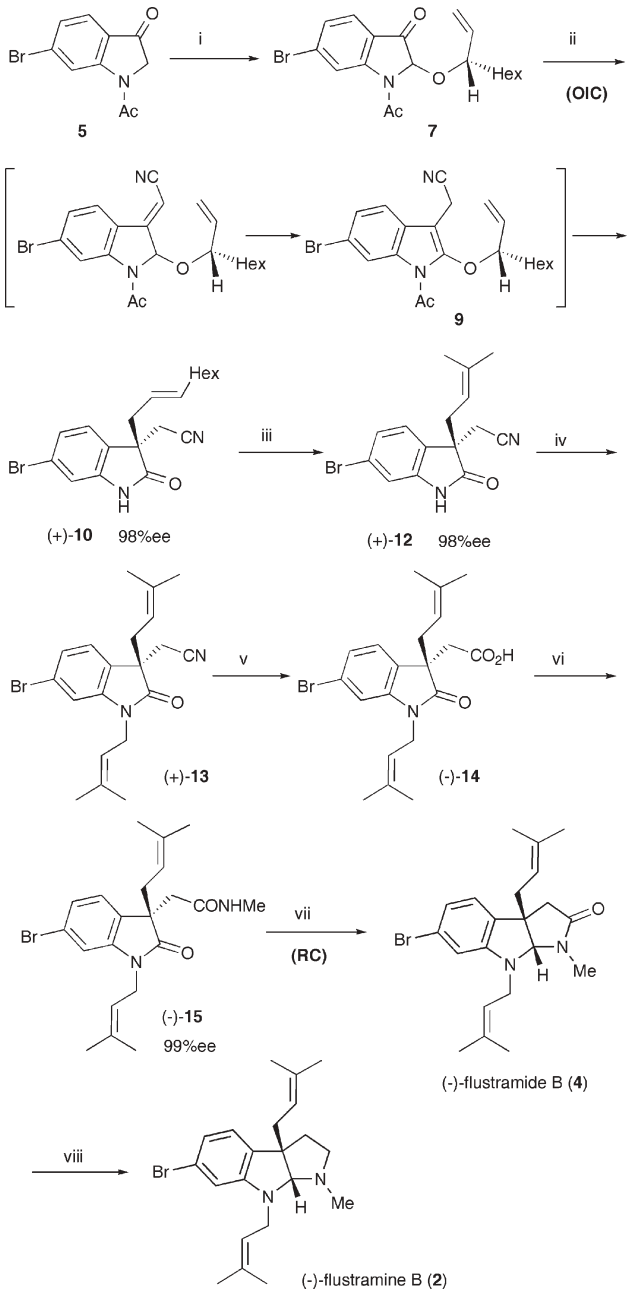
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b512485a

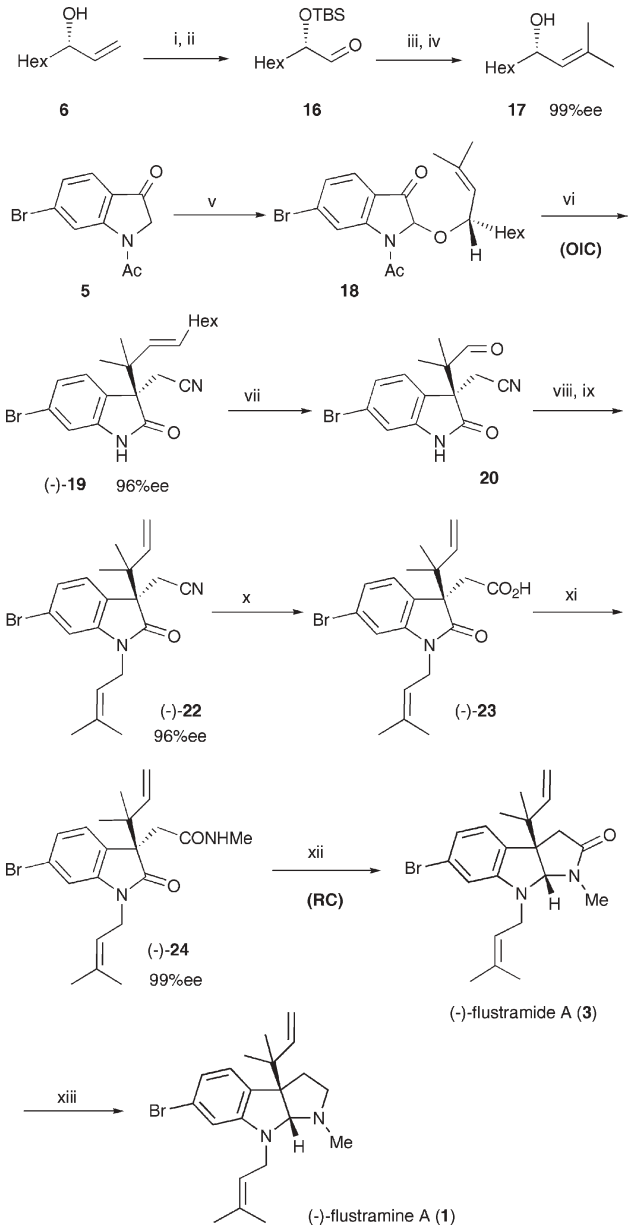
Recently we have evolved our synthetic methodology using the domino olefination/isomerization/Claisen rearrangement (OIC) and reductive cyclization (RC) for construction of the pyrrolo[2,3-*b*]indole architecture.[15–17] Herein we report the first enantioselective total synthesis of (−)-flustramine A (**1**) and (−)-flustramides A (**3**) and B (**4**), along with the second synthesis of (−)-flustramine B (**2**), following a short and simple approach, which is also diversity oriented.

Initially the synthesis of flustramine B (**2**) and flustramide B (**4**) was performed as illustrated in Scheme 1. Bromination of 6-bromoindolin-3-one **5**[18] and substitution with (*S*)-1-nonen-3-ol[19] (**6**, 98% ee) in the presence of MS 4A were carried out successively to a diastereoisomer-mixture of 2-(1-nonen-3-yloxy)-indolin-3-one **7** in 50% yield for two steps. When **7** was allowed to react with cyanomethylphosphonate **8** in the presence of *t*-BuOK at −78 °C to room temperature for 2.5 h, Claisen rearrangement of intermediary 2-(1-nonen-3-yloxy)-3-cyanomethylindole **9**, generated *in situ* by olefination of **8** followed by isomerization, took place stereoselectively to afford (*S*),(*E*)-3-cyanomethyl-3-(2-nonenyl)indolin-2-one **10** with highly enantiomeric excess (98% ee) in 70% yield.[20] For conversion of the nonenyl group in **10** to a prenyl group, a sequence of oxidative cleavage of the C–C double bond of **10** with ozone and Wittig olefination with 2-propylidenephosphorane **11** was carried out to provide 3-prenylindolin-2-one **12** in 54% yield for two steps.[21] Treatment of **12** with prenyl bromide in the presence of NaH gave *N*-prenyl derivative **13** in 97% yield. Selective hydrolysis of the nitrile **13** with NaOH in refluxing MeOH afforded the corresponding acid **14** in quantitative yield. Successive treatment of **14** with pentafluorophenol and EDC, and with methylamine facilitated condensation to give *N*-methylamide **15** (75%, 99% ee). When the amide **15** was treated with alane-*N*,*N*-dimethylethylamine complex at −15 °C for 5 min,[22] chemoselective reduction of the lactam carbonyl group of **15** proceeded smoothly without reduction of the side chain amide and debromination, and continuous cyclization produced flustramide B (**4**) $[\alpha]_D^{18}$ −104.2 (*c* 1.75, EtOH) {lit.[4b] $[\alpha]_D^{20}$ −180.0 (*c* 0.47, EtOH)} in 95% yield.[23] Furthermore, **4** was reduced with the alane complex[12b] at room temperature to afford flustramine B (**2**, 97%) $[\alpha]_D^{18}$ −103.5 (*c* 0.75, EtOH) {lit. $[\alpha]_D^{20}$ −511 (*c* 0.0039, EtOH)[2b] and $[\alpha]_D^{23}$ −93.5 (*c* 1.5, EtOH)[14]}.[23]

Next, we synthesized flustramine A (**1**) and flustramide A (**3**) by a similar strategy (Scheme 2). Initially, optically active (*S*)-2-methyl-2-decen-4-ol (**17**) was prepared as follows. TBDMS-protection of the alcohol (*S*)-**6** (99% ee) followed by OsO_4–$NaIO_4$ oxidation provided α-silyloxy aldehyde **16**.[24] Wittig olefination of **16** with ylide **11** followed by standard deprotection with TBAF



Scheme 1 *Reagents and conditions*: i, Br_2, CH_2Cl_2, 0 °C, 10 min, then (*S*)-1-nonen-3-ol (**6**), MS 4A, MeCN/DMF, rt, 9 d, 50%; ii, $(EtO)_2P(O)CH_2CN$ **8**, *t*-BuOK, DMF, −78 °C to rt, 2.5 h, 70%; iii, O_3, CH_2Cl_2/MeOH, −78 °C, then Ph_3P, −78 °C to rt, then $Ph_3P{=}CMe_2$ **11**, THF/HMPA, 0 °C, 1 h, 54%; iv, NaH, 1-bromo-3-methyl-2-butene, DMF, 0 °C, 10 min, 97%; v, 35% aq. NaOH, MeOH, reflux, 7 h, >99%; vi, EDAC·HCl, C_6F_5OH, Et_3N, THF, rt, 0.5 h, then $MeNH_2$ gas, rt, 75%; vii, $AlH_3{\cdot}EtNMe_2$, THF, −15 °C, 5 min, 95%; viii, $AlH_3{\cdot}EtNMe_2$, THF, rt, 5 min, 97%.



Scheme 2 *Reagents and conditions*: i, TBSCl, imidazole, rt, 24 h, 85%; ii, OsO_4, NMO, MeCN, 2 h, then $NaIO_4$, 1,4-dioxane/H_2O, rt, 0.5 h, 78%; iii, $Ph_3P{=}CMe_2$ **11**, THF, −78 °C to rt, 1 h, 73%; iv, TBAF, THF, rt, 0.5 h, 80%; v, Br_2, CH_2Cl_2, 0 °C, 10 min, then (*S*)-2-methyldec-2-en-4-ol (**17**), MS 4A, MeCN/DMF, rt, 6 d, 64%; vi, $(EtO)_2P(O)CH_2CN$ **8**, *t*-BuOK, DMF, −78 °C to rt, 2.5 h, 70%; vii, O_3, CH_2Cl_2/MeOH, −78 °C, then Ph_3P, −78 °C to rt, 97%; viii, NaH, 1-bromo-3-methyl-2-butene, DMF, 0 °C, 10 min, 77%; ix, $Ph_3P{=}CH_2$ **21**, THF, rt, 1 h, 83%; x, 35% aq. NaOH, MeOH, reflux, 24 h, 88%; xi, EDAC·HCl, C_6F_5OH, Et_3N, THF, rt, 0.5 h, then $MeNH_2$ gas, rt, 76%; xii, $AlH_3{\cdot}EtNMe_2$, THF, −15 °C, 5 min, 92%; xiii, $AlH_3{\cdot}EtNMe_2$, THF, rt, 5 min, 90%.

afforded (*S*)-alcohol **17**[25] (99% ee) in moderate overall yield. Successive bromination of **5** and substitution with **17** in the presence of MS 4A furnished 2-(2-methyl-2-decen-4-yloxy)indolin-3-one **18** in 64% yield. Horner–Wadsworth–Emmons olefination of **18** with **8** in the presence of *t*-BuOK at −78 °C to room temperature for 2.5 h proceeded smoothly with consecutive isomerization, Claisen rearrangement and deacylation to provide (*R*),(*E*)-3-cyanomethyl-3-(2-methyl-3-decen-2-yl)indolin-2-one **19** (70%, 96% ee).[26] Transformation of **19** to the reverse-prenyl derivative **22** was tried in a similar manner as above (from **10** to **13**). Ozonolysis of **19** produced readily an unstable aldehyde **20**, but several attempts to effect Wittig reaction of **20** with methylidenephosphorane **21** failed. We performed another access to **22** *via* *N*-prenylation of **20** prior to Wittig olefination. Thus,

aldehyde **20** underwent *N*-prenylation followed by Wittig olefination with **21** to give the desired reverse-prenyl product **22** in 63% overall yield. After alkaline hydrolysis of the nitrile **22**, condensation of the resulting acid **23** with methylamine through pentafluorophenol activated ester using EDC afforded *N*-methylamide **24**, which was recrystallized with ethyl acetate–hexane to give the optically pure product (99% ee, 67% overall yield form **22**). Reduction of **24** with the alane complex at −15 °C took place smoothly with cyclization to form flustramide A (**3**) $[\alpha]_D^{18}$ −73.2 (*c* 1.09, EtOH) in 92% yield.[23] Additional alane-reduction of **3** at room temperature[12b] led to complete construction of flustramine A (**1**, 90%) $[\alpha]_D^{18}$ −139.4 (*c* 0.73, EtOH) (lit.[3] $[\alpha]_D^{22}$ −40.0 (*c* 0.1, EtOH)).[23]

In summary, we have completed the asymmetric total synthesis of four marine indole alkaloids, flustramines A (**1**), B (**2**), and flustramides A (**3**), B (**4**) in a concise fashion. The highlights of our synthesis include the domino reactions (olefination/isomerization/Claisen rearrangement) for highly enantioselective construction of the asymmetric quaternary carbon center and the chemoselective reduction–cyclization. Further application of this methodology to asymmetric total synthesis of a variety of pyrrolo[2,3-*b*]indole alkaloids is currently in progress in our laboratory.

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20 The stereochemistry can be tentatively assigned by our previous results of an analogous debromo version[17] and confirmed by completion of the total synthesis of **2**.

21 Oxidative fission produced an unstable aldehyde, which was used without further purification in the next reaction.

22 When alane-reduction of **15** at room temperature was carried out, flustramine B (**2**) was directly obtained, but the yield was low (34%).

23 All spectra of the synthetic products **1–4** agreed with those of isolated products[1–3] and synthetic materials in racemic form,[12] respectively.

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