



A Short Route to "Reverse-Prenylated" Pyrrolo[2,3-*b*]indoles via Tandem Olefination and Claisen Rearrangement of 2-(3,3-Dimethylallyloxy)indol-3-ones: First Total Synthesis of Flustramine C

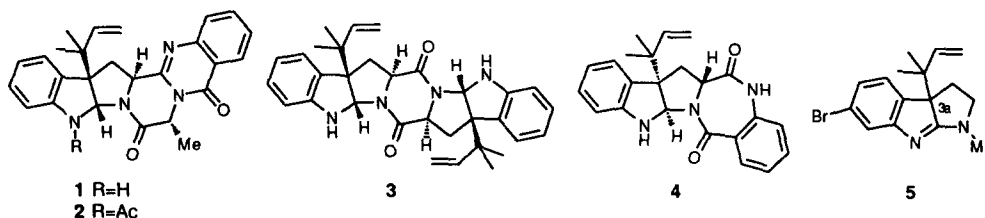
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Abstract: The Wittig or Horner-Emmons reaction of 1-acetyl-2-(3,3-dimethylallyloxy)indol-3-ones proceeded via tandem olefination, isomerization, Claisen rearrangement, and deacetylation to give 3-cyanomethyl-3-(1,1-dimethylallyl)indol-2-ones in good yields, which were reduced with Red-Al® to afford pyrrolo[2,3-*b*]indoles having the 1,1-dimethylallyl group at the 3a-position. The first total synthesis of the marine alkaloid flustramine C was also described.

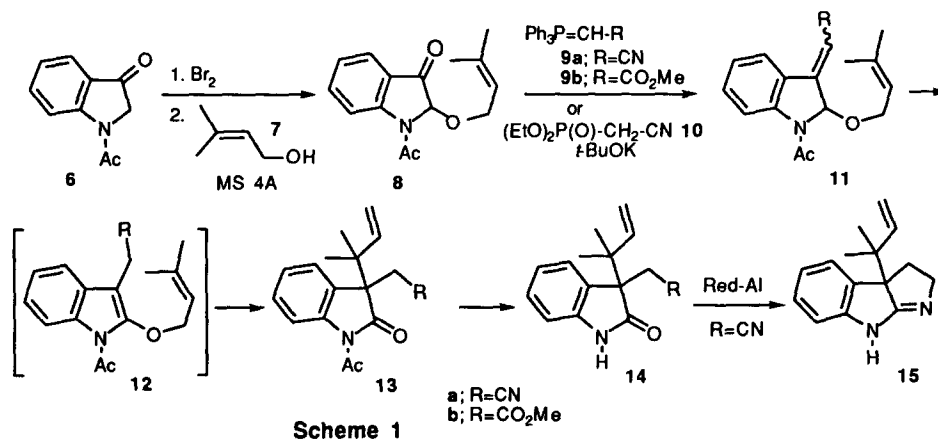
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The pyrrolo[2,3-*b*]indole ring system possessing the 1,1-dimethylallyl ("reverse-prenyl") group at the 3a-site represents a key structural subunit in a number of biological important natural products such as ardeemin (1),¹ 5-*N*-acetylardeemin (2),¹ amauiromine (3),² aszonalenin (4),³ and flustramine C (5).⁴ Three routes to 3a-(1,1-dimethylallyl)pyrrolo[2,3-*b*]indole nucleus were reported, via alkylation of tryptamine with 1,1-dimethylpropargyl chloride,⁵ thio-Claisen rearrangement,⁶ and direct substitution of 3a-phenylselenopyrrolo[2,3-*b*]indole with prenyl tributylstannane.⁷ Our interest in developing a general synthetic strategy to these and other related compounds necessitated the introduction of 1,1-dimethylallyl group to the corresponding 3a-position of pyrrolo[2,3-*b*]indole structure. Recently, we have shown the Wittig reaction of indolin-3-ones as a useful method for preparing 3-substituted indoles,⁸ and the Claisen rearrangement of 2-(3,3-dimethylallyloxy)indoles as a manner for introducing 1,1-dimethylallyl moiety at the 2-site of the indole nucleus.⁹ In this paper we describe an efficient method for synthesis of 3a-(1,1-di-



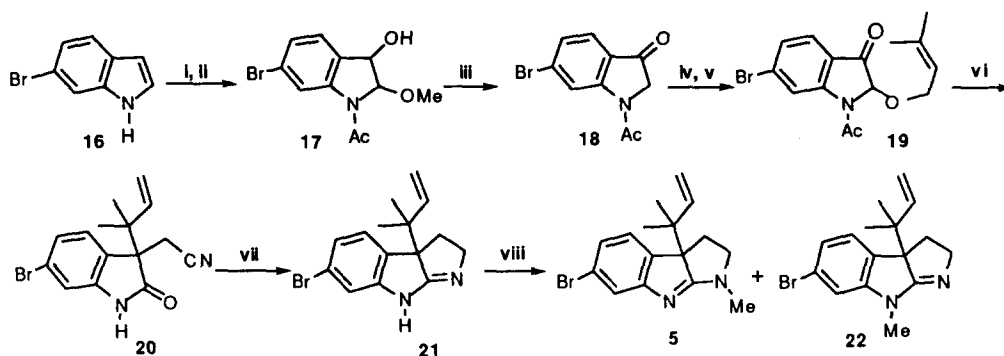
methylallyl)pyrrolo[2,3-*b*]indole via tandem olefination, isomerization, and Claisen rearrangement of 2-(3,3-dimethylallyloxy)indolin-3-one (**8**) to 3-substituted 3-(1,1-dimethylallyl)indol-2-ones (**13**). We have applied this methodology to the first total synthesis of the marine alkaloid flustramine C (**5**).

The starting 2-(3,3-dimethylallyloxy)indolin-3-one (**8**)¹⁰ was obtained in 73% overall yield by the bromination¹¹ of readily available indolin-3-one (**6**)¹² followed by substitution with prenyl alcohol (**7**) in the presence of molecular sieves (MS) 4A. The Wittig reaction of **8** with cyanomethylidene-triphenylphosphorane (**9a**) in refluxing toluene for 5 h gave a mixture (*E* : *Z* = 1 : 3) of *E*- and *Z*-isomers of the 3-alkylideneindoline (**11a**) in 70% yield. Prolonged heating of **11a** under the same conditions failed to isomerize to an indole (**12a**). When **11a** was treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) at room temperature, it underwent smoothly successive isomerization and Claisen rearrangement affording indolin-2-ones (**13a**, 13%) and (**14a**, 47%),¹³ which have the reversed prenyl group at the desired position. The 'one pot' procedure of these reactions achieved the synthetic purpose, namely the reaction of **8** with **9a** followed by treatment of the resulting mixture with DBU provided **13a** (14%) and **14a** (72%). Similarly, the 'one pot' reaction of **8** with **9b** gave the corresponding products, **13b** (39%) and **14b** (35%). When the reaction of **8** was performed using cyanomethylphosphonate (**10**) with potassium *tert*-butoxide instead of the ylides (**9**), the tandem olefination, isomerization, Claisen rearrangement, and deacetylation proceeded more smoothly at -60 °C and then at room temperature for 5 h to afford **14a** in quantitative overall yield.



Transformation of the indolin-2-one **14a** to pyrrolo[2,3-*b*]indole (**15**) was achieved by reductive cyclization of **14a** using Red-Al^{®14} to give **15** in 73% yield. The present methodology is useful for the synthesis of 3a-(1,1-dimethylallyl)pyrrolo[2,3-*b*]indole derivatives, and we next applied this method to synthesis of flustramine C (**5**).

6-Bromoindolin-3-one (**18**) was readily prepared from 6-bromoindole (**16**)¹⁵ by N-acetylation followed by molybdenum peroxide oxidation¹⁶ and demethoxylation¹² of the oxidation product (**17**) with tin (IV) chloride in 43% overall yield. Bromination of **18** followed by substitution with prenyl alcohol (**7**) gave the ether (**19**) in 89% yield. The tandem reaction of **19** to the indolin-2-one (**20**) (73%) was then accomplished by treatment with the phosphonate (**10**). Reduction of **20** with Red-Al® afforded the pyrrolo[2,3-*b*]indole (**21**) (89%), which was alkylated using methyl iodide in the presence of sodium bicarbonate to give flustramine C (**5**)⁴, **17** (38%) together with its isomer (**22**) (29%).



Scheme 2. Reagents and Conditions : I, AcCl, 33 % NaOH, Bu₄NHSO₄; II, MoO₃·HMPA, MeOH; III, SnCl₄; IV, Br₂; V, Me₂C=CHCH₂OH **7**, MS 4A; VI, (EtO)₂P(O)CH₂CN **10**, t-BuOK; VII, Red-Al; VIII, MeI, NaHCO₃

In summary, we have demonstrated the first total synthesis of flustramine C using the tandem olefination, isomerization, Claisen rearrangement, and deacetylation of 2-(3,3-dimethylallyloxy)indolin-3-ones. This tandem reaction is a useful strategy for constructing pyrrolo[2,3-*b*]indole alkaloids involving the "reverse-prenyl" group at 3a-position.

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13. Compound (**14a**) mp: 154-155 °C; IR (CHCl_3): ν 3434, 2255, 1716 cm^{-1} ; ^1H -NMR (270 MHz, CDCl_3): δ 1.08 (3H, s), 1.16 (3H, s), 2.86 (1H, d, $J = 14.5$ Hz), 3.01 (1H, d, $J = 14.5$ Hz), 5.99 (1H, d, $J = 17.5$ Hz), 5.22 (1H, d, $J = 10.9$ Hz), 6.08 (1H, dd, $J = 17.5, 10.9$ Hz), 6.92 (1H, d, $J = 7.6$ Hz), 7.07 (1H, t, $J = 7.6$ Hz), 7.27 (1H, d, $J = 7.6$ Hz), 7.29 (1H, t, $J = 7.6$ Hz), 8.12 (1H, br s); HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ [M^+] 240.1263, found 240.1263.
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17. Flustramine C (**5**); IR (CHCl_3): ν 1636, 1586, 1565 cm^{-1} ; ^1H -NMR (270 MHz, CDCl_3): δ 0.89 (3H, s), 0.99 (3H, s), 2.06 (1H, ddd, $J = 8.9, 9.9, 12.9$ Hz), 2.35 (1H, dd, $J = 6.6, 12.9$ Hz), 3.02 (3H, s), 3.39 (1H, t, $J = 9.9$ Hz), 3.94 (1H, ddd, $J = 6.6, 8.9, 9.9$ Hz), 5.04 (1H, d, $J = 17.2$ Hz), 5.06 (1H, d, $J = 10.9$ Hz), 6.01 (1H, dd, $J = 10.9, 17.2$ Hz), 6.906 (1H, d, $J = 7.9$ Hz), 6.908 (1H, d, $J = 7.9$ Hz), 7.20 (1H, t, $J = 1.0$ Hz); ^{13}C -NMR (67.8 MHz, CDCl_3): 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 ($\text{M}+2$, 32%), 318 (M^+ , 33), 251 (99), 249 (100), 210 (4), 208 (5), 170 (42), 129 (13), 69 (5); HRMS calcd for $\text{C}_{16}\text{H}_{19}\text{BrN}_2$ [M^+] 318.0732, found 318.0730.

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