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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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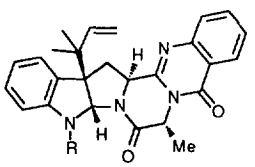
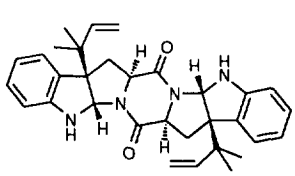
Abstract: The Wittig or Horner-Emmons reaction of 1-acetyl-2-(3,3-dimethylallyloxy)indol-3-ones proceeded *via* tandem olefination, isomerization, Claisen rearrangement, and deacetylation to give 3-cyanomethyl-3-(1,1-dimethylallyl)indol-2-ones in good yields, which were reduced with Red-Al® to afford 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.

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] amauromine (**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-



1 R=H
2 R=Ac



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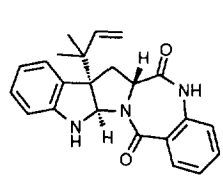

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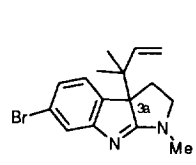

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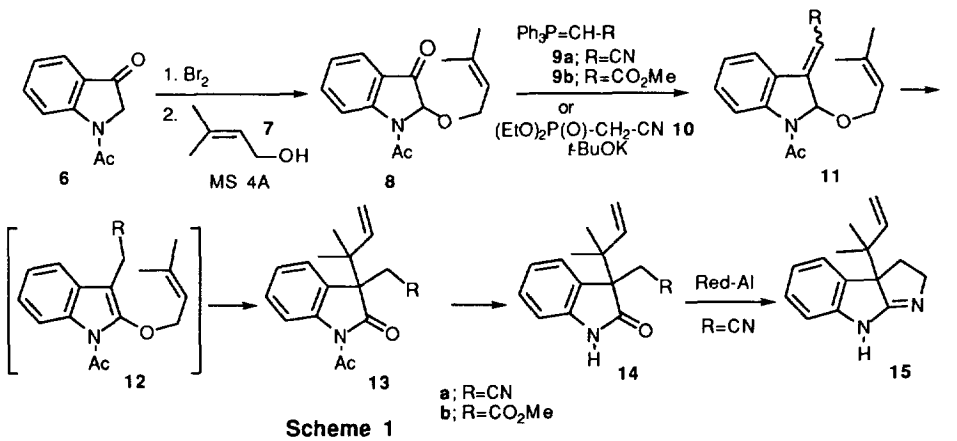
methylallyl)pyrrolo[2,3-*b*]indole *via* tandem olefination, isomerization, and Claisen rearrangement of 2-(3,3-dimethylallyloxy)indolin-3-one (**8**) to 3-substituted 3-(1,1-dimethylallyl)indol-2-ones (**13**). We have applied this methodology to the first total synthesis of the marine alkaloid flustramine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

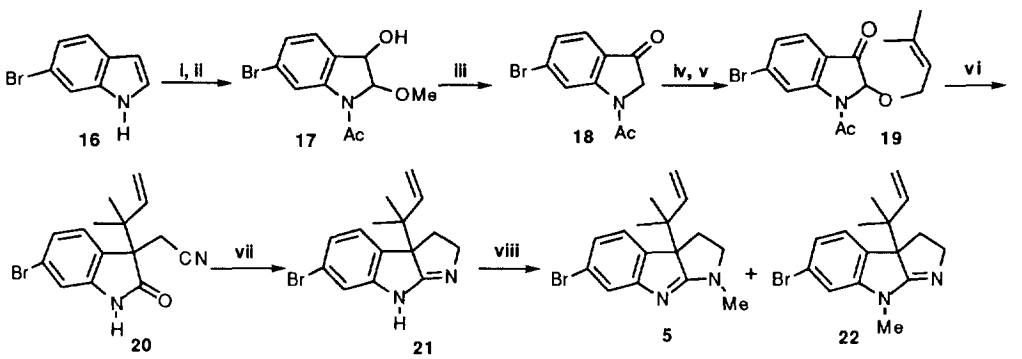
The starting 2-(3,3-dimethylallyloxy)indolin-3-one (**8**)[10] was obtained in 73% overall yield by the bromination[11] of readily available indolin-3-one (**6**)[12] followed by substitution with prenyl alcohol (**7**) in the presence of molecular sieves (MS) 4A. The Wittig reaction of **8** with cyanomethylidene-triphenylphosphorane (**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.



Scheme 1

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 oxidation[16] and demethoxylation[12] 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, Bu_4NHSO_4; **ii**, MoO_5·HMPA, MeOH; **iii**, $SnCl_4$; **iv**, Br_2; **v**, $Me_2C{=}CHCH_2OH$ **7**, MS 4A; **vi**, $(EtO)_2P(O)CH_2CN$ **10**, *t*-BuOK; **vii**, Red-Al; **viii**, MeI, $NaHCO_3$

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}; ^{1}H-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 $C_{15}H_{16}N_2O$ [M$^+$] 240.1263, found 240.1263.
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17. Flustramine C (**5**); IR ($CHCl_3$): ν 1636, 1586, 1565 cm^{-1}; ^{1}H-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 (M+2, 32%), 318 (M$^+$, 33), 251 (99), 249 (100), 210 (4), 208 (5), 170 (42), 129 (13), 69 (5); HRMS calcd for $C_{16}H_{19}BrN_2$ [M$^+$] 318.0732, found 318.0730.

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