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TETRAHEDRON
LETTERS

Total Synthesis of Didemnimide A and B

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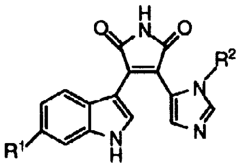
Abstract: The total synthesis of didemnimide A and didemnimide B, novel predator-deterrent alkaloids from the Caribbean mangrove ascidian *Didemnum conchyliatum*, is described.

Didemnimides A (**1**), B (**2**), C (**3**), and D (**4**) were recently isolated,[1] and represent the first members of a novel class of indole-maleimide-imidazole fused tricyclic compounds. To date, only the synthesis of didemnimide C (**3**), which utilized a Stille coupling, has been reported.[2] The structural similarity of the didemnimides with various bisindolylmaleimides, which have been the central framework for several biologically active compounds[3], arrested our attention. Recently, Faul et al.,[4] reported a new method for the synthesis of unsymmetrical bisindolylmaleimides via a K^+ *t*-BuO$^-$ catalyzed condensation of indole-3-acetamide with methyl indolyl-3-glyoxylates. We herein describe the application of this methodology to achieve the total synthesis of didemnimides A (**1**) and B (**2**).



	(1)	(2)	(3)	(4)
R¹	H	Br	H	Br
R²	H	H	CH_3	CH_3

The preparation of methyl indolyl-3-glyoxylate (**5**) and its 6-bromo analogue (**6**) was accomplished by treatment of indole (**7**) or 6-bromoindole[5] (**8**) with oxalyl chloride in Et_2O and the subsequent treatment of the corresponding acid chlorides with methanol to afford (**5**) and (**6**) in 83 and 72% yields, respectively. The readily available imidazole acetonitrile[6] (**9**) was reacted with trityl chloride to give the trityl protected imidazole acetonitrile (**10**) in 95% yield. Partial hydrolysis of the nitrile (**10**) was achieved under KOH/ *t*-BuOH conditions[7] to give the desired acetamide (**11**) in 95% yield .

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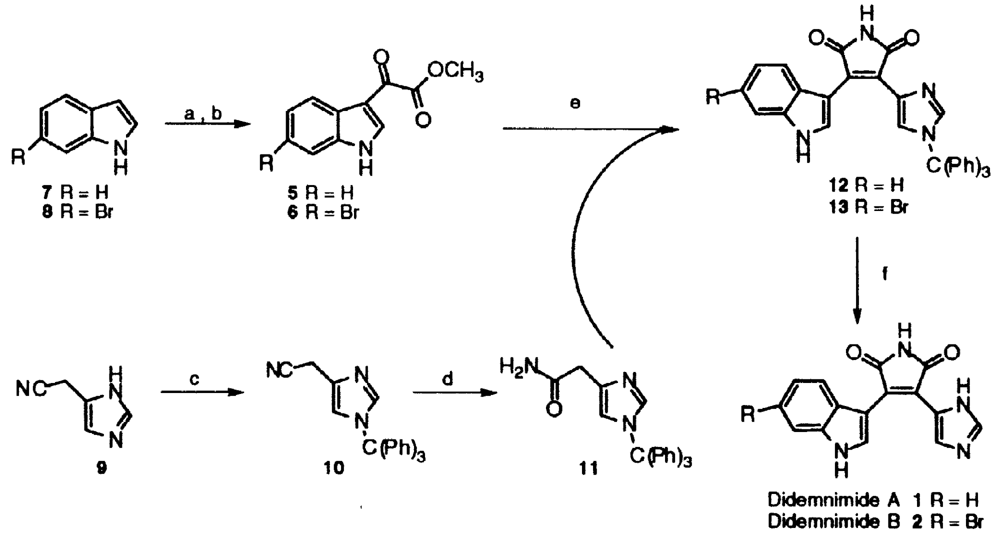
Attempted base condensation of (**5**) and (**11**) using the K^+t-BuO^- conditions gave only trace amounts of the desired condensation product (**12**) and returned unreacted starting materials. However, the desired condensation of (**5**) and (**11**) was achieved via K_2CO_3 / CETAB in refluxing benzene with a Dean Stark trap in 70% yield. Likewise, the condensation of (**6**) and (**11**), using K_2CO_3 / CETAB conditions, afforded (**13**) in 40% yield. Subsequent deprotection of (**12**) and (**13**) with TFA in CH_2Cl_2 gave didemnimides A (**1**) and B (**2**) in 91 and 77% yields, respectively. The properties of didemnimides A (**1**) and B (**2**) (^{1}H-NMR, ^{13}C-NMR, IR, mp, UV-vis, HRMS) were in accord with previously reported values.[1,8]



Scheme 1

Reagents and Conditions: a) oxalyl chloride (1.1 equiv.), Et_2O, 0 °C to rt; b) MeOH (xs), rt, 24 h; c) trityl chloride (1.1 equiv.), CH_2Cl_2, Et_3N (1.1 equiv.), rt, 24 h; d) powdered KOH (6 equiv.), *t*-BuOH, reflux, 30 min; e) K_2CO_3 (7 equiv.), CETAB (0.07 equiv.), benzene (Dean Stark), reflux, 48 h; f) TFA (8 equiv.), CH_2Cl_2, rt, 12 h.

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8. Compound **1**: orange crystals (CH_3CN/H_2O) mp 235-238 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ 12.40 (bs, 1H), 11.69 (bs, 1H), 10.90 (bs, 1H), 8.01 (bs, 1H), 7.67 (bs, 2H), 7.42 (d, 1H, *J*=7.42 Hz), 7.09 (m, 2H), 6.87 (m, 1H). ^{13}C NMR (360MHz, DMSO-d_6) δ 172.58, 136.23, 130.45, 128.31, 125.90, 121.54, 119.36, 111.70, 104.88. HRMS calcd for $C_{15}H_{10}N_4O_2$: 278.0804, found: 278.0798. Compound **2**: orange solid, mp 334-335 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ 12.44 (bs, 1H), 11.72 (bs, 1H), 10.87 (bs, 1H), 8.04 (s, 1H), 7.75 (s, 1H), 7.67 (s, 1H), 7.02 (bs, 2H). ^{13}C NMR (360 MHz, DMSO-d_6) δ 172.68, 172.54, 136.95, 131.21, 130.76, 127.31, 126.67, 125.09, 123.55, 121.94, 120.14, 114.02, 105.19. HRMS calcd for $C_{15}H_9{}^{81}BrN_4O_2$: 357.9888, found: 357.9875.