

Total Synthesis of Didemnimide A and B

Terry V. Hughes and Michael P. Cava*

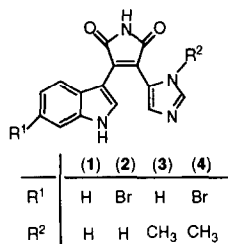
Department of Chemistry, The University of Alabama, Box 870336
Tuscaloosa, AL 35487-0336, U.S.A.

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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.

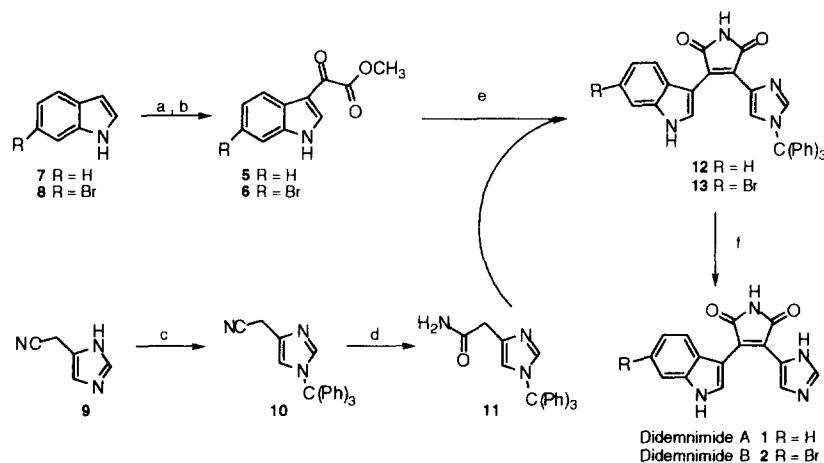
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Didemnimides A (1), B (2), C (3), and D (4) were recently isolated,¹ and represent the first members of a novel class of indole-maleimide-imidazole fused tricyclic compounds. To date, only the synthesis of didemnimide C (3), which utilized a Stille coupling, has been reported.² The structural similarity of the didemnimides with various bisindolylmaleimides, which have been the central framework for several biologically active compounds³, arrested our attention. Recently, Faul et al.,⁴ reported a new method for the synthesis of unsymmetrical bisindolylmaleimides via a $K^+ t\text{-BuO}^-$ 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).



The preparation of methyl indolyl-3-glyoxylate (5) and its 6-bromo analogue (6) was accomplished by treatment of indole (7) or 6-bromoindole⁵ (8) with oxalyl chloride in Et₂O 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 acetonitrile⁶ (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 conditions⁷ to give the desired acetamide (11) in 95% yield.

Attempted base condensation of (5) and (11) using the $K^+t\text{-BuO}^-$ 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) (1H -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.), $t\text{-BuOH}$, 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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- Compound 1: orange crystals (CH_3CN/H_2O) mp 235-238 °C. 1H 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. 1H 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.