SYNTHESIS OF AMPHIMEDINE, A NEW FUSED AROMATIC ALKALOID FROM A PACIFIC SPONGE, *Amphimedon* sp.

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Abstract ——Synthesis of the cytotoxic fused pentacyclic aromatic alkaloid, amphimedine **1**, is described.

Although marine organisms have been a rich source of structurally diverse natural products, relatively few alkaloids have been isolated from marine sources.[1]

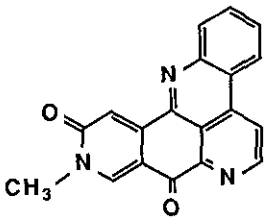
In 1983 Schmitz and co-workers reported the isolation of a novel cytotoxic fused aromatic alkaloid, named amphimedine **1**, from an *Amphimedon* sp. of sponge found near Guam island.[2] The structure **1** was assigned on the basis of an extensive long-range heterocorrelation and carbon-carbon correlation analyses.

To date, the structurally related fused aromatic alkaloids include calliactine **2**,[3] 2-bromo-leptoclinidinone **3**,[4] ascididemin **4**,[5] petrosamine **5**,[6] and cystodytins A, B, and C **6**.[7]

Their highly fused structures have proven not only to be challenging structural elucidation problems and but also to be challenging targets for synthesis.

Although a few synthetic studies[8] toward them have been reported recently, no total synthesis has yet been accomplished. In this paper, we report the first synthesis of amphimedine **1**.

Our starting material was the *o*-nitrobenzoylacetanilide **7** [mp 93.5-95°C; ms m/z 344 (M^+)], which was prepared in quantitative yield by heating 2,5-dimethoxyaniline with ethyl *o*-nitrobenzoylacetate in toluene and a slight amount of pyridine at 140°C for 6 h. Cyclization of **7** in 80% H_2SO_4 at 75°C for 30 min gave in 53% yield the quinolone **8** [mp 208-209°C; ms m/z 326 (M^+)], which was converted to the 2-chloroquinoline **9** [mp 225-226°C; ms m/z 346 (M^++2)] in 66% yield using $PCl_5/POCl_3$ at 70°C for 45 min. Oxidative demethylation of **9** with ceric ammonium nitrate (CAN)[9] in aqueous CH_3CN at 0°C for 15 min afforded the quinolinequinone **10** [mp 188-190°C(decomp); ms m/z 316 (M^++2)] in 77% yield.



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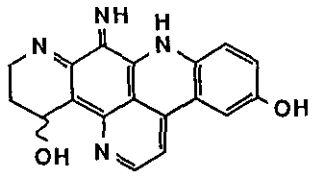

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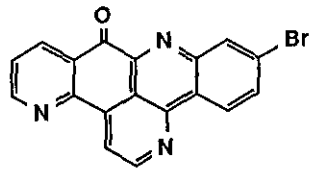

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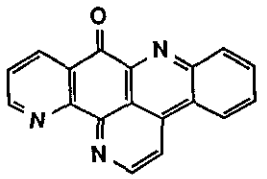

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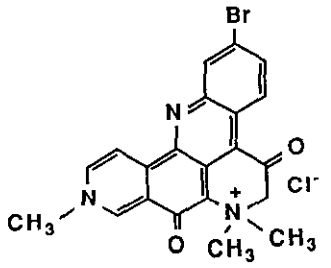

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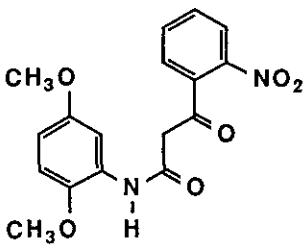
The crucial step, formation of an isoquinolone ring, was performed according to the procedure of Ghosez and co-workers.[10] The Diels-Alder reaction of **10** with 2-aza-1,3-bis(tert-butyldimethylsilyloxy)-1,3-butadiene **11**[10] in $CHCl_3$ at 35°C for 8 h gave a mixture of crude adducts after acidic workup; *which was methylated with* CH_3I/K_2CO_3/tris[2-(2-methoxyethoxy)ethyl]amine[11] in DMF at room temperature for 1 h to provide two N-methylisoquinolones [**12** (7%) and **13** (8%)] after silica gel chromatography [**12:** mp 286-288°C; ms m/z 397 (M^++2, 4), 395 (M^+, 11), 351 (34), 349 (100); ^{1}H-nmr (400MHz, $CDCl_3$) δ 3.73 (3H, s), 7.03 (1H, s), 7.26 (1H, dd, J = 1.2, 7.3 Hz), 7.48 (1H, s), 7.72 (1H, ddd, J = 1.2, 7.6, 8.2 Hz), 7.80 (1H, ddd, J = 1.2, 7.3, 7.6 Hz), 8.38 (1H, dd, J = 1.2, 8.2 Hz), 8.67 (1H, s). **13**: mp > 300°C; ms m/z 397 (M^++2, 1), 395 (M^+, 3), 351 (37), 349 (100); ^{1}H-nmr (400MHz, $CDCl_3$) δ: 3.64 (3H, s), 7.29 (1H, dd, J = 1.2, 7.3 Hz), 7.35 (1H, s), 7.51 (1H, s), 7.70 (1H, ddd, J = 1.2, 7.6, 8.2 Hz), 7.79 (1H, ddd, J = 1.2, 7.3, 7.6 Hz), 8.32 (1H, s), 8.35 (1H, dd, J = 1.2, 8.2 Hz)].

Finally, catalytic hydrogenation of **12** with 10% Pd-C/Et_3N in MeOH at room temperature for 20 h *afforded in 13% yield amphimedine* **1** [mp > 300°C; high-resolution ms Calcd for $C_{19}H_{11}N_3O_2$: 313.0852, Found 313.0857; uv (EtOH): λ_{max} nm (ε) 235 (38,000), 281 (10,000), 340 (7,000); ms

m/z 313 (M^+, 100), 298 (41); ir (KBr): ν max 1680, 1640 cm^{-1}; ^{1}H-nmr (400MHz, 2:1 $CF_3COOD:CDCl_3$) δ 4.09 (3H, s), 8.21 (1H, t like), 8.38 (1H, t like), 8.49 (1H, s), 8.69 (1H, d, J = 8.1 Hz), 8.97 (1H, d, J = 8,1 Hz), 9.19 (1H, s), 9.32 (1H, d, J = 6.5 Hz), 9.51 (1H, d, J = 6.5 Hz); ^{13}C-nmr (100.4 MHz, 2:1 $CF_3COOD:CDCl_3$) δ 40.03, 114.36, 115.08, 119.16, 120.85, 125.38, 125.58, 133.28, 133.65, 137.72, 139.64, 139.94, 144.41, 145.62, 146.47, 147.76, 148.11, 166.34, 173.58]. Synthetic amphimedine had spectral properties (^{1}H-, ^{13}C-nmr, HRms, uv) and HPLC mobility identical with those of a natural specimen.

In a similar manner the regio isomer **13** afforded an isomer **14** of amphimedine in 11% yield [mp > 300°C; ms m/z 313 (M^+, 100), 298 (69), 285 (23); ^{1}H-nmr (400MHz, 2:1 $CF_3COOD:CDCl_3$)



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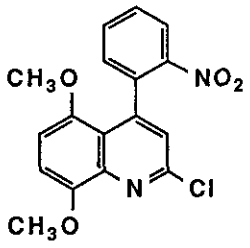

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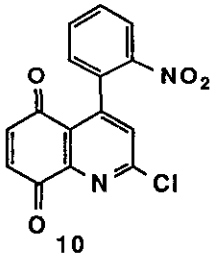

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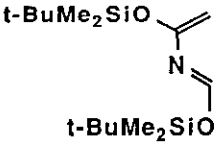

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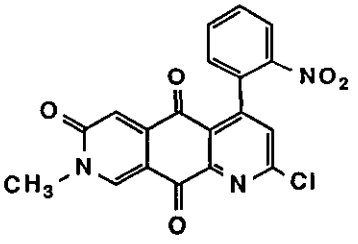

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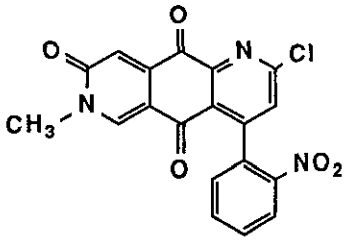

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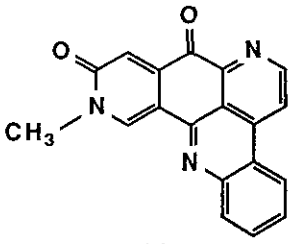

14

δ 4.10 (3H, s), 7.92 (1H, s), 8.15 (1H, t like), 8.34 (1H, t like), 8.53 (1H, d, J = 8.5 Hz), 8.91 (1H, d, J = 8.1 Hz), 9.45 (2H, s like), 9.68 (1H, s)].

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