TOTAL SYNTHESIS OF EILATIN

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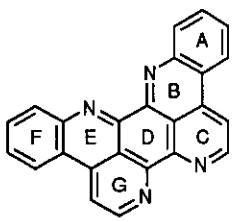
Abstract —— Synthesis of the symmetrical pentacyclic fused aromatic alkaloid called eilatin (**1**) is described.

Since 1983 when amphimedine (**2**) was isolated from marine organisms,[1] the number of polycyclic aromatic alkaloids including benzo[*de*][3,6]phenanthroline ring (**3**) has increased rapidly.

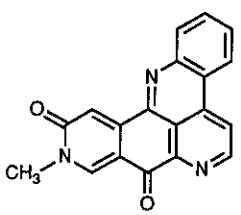
Eilatin (**1**),[2] right yellow solid mp > 310°C, is a heptacyclic alkaloid from the Purple Red Sea tunicate *Eudistoma* sp. and has a highly symmetrical structure which was determined by extensive use of ^{1}H- and ^{13}C-nmr spectroscopy and a single-crystal X-ray analysis.



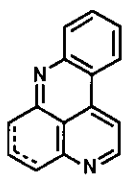
Eilatin **1**

During the last several years amphimedine (**2**),[3] ascididemin (**4**),[4] 2-bromo-leptoclinidinone (**5**),[5] cystodytins (**6**)[6] were synthesized.

Eilatin (**1**) belongs to a group of polycyclic marine alkaloids that possess benzo[*de*][3,6]phenanthroline ring (**3**). In this paper we wish to report the first total synthesis of eilatin (**1**).



Amphimedine **2**



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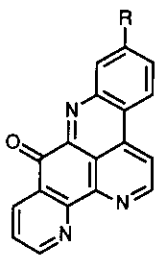
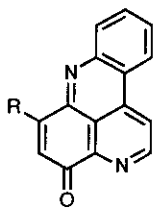


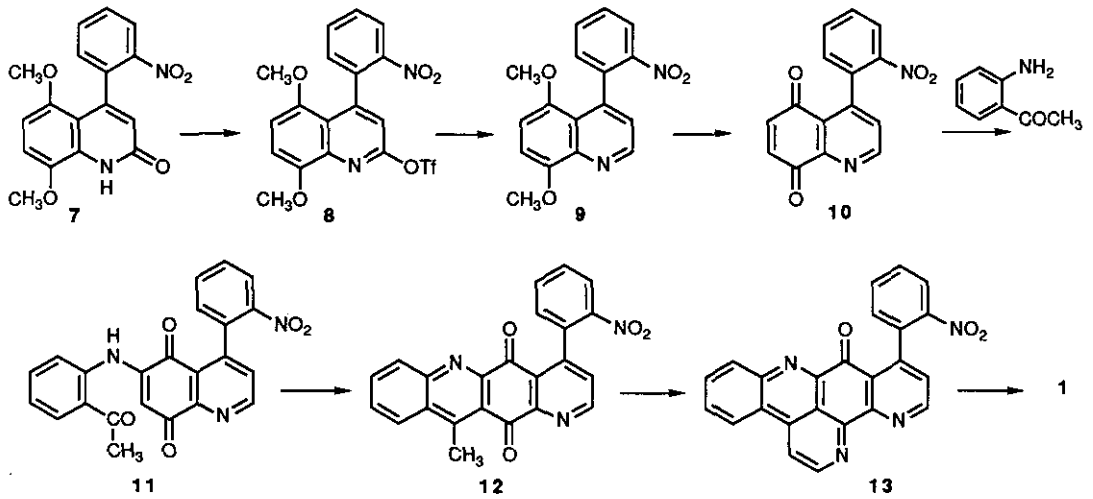
R=H Ascididemin **4**
R=Br 2-Bromoleptoclinidinone **5**



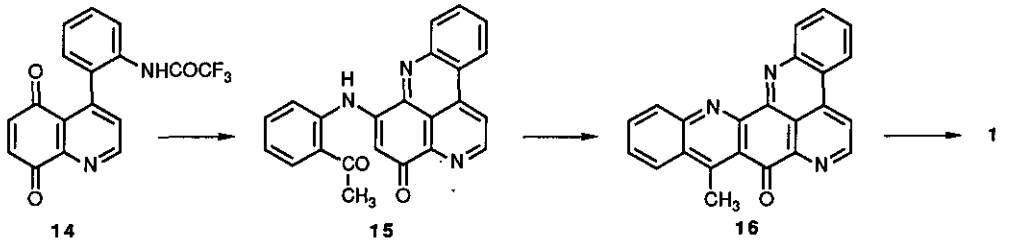
Cystodytins **6**

Reaction of the readily available 2-quinolinone (**7**), the intermediate of our amphimedine synthesis,[3b] with trifluoromethanesulfonic anhydride in dichloromethane containing triethylamine at -20°C for 30 min under an argon atomosphere furnished the desired aryl triflate (**8**) in 93% yield. Palladium catalyzed triethylammonium formate reaction[7] of aryl triflate (**8**) in DMF at 0 - 60°C for 2 h gave quinoline (**9**) in 87% yield. Oxidative demethylation of **9** with cerium (IV) ammonium nitrate (CAN) in aqueous acetonitrile afforded the *p*-quinone

(**10**) in 60% yield. *p*-Quinone (**10**) reacted with 2-aminoacetophenone in the presence of cerium ion at room temperature for 3 h to afford the desired product, 6-(2-acetylanilino)-4-(2-nitrophenyl)quinoline-5,8-dione (**11**) regioselectively[8] in 54% yield. Cyclization of **11** to the tetracyclic quinone (**12**) proceeded at 60°C for 15 min with concentrated sulfuric acid in acetic acid in 80% yield. The formation of ring G was accomplished by means of the one pot annulation method.[9] Treatment of **12** with *N,N*-dimethylformamide diethyl acetal in DMF at 120°C for 30 min followed by ammonium chloride in acetic acid gave the pentacyclic compound (**13**) in 75% yield. In the last step catalytic hydrogenation of **13** with 10% Pd-C in ethanol at room temperature for 1.5h afforded eilatin (**1**) in 85% yield.



Eilatin (**1**) was also synthesized from 4-[2-(trifluoroacetylamino)phenyl]quinoline-5,8-dione (**14**)[3a] in a similar manner. Condensation of **14** with 2-aminoacetophenone afforded the benzophenanthroline (**15**) in 52% yield. Cyclization of **15** gave hexacyclic compound (**16**) in 75% yield. Finally, synthesis of eilatin (**1**) was accomplished by the one pot annulation of ring G. The synthetic eilatin (**1**) had spectral properties (^{1}H- and ^{13}C-nmr) identical with those of a natural specimen.



ACKNOWLEDGEMENT

We are grateful to Prof. Y. Kashman (Tel Aviv University) for kindly providing the copies of the ^{1}H- and ^{13}C-nmr spectra of natural eilatin. This work was partly supported by a Grant-in-Aid for Scientific Research (No. 03671018) from the Ministry of Education, Science and Culture, Japan.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-Nmr spectra were measured at 270 MHz in $CDCl_3$ with tetramethylsilane as an internal standard. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography (flash chromatography) was performed with silica gel 60 (230-400 mesh).

2-Trifluoromethanesulfonyl-5,8-dimethoxy-4-(2-nitrophenyl)quinoline (8) Trifluoromethanesulfonic anhydride (2.8 ml, 16.6 mmol) was added dropwise to a solution of 5,8-dimethoxy-4-(2-nitrophenyl)-2(1*H*)qunolinone (**7**) (2.7 g, 8.3 mmol) in dry methylene chroride (140 ml) containing triethylamine (3.5 ml, 25 mmol) at -20°C for 30 min under argon atomosphere. The reaction mixture was kept -20°C for 30 min, diluted with water (100 ml) and basified with saturated $NaHCO_3$ (20 ml). The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The organic extracts were combined, wash with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 1:1) to afford **8** (3.53 g, 93%). mp 144-145°C (yellow needles from $CHCl_3$-hexane). *Anal.* Calcd for $C_{18}H_{13}N_2O_7F_3S$: C, 47.17; H, 2.86; N, 6.11. Found: C, 46.93; H, 2.88; N, 6.04. Ms *m/z* (%): 458 (M^+, 100), 325 (98). Ir (KBr): 1516, 1350 cm^{-1}. ^{1}H-Nmr δ: 3.41 (3H, s), 4.04 (3H, s), 6.73 (1H, d, *J*=8.6 Hz), 7.08 (1H, s), 7.32 (1H, dd, *J*=7.6, 1.3 Hz), 7.62 (1H, td, *J*=7.6, 1.3 Hz), 7.71 (1H, td, *J*=7.6, 1.3 Hz), 7.85 (1H, d, *J*=8.6 Hz), 8.24 (1H, dd, *J*=7.9, 1.3 Hz).

5,8-Dimethoxy-4-(2-nitrophenyl)quinoline (9) 99% Formic acid (1.2 ml, 30.8 mmol) was added dropwise to a mixture of 2-trifluoromethanesulfonyl-5,8-dimethoxy-4-(2-nitrophenyl)qunoline (**8**) (3.5 g, 7.6 mmol), triethylamine (6.5 ml, 46 mmol), palladium acetate (350 mg, 1.55 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (1.71 mg, 3.1 mmol) in DMF (75 ml) at 0°C for 10 min under argon atomosphere. The reaction mixture was warmed gradually to 60°C for 2 h, diluted with water (1.5 l), basified with saturated $NaHCO_3$, extracted with $CHCl_3$ (3 x 250 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-MeOH 10:1) to afford **9** (2.2 g, 92%). mp 160-161°C (orange needles from $CHCl_3$-ether). *Anal.* Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55;

N, 9.03. Found: C, 65.78; H, 4.61; N, 8.99. Ms *m/z* (%): 310 (M^+, 100), 295 (70), 248 (68), 220 (47). Ir (KBr): 1512, 1342 cm^{-1}. ^{1}H-Nmr δ: 3.41 (3H, s), 4.07 (3H, s), 6.69 (1H, d, *J*=8.6 Hz), 6.97 (1H, d, *J*=8.6 Hz), 7.21 (1H, d, *J*=4.6 Hz), 7.31 (1H, dd, *J*=7.6, 1.3 Hz), 7.56 (1H, td, *J*=7.6, 1.3 Hz), 7.66 (1H, td, *J*=7.6, 1.3 Hz), 8.19 (1H, dd, *J*=7.9, 1.3 Hz), 8.97 (1H, d, *J*=4.6 Hz).

4-(2-Nitrophenyl)quinoline-5,8-dione (10) A solution of CAN (17.7 g, 32.3 mmol) in water (25 ml) was added dropwise to **9** (2 g, 6.45 mmol) dissolved in acetonitrile-water (3:1, 400 ml) at 0°C. The mixture was left at 0°C for 5 min, poured into water (1.5 l) and extracted with $CHCl_3$ (3 x 300 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with hexane-ethyl acetate 1:2) to afford **10** (1.08 g, 60 %). mp 145-147°C (decomp.)(light orange needles from $CHCl_3$-ether). *Anal.* Calcd for $C_{15}H_8N_2O_4$: C, 64.29; H, 2.88; N, 10.00. Found: C, 64.06; H, 2.97; N, 9.76. Ms *m/z* (%): 282 (M^++2, 3), 234 (100), 206 (52). Ir (KBr): 1680, 1666, 1520, 1348 cm^{-1}. ^{1}H-Nmr δ: 6.87 (1H, d, *J*=10.6 Hz), 7.14 (1H, d, *J*=10.6 Hz), 7.23 (1H, dd, *J*=7.6, 1.3 Hz), 7.44 (1H, d, *J*=5.0 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 7.76 (1H, td, *J*=7.6, 1.3 Hz), 8.32 (1H, dd, *J*=7.9, 1.3 Hz), 9.09 (1H, d, *J*=5.0 Hz).

6-Acetylanilino-4-(2-nitrophenyl)quinoline-5,8-dione (11) A mixture of *p*-quinone (**10**) (284 mg, 1 mmol), $CeCl_3 \cdot 7H_2O$ (391 mg, 1.05 mmol) and 2-aminoacetophenone(142 mg, 1.05 mmol) in EtOH(55 ml) was stirred at room temperature for 3 h. The mixture was diluted with water (200 ml) and extracted with $CHCl_3$ (3 x 50 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-MeOH-$CHCl_3$ 8:1:1) to afford **11** (224 mg, 54 %). mp 225°C (red powder from $CHCl_3$-ether). *Anal.* Calcd for $C_{23}H_{15}N_3O_5 \cdot 1/5H_2O$: C, 66.77; H, 3.75; N, 10.16. Found: C, 66.49; H, 3.71; N, 9.90. Ms *m/z* (%): 413 (M^+, 15), 349 (100), 320 (14). High resolution ms Calcd for $C_{23}H_{15}N_3O_5$: 413.1011, Found 413.1025. Ir (KBr): 1676, 1522, 1344 cm^{-1}. ^{1}H-Nmr δ: 2.62 (3H, s), 6.91 (1H, s), 7.18 (1H, ddd, *J*=8.3, 6.9, 1.3 Hz), 7.26 (1H, dd, *J*=7.6, 1.3 Hz), 7.36 (1H, d, *J*=5.0 Hz), 7.57 (1H, td, *J*=8.3, 1.3 Hz), 7.62 (1H, dd, *J*=8.3, 1.3 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 7.75 (1H, td, *J*=7.6, 1.3 Hz), 7.92 (1H, dd, *J*=6.9, 1.3 Hz), 8.33 (1H, dd, *J*=7.9, 1.3 Hz), 9.05 (1H, d, *J*=5.0 Hz), 10.96 (1H, s).

11-Methyl-4-(2-nitrophenyl)pyrido[2,3-*b*]acridine-5,12-dione (12) A solution of **11** (170 mg, 0.41 mmol) in 10% H_2SO_4-acetic acid (1.3 ml) was stirred at 60°C for 15 min. The reaction mixture was diluted with water (25 ml) and ajusted pH 7 with saturated $NaHCO_3$, extracted with $CHCl_3$ (3 x 10 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-$CHCl_3$-MeOH 90:10:1) to afford **12** (135 mg, 83 %). mp 272-274°C (decomp.)(yellow needles from

$CHCl_3$-ether). *Anal.* Calcd for $C_{23}H_{13}N_3O_4$: C, 69.87; H, 3.31; N, 10.63. Found: C, 69.64; H, 3.44; N, 10.41. Ms *m/z* (%): 395 (M^+, 10), 349 (100), 320 (16). Ir (KBr): 1684, 1518, 1346 cm^{-1}. ^{1}H-Nmr δ: 3.34 (3H, s), 7.29 (1H, dd, *J*=7.6, 1.3 Hz), 7.50 (1H, d, *J*=5.0 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 7.73 (1H, td, *J*=7.6, 1.3 Hz), 7.78 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 7.90 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 8.32-8.39 (3H, m), 9.17 (1H, d, *J*=5.0 Hz).

10-(2-Nitrophenyl)-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (13) A solution of **12** (41 mg, 0.103 mmol) and *N,N*-dimethylformamide diethyl acetal (58 mg, 0.4 mmol) in DMF (0.6 ml) was stirred at 120°C for 30 min. Acetic acid (1 ml) and ammonium chloride (96 mg, 1.8 mmol) were added to the reaction mixture. The whole was stirred at 115°C for 30 min, diluted with water (20 ml) and extracted with $CHCl_3$ (3 x 4 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-MeOH-$CHCl_3$ 10:1:1) to afford **13** (31 mg, 75 %). mp > 300°C (yellow needles from $CHCl_3$-hexane). *Anal.* Calcd for $C_{24}H_{12}N_4O_3 \cdot 1/4H_2O$: C, 70.49; H, 2.96; N, 13.71. Found: C, 70.50; H, 3.15; N, 13.47. Ms *m/z* (%): 358 (100). Ir (KBr): 1680, 1518, 1346 cm^{-1}. ^{1}H-Nmr δ: 7.31 (1H, dd, *J*=7.6, 1.3 Hz), 7.42 (1H, d, *J*=4.6 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 7.76 (1H, td, *J*=7.6, 1.3 Hz), 7.93 (1H, td, *J*=7.3, 1.7 Hz), 7.99 (1H, td, *J*=7.3, 1.7 Hz), 8.39 (1H, dd, *J*=7.6, 1.3 Hz), 8.50 (1H, dd, *J*=7.6, 2.0 Hz), 8.58 (1H, d, *J*=5.6 Hz), 8.70 (1H, dd, *J*=7.6, 2.0 Hz), 9.22 (1H, d, *J*=4.6 Hz), 9.35 (1H, d, *J*=5.3 Hz).

Eilatin (1) The compound (**13**) (8 mg, 0.02 mmol) in EtOH (30ml) was hydrogenated at 1 atom for 1.5 h using 10% palladium on carbon (16 mg) as a catalyst. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed (eluting with $CHCl_3$) to afford eilatin (**1**) (6 mg, 85 %). mp > 300°C (yellow needles from $CHCl_3$). Ms *m/z* (%): 356 (M^+, 100), 178 (24). High resolution ms Calcd for $C_{24}H_{12}N_4$: 356.1062, Found 356.1055. Uv (MeOH): λ_{max} nm (ε) 240 (47600), 275 (35400), 284 (37700), 295 (24800), 367 (13200), 385 (21700), 407 (30500), 432 (27100). ^{1}H-Nmr δ: 7.87 (1H, ddd, *J*=7.9, 6.9, 1.0 Hz), 8.00 (1H, ddd, *J*=8.3, 6.9, 1.3 Hz), 8.57 (1H, d, *J*=5.6 Hz), 8.67 (1H, dd, *J*=7.9, 1.0 Hz), 8.69 (1H, dd, *J*=8.3, 1.3 Hz), 9.31 (1H, d, 5.6 Hz). ^{13}C-Nmr δ: 117.0, 118.9, 122.6, 122.8, 129.2, 131.5, 132.6, 138.6, 146.2, 149.2, 150.0, 150.5.

10-(2-Acetylanilino)-8*H*-benzo[4,3,2-*de*][3,6]phenanthrolin-8-one (15) Condensation of **14** with 2-aminoacetophenone was carried out by the same procedure as used for **10**. Yield 52 %. mp 267-270°C (decomp.)(light orange powder from $CHCl_3$-ether). *Anal.* Calcd for $C_{23}H_{15}N_3O_2 \cdot 1/2H_2O$: C, 73.79; H, 4.41; N, 11.22. Found: C, 73.73; H, 4.16; N, 11.13. Ms *m/z* (%): 365 (M^+, 65), 347 (100), 322 (85). High resolution ms Calcd for $C_{23}H_{15}N_3O_2$: 365.1164, Found 365.1159. Ir (KBr): 1640 cm^{-1}. ^{1}H-Nmr δ:

2.74 (3H, s), 6.97 (1H, s), 7.21 (1H, td, *J*=7.3, 1.0 Hz), 7.61 (1H, td, *J*=7.3, 1.3 Hz), 7.81-7.86 (2H, m), 7.94 (1H, td, *J*=8.3, 1.3 Hz), 7.99 (1H, dd, *J*=8.3, 1.3 Hz), 8.47 (1H, d, *J*=5.6 Hz), 8.48 (1H, dd, *J*=8.3, 1.0 Hz), 8.58 (1H, br d, *J*=7.9 Hz), 9.18 (1H, d, *J*=5.6 Hz), 12.06 (1H, br s).

9-Methyl-8*H*-acridino[2,3,4-*de*][3,6]phenanthrolin-8-one (16) Cyclisation of **15** was carried out by the same procedure as used for **11.** Yield 75 %. mp > 300°C (green yellow powder from $CHCl_3$-ether). *Anal.* Calcd for $C_{23}H_{13}N_3O \cdot 1/4H_2O$: C, 78.51; H, 3.72; N, 11.94. Found: C, 78.32; H, 3.87; N, 11.80. Ms *m/z* (%): 347 (M^+, 100), 318 (20), 291 (8). High resolution ms Calcd for $C_{23}H_{13}N_3O$: 347.1059, Found 347.1055. Ir (KBr): 1666 cm^{-1}. ^{1}H-Nmr δ: 3.43 (3H, s), 7.76 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 7.87 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 7.95 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 8.01 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz), 8.42 (1H, br d, *J*=7.9 Hz), 8.60 (1H, br d, *J*=7.6 Hz), 8.66 (1H, br d, *J*=7.9 Hz), 8.69 (1H, d, *J*=5.3 Hz), 8.72 (1H, br d, *J*=7.6 Hz), 9.35 (1H, d, *J*=5.3 Hz).

Eilatin (1) Eilatin (**1**) was obtained in 41% yield from **16** by the same procedure as used for **12.**

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Received, 17th December, 1992