Tetrahedron Letters, Vol. 34, No. 11, pp. 1827-1830, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Two Step Biomimetic Total Synthesis of Eilatin

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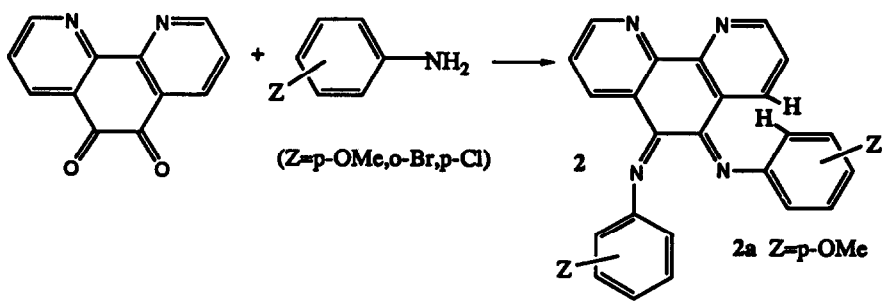
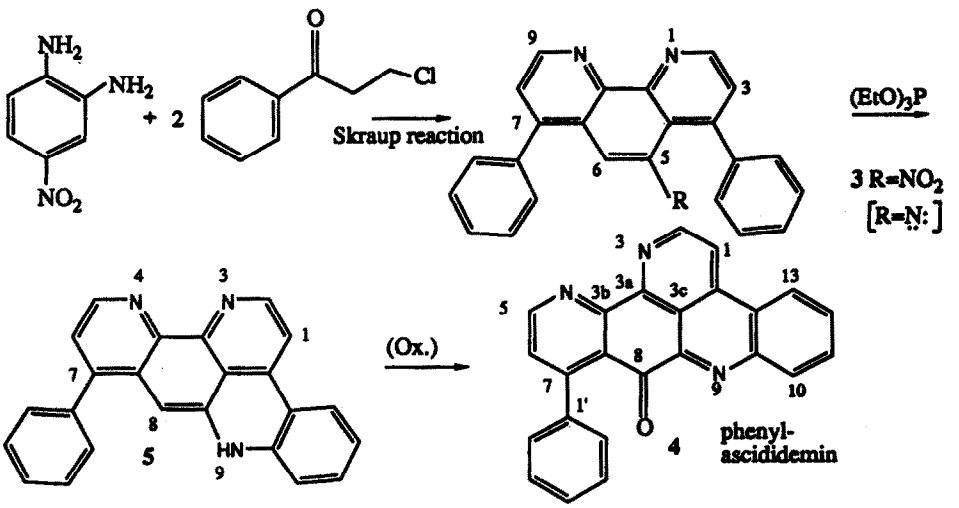
Abstract: The symmetrical tetraaza heptacyclic alkaloid eilatin (1) was synthesized in a biomimetic two step reaction from catechol and monotrifluoro kynuramine (6) under oxidative conditions in the first step (aq. EtOH, $NaIO_3$) and basic conditions (ammoniacal MeOH, DMAP) in the second. Two other unsuccessful approaches, one leading to 7-phenylascididemin, are described.

Several years ago[1] we reported the isolation and structure elucidation of six new alkaloids from the ascidian *Eudistoma sp.*[1]. Most outstanding among the six was the symmetrical heptacyclic alkaloid eilatin (1). From that time, and more so recently, because of the interesting biological activity of 1[2], we have tried many synthetic approaches which failed. Thus, e.g., we have prepared from 1,10-phenanthroline-5,6-dione a series of double Schiff bases (2) and have tried, without success, to perform a double cyclisation of these molecules to obtain 1.

Observation of the NMR spectra of the latter compounds (2), e.g., the spectrum of **2a** - the di p-methoxyphenyl deep blue compound[3], clearly pointed to a complex mixture of unsymmetrical conformers which could not easily be equilibrated by warming up **2a** in solution.

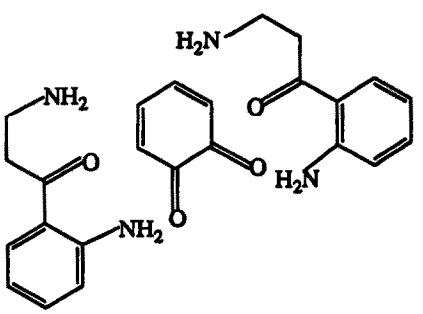


In another approach we have performed a double Skraup reaction between 4-nitro-o-phenylenediamine and two molecules of 3'-chloropropiophenone to afford in ca. 15% yield 4,7-diphenyl-5-nitro-1,10-phenanthroline (3)[4]. Heating the solution of the latter compound (3) in dodecane at 180° under N_2 for 2 hours, in the presence of $(EtO)_3P$ gave *via* the nitrene[5] the unexpected ketone 4 which by careful 2D NMR study (COSY, d-NOE, HMQC and HMBC) was determined to be 7-phenylascididemin[6,7]. Repeating the reaction under oxygen free argon gave the originally expected compound 5[8], which under oxygen atmosphere was transformed into 4. All attempts to prepare eilatin (1) from compound 4 (e.g., by reacting it under different conditions with HN_3) failed.



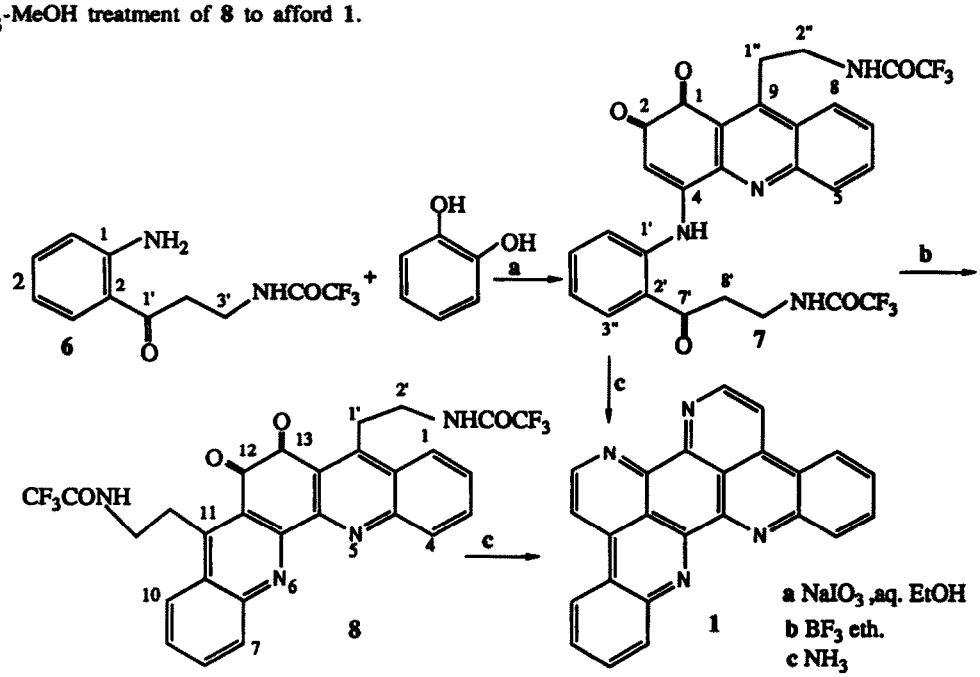
From the above data and several other experiments we concluded that it will be hard if not impossible to synthesise **1** in a synthesis which will in its last step require cyclisation of one or two aromatic rings (as in case of **4** and **2**, respectively) because of the severe repulsion between the protons and/or other substituents on the latter rings (both in **2** and **4** the substituting phenyl(s) seem to be out of plane with the rest of the molecule). Therefore the preferred way to go should involve closure of a piperidine ring(s) which then will readily be oxidized to the required pyridine ring(s).

Based on a novel biomimetic synthesis of pyrido[2,3,4-*kl*]acridines[9] we have decided on the following strategy towards **1**:



In the event, the mono protected trifluoroacetyl kynuramine **6** was reacted with catechol under oxidative conditions (aq. EtOH, $NaIO_3$)[10]. This reaction afforded compound **7**, whose structure was determined by 2D

NMR measurements (500 MHz, COSY, HMQC, HMBC) to be a 1,2-acridinedione derivative 7[11]. Basic treatment of 7 (NH_3-MeOH, cat. DMAP) afforded directly eilatin 1. Having in 7 all functionalities in the right position seems to have a strong and crucial driving force towards the formation of eilatin. Alternatively, the last step towards the goal compound could have been divided into two, namely, BF_3 etherate cyclisation to the dibenzo-1,10-phenanthroline-5,6-dione derivative 8[9,12] and sequentially mild NH_3-MeOH treatment of 8 to afford 1.



The readily and very simple biomimetic reaction shown above, suggests kynuramine and o-benzoquinone, or hydroquinone, both natural products, to be potential biosynthetic precursors of eilatin.

References and Notes

1. Rudi, A.; Kashman, Y., J. Org. Chem. 1989, 54, 5331.
2. Eilatin was found to possess potent cellular growth regulatory properties and to affect cAMP-mediated cellular processes. Schochet, N.R., et al, submitted for publication.
3. 1,10-phenanthroline-5,6-dione was refluxed with p-anisidine in acetic acid for 30 minutes. After evaporation the crude product was purified on a silica gel column (65%); dark blue oil, $C_{26}H_{20}N_4O_2$, m/z M^+ 420 (100%), 308, (75%); λmax (CH_3CN) 605 (13800), 430 (11100), 290 (39400); IR (KBr) 1590, 1260, 1000, 850, 810 cm^{-1}; δ_H ($CDCl_3$-d_4MeOH; 10:1): δ_H 9.61 (1H, dd, J=1.5, 3.5 Hz), 9.25 (1H, dd, J=1.5, 7.5 Hz), 9.14 (1H, dd, J=1.5, 3.5 Hz), 8.32 (1H, d, J=8 Hz), 8.01 (2H, dd, J=3.5, 7.5 Hz),

7.86 (1H, dd, J=1.5, 7.5 Hz), 7.80 (2H, d, J=9 Hz), 7.75 (1H, d, J=8 Hz), 7.46 (2H, dd, J=3.5, 7.5 Hz), 7.45 (2H, d, J=9 Hz), 7.31 (2H, d, J=9 Hz), 7.02 (2H, d, J=9 Hz), 3.76 (3H, s), 3.59 (3H, s); δ_C (5% CD_3OD/$CDCl_3$); 161.6s, 158.6s, 155.3s, 152.3d, 151.7d, 149.0s, 144.8s, 144.1s, 139s, 135.3d, 133.4d, 133.0d, 131.0s, 129.5s, 128.0d, 126.2s, 125.1d, 124.4d, 122.2d, 119.5s, 117.0d, 114.5d, 56.6q, 55.9q.

4. 4-Nitro-o-phenylenediamine was reacted with β-chloropropiophenone under the Skraup reaction conditions to afford in 15% compound 3; amorphous yellow powder; m/z 377 (100%) ($C_{24}H_{15}N_3O_2$): δ_H ($CDCl_3$) δ 9.32 (1H, d, J=4.7 Hz), 9.26 (1H, d, J=4.7), 8.31 (1H, s), 7.70 (1H, d, J=4.7), 7.68 (1H, d, J=4.7), 7.36-7.59 (10H, m); δ_C ($CDCl_3$): 152.2d, 150.7d, 150.1s, 147.6s, 147.0s, 146.7s, 138.2s, 136.1s, 129.5d, 129.3d, 129.0d, 128.6d, 127.8s, 127.4d, 126.2d, 124.3s, 123.8d, 122.8d, 118.8s; IR(KBr): 1610, 1530, 1490, 1410, 1380, 1350, 1260, 1180, 1090, 1020, 900, 850, 820, 800, 780, 760, 690, 650 cm^{-1}; UV (MeOH), 266, 222 nm.
5. Cadogen, J.I., Quart. Rev. 1968, 22, 122.
6. Compound 4; m/z: MH^+ 360 (100%) ($C_{24}H_{13}N_3O$); δ_H (d_6-DMSO): δ 9.25 (d, H-2, J=5.0 Hz), 9.05 (d, H-5, J=5.0 Hz), 9.03 (dd, H-13, J=7.5, 1.0 Hz), 8.94 (d, H-1, J=5.0 Hz), 8.55 (d, H-6, J=5.0 Hz), 8.35 (d, H-10, J=8.0 Hz), 8.06 (dt, H-11, J=8.0, 1.0 Hz), 8.02 (dt, H-12, J=7.5, 1.0 Hz), 7.94bs (5H) (H-2′-6′); δ_C 182.1s (C8), 153.6s (C3b), 153.4s (C8a), 152.1d (C5), 150.1s (C3a), 149.8d (C2), 140.2s (C13b), 137.4d (C10), 132.3d (C11), 132.0s (C7), 130.7d (C12), 128.5d (C6), 147.8s (C9a), 145.4s (C7a), 128.1-128.5 (C1′-6′), 124.5d (C13), 123.3s (C13a), 117.8d (C1), 117.7s (C3c); IR (KBr) 1682, 1600, 1428, 1201, 1170, 770 cm^{-1}; UV (MeOH); 366, 308, 264, 244, 219 nm.
7. (a) Kobayashi, J.; Cheng, J.F.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Nozoe, S., Tet. Letters, 1988, 29, 1177; (b) Moody, C.J.; Rees, C.W.; Thomas, R., Tet. 1992, 48, 3589.
8. Compound 5, unstable oil; δ_H ($CDCl_3$): 8.89d (J=5.2), 8.73d (J=5.2) (H-2 & 5), 7.76d (J=8, H-13(10)), 7.50m (Ph), 7.27m (2H), 6.80m (3H), 6.68s (H-8).
9. Gellerman, G.; Rudi, A.; Kashman, Y., Tet. Letters, previous report.
10. Tindale, C.R., Aust. J. Chem. 1984, 37, 611 and references therein.
11. 3′-Trifluorokynuramine (6) (δ_H 7.62d (J=8, H-3), 7.24t & 6.58t (J=8, H-4,5), 6.61d (J=8, H-6), 3.76m (2H-3′), 3.19t (2H-2′) was reacted with catechol in aq. EtOH in the presence of 5 equivalents of $NaIO_3$[10]. After 24 hours the ppt was filtered and chromatographed on a silica gel column to afford compound 7 (ca. 15%), mp 249-251° (CH_2Cl_2), orange crystals, $C_{28}H_{20}F_6N_4O_5$ m/z: 606, M (1.5%), 493, M-NH_2COCF_3 (35%), 380, M-2NH_2COCF_3 (50%); vmax 3320, 1717, 1611, 1576, 1526 cm^{-1}; $\delta_H CDCl_3$-d_4-MeOH 9:1): 8.52d (J=8.0, H-5), 8.30d (J=8.0, H-8), 7.97d (J=8.0, H-3′), 7.92t (J=8.0, H-7), 7.80t (J=8.0, H-6), 7.69d (J=8.0, H-6′), 7.62t (J=8.0, H-5′), 7.32t (J=8.0, H-4′), 6.67s (H-3), 3.83t, 3.67t, 3.58t, 3.33t (2H each); δ_C 201.6s (C7′), 183.1s (C1), 162.1 ($\underline{C}OCF_3$), 151.7s (C9), 151.4s (C4), 147.3s (C8a), 146.2s (C4a), 138.2s (C1′), 134.3d (C5′), 133.5d (C7), 131.4d (C3′), 130.8d (C8), 130.0d (C6), 128.5 (C8b), 127.5s (C2′), 125.8d (C5), 125.2d (C4′), 123.4d (C6′), 103.3d (C3), 39.3t, 38.8t, 34.9t, 27.8t.
12. Compound 8 was obtained from 7 after 24 hours in CH_2Cl_2 in the presence of BF_3 etherate; amorphous yellow powder, $C_{28}H_{18}F_6N_4O_4$ m/z M, 588 (1.5%); δ_H ($CDCl_3$): 8.58d (J=8, H-1 & 10), 8.46d (J=8, H-4 & 7), 8.04t (J=8) & 7.82t (J=8) (H-2, 3, 8 & 9), 3.89m (2x2H), 3.78m (2x2H).

(Received in UK 14 December 1992)