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First total synthesis of the 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline annoretine

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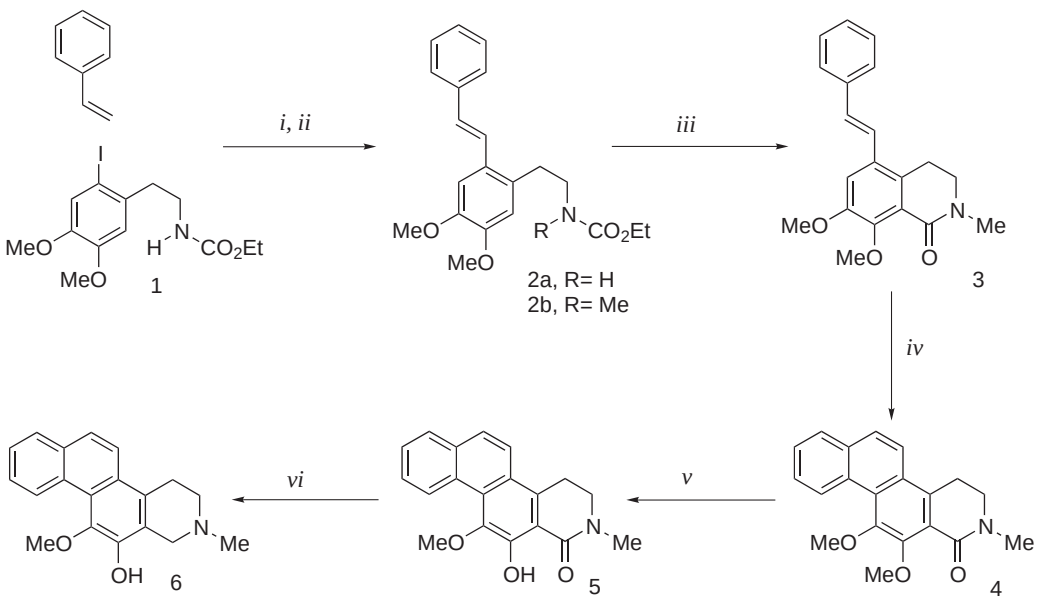
Abstract—Here we describe the first total synthesis of the 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline (**6**) annoretine from *N*-carbethoxy-*o*-styrylphenylethylamines **2**. The key steps were the Bischler–Napieralski reaction to form the isoquinoline unit and photocyclization of the resulting 5-styrylisoquinoline **3** to naphtoisoquinoline **4**.

The only natural products containing the 1,2,3,4-tetrahydronaphtho[2,1-*f*] isoquinoline skeleton are the relatively recently discovered alkaloids annoretine (**6**)[1] and litebamine.[2] This explains why the 1,2,3,4-tetrahydronaphtho[2,1-*f*] isoquinoline skeleton has received little chemical attention apart from a preliminary study of synthetic approaches[3] and a biomimetic synthesis from its probably biogenetic precursor boldine.[4,5] However, pharmacological studies have established the antiplatelet effects and the anti-acetylcholinesterase activity of litebamine and the cytotoxic properties of annoretine.[6] Additionally, tetrahydronaphtho[2,1-*f*]-isoquinolines are potential antibacterials and antitumorals because they have a tetracyclic ring system that



Scheme 1. $Pd(OAc)_2$ (10% molar), Ph_3P, Et_3N, MeCN, argon, 80°C, 24 h; (ii) (a) NaH, THF, rt, 30 min; (b) MeI, rt, 3 h; (iii) 5:3 Tf_2O/DMAP, CH_2Cl_2, argon, 0°C, 1 h; (iv) UV light, I_2, O_2, 95:5 Et_2O/CH_2Cl_2, 2 h; (v) BCl_3, CH_2Cl_2, argon, rt, 15 min; (vi) $LiAlH_4$, THF, rt, 5 h.

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is similar to that of the carcinogenic hydrocarbon chrysene but, like the ring system of antibacterial and antitumoral benzophenanthridine alkaloids, includes a nitrogen atom.[7] Here we briefly describe the first total synthesis of annoretine starting from the key *N*-carbethoxy-*o*-styrylphenylethylamines **2**.

N-Carbethoxy-*o*-iodohomoveratrylamine (**1**) was easily prepared in 75% yield in a two-step sequence starting from homoveratrylamine.[8] Heck coupling[9] of **1** to styrene gave the *E* isomer of *N*-carbethoxy-*o*-styrylphenylethylamine **2a** (Scheme 1) as a yellow oil (yield 70%). Treatment of this carbamate with MeI then afforded a 100% yield of *N*-methylcarbamate **2b**, which when subjected to Bischler–Napieralski[10] cyclization conditions (5:3 Tf_2O/DMAP) gave isoquinolinone **3** in 75% yield. Construction of the phenanthrene ring system was completed by photocyclization[11] of isoquinolinone **3** in oxygenated 95:5 ether–dichloromethane containing one equivalent of iodine. The resulting 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolinone **4** was obtained in 40% yield as a yellow solid, mp 134–136°C (AcOEt).

The substitution pattern of annoretine was easily established by treatment of **4** with BCl_3, which selectively and quantitatively removed the methyl group of the methoxy substituent at position 12 (a process favored by the carbonyl group). NOEs and NMR correlation experiments (HMBC and HMQC) allowed unambiguous identification of the structure of compound **5**. Final treatment of **5** with $LiAlH_4$ afforded annoretine[12] in 75% yield as a white solid, mp 160–163°C (MeOH, sublimation). We note that this synthesis confirms the structure proposed for annoretine.[1]

The above route to annoretine is currently being applied to the synthesis of litebamine and a series of non-natural tetrahydronaphtho[2,1-*f*]isoquinolines with a view to systematic study of their chemical and biological properties.

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12. All new compounds gave satisfactory analytical and spectroscopic data.
(a) Selected spectroscopic data for annoretine (**6**): ^{1}H NMR (δ, ppm, Cl_3CD): 2.57 (s, 3H, -NCH_3), 2.85 (t, J=5.9 Hz, 2H, -CH_2-), 3.27 (t, J=5.9 Hz, 2H, -CH_2-), 3.77 (s, 2H, -CH_2-), 3.79 (s, 3H, -OCH_3), 7.55–7.78 (m, 3H, 3×Ar-H), 7.82–7.87 (m, 2H, 2×Ar-H), 9.34–9.38 (m, 1H, Ar-H). ^{13}C NMR (δ, ppm, Cl_3CD): 26.76 (-CH_2-), 45.92 (-NCH_3), 52.48 (-CH_2-), 53.04 (-CH_2-), 60.08 (-OCH_3), 121.85 (C), 121.89 (Ar-H), 123.15 (C), 124.94 (Ar-H), 125.42 (C), 126.17 (Ar-H), 126.63 (Ar-H), 127.00 (Ar-H), 127.15 (C), 128.19 (Ar-H), 128.91 (C), 132.37 (C), 141.47 (C), 144.73 (C). MS (m/z, %): 293 (M^+, 97), 250 (100).
(b) Crystallographic data for annoretine (**6**): $C_{19}H_{19}NO_2$, M=293.35, T=293(2) K. Triclinic, space group $P\bar{1}$ with a=11.5575(17), b=12.0696(16), c=13.271(3) Å; α=112.933(13), β=111.403(14), γ=97.794(14)°; U=1501.7(4) Å^3, D_{calcd} (Z=4)=1.298 g cm^{-3}. $F(000)$=624, μ(Cu Kα)=6.66 cm^{-1}; 6453 unique data ($2\theta_{max}$=150°), 6177 with $I>2\sigma(I)$; conventional $R_1[I>2\sigma(I)]$=0.0413, wR_2 [all data]=0.1323, GOF [all data]=1.017. Data were obtained on an Enraf–Nonius CAD4-Mach3 diffractometer (graphite crystal monochromator, λ=1.5418 Å) using the $\omega=2\theta$ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least-squares on F^2 (SHELXL-93) using all data; $wR_2=[(\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.