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First Total Synthesis of 1,2,3,4-Tetrahydronaphtho[2,1-*f*]isoquinolines

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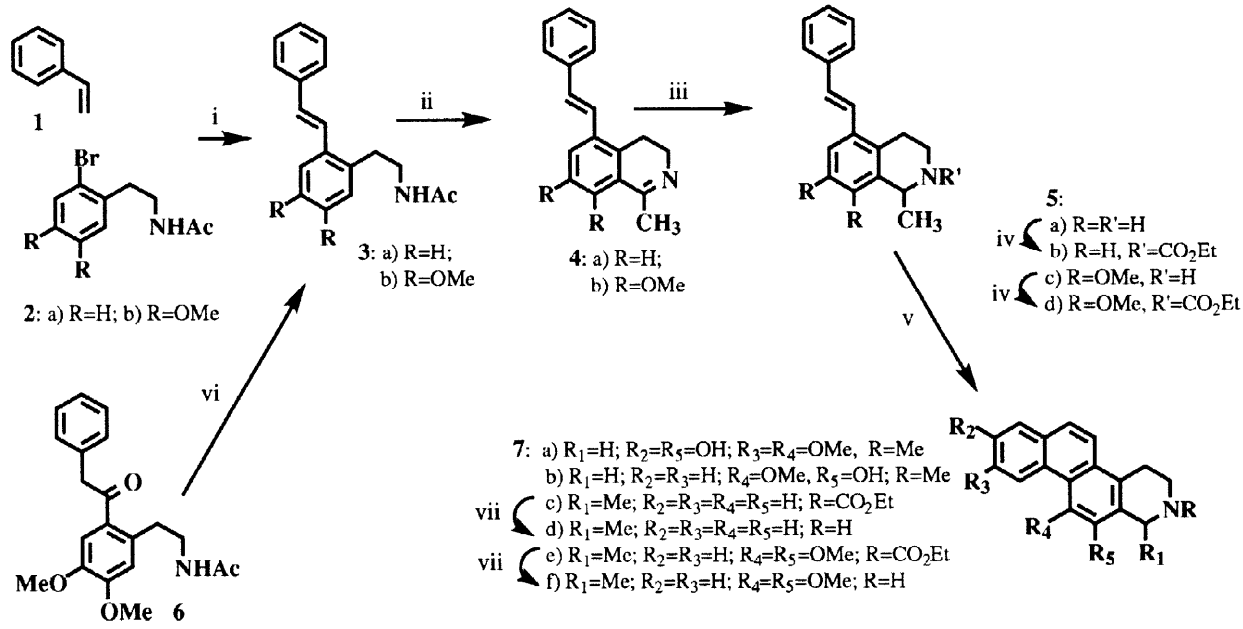
Abstract. *Here we describe the first total synthesis of 1,2,3,4-tetrahydronaphtho[2,1-f]isoquinolines (7) from N-acyl-o-styrylphenylethylamines 3. It proceeds by the Bischler-Napieralski reaction to form the isoquinoline unit and photocyclization of the resulting 5-styrylisoquinolines 5.* © 1998 Elsevier Science Ltd. All rights reserved.

5-Styrylisoquinolines **5** and naphtho[2,1-*f*]isoquinolines **7** have hitherto received little chemical attention. Partial synthesis of 5-styrylisoquinolines has only recently been described,[1] and 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines were ignored[2] until the isolation of litebamine (**7a**)[3] and anoretine (**7b**)[4] prompted partial syntheses of litebamine[1,5] from its probable biogenetic precursor,[3] the aporphine boldine. However naphthoisoquinolines may have antineoplastic properties: their tetracyclic ring system is similar to that of the carcinogenic hydrocarbon chrysene, but like the ring system of antibacterial and antitumoral benzophenanthridine alkaloids, includes a nitrogen atom.[6]

Here we briefly sketch the first total synthesis of 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines. The key *o*-styrylphenylethylacetamides **3** were obtained by two complementary routes.



Scheme: *(i) $Pd(OAc)_2$ (5% molar), Ph_3P, Et_3N, MeCN, argon, 130°C, 3 days. (ii) $POCl_3$, MeCN, argon, reflux, 18 h. (iii) $NaBH_4$, MeOH, r.t., 3 h. (iv) Et_3N, $ClCO_2Et$, r.t., 3 h. (v) UV light, I_2, O_2, Et_2O: CH_2Cl_2 (95:5), 2 h. (vi) a) $NaBH_4$, THF, r.t., 3.5 h. b) 10% aq. HCl, dioxan, reflux, 45 min. (vii) 10% aq. NaOH, MeOH, reflux, 30 min.*

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Heck coupling[7] of *o*-bromophenylethylacetamide (**2a**) to styrene gave the *E* isomer of *o*-styrylphenylethylacetamide **3a**, as a yellow solid [81% yield, m.p. 140-142°C (MeOH)]. This amide was subjected to Bischler-Napieralski[8] cyclization and the resulting unstable dihydroisoquinoline **4a** was directly reduced to 5-styryltetrahydroisoquinoline **5a** (80% yield, oil) by treatment with $NaBH_4$ in methanol at room temperature. Heck coupling of styrene to the electron rich *o*-bromophenylethylacetamide **2b**, afforded only a 30% yield of styrylamide **3b**, but efficient preparation of **3b** (90% overall yield) was accomplished by acidic hydrolysis[9] of the corresponding *N*-acetyl-1-benzyldihydroisoquinoline to *o*-phenylacetylphenyl-ethylacetamide **6**, treatment of **6** with $NaBH_4$ in THF, and reflux of an acidified solution of the resulting hydroxyamide in dioxan. Amide **3b** was transformed into 5-styryltetrahydroisoquinoline **5c**[10] via 5-styryldihydroisoquinoline **4b** as above (60% overall yield).

Photochemically promoted cyclization[11] of the *N*-protected styrylisoquinoline **5b** was carried out in oxygenated 95:5 ether-dichloromethane containing traces of iodine. The resulting *N*-protected naphthoisoquinoline **7c**, obtained in 30% yield as a white solid of m.p. 176-178 °C (MeOH), was transformed into naphthoisoquinoline **7d** by removal of the *N*-ethoxycarbonyl group. Similarly, irradiation of **5d**, the *N*-ethoxycarbonyl derivative of **5c**, afforded a 60% yield of the desired dimethoxylated naphthoisoquinoline **7e**, from which **7f** was obtained as an oil by removal of the ethoxycarbonyl group.

This first total synthesis of 5-styrylisoquinolines and naphtho[2,1-*f*]isoquinolines seems likely to be of general interest. We are continuing work in this area to prepare a series of 5-styrylisoquinolines and naphthoisoquinolines, including litebamine (**7a**) and anoretine (**7b**), for systematic study of their chemical and biological properties.

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10. All new compounds gave satisfactory analytical and spectroscopic data. Selected spectroscopic data: Compound **5c**: ^1H NMR (∂, ppm, Cl_3CD): 1.48 (m, 3H, $-CH_3$), 2.73-2.78 (m, 2H, $-CH_2-$), 3.11-3.84 (m, 2H, $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-OCH_3$), 4.36 (q, J=6.7 Hz, 1H, -CH-), 5.90 (bs, 1H, -NH), 6.90 (d, J=16.0 Hz, 1H, -C=CH-), 7.07 (s, 1H, Ar-H), 7.27 (d, J=16.0 Hz, 1H, -C=CH-) y 7.29-7.53 (m, 5H, 5xAr-H). Compound **7d**: ^1H NMR (∂, ppm, Cl_3CD): 1.56-1.58 (m, 3H, $-CH_3$), 1.89 (bs, 1H, -NH), 3.18-3.46 (m, 4H, 2x-CH_2), 4.33 (m, 1H, -CH-), 7.47 (d, J=8.7 Hz, 1H, Ar-H), 7.55-7.69 (m, 2H, 2xAr-H), 7.79 (m, 1H, Ar-H), 7.88 (m, 1H, Ar-H), 7.93 (d, J=8.9 Hz, 1H, Ar-H), 8.54 (m, 1H, Ar-H), 8.69 (m, 1H, Ar-H). MS (m/z, %): 247 (M^+, 7), 232 (100). Compound **7f**: ^1H NMR (∂, ppm, Cl_3CD): 1.58-1.66 (m, 3H, $-CH_3$), 2.79-3.08 (m, 2H, $-CH_2-$), 3.22-3.39 (m, 2H, $-CH_2-$), 3.95 (s, 3H, $-OCH_3$), 3.98 (s, 3H, $-OCH_3$), 4.61 (m, 1H, -CH-), 7.58-7.78 (m, 3H, 3xAr-H), 7.82-7.98 (m, 2H, 2xAr-H), 9.63 (m, 1H, Ar-H). MS (m/z, %): 307 (M^+, 15), 293 (22), 292 (100).
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