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Transition Metal Complexes in Organic Synthesis, Part 35.[1]

First Total Synthesis of Furostifoline

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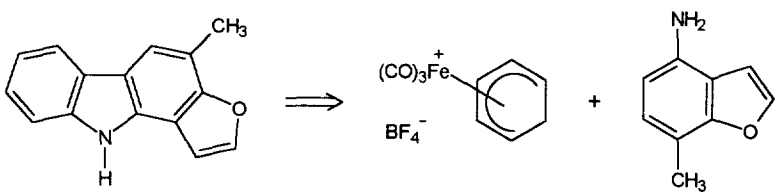
Abstract: The first total synthesis of the furo[3,2-*a*]carbazole alkaloid furostifoline was achieved using a convergent iron-mediated construction of the carbazole nucleus.

A large number of novel carbazole alkaloids have been isolated from natural sources over the past years.[2] The continuing interest of synthetic organic chemists in these natural products derives from the fact, that many derivatives have unprecedented structural features and exhibit useful biological activities. Many research groups developed novel synthetic methodologies directed towards the total synthesis of carbazole alkaloids.[3] Our group focussed on the elaboration of convergent total syntheses *via* transition metal-mediated reactions.[4] For the synthesis of highly oxygenated carbazoles we developed an efficient process involving oxidative cyclization of appropriately functionalized tricarbonyl(η^4-1,3-cyclohexadiene)iron complexes.[5] Although of broad scope for the synthesis of 1-oxygenated, 3-oxygenated, 3,4-dioxygenated, and 3,4,6-trioxygenated carbazole alkaloids,[1,6] the method was only of limited success for the synthesis of 2-oxygenated carbazole derivatives.[7] Because of this drawback we recently developed a novel molybdenum-mediated construction of the carbazole framework which is complementary to the iron-mediated approach.[8,9] In the present study, we wish to report that our iron-mediated carbazole synthesis is useful for the synthesis of furo[3,2-*a*]carbazole alkaloids which is demonstrated by the first total synthesis of furostifoline.[10]

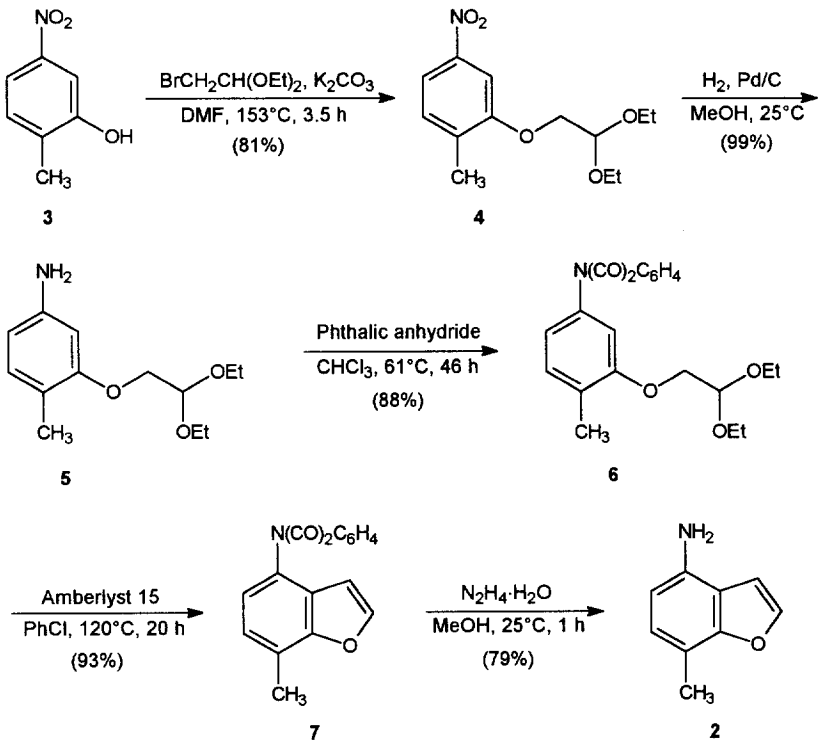


Furostifoline **1** **2**

Scheme 1

Retrosynthesis of furostifoline based on the iron-mediated construction of the carbazole nucleus leads to the iron complex salt **1** and 4-amino-7-methylbenzofuran **2** as the potential synthetic precursors (Scheme 1). Both building blocks should be combined in a consecutive iron-mediated C–C and C–N bond formation by regioselective electrophilic substitution of **2** with **1** followed by oxidative cyclization of the resulting transition metal complex to the carbazole. The complex salt **1** is readily available in large quantities by 1-aza-1,3-butadiene catalyzed complexation of 1,3-cyclohexadiene[11] and subsequent hydride abstraction with triphenylcarbenium tetrafluoroborate.[12] A simple route to the 4-aminobenzofuran **2** is outlined in Scheme 2.

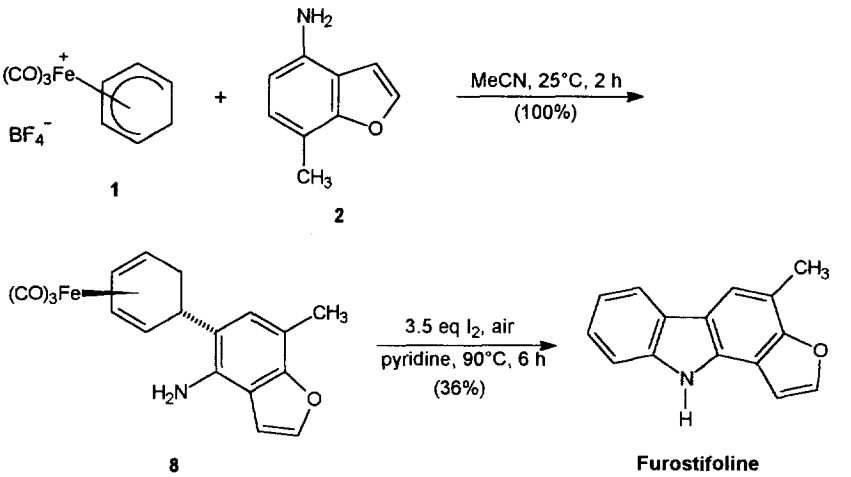
The nitrophenol **3** is easily prepared from the corresponding nitroaniline[13] and served already as precursor in our molybdenum-mediated total synthesis of dihydroxygirinimbine.[9] Bromoacetaldehyde diethylacetal was used as C_2 moiety for the annulation of the furan ring.[14] Alkylation of the nitrophenol **3** with bromoacetaldehyde diethylacetal in presence of potassium carbonate in *N,N*-dimethylformamide under reflux afforded the ether **4** which was hydrogenated to the arylamine **5**. Prior to cyclization of the furan ring the amino group was protected by transformation into the phthalic imide **6**. Annulation of the furan ring was then achieved by amberlyst 15 promoted cyclization[15] in chlorobenzene at 120°C and provided the protected aminobenzofuran 7 in 93% yield. Cleavage of the imide by treatment with hydrazine in methanol at room temperature afforded the required 4-amino-7-methylbenzofuran **2**.[16] By the present 5-step-sequence, **2** is available on a multigram scale in 52% overall yield based on the nitrophenol **3**.



Scheme 2

The reaction of the 4-aminobenzofuran **2** with the dicarbonyl(η^4-1,3-cyclohexadiene)(η^5-cyclopentadienyl)-molybdenum hexafluorophosphate[8,9] gave the desired molybdenum complex only in 7% yield. However, electrophilic aromatic substitution reaction of **2** with the complex salt **1** took place exclusively in the 5-position and provided regio- and diastereoselectively the iron complex **8** in quantitative yield (Scheme 3). According to the spectral data of **8**,[16] the regioselectivity (electrophilic substitution *ortho* relative to the amino function) and the diastereoselectivity (nucleophilic attack of the amine *anti* to the tricarbonyliron fragment) of this reaction were the same as previously found in analogous cases.[17] All attempted oxidative cyclizations using different manganese dioxides (commercial MnO_2 and very active MnO_2) as well as ferricenium hexafluorophosphate as

the oxidants resulted exclusively in decomposition. Cyclization of complex **8** with concomitant aromatization was finally achieved by oxidation in the air with an excess of iodine in pyridine at 90°C[7,18] and afforded directly the furo[3,2-*a*]carbazole alkaloid **furostifoline**.



Scheme 3

The spectral data (UV, IR, ^{1}H-NMR, and MS) of synthetic furostifoline[16] are in full agreement with those reported by Furukawa and coworkers for the alkaloid, which was obtained from the root bark of *Murraya euchrestifolia*.[10] The natural product was described as an oil, whereas we obtained furostifoline as colorless crystals (m.p. 174-175°C).

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15. Amberlyst 15 from Fluka (art. 06423).
16. 4-Amino-7-methylbenzofuran **2**: Light yellow oil, b.p. 60-62°C/0.06 Torr; UV (MeOH): λ = 219, 259, 297 nm; IR (film): ν = 3354 (br), 2922, 1635, 1505, 1359, 1299, 1177, 1144, 1041, 878, 809, 770, 732, 622 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.60 (br s, 2 H), 6.40 (d, J = 7.7, 1 H), 6.64 (d, J = 2.2, 1 H), 6.87 (d, J = 7.7, 1 H), 7.50 (d, J = 2.2, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.46 (CH_3), 103.46 (CH), 107.62 (CH), 112.09 (C), 115.77 (C), 125.68 (CH), 137.78 (C), 143.07 (CH), 154.77 (C); MS (20°C): *m/z* (%) = 147 (M^+, 100), 146 (99), 91 (6), 74 (5); HRMS: Calc. for C_9H_9NO (M^+): 147.0684; found: 147.0674.

    Tricarbonyl(η^4-cyclohexa-1,3-diene)iron complex **8**: Yellow crystals, m.p. 116°C; UV (MeOH): λ = 225, 301 nm; IR (KBr): ν = 3445, 3365, 3005, 2846, 2039, 1949, 1631, 1480, 1155, 745, 625 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.65 (br d, J = 15.3, 1 H), 2.40 (ddd, J = 15.3, 11.1, 4.0, 1 H), 2.40 (d, J = 0.7, 3 H), 3.15-3.22 (m, 2 H), 3.49 (dt, J = 11.1, 3.7, 1 H), 3.71 (br s, 2 H), 5.49-5.55 (m, 2 H), 6.62 (d, J = 2.3, 1 H), 6.81 (s, 1 H), 7.51 (d, J = 2.3, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.66 (CH_3), 31.62 (CH_2), 38.54 (CH), 60.34 (CH), 65.71 (CH), 84.93 (CH), 85.64 (CH), 103.42 (CH), 112.05 (C), 116.26 (C), 122.84 (C), 124.28 (CH), 134.17 (C), 143.51 (CH), 153.18 (C), 212.05 (3 CO); MS (75°C): *m/z* (%) = 365 (M^+, 20), 337 (6), 309 (37), 281 (70), 279 (100), 223 (41), 203 (81), 147 (42). Anal. Calc. for $C_{18}H_{15}FeNO_4$: C, 59.20; H, 4.14; N, 3.84. Found: C, 59.27; H, 4.26; N, 3.98.

    Furostifoline: Colorless crystals, m.p. 174-175°C; UV (MeOH): λ = 211, 226, 237, 260, 274, 296, 319, 333 nm; IR (KBr): ν = 3415, 1457, 1445, 1361, 1308, 1159, 1044, 878, 747, 679 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.67 (d, J = 0.8, 3 H), 6.97 (d, J = 2.2, 1 H), 7.25 (dt, J = 0.9, 7.5, 1 H), 7.37 (ddd, J = 7.5, 7.2, 1.1, 1 H), 7.47 (br d, J = 8.0, 1 H), 7.71 (d, J = 2.2, 1 H), 7.77 (br s, 1 H), 8.05 (br d, J = 7.7, 1 H), 8.21 (br s, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.45 (CH_3), 103.72 (CH), 110.74 (CH), 111.37 (C), 114.29 (C), 116.68 (CH), 117.85 (C), 119.58 (CH), 119.63 (CH), 124.01 (C), 124.30 (CH), 131.00 (C), 138.87 (C), 143.76 (CH), 154.05 (C); MS (45°C): *m/z* (%) = 221 (M^+, 100), 220 (56), 191 (11), 110 (6). Anal. Calc. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.62; H, 5.35; N, 6.41.
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