Transition Metal Complexes in Organic Synthesis, Part 63;[1] Convergent Iron-Mediated Syntheses of the Furo[3,2-*a*]carbazole Alkaloid Furostifoline

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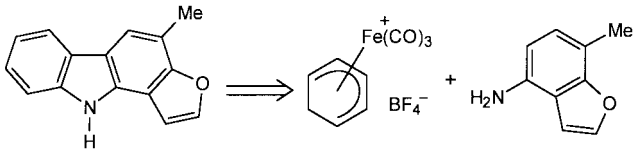
Abstract: Two highly efficient routes to the furo[3,2-*a*]carbazole alkaloid furostifoline are described. Both syntheses use the iron-mediated arylamine cyclization as the key-step and lead to the natural product in seven and five steps, respectively.

Key words: benzofurans, carbazole alkaloids, tricarbonyliron complexes, electrophilic substitution, oxidative cyclization

Over the past decades many biologically active carbazole alkaloids with challenging new structures were isolated from different natural sources.[2-5] The strong interest of many research groups in these natural products led to the development of novel methodologies for the synthesis of carbazole alkaloids.[6-10] We developed an efficient and highly convergent iron-mediated construction of the carbazole framework which was applied to the total synthesis of a broad range of carbazole alkaloids. The key-steps of our approach are the consecutive C−C and C−N bond formations, which are mediated by a tricarbonyliron fragment between its coordinated cyclohexa-1,3-diene ligand and a fully functionalized arylamine.[10,11]

In 1990, Furukawa and his group at Nagoya reported the isolation and structural elucidation of furostifoline **1**.[12] Furostifoline was obtained from the root bark of *Murraya euchrestifolia* Hayata (Rutaceae), a shrub growing in Taiwan where extracts of the leaves and bark of this plant have been used as a folk medicine. Furostifoline was the first carbazole alkaloid exhibiting a furo[3,2-*a*]carbazole framework. Because of its unprecedented framework and pharmacological potential, furostifoline attracted the attention of several synthetic organic groups. In 1996, we described the first total synthesis of furostifoline by application of our convergent iron-mediated formation of the carbazole nucleus.[13] Further total syntheses were reported in 1998 by the groups of Beccalli and Hibino using different electrocyclic ring closures as key-step.[14,15] More recently, Timári and co-workers elaborated an additional synthesis of furostifoline using a palladium-catalyzed cross-coupling followed by a regioselective nitrene insertion.[16] In this paper, we describe the full experimental details of our first furostifoline synthesis[13] and an alternative approach featuring a reversal of the sequence of the two cyclization reactions.

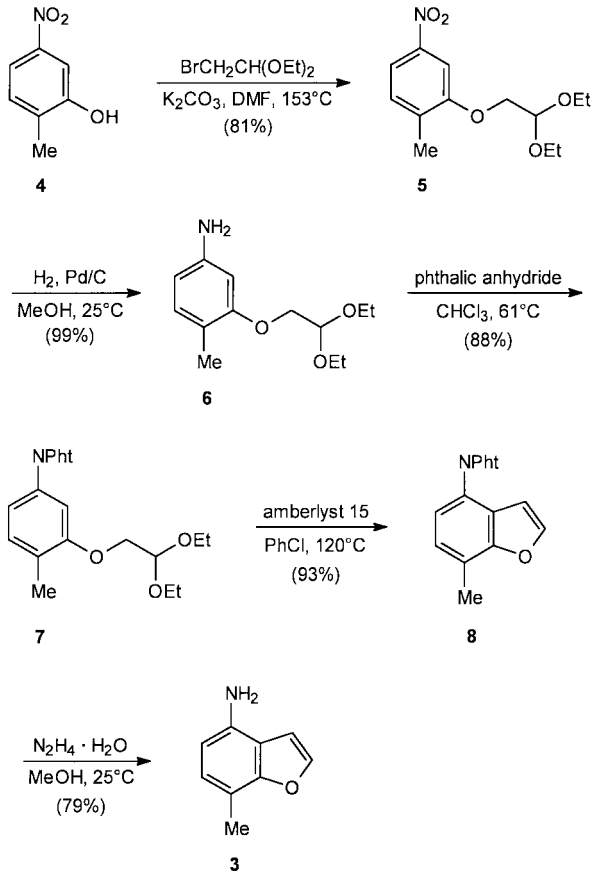
The retrosynthetic analysis of furostifoline **1** leads to the iron complex salt **2** and 4-amino-7-methylbenzofuran (**3**) as precursors for a highly convergent iron-mediated synthesis (Scheme 1). In this approach the whole benzofuran moiety of the natural product is already completed at the stage of the arylamine precursor and the two building blocks only have to be combined by the final iron-mediated consecutive C−C and C−N bond formation furnishing the carbazole framework. The iron complex salt **2** is readily prepared on a large scale using our 1-azabuta-1,3-diene catalyzed complexation of cyclohexa-1,3-diene[17] followed by hydride abstraction with triphenylcarbenium tetrafluoroborate.[18] For the synthesis of 4-amino-7-methylbenzo[*b*]furan (**3**), we devised a straightforward route (Scheme 2).



1 Furostifoline **2** **3**

Scheme 1

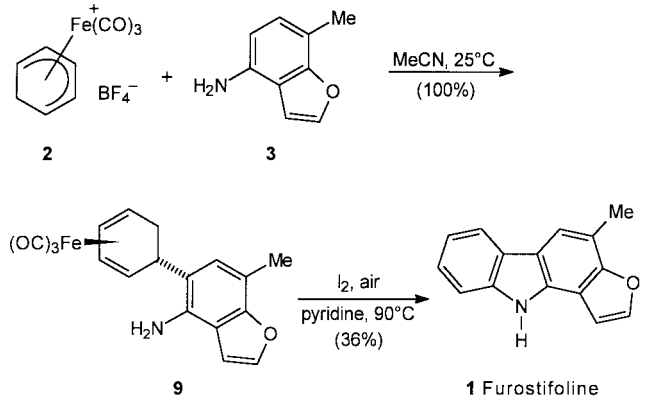
Following a literature procedure, 2-methyl-5-nitrophenol (**4**) is easily prepared by treatment of 2-methyl-5-nitroaniline with nitrous acid with heating.[19] Compound **4** previously served as starting material for our molybdenum-mediated total synthesis of the pyrano[3,2-*a*]carbazole alkaloid dihydroxygirinimbine.[20] For the annulation of the furan ring at the nitrophenol **4**, we used bromoacetaldehyde diethyl acetal, which represents a well-established C_2-building block for the synthesis of benzofurans via ether formation, and subsequent amberlyst 15 catalyzed cyclization.[21,22] The alkylation of the nitrophenol **4** with 2-bromo-1,1-diethoxyethane in *N*,*N*-dimethylformamide at reflux in the presence of potassium carbonate provided the 2-aryloxy-1,1-diethoxyethane **5**. The reaction of the nitroaryl ether **5** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C provided the desired 7-methyl-4-nitrobenzo[*b*]furan in only 6% yield and led by cleavage of the ether to the nitrophenol **4** as major product (see experimental section). Catalytic hydrogenation of the nitro derivative **5** using palladium on activated carbon afforded the arylamine **6**. All attempts to achieve a cyclization of the unprotected arylamine **6** with amberlyst 15, polyphosphoric acid, or boron trifluoride etherate resulted in complete decomposition. Therefore, the amino group was protected prior to the furan formation by conversion to the



Scheme 2

phthalimide **7**. The subsequent annulation of the furan ring by the amberlyst 15 catalyzed cyclization in chlorobenzene at 120 °C afforded the protected aminobenzofuran **8**.[21,22] Removal of the phthaloyl protecting group by treatment of **8** with hydrazine hydrate in methanol at room temperature provided 4-amino-7-methylbenzo[*b*]furan (**3**). The present 5-step-sequence can be carried out easily on a multigram scale and provides compound **3** in 52% overall yield based on the nitrophenol **4**.

The C–C bond formation by electrophilic aromatic substitution at the aminobenzofuran **3** with the iron complex salt **2** in acetonitrile at room temperature afforded quantitatively the iron complex **9** (Scheme 3). The attempted oxidative cyclization of complex **9** with a range of reagents (commercial manganese dioxide, very active manganese dioxide, and ferricenium hexafluorophosphate) failed and resulted exclusively in decomposition of the starting material. An alternative reagent for the iron-mediated arylamine cyclization is iodine in pyridine,[23] although it was demonstrated that this oxidant often leads to simple demetalation with only minor amounts of cyclization products.[24,25] More recently, iodine in pyridine was successfully utilized for the first double iron-mediated arylamine cyclization to indolo[2,3-*b*]carbazole.[26] Oxidative cyclization of complex **9** with concomitant aromatization was achieved by treatment with an excess of iodine in pyridine at 90 °C in the air and provided furostifoline **1** in 36% yield.



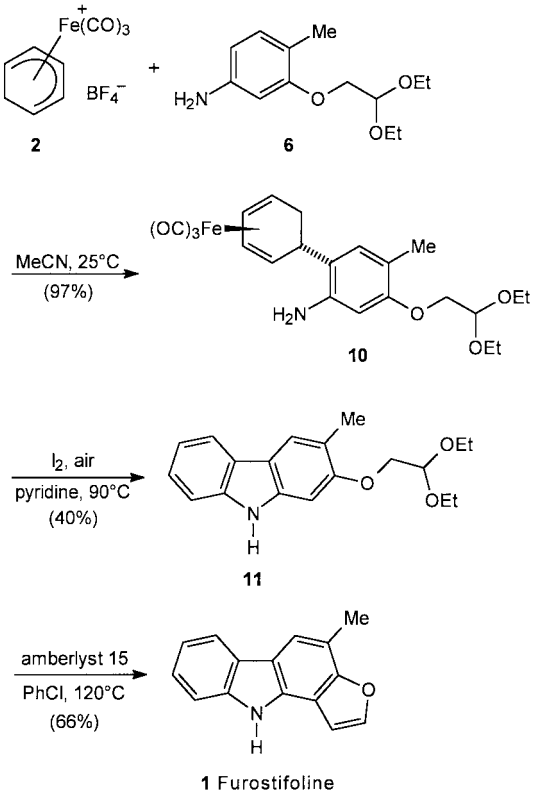
Scheme 3

In a novel approach to the furo[3,2-*a*]carbazole alkaloid furostifoline we realized a reversal of the two cyclization reactions by first forming the carbazole nucleus and then fusing the furan ring (Scheme 4). This second synthesis is shorter because an intermediate protection of the amino function is not necessary. Electrophilic substitution at the arylamine **6** by reaction with the iron complex salt **2** in acetonitrile at room temperature provided in high yield the iron complex **10**. Although one equivalent of tetrafluoroboric acid was generated during this process, the acetal protecting group in the side chain stayed intact. At this stage, the carbazole heterocycle was first formed by an iron-mediated arylamine cyclization of complex **10** with iodine in pyridine, which afforded the carbazole **11** in 40% yield. Annulation of the furan ring by reaction of the carbazole **11** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C led directly to furostifoline **1** in 66% yield.

The spectral data of our synthetic furostifoline are in full agreement with those described by Furukawa for the natural product (UV, IR, ^{1}H NMR, and MS).[12] We obtained furostifoline as colorless crystals with a melting point of 174–175 °C, whereas the natural product was isolated as a colorless oil.[12]

In conclusion, our first synthesis provides furostifoline in seven steps and 19% overall yield based on the nitrophenol **4**, while our second synthesis leads to the natural product in only five steps and 21% overall yield based on the same starting material.

All reactions were carried out in dry solvents under an inert gas atmosphere unless otherwise stated. Flash chromatography: Merck silica gel (0.03–0.06 mm). Amberlyst 15 was obtained from Fluka.[22] Mps: Büchi 535. UV spectra: Perkin–Elmer Lambda 2 (UV/VIS spectrometer). IR spectra: Bruker IFS 88 (FT-IR). ^{1}H NMR and ^{13}C NMR spectra: Bruker AM-400 and Bruker DRX 500; internal standard: TMS or the signal of the deuterated solvent; δ in ppm;



Scheme 4

coupling constants (*J*) in Hz. MS: Finnigan MAT-90; ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid.

3-(2,2-Diethoxyethoxy)-4-methylnitrobenzene (5)
Bromoacetaldehyde diethyl acetal (14.2 g, 71.8 mmol) was added to a refluxing mixture of 2-methyl-5-nitrophenol (**4**) (10.0 g, 65.3 mmol) and potassium carbonate (10.9 g, 79.0 mmol) in *N*,*N*-dimethyl formamide (40 mL) over 45 min. The reaction mixture was stirred for an additional 3.5 h at reflux and cooled to r.t. The mixture was poured into NaOH (1%, 180 mL) and the aqueous layer was extracted with Et_2O (2 x 80 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4). After removal of the solvent, the residue was distilled in vacuo to provide the acetal **5** as a pale yellow oil, yield: 14.3 g (81%), bp: 122 °C/0.3 Torr.

UV (MeOH): λ = 210, 229, 279, 323 nm.

IR (film): ν = 2977, 2931, 2884, 1522, 1346, 1253, 1133, 1071, 866, 815, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 6H, *J* = 7.1 Hz), 2.32 (s, 3H), 3.68 (dq, 2H, *J* = 9.3, 7.1 Hz), 3.81 (dq, 2H, *J* = 9.3, 7.1 Hz), 4.09 (d, 2H, *J* = 5.2 Hz), 4.90 (t, 1H, *J* = 5.2 Hz), 7.26 (d, 1H, *J* = 8.1 Hz), 7.67 (d, 1H, *J* = 2.1 Hz), 7.76 (dd, 1H, *J* = 8.1, 2.1 Hz).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.37 (2 CH_3), 16.64 (CH_3), 63.00 (2 CH_2), 69.19 (CH_2), 100.38 (CH), 105.82 (CH), 115.99 (CH), 130.60 (CH), 135.21 (C), 147.10 (C), 156.86 (C).

MS (35 °C): *m/z* (%) = 269 (M^+, 1), 178 (12), 103 (100), 75 (42), 47 (32).

HRMS: *m/z* calcd for $C_{13}H_{19}NO_5$ (M^+): 269.1263. Found: 269.1253.

7-Methyl-4-nitrobenzo[*b*]furan
A mixture of the nitroaryl ether **5** (3.96 g, 14.7 mmol) and amberlyst 15 (400 mg) in dry chlorobenzene (10 mL) was stirred at 120 °C for 2 days. TLC analysis, at this stage, indicated that the major product was the nitrophenol **4**. After cooling to r.t., the reaction mixture was filtered and the filter washed with Et_2O (50 mL). The combined filtrates were washed with NaOH (5%, 3 x 30 mL) to remove the nitrophenol **4**, then with H_2O (50 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography (CH_2Cl_2) of the residue on silica gel provides 7-methyl-4-nitrobenzofuran as light yellow crystals, yield: 166 mg (6%), mp: 110−111 °C (acetone).

UV (MeOH): λ = 193, 224, 307 nm.

IR (drift): ν = 3173, 3137, 1511, 1324, 1127, 815, 784, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3H), 7.18 (d, 1H, *J* = 8.3 Hz), 7.47 (d, 1H, *J* = 2.2 Hz), 7.82 (d, 1H, *J* = 2.2 Hz), 8.09 (d, 1H, *J* = 8.3 Hz).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.47 (CH_3), 107.33 (CH), 119.85 (CH), 122.56 (C), 124.57 (CH), 129.82 (C), 139.05 (C), 148.13 (CH), 154.61 (C).

MS (20 °C): *m/z* (%) = 177 (M^+, 100), 147 (35), 131 (45), 102 (11), 91 (12), 77 (35).

HRMS: *m/z* calcd for $C_9H_7NO_3$ (M^+): 177.0426. Found: 177.0436.

Anal. calcd for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.76; H, 4.01; N, 7.70.

3-(2,2-Diethoxyethoxy)-4-methylaniline (6)
Palladium on activated carbon (10%, 970 mg) was added to a solution of the nitrobenzene **5** (9.69 g, 36.0 mmol) in MeOH (100 mL). The solution was stirred vigorously under a H_2 atm until no further uptake of H_2 was detected. The reaction mixture was filtered over a short path of Celite (which was subsequently washed with MeOH) and the solvent was removed. The residue was subjected to flash chromatography (Et_2O) on silica gel to afford the arylamine **6** as a light red oil, yield: 8.48 g (99%).

UV (MeOH): λ = 204, 237, 288 nm.

IR (film): ν = 3450, 3365, 2976, 2932, 1622, 1514, 1183, 1130, 1072, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 6H, *J* = 7.1 Hz), 2.11 (s, 3H), 3.54 (br s, 2H), 3.64 (dq, 2H, *J* = 9.4, 7.1 Hz), 3.77 (dq, 2H, *J* = 9.4, 7.1 Hz), 3.93 (d, 2H, *J* = 5.3 Hz), 4.83 (t, 1H, *J* = 5.3 Hz), 6.17−6.21 (m, 2H), 6.87 (d, 1H, *J* = 7.8 Hz).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.37 (3 CH_3), 62.80 (2 CH_2), 68.79 (CH_2), 99.54 (CH), 100.81 (CH), 107.21 (CH), 116.55 (C), 131.01 (CH), 145.61 (C), 157.35 (C).

MS (20 °C): *m/z* (%) = 239 (M^+, 66), 148 (16), 123 (14), 122 (14), 106 (15), 103 (100), 75 (46), 47 (27).

HRMS: *m/z* calcd for $C_{13}H_{21}NO_3$ (M^+): 239.1521. Found: 239.1530.

3-(2,2-Diethoxyethoxy)-4-methylphthaloylimidobenzene (7)
A mixture of the arylamine **6** (2.34 g, 9.78 mmol) and phthalic anhydride (1.63 g, 11.0 mmol) was stirred in $CHCl_3$ (30 mL) at reflux for 27 h. Additional phthalic anhydride (250 mg, 1.69 mmol) was added to the reaction mixture, which was stirred further at reflux for 19 h. The solvent was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel to afford the phthalimide **7** as a colorless solid, yield: 3.18 g (88%), mp: 110−111 °C.

UV (MeOH): λ = 197, 218, 279 nm.

IR (drift): ν = 2977, 2930, 2892, 1720, 1515, 1393, 1260, 1133, 1109, 1082, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, 6H, *J* = 7.1 Hz), 2.28 (s, 3H), 3.65 (dq, 2H, *J* = 9.3, 7.1 Hz), 3.78 (dq, 2H, *J* = 9.3, 7.1 Hz), 4.03 (d, 2H, *J* = 5.2 Hz), 4.88 (t, 1H, *J* = 5.2 Hz), 6.89 (d, 1H,

J = 1.8 Hz), 6.94 (dd, 1H, *J* = 7.9, 1.8 Hz), 7.25 (d, 1H, *J* = 7.9 Hz), 7.75−7.79 (m, 2H), 7.90−7.93 (m, 2H).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.25 (2 CH_3), 16.00 (CH_3), 62.66 (2 CH_2), 68.81 (CH_2), 100.45 (CH), 109.75 (CH), 118.75 (CH), 123.55 (2 CH), 127.11 (C), 129.98 (C), 130.64 (CH), 131.63 (2 C), 134.25 (2 CH), 156.75 (C), 167.24 (2 C=O).

MS (100 °C): *m/z* (%) = 369 (M^+, 10), 278 (14), 103 (100), 75 (26), 47 (20).

HRMS: *m/z* calcd for $C_{21}H_{23}NO_5$ (M^+): 369.1576. Found: 369.1566.

Anal. calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.32; H, 6.06; N, 3.91.

7-Methyl-4-phthaloylimidobenzo[*b*]furan (8)

A mixture of the phthalimide **7** (665 mg, 1.80 mmol) and amberlyst 15 (70 mg) in chlorobenzene (1 mL) was stirred at 120 °C for 20 h. After cooling to r.t., the reaction mixture was diluted with CH_2Cl_2 and filtered. The solvent was evaporated and the residue was recrystallized from tetrachloromethane to give the benzofuran **8** as pale yellow crystals, yield: 465 mg (93%), mp: 183 °C.

UV (MeOH): λ = 215, 237, 255 nm.

IR (drift): ν = 1724, 1505, 1383, 882, 806, 717 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3H), 6.61 (d, 1H, *J* = 2.2 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 7.66 (d, 1H, *J* = 2.2 Hz), 7.79−7.82 (m, 2H), 7.96−7.99 (m, 2H).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.03 (CH_3), 105.40 (CH), 121.85 (C), 121.90 (CH), 122.59 (C), 123.82 (2 CH), 124.49 (C), 125.23 (CH), 131.95 (2 C), 134.41 (2 CH), 145.24 (CH), 154.56 (C), 167.17 (2 C=O).

MS (65 °C): *m/z* (%) = 277 (M^+, 100), 233 (5), 204 (6), 130 (4), 104 (4), 76 (9).

HRMS: *m/z* calcd for $C_{17}H_{11}NO_3$ (M^+): 277.0739. Found: 277.0753.

Anal. calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.45; H, 4.04; N, 5.01.

4-Amino-7-methylbenzo[*b*]furan (3)

Hydrazine hydrate (85%, 2.7 mL) was added dropwise to a stirred suspension of the benzofuran **8** (1.67 g, 6.02 mmol) in MeOH (50 mL) and the resulting orange colored solution was stirred for 1 h at r.t. After removal of the solvent, the residue was extracted with Et_2O (3 x 50 mL). The combined organic layers were evaporated and the residue was distilled in vacuo to afford the aminobenzofuran **3** as a light yellow oil, yield: 719 mg (81%), bp: 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, 3H), 3.60 (br s, 2H), 6.40 (d, 1H, *J* = 7.7 Hz), 6.64 (d, 1H, *J* = 2.2 Hz), 6.87 (d, 1H, *J* = 7.7 Hz), 7.50 (d, 1H, *J* = 2.2 Hz).

^{13}C NMR and DEPT (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: *m/z* calcd for C_9H_9NO (M^+): 147.0684. Found: 147.0674.

[(1-4-η)-5-(4-Amino-7-methylbenzo[*b*]furan-5-yl)cyclohexa-1,3-diene]tricarbonyliron (9)

A solution of the aminobenzofuran **3** (112 mg, 0.761 mmol) and tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**2**) (116 mg, 0.379 mmol) in degassed MeCN (2 mL) was stirred for 3.5 h at r.t. The solvent was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel to provide the iron complex **9** as yellow crystals, yield: 139 mg (100%), mp: 116 °C.

UV (MeOH): λ = 210 (sh), 225, 301 nm.

IR (drift): ν = 3445, 3365, 3005, 2938, 2846, 2039, 1949, 1631, 1480, 1155, 745, 625 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (br d, 1H, *J* = 15.3 Hz), 2.40 (ddd, 1H, *J* = 15.3, 11.1, 4.0 Hz), 2.40 (d, 3H, *J* = 0.7 Hz), 3.15−3.22 (m, 2H), 3.49 (dt, 1H, *J* = 11.1, 3.7 Hz), 3.71 (br s, 2H), 5.49−5.55 (m, 2H), 6.62 (d, 1H, *J* = 2.3 Hz), 6.81 (s, 1H), 7.51 (d, 1H, *J* = 2.3 Hz).

^{13}C NMR and DEPT (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).

HRMS: *m/z* calcd for $C_{18}H_{15}FeNO_4$ (M^+): 365.0350. Found: 365.0334.

Anal. calcd 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 (4-Methyl-10*H*-furo[3,2-*a*]carbazole) (1)

Iodine (2.08 g, 8.20 mmol) was added to a solution of the iron complex **9** (1.00 g, 2.74 mmol) in pyridine (30 mL) at 90 °C. After stirring for 4 h at 90 °C in the air, additional iodine (340 mg, 1.34 mmol) was added to the dark brown solution. The reaction mixture was stirred further for 2 h at 90 °C and was cooled to r.t. A solution of sodium thiosulfate (10 g) and citric acid (5 g) in H_2O (60 mL) was added and the mixture was extracted with Et_2O (2 x 80 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to flash chromatography (hexane/EtOAc/Et_3N, 6:3:1) on silica gel to afford furostifoline **1** as colorless crystals, yield: 215 mg (36%), mp: 174−175 °C (cyclohexane).

UV (MeOH): λ = 211, 226, 237, 260, 274, 296, 319, 333 nm.

IR (drift): ν = 3415, 1457, 1445, 1361, 1308, 1159, 1044, 878, 747, 735, 679 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67 (d, 3H, *J* = 0.8 Hz), 6.97 (d, 1H, *J* = 2.2 Hz), 7.25 (dt, 1H, *J* = 0.9, 7.5 Hz), 7.37 (ddd, 1H, *J* = 7.5, 7.2, 1.1 Hz), 7.47 (br d, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 2.2 Hz), 7.77 (br s, 1H), 8.05 (br d, 1H, *J* = 7.7 Hz), 8.21 (br s, 1H).

^{13}C NMR and DEPT (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).

HRMS: *m/z* calcd for $C_{15}H_{11}NO$ (M^+): 221.0841. Found: 221.0830.

Anal. calcd 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.

[(1-4-η)-5-{2-Amino-4-(2,2-diethoxyethoxy)-5-methylphenyl}cyclohexa-1,3-diene]tricarbonyliron (10)

A solution of the arylamine **6** (1.00 g, 4.19 mmol) and tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**2**) (640 mg, 2.09 mmol) in degassed MeCN (20 mL) was stirred for 3 h at r.t. The solvent was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel to provide the iron complex **10** as light yellow crystals, yield: 930 mg (97%), mp: 91−92 °C.

UV (MeOH): λ = 205, 296 nm.

IR (drift): ν = 3451, 3370, 2983, 2940, 2889, 2042, 1967, 1949, 1920, 1626, 1511, 1058, 618 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 6H, *J* = 7.1 Hz), 1.57 (br d, 1H, *J* = 15.1 Hz), 2.11 (s, 3H), 2.33 (ddd, 1H, *J* = 15.1, 11.1, 3.9 Hz), 3.12 (m, 1H), 3.17 (m, 1H), 3.31 (dt, 1H, *J* = 11.1, 3.5 Hz), 3.47 (br s, 2H), 3.63 (dq, 2H, *J* = 9.2, 7.1 Hz), 3.76 (dq, 2H, *J* = 9.2, 7.1 Hz), 3.90 (d, 2H, *J* = 5.2 Hz), 4.80 (t, 1H, *J* = 5.2 Hz), 5.49 (m, 2H), 6.11 (s, 1H), 6.81 (s, 1H).

^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 15.38 (2 CH_3), 15.56 (CH_3), 31.35 (CH_2), 38.33 (CH), 60.29 (CH), 62.77 (2 CH_2), 65.34 (CH), 68.99 (CH_2), 84.94 (CH), 85.66 (CH), 100.20 (CH), 100.77 (CH), 116.92 (C), 122.47 (C), 129.00 (CH), 142.16 (C), 155.62 (C), 212.07 (3 CO).

MS (90 °C): *m/z* (%) = 457 (M^+, 20), 429 (1), 412 (5), 401 (14), 373 (100), 371 (12), 317 (18), 315 (17), 301 (21), 299 (16), 257 (22), 255 (32), 253 (20), 223 (21), 103 (31).

HRMS: *m/z* calcd for $C_{22}H_{27}FeNO_6$ (M^+): 457.1188. Found: 457.1179.

Anal. calcd for $C_{22}H_{27}FeNO_6$: C, 57.78; H, 5.95; N, 3.06. Found: C, 57.89; H, 5.94; N, 3.16.

2-(2,2-Diethoxyethoxy)-3-methylcarbazole (11)

Iodine (2.60 g, 10.2 mmol) was added to a solution of the iron complex **10** (1.34 g, 2.93 mmol) in pyridine (35 mL) at 90 °C. After stirring for 6 h at 90 °C in the air, the dark brown solution was cooled to r.t. A solution of sodium thiosulfate (13 g) and citric acid (7 g) in H_2O (60 mL) was added and the mixture was extracted with Et_2O (2 x 80 mL). The combined organic layers were washed with H_2O (4 x 80 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by flash chromatography (hexane/EtOAc, 2:1) on silica gel to afford the carbazole **11** as colorless crystals, yield: 364 mg (40%), mp: 110−111 °C (hexane).

UV (MeOH): λ = 211, 229 (sh), 235, 250 (sh), 256, 301, 331 nm.

IR (drift): ν = 3402, 2976, 2930, 1633, 1610, 1473, 1458, 1348, 1306, 1231, 1185, 1142, 1072, 751, 724 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, 6H, *J* = 7.2 Hz), 2.37 (s, 3H), 3.69 (dq, 2H, *J* = 9.7, 7.2 Hz), 3.81 (dq, 2H, *J* = 9.7, 7.2 Hz), 4.06 (d, 2H, *J* = 5.6 Hz), 4.91 (t, 1H, *J* = 5.6 Hz), 6.76 (s, 1H), 7.17 (m, 1H), 7.31 (m, 2H), 7.77 (s, 1H), 7.87 (br s, 1H), 7.93 (d, 1H, *J* = 8.2 Hz).

^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 15.44 (2 CH_3), 16.74 (CH_3), 63.03 (2 CH_2), 69.37 (CH_2), 93.69 (CH), 101.00 (CH), 110.36 (CH), 116.60 (C), 119.31 (CH), 119.37 (CH), 119.49 (C), 121.57 (CH), 123.46 (C), 124.26 (CH), 139.09 (C), 139.43 (C), 156.33 (C).

MS (95 °C): *m/z* (%) = 313 (M^+, 93), 268 (8), 197 (38), 196 (41), 180 (15), 168 (13), 167 (22), 103 (100), 75 (37), 47 (24).

HRMS: *m/z* calcd for $C_{19}H_{23}NO_3$ (M^+): 313.1678. Found: 313.1662.

Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.61; H, 7.36; N, 4.59.

Furostifoline (4-Methyl-10*H*-furo[3,2-*a*]carbazole) (1)

A mixture of the carbazole **11** (32 mg, 0.102 mmol) and a catalytic amount of amberlyst 15 in chlorobenzene (1 mL) was stirred at 120 °C for 7 h. The solvent was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel to provide furostifoline **1** as colorless crystals, yield: 15 mg (66%). Spectral data, see above.

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References

(1) Part 62: Knölker, H.-J.; Cämmerer, S. *Tetrahedron Lett.* **2000**, *41*, 5035.
(2) Chakraborty, D. P. In *Prog. Chem. Org. Nat. Prod.*, Vol. 34; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1977; p 299.
(3) Bhattacharyya, P.; Chakraborty, D. P. In *Prog. Chem. Org. Nat. Prod.*, Vol. 52; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1987; p 159.
(4) Chakraborty, D. P.; Roy, S. In *Prog. Chem. Org. Nat. Prod.*, Vol. 57; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer: Wien, 1991; p 71.
(5) Chakraborty, D. P. In *The Alkaloids*, Vol. 44; Cordell, G. A., Ed.; Academic Press: New York, 1993; p 257.
(6) Pindur, U. *Heterocycles* **1988**, *27*, 1253.
Pindur, U. *Chimia* **1990**, *44*, 406.
Pindur, U.; Rogge, M. *Chimia* **1992**, *46*, 441.
Pindur, U. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich (CT), 1995; p 121.
(7) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967.
(8) Moody, C. J. *Synlett* **1994**, 681.
(9) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443.
Hibino, S.; Sugino, E. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich (CT), 1995; p 205.
(10) Knölker, H.-J. In *40 Jahre Fonds der Chemischen Industrie 1950−1990*; Verband der Chemischen Industrie, Ed.; Frankfurt, 1990; p 219.
Knölker, H.-J. In *Organic Synthesis via Organometallics*; Dötz, K. H., Hoffmann, R. W., Eds.; Vieweg: Braunschweig, 1991; p 119.
Knölker, H.-J. *Synlett* **1992**, 371.
Knölker, H.-J. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich (CT), 1995; p 173.
Knölker, H.-J. In *Transition Metals for Organic Synthesis*, Vol. 1; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 534.
Knölker, H.-J. *Chem. Soc. Rev.* **1999**, *28*, 151.
(11) Fore more recent applications, see: Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron* **1999**, *55*, 10391.
Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1999**, *40*, 6915.
Knölker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett.* **2000**, *41*, 1171.
Knölker, H.-J.; Baum, E.; Reddy, K. R. *Chirality* **2000**, *12*, 526.
(12) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1548.
(13) For a preliminary communication, see: Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett.* **1996**, *37*, 9183.
(14) Beccalli, E. M.; Clerici, F.; Marchesini, A. *Tetrahedron* **1998**, *54*, 11675.
(15) Hagiwara, H.; Choshi, T.; Fujimoto, H.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **1998**, *46*, 1948.
(16) Soós, T.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **1999**, *40*, 8607.
(17) Knölker, H.-J.; Baum, E.; Gonser, P.; Rohde, G.; Röttele, H. *Organometallics* **1998**, *17*, 3916.
Knölker, H.-J. *Chem. Rev.* **2000**, *100*, 2941.
(18) Fischer, E. O.; Fischer, R. D. *Angew. Chem.* **1960**, *72*, 919.
(19) Ullmann, F.; Fitzenkam, R. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 3787.

Astle, M. J.; Cropper, W. P. *J. Am. Chem. Soc.* **1943**, *65*, 2398.
Cohen, T.; Dietz, A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053.
(20) Knölker, H.-J.; Hofmann, C. *Tetrahedron Lett.* **1996**, *37*, 7947.
(21) Röhrkasten, R.; Konrad, M. In *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E6b; Kreher, R. P., Ed.; Thieme: Stuttgart, 1994; p 94.
(22) Amberlyst 15 from Fluka (art. 06423).
(23) Birch, A. J.; Liepa, A. J.; Stephenson, G. R. *Tetrahedron Lett.* **1979**, 3565.
Birch, A. J.; Liepa, A. J.; Stephenson, G. R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 713.
(24) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B. *Chem. Ber.* **1992**, *125*, 2783.
(25) Knölker, H.-J.; Bauermeister, M. *J. Indian Chem. Soc.* **1994**, *71*, 345.
(26) Knölker, H.-J.; Reddy, K. R. *Tetrahedron Lett.* **1998**, *39*, 4007.
Knölker, H.-J.; Reddy, K. R. *Tetrahedron* **2000**, *56*, 4733.

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