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Transition Metal-Diene Complexes in Organic Synthesis - 16.[1]
Iron-Mediated Total Synthesis of 1-Oxygenated Carbazole Alkaloids

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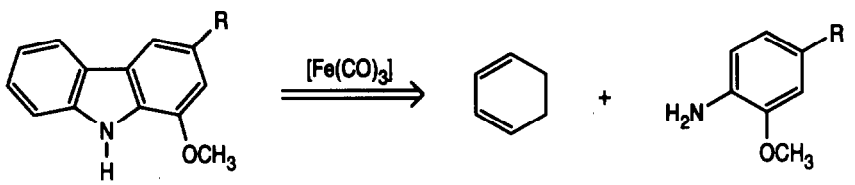
Abstract: Using a methodology of consecutive iron-induced C-C and C-N bond formation we describe the total synthesis of murrayafoline A, murrayaquinone A, koenoline, murrayanine, mukoeic acid, and mukonine.

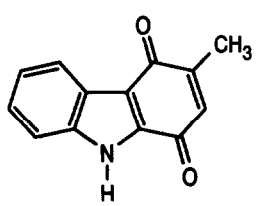
Introduction

The vast majority of naturally occurring carbazole alkaloids have been isolated from higher plants of the genus *Murraya* (*Rutaceae* family), trees growing in southern Asia.[2] The extracts of leaves and bark of this tree have been used as folk medicine for analgesia and local anesthesia, and for the treatment of eczema, rheumatism, and dropsy. In search for the biologically active metabolites of *Murraya* numerous carbazole alkaloids have been found including a whole family of 1-methoxycarbazoles and a carbazolequinone alkaloid which obviously derive from the parent compound murrayafoline A (Scheme 1).[2]



Murrayafoline A R = CH_3
Koenoline R = CH_2OH
Murrayanine R = CHO
Mukoeic acid R = COOH
Mukonine R = $COOCH_3$

1a R = CH_3
1b R = $COOCH_3$



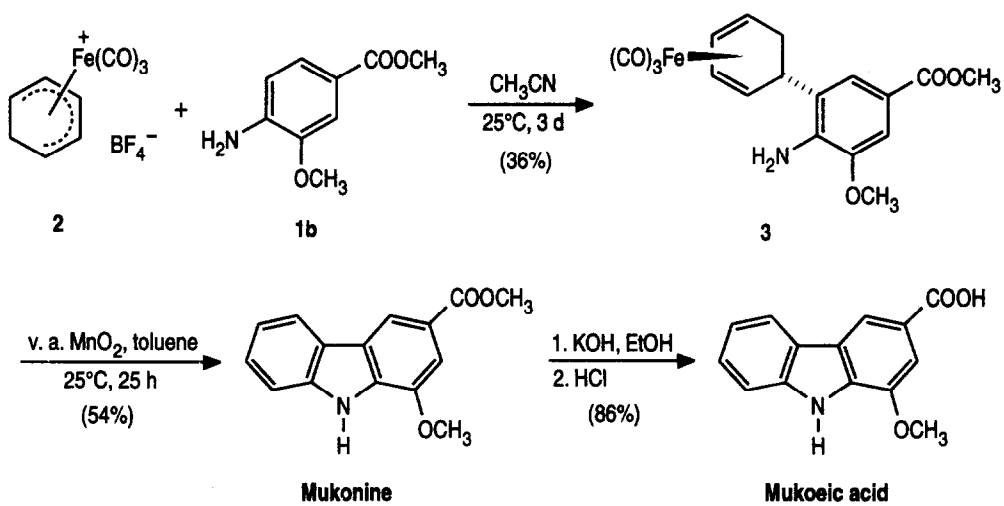
Murrayaquinone A

Scheme 1

Murrayanine, isolated in 1964 by Chakraborty from the stem bark of the Indian medicinal plant *Murraya koenigii* Spreng., was the first tricyclic carbazole alkaloid isolated from natural sources.[3] The same alkaloid was later identified in extracts of the roots of *Clausena heptaphylla*, a plant also belonging to the *Rutaceae* family.[4] The isolation of mukoeic acid, the first carbazole carboxylic acid from plant sources,[5] and its corresponding methyl ether, mukonine,[2b] from the stem bark of *Murraya koenigii* Spreng. has been reported by Chakraborty also. The cytotoxic carbazole alkaloid koenoline was isolated from the root bark of *Murraya koenigii*.[6] Murrayafoline A, the parent compound, and murrayaquinone A, the first carbazolequinone alkaloid from a natural source, were isolated from the root bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[7] The co-occurrence of these alkaloids in plants of the same genus indicates that they are biosynthesized by *in vivo* oxidation of murrayafoline A.[2,5,6] Moreover, it is interesting from the biogenetic point of view that a seasonal variation of the carbazolequinone constituents has been observed for *Murraya euchrestifolia*.[7b]

The broad range of useful biological activities which have been reported for the plant exctracts of *Murraya* species prompted several groups to develop strategies for total syntheses of the 1-oxygenated carbazole alkaloids.[8] We developed a short and convergent synthesis providing access to all of the six 1-oxygenated carbazole alkaloids described above.[9] The retrosynthetic analysis is based on our iron-mediated construction of the carbazole ring system indicated in Scheme 1, a disconnection, which suggests cyclohexadiene and the corresponding arylamines **1a** and **1b** as starting materials. The two crucial steps of our synthetic approach are first, C-C bond formation by electrophilic aromatic substitution of the arylamines by the tricarbonyliron-complexed cyclohexadienylium cation and second, C-N bond formation and aromatization by iron-mediated oxidative cyclization.[10] This strategy has already been applied to the total synthesis of several members of the carbazomycin alkaloids[11] and further carbazole derivatives.[12]

Synthesis of Mukonine and Mukoeic acid



2 **1b** **3**

Mukonine **Mukoeic acid**

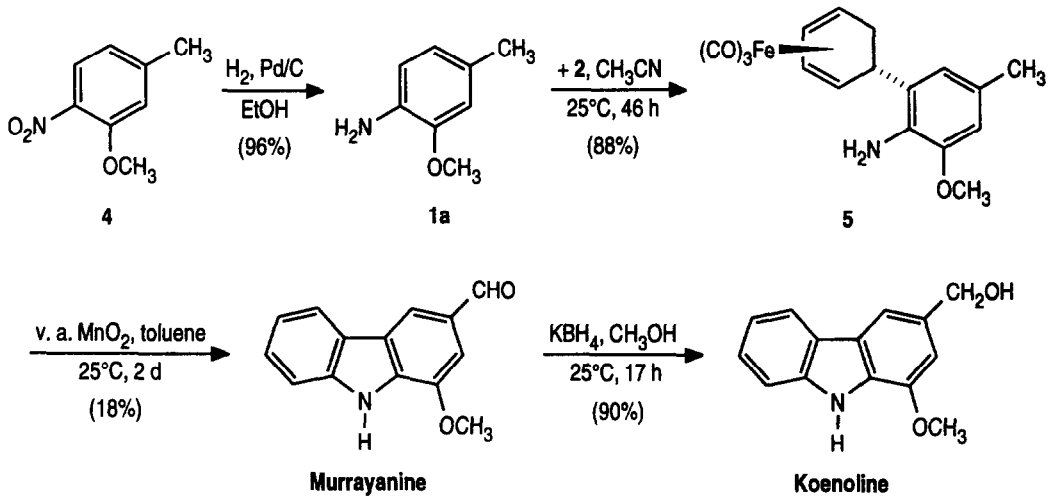
Scheme 2

1-Aza-1,3-butadiene-catalyzed complexation of 1,3-cyclohexadiene with pentacarbonyliron[13] followed by hydride abstraction using triphenylcarbenium tetrafluoroborate[14] affords the tricarbonyl[(1-5-η)-cyclohexadienylium]iron tetrafluoroborate **2** on a large scale in virtually quantitative overall yield. Electrophilic

substitution of the commercial arylamine **1b** by the iron-complexed cation **2** in acetonitrile at room temperature provides regio- and stereoselectively the iron complex **3** in 36% yield (Scheme 2). Surprisingly, the yield of **3** obtained in acetonitrile at reflux was even lower. The only moderate yield is ascribed to the decreased nucleophilicity of the arylamine **1b** compared to previous systems which have been applied to this reaction.[11,12] The regiochemistry of **3** was confirmed in the ^{1}H-NMR spectrum by the two signals of aromatic protons (7.54 ppm and 7.32 ppm) which exhibit only a small *meta* coupling (J = 1.7 Hz). The stereochemistry (*anti* orientation of the arylamine moiety relative to the tricarbonyliron group) was assigned based on the chemical shift of the signal of the tertiary proton (3.38 ppm). Similar downfield shifts of protons caused by the effect of magnetic anisotropy of the iron atom have been found in related complexes reported earlier.[11,12] The same spectral considerations have been used to determine the selectivity of the other electrophilic substitutions of arylamines with **2** described in this paper.

Oxidative cyclization of complex **3** with very active manganese dioxide (v. a. MnO_2)[15] at room temperature in toluene afforded mukonine in 54% yield (Scheme 2). This is the best result of an iron-mediated arylamine cyclization which has been obtained so far.[16] Finally ester cleavage of mukonine provided mukoeic acid. The spectral data of both carbazole alkaloids were in full agreement with those reported by Chakraborty for the natural products.[2b,5] This synthesis leads to mukoeic acid in 3 steps and 17% overall yield based on the iron-complexed cation **2**.

Synthesis of Murrayanine and Koenoline

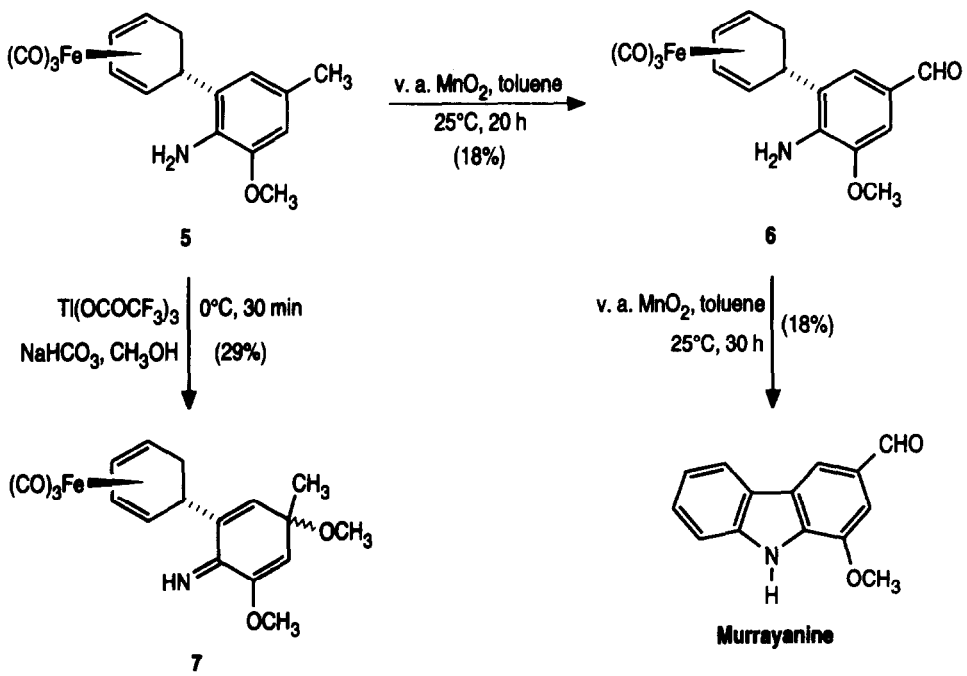


Scheme 3

Hydrogenation of the commercial nitroaryl derivative **4** afforded the required arylamine **1a**. Subsequent treatment of **1a** with the iron-complexed cation **2** in acetonitrile gave after 46 h at room temperature the iron complex **5** in 88% yield (Scheme 3). TLC control of the electrophilic substitution indicated instantaneous formation of an intermediate product which in the course of 46 h rearranges to the desired complex **5**. The final product **5** is slightly more polar than the intermediate compound. In agreement with similar results reported previously[1,12b] we assume that the intermediate kinetic product is the *N*-alkylated arylamine. However, since the intermediate complex was not of interest from the synthetic point of view we made no

attempt to isolate it. Oxidative cyclization of complex **5** with very active manganese dioxide[15] in toluene at room temperature proceeded with concomitant oxidation of the methyl group and provided after 2 days directly murrayanine. Borohydride reduction of murrayanine afforded the cytotoxic carbazole alkaloid koenoline (Scheme 3). Again, the spectral data of both alkaloids could be compared with those reported for the natural products in the literature.[3,4,6] The route described above provides koenoline in 4 steps and 14% overall yield based on the nitroaryl derivative **4**.

The one-pot conversion of the iron complex **5** to murrayanine is rationalized by the following four-step sequence. First, oxidation of the methyl to the formyl group. Second, cyclizing dehydrogenation to a 4a,9a-dihydro-9*H*-carbazole. Third, aromatization to a 20-electron complex and fourth, spontaneous demetalation to murrayanine. Tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazoles have previously been shown to represent intermediates of the iron-mediated arylamine cyclization.[11a,c,d] The sequence proposed for the arylamine cyclization to murrayanine derives support by chemoselective oxidation of **5** using very active manganese dioxide (Scheme 4).



Scheme 4

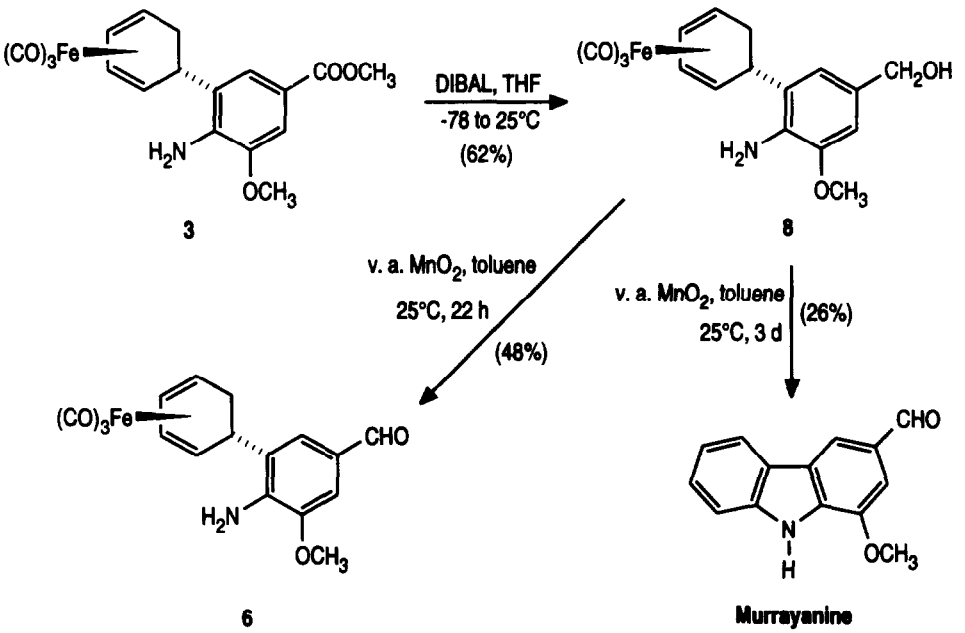
Incomplete oxidation of complex **5** was achieved by treatment with very active manganese dioxide in toluene for only 20 h (the reaction was carefully monitored by TLC). This reaction provided the non-cyclized aldehyde **6** in 18% yield. On further reaction with very active manganese dioxide the complex **6** was transformed to murrayanine. These results demonstrate that the oxidation of the methyl group in complex **5** is much faster than the cyclization of the aldehyde **6** and that the latter is an intermediate of the cyclization to murrayanine.

On the attempt to achieve an oxidation of complex **5** using thallium(III) trifluoroacetate we isolated the iron complex **7** in 29% yield as a 1:1 mixture of diastereoisomers. The formation of complex **7** is explained by an

oxidation of the amino group with the thallium(III) reagent generating a nitrenium cation intermediate which is trapped by methanol as a nucleophile in the position *para* relative to the amino group, thus giving rise to the cross-conjugated dienimine. Similar products have been obtained previously on oxidation with thallium(III) trifluoroacetate and the mechanism has been described in detail.[12b] The corresponding cyclic dienimine product was not observed for the cyclization of complex **5** with thallium(III) trifluoroacetate.

Synthesis of Murrayanine *via* the Mukonine Precursor

To elaborate an alternative access to murrayanine and koenoline we used the mukonine precursor **3** as starting material. Compound **3** offers the advantage that the *para* amino methyl group is already oxidized.

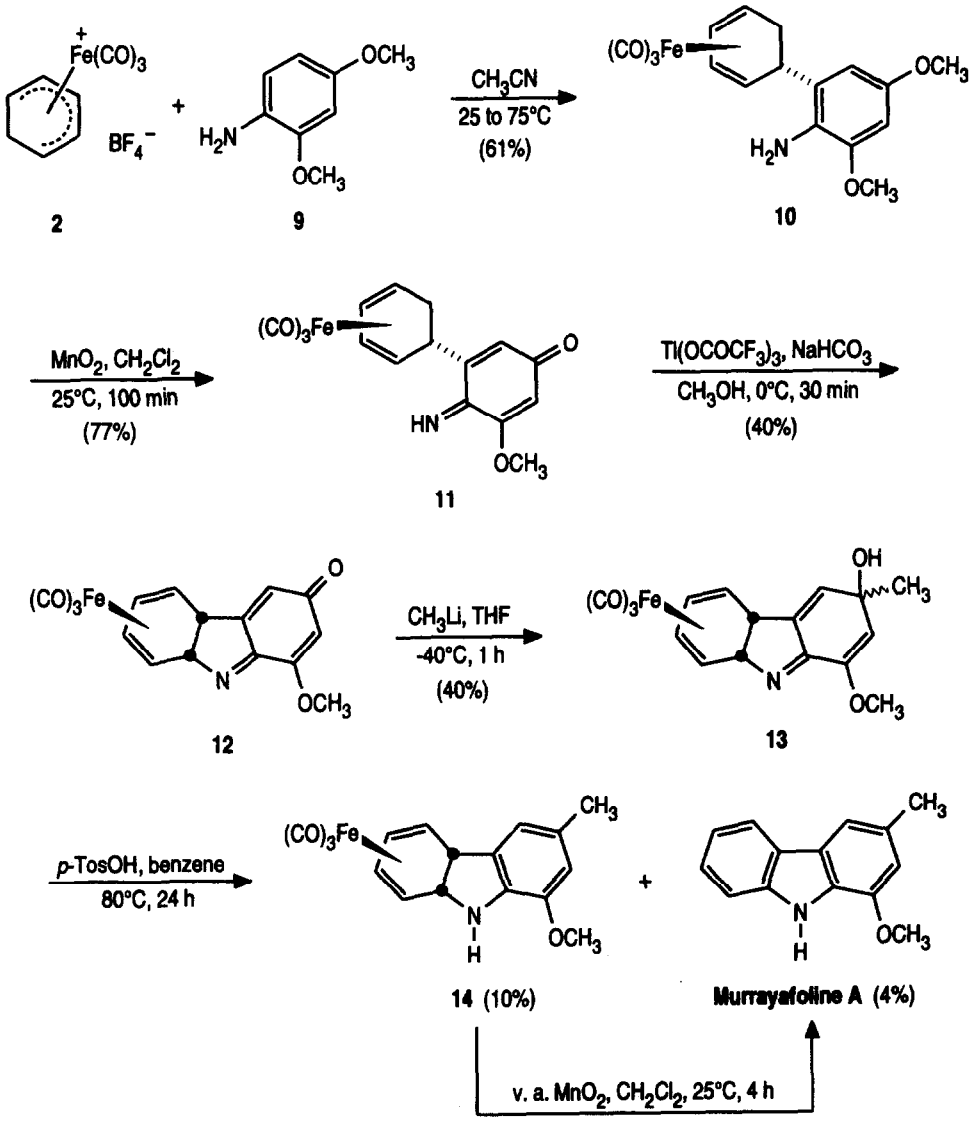


Scheme 5

Reduction of the ester group in **3** using DIBAL afforded the benzylic alcohol **8** in 62% yield. Using very active manganese dioxide the direct transformation of complex **8** to murrayanine was achieved in 26% yield. By careful control of the equivalents of manganese dioxide and of the reaction time (see experimental section) a chemoselective oxidation of **8** to **6** could be achieved. It has been shown above that complex **6** is transformed to murrayanine (Scheme 4). Therefore, it is concluded that the arylamine cyclization of **8** to murrayanine involves a similar sequence of oxidations as described above for the cyclization of **5** to murrayanine. The advantage of the present reaction is, that the oxidation of the benzylic alcohol in **8** to the formyl group proceeds much easier than the oxidation of the methyl group in **5** to the formyl group. TLC control of both reactions confirms the much cleaner course of the oxidation of the benzylic alcohol **8**. However, the yield of murrayanine based on the iron-complexed cation **2** is much better using the arylamine **1a** (2 steps, 16% overall yield) compared to the route starting with **1b** (3 steps, 6% overall yield) due to the low yield of the C-C coupling of **1b** with **2**. Therefore, the direct route to murrayanine and koenoline using the arylamine **1a** is superior.

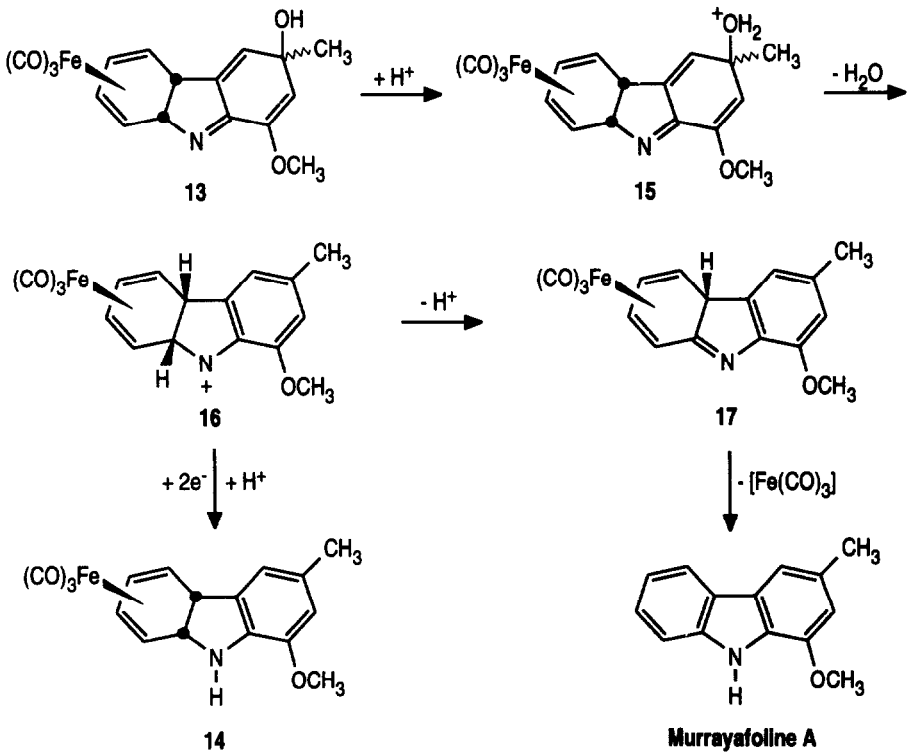
Synthesis of Murrayafoline A and Murrayaquinone A

The results described above demonstrated that a direct synthesis of murrayafoline A by the iron-mediated construction of the carbazole framework using the arylamine **1a** is not feasible with our standard oxidizing reagents. This is because the concomitant oxidation of the methyl group on cyclization of complex **5** could not be avoided. Therefore, we applied the iron-mediated iminoquinone cyclization to the synthesis of murrayafoline A. The methyl group of murrayafoline A should be introduced by nucleophilic addition of a methyl-Grignard reagent or methyllithium to the carbonyl group of the resulting tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one.



Scheme 6

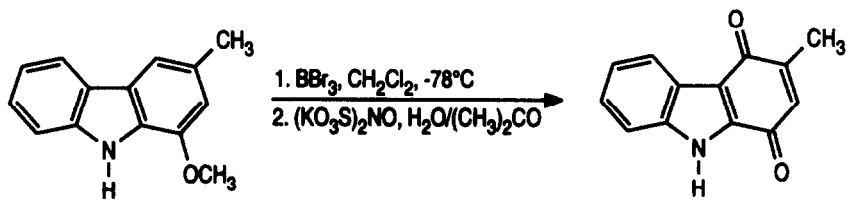
Electrophilic substitution of 2,4-dimethoxyaniline **9** with the iron-complexed cation **2** provided complex **10** in 61% yield (Scheme 6). A direct iron-mediated iminoquinone cyclization, as observed previously in other cases,[12a] was not achieved with the iron complex **10** (oxidation with thallium(III) trifluoroacetate afforded the non-cyclized iminoquinone **11** in 10% yield). Therefore, the two-step procedure[12a] with isolation of the intermediate non-cyclized iminoquinone had to be used. Oxidation of complex **10** using commercial manganese dioxide[17] provided in 77% yield the non-cyclized iminoquinone **11**. In contrast to related compounds,[12a] the attempt to cyclize complex **11** with very active manganese dioxide[15] led only to decomposition. However, oxidative cyclization of **11** with thallium(III) trifluoroacetate afforded the desired cyclized iminoquinone complex **12** in 40% yield. This variation of our standard protocol for the synthesis of tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-ones[12a] gave the best access to the present derivative. No product formation was observed on addition of methylmagnesium chloride to the iron complex **12**. But, addition of methyllithium to **12** in tetrahydrofuran at -40°C provided the tertiary carbinol **13** in 40% yield as a 1:1 diastereomeric mixture. With complex **13** in hand we attempted to effect a direct transformation to the natural product by taking advantage of the potential aromatization of this compound to the carbazole system as driving force for the process. Elimination of water with concomitant aromatization and demetalation to afford directly murrayafoline A was achieved on treatment of the complex **13** with *p*-toluenesulfonic acid in benzene at reflux for 24 h. However, the yield of murrayafoline A was only 4% and we got the corresponding tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **14** in 10% yield (Scheme 6). Complex **14** was smoothly converted to murrayafoline A with very active manganese dioxide.[18]



Scheme 7

The mechanism we propose for the transformation of complex **13** to murrayafoline A and **14** is described in Scheme 7. Protonation of the carbinol **13** to **15** followed by elimination of water generates the nitrenium cation **16**. Similar nitrenium cations have been proposed as intermediates in the thallium(III) trifluoroacetate oxidation of *p*-methylarylamine substituted tricarbonyl[η^4-cyclohexadiene]iron complexes. In this case, however, the reverse reaction, attack of a nucleophile (methanol) in the position *para* to the nitrogen, was observed (*cf.* the synthesis of complex **7** described above and ref.[12b]). Proton loss of **16** affords the imine complex **17**. Finally, imine-enamine tautomerization of **17** gives an intermediate 20-electron complex which demetalates instantaneously to murrayafoline A. The tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **14** is believed to be formed by reduction of the nitrenium cation **16** followed by protonation of the resulting anion. The electrons required for this process might well be delivered from amorphous iron produced by the demetalation of the aromatized carbazole.

Our synthetic murrayafoline A was identical in all spectral data (UV, IR, MS and ^{1}H-NMR) and by TLC comparison with an authentic sample of the natural product,[7] kindly provided by Professor H. Furukawa.



Murrayafoline A **Murrayaquinone A**

Scheme 8

Cleavage of the methyl ether and subsequent oxidation of the resulting 1-hydroxy-3-methyl-9*H*-carbazole with Fremy's salt has been shown to transform murrayafoline A into murrayaquinone A.[8f] The carbazole-quinone alkaloid murrayaquinone A has recently been found to exhibit cardiotonic activity.[19]

Conclusion

The methodology of consecutive iron-induced C-C and C-N bond formation has been applied to a novel and straightforward access to 1-methoxycarbazole alkaloids. The present results extend the synthetic scope of our iron-mediated synthesis of the carbazole framework significantly, since we described the synthesis of a whole biogenetically related series of 1-oxygenated alkaloids. These alkaloids are of interest because of their useful biological activities. Especially intriguing is the hitherto unprecedented four-step oxidation of the iron complex **5** which represents the key step of the total synthesis of the cytotoxic carbazole alkaloid koenoline. However, with 2-methoxy substituted arylamines an "*ortho* analogue" of our iron-mediated iminoquinone cyclization which would lead to 4b,8a-dihydrocarbazol-1-ones could not be realized and an optimization of the iron-mediated approach to murrayafoline A remains to be achieved.

EXPERIMENTAL SECTION

Flash chromatography: Baker silica gel (0.03-0.06 mm). Melting points: Reichert hot stage. UV: Beckman 3600. IR: Bruker IFS 25, Perkin-Elmer 882 and 1710 (FTIR). ^{1}H-NMR and ^{13}C-NMR: Bruker WP-200, AM-300, and WM-400; internal standard: tetramethylsilane or chloroform; coupling constants in Hz. Mass spectra: Finnigan MAT-312; ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid. All reactions were carried out by using dry and degassed solvents in an inert gas atmosphere.

Tricarbonyl[(1-4-η)-5-(2-amino-3-methoxy-5-methoxycarbonylphenyl)-1,3-cyclohexadiene]iron (3)
A solution of the complex salt **2** (306 mg, 1.00 mmol) in acetonitrile (5 ml) was added to a solution of the arylamine **1b** (400 mg, 2.21 mmol) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature for 3 days. Removal of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:6) of the residue on silica gel provided 143 mg (36%) of the iron complex **3** as yellow crystals, m.p. 160-162°C. IR (KBr): ν 2045, 1968, 1952, 1699, 1617, 1437, 1312, 1225, 618, 564 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.54 (d, J = 1.7, 1 H), 7.32 (d, J = 1.7, 1 H), 5.56 (m, 2 H), 4.24 (br s, 2 H), 3.88 (s, 6 H), 3.38 (dt, J = 11.1, 3.8, 1 H), 3.18 (m, 2 H), 2.40 (ddd, J = 15.1, 11.1, 3.9, 1 H), 1.58 (m, 1 H); ^{13}C-NMR and DEPT (75 MHz, $CDCl_3$): δ 211.8 (CO), 167.4 (C=O), 146.2 (C), 138.5 (C), 129.0 (C), 121.7 (CH), 118.7 (C), 109.0 (CH), 85.9 (CH), 85.2 (CH), 63.8 (CH), 60.0 (CH), 55.8 (CH_3), 51.7 (CH_3), 38.9 (CH), 30.9 (CH_2); MS (110°C): *m/z* 399 (M^+, 11), 371 (15), 358 (10), 343 (31), 314 (100), 312 (58), 287 (10), 226 (26), 208 (43); HRMS calcd for $C_{18}H_{17}FeNO_6$ (M^+): 399.0405, found: 399.0405.

Methyl 1-Methoxy-9*H*-carbazole-3-carboxylate (Mukonine)
Very active manganese dioxide[15] (275 mg) was added to a solution of the iron complex **3** (55 mg, 0.14 mmol) in toluene (5 ml) and the heterogeneous reaction mixture was stirred at room temperature under TLC control. After 7 h further very active manganese dioxide (275 mg) was added. The entire reaction time was 25 h, after which the oxidizing reagent was removed by filtration through a short path of Celite. Evaporation of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:6) of the residue on silica gel afforded 19 mg (54%) of **mukonine** as light yellow crystals, m.p. 169-170°C. UV (MeOH): λ 205, 218, 234, 245 (sh), 267 (sh), 275, 310, 318, 332 (sh) nm; IR (KBr): ν 3373, 1698, 1610, 1587, 1450, 1435, 1351, 1313, 1259, 1245, 1227, 765 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.54 (br s, 1 H), 8.47 (dd, J = 1.2, 0.5, 1 H), 8.09 (br d, J = 7.7, 1 H), 7.59 (d, J = 1.2, 1 H), 7.50-7.23 (m, 3 H), 4.04 (s, 3 H), 3,98 (s, 3 H); MS (70°C): *m/z* 255 (M^+, 30), 240 (15), 224 (12), 212 (6), 196 (6), 44 (100); HRMS calcd for $C_{15}H_{13}NO_3$ (M^+): 255.0895, found: 255.0894.

1-Methoxy-9*H*-carbazole-3-carboxylic acid (Mukoeic acid)
Mukonine (32 mg, 0.13 mmol) was dissolved in 10% ethanolic KOH solution (4 ml) and heated at reflux for 5 h. The solvent was removed *in vacuo*, the residue acidified with 2 N HCl, and the aqueous layer extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. Flash chromatography (diethyl ether) of the residue on silica gel provided 26 mg (86%) of **mukoeic acid** as colorless crystals, m.p. 215°C. UV (MeOH): λ 205, 234, 243 (sh), 267 (sh), 273, 308, 318, 330 (sh) nm; IR (KBr): ν 3416, 2927, 1680, 1609, 1588, 1454, 1404, 1342, 1309, 1255, 1227,

1202, 767, 737 cm^{-1}; ^{1}H-NMR (200 MHz, $[CD_3]_2CO$): δ 10.80 (br s, 1 H), 8.53 (s, 1 H), 8.22 (d, *J* = 7.8, 1 H), 7.62 (m, 2 H), 7.46 (m, 1 H), 7.28 (d, *J* = 7.9, 1 H), 4.08 (s, 3 H); MS (180°C): *m/z* 241 (M^+, 100), 226 (59), 198 (22), 170 (12), 153 (12); HRMS calcd for $C_{14}H_{11}NO_3$ (M^+): 241.0739, found: 241.0739.

2-Methoxy-4-methylaniline (1a)

To a solution of 2-nitro-5-methylanisole **4** (3.18 g, 19.0 mmol) in ethanol (120 ml) was added 10% palladium on activated carbon (319 mg). Compound **4** was hydrogenated by vigorous stirring of this mixture in an hydrogen atmosphere (1.2 atm) until no further hydrogen uptake was detected. The catalyst was removed by filtration through a short path of Celite and the solvent was evaporated *in vacuo*. A purification of the arylamine **1a** was achieved by sublimation (75°C/0.04 mbar). Yield of **1a**: 2.51 g (96%), colorless crystals, m.p. 25-27°C. IR ($CHCl_3$): ν 3370, 3024, 3010, 1520, 1466, 1278, 1244, 1209, 1159, 1040 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.60 (m, 3 H), 3.82 (s, 3 H), 3.58 (br s, 2 H), 2.26 (s, 3 H); ^{13}C-NMR and DEPT (100 MHz, $CDCl_3$): δ 147.3 (C), 133.5 (C), 128.0 (C), 121.1 (CH), 115.0 (CH), 111.5 (CH), 55.3 (CH_3), 20.9 (CH_3); MS (25°C): *m/z* 137 (M^+, 71), 122 (100), 106 (6), 94 (72), 77 (35); HRMS calcd for $C_8H_{11}NO$ (M^+): 137.0841, found: 137.0841.

Tricarbonyl[(1-4-η)-5-(2-amino-3-methoxy-5-methylphenyl)-1,3-cyclohexadiene]iron (5)

A solution of the complex salt **2** (482 mg, 1.58 mmol) in acetonitrile (6 ml) was added to a solution of the arylamine **1a** (475 mg, 3.47 mmol) in acetonitrile (3 ml). The reaction mixture was stirred at room temperature for 46 h. Removal of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:6) of the residue on silica gel gave 495 mg (88%) of the iron complex **5** as light yellow crystals, m.p. 86-88°C. IR (KBr): ν 3391, 2917, 2038, 1964, 1586, 1489, 1466, 1290, 1190, 1156, 833, 621, 564 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.54 (br s, 1 H), 6.48 (br s, 1 H), 5.50 (m, 2 H), 3.80 (s, 3 H), 3.63 (br s, 2 H), 3.40 (dt, *J* = 11.1, 3.7, 1 H), 3.17 (m, 2 H), 2.37 (ddd, *J* = 15.2, 11.1, 4.0, 1 H), 2.26 (s, 3 H), 1.60 (ddd, *J* = 15.2, 3.7, 2.6, 1 H); ^{13}C-NMR and DEPT (100 MHz, $CDCl_3$): δ 212.0 (CO), 147.6 (C), 131.1 (C), 130.4 (C), 127.6 (C), 119.1 (CH). 109.3 (CH), 85.7 (CH), 85.0 (CH), 65.1 (CH), 60.4 (CH), 55.7 (CH_3), 38.9 (CH), 31.3 (CH_2), 21.3 (CH_3); MS (25°C): *m/z* 355 (M^+, 4), 327 (6), 299 (7), 271 (19), 269 (16), 213 (7), 192 (18), 176 (38), 137 (71), 122 (100). Anal. Calcd for $C_{17}H_{17}FeNO_4$: C, 57.49; H, 4.82; N, 3.94. Found: C, 57.59; H, 4.88; N 3.99.

1-Methoxy-9*H*-carbazole-3-carbaldehyde (Murrayanine)

Very active manganese dioxide[15] (270 mg) was added to a solution of the iron complex **5** (54 mg, 0.15 mmol) in toluene (7 ml). The heterogeneous reaction mixture was stirred at room temperature for 24 h and further very active manganese dioxide (270 mg) was added. The entire reaction time was 2 days, after which the oxidizing reagent was removed by filtration through a short path of Celite. Removal of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:3) of the residue on silica gel afforded 6 mg (18%) of **murrayanine** as colorless crystals, m.p. 154-156°C. UV (MeOH): λ 222 (sh), 238, 249, 274, 287, 335 nm; IR (KBr): ν 3170, 2922, 2853, 1662, 1625, 1609, 1581, 1503, 1344, 1316, 1256, 1241, 1142, 848, 824, 773, 751, 726 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 10.05 (s, 1 H), 8.63 (br s, 1 H), 8.20 (br s, 1 H), 8.12 (dd, *J* = 7.7, 0.7, 1 H), 7.55-7.28 (m, 4 H), 4.07 (s, 3 H); MS (60°C): *m/z* 226 (MH^+, 53), 225 (M^+, 11), 224 (30), 212 (27), 210 (21), 183 (18), 182 (14), 181 (25), 165 (31), 153 (30), 57 (100); HRMS calcd for $C_{14}H_{11}NO_2$ (M^+): 225.0790, found: 225.0789.

1-Methoxy-3-hydroxymethyl-9*H*-carbazole (Koenoline)

A solution of KBH_4 (40 mg, 0.74 mmol) in methanol (15 ml) was added to a solution of **murrayanine** (41 mg, 0.18 mmol) in methanol (5 ml) and the reaction mixture was stirred at room temperature for 17 h. The major part of the solvent was removed in vacuo, the residue taken up in water, acidified with 2 N HCl, and the aqueous layer was extracted several times with diethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. Flash chromatography (ethyl acetate/light petroleum, 1:2) of the residue on silica gel provided 37 mg (90%) of **koenoline** as light brown crystals, m.p. 127-129°C. UV (MeOH): λ 226, 243, 252, 259, 280, 290, 323, 337 nm; IR (KBr): ν 3417, 2927, 1588, 1505, 1454, 1397, 1338, 1312, 1283, 1262, 1233, 1135, 1105, 1040, 1012, 750, 736, 562 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.41 (br s, 1 H), 7.98 (dd, J = 7.8, 0.7, 1 H), 7.59 (br s, 1 H), 7.39 (m, 2 H), 7.20 (m, 1 H), 6.87 (d, J = 1.1, 1 H), 4.78 (s, 2 H), 3.91 (s, 3 H), 2.31 (br s, 1 H); ^{13}C-NMR and DEPT (75 MHz, $CDCl_3$): δ 145.8 (C), 139.5 (C), 133.0 (C), 129.5 (C), 125.8 (CH), 124.1 (C), 123.6 (C), 120.5 (CH), 119.5 (CH), 111.7 (CH), 111.1 (CH), 105.7 (CH), 66.5 (CH_2), 55.6 (CH_3); MS (150°C): *m/z* 227 (M^+, 100), 212 (26), 210 (48), 198 (30), 196 (14), 183 (25), 182 (26), 167 (59), 154 (44), 139 (23); HRMS calcd for $C_{14}H_{13}NO_2$ (M^+): 227.0946, found: 227.0947.

Tricarbonyl[(1-4-η)-5-(2-amino-3-methoxy-5-formylphenyl)-1,3-cyclohexadiene]iron (6)

Very active manganese dioxide[15] (330 mg) was added to a solution of the iron complex **5** (55 mg, 0.15 mmol) in toluene (6 ml) and the heterogeneous reaction mixture was stirred at room temperature for 20 h. The oxidizing reagent was removed by filtration through a short path of Celite. Evaporation of the solvent *in vacuo* and flash chromatography (ethyl acetate/light petroleum, 1:4) of the residue on silica gel provided 10 mg (18%) of the iron complex **6** as yellow crystals, m.p. 163°C. IR (KBr): ν 3487, 3348, 2925, 2043, 1994, 1965, 1947, 1662, 1620, 1568, 1494, 1459, 1435, 1344, 1293, 1258, 1150, 623, 560 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.74 (s, 1 H), 7.31 (d, J = 1.3, 1 H), 7.19 (d, J = 1.3, 1 H), 5.58 (m, 2 H), 4.44 (br s, 2 H), 3.90 (s, 3 H), 3.38 (dt, J = 11.1, 3.6, 1 H), 3.19 (m, 2 H), 2.43 (ddd, J = 15.1, 11.1, 4.0, 1 H), 1.60 (m, 1 H); ^{13}C-NMR and DEPT (75 MHz, $CDCl_3$): δ 211.6 (CO), 190.7 (CHO), 146.7 (C), 140.3 (C), 128.8 (C), 126.6 (C), 124.9 (CH), 106.6 (CH), 86.0 (CH), 85.0 (CH), 63.3 (CH), 59.8 (CH), 55.8 (CH_3), 38.6 (CH), 30.9 (CH_2); MS (110°C): *m/z* 369 (M^+, 10), 341 (25), 313 (47), 285 (98), 283 (73), 268 (23), 227 (18), 206 (100); HRMS calcd for $C_{17}H_{15}FeNO_5$ (M^+): 369.0300, found: 369.0299.

1-Methoxy-9*H*-carbazole-3-carbaldehyde (Murrayanine)

Very active manganese dioxide[15] (225 mg) was added to a solution of the iron complex **6** (45 mg, 0.12 mmol) in toluene (4 ml). After 24 h of stirring at room temperature further very active manganese dioxide (225 mg) was added to the reaction mixture. The entire reaction time was 30 h, after which the oxidizing reagent was removed by filtration through a short path of Celite. Removal of the solvent *in vacuo* and flash chromatography (ethyl acetate/light petroleum, 1:3) of the residue on silica gel afforded 5 mg (18%) of **murrayanine** as colorless crystals; spectral data, see above.

Tricarbonyl[(1-4-η)-5-(6-imino-3,5-dimethoxy-3-methylcyclohexa-1,4-dienyl)-1,3-cyclohexadiene]iron (7)

Sodium bicarbonate (53 mg, 0.63 mmol) and then thallium(III) trifluoroacetate (219 mg, 0.40 mmol) were added to a solution of the iron complex **5** (68 mg, 0.19 mmol) in methanol (4 ml) at 0°C and the reaction

mixture was stirred for 30 min at 0°C. Subsequently a saturated aqueous solution of sodium carbonate was added, the mixture was stirred for 5 min at room temperature, filtered through a short path of Celite, and the Celite was washed with ethyl acetate. The combined filtrates were poured into a saturated aqueous solution of sodium bicarbonate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo*. Flash chromatography (ethyl acetate/light petroleum, 1:6) of the residue on silica gel provided 21 mg (29%) of the iron complex **7** as red crystals (1:1 mixture of diastereoisomers). IR (KBr): ν 3280, 2040, 1957, 1632, 1588, 1250, 1233, 1105, 1078, 1058, 626, 565 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$): δ 10.16 (br s, 1 H), 6.07 (m, 1 H), 5.43 (m, 2 H), 5.02/5.00 (s, 1 H), 3.80-3.50 (m, 1 H), 3.64 (s, 3 H), 3.20-2.90 (m, 2 H), 3.04/2.97 (s, 3 H), 2.55-2.15 (m, 1 H), 1.50-1.20 (m, 1 H), 1.38/1.33 (s, 3 H); MS (120°C): *m/z* 357 (M^+-CO, 8), 326 (19), 302 (72), 300 (67), 268 (100), 254 (60), 253 (82), 213 (42), 198 (57), 177 (94), 167 (40), 154 (33), 128 (28), 112 (39); HRMS calcd for $C_{17}H_{19}FeNO_4$ (M^+-CO): 357.0663, found: 357.0662.

Tricarbonyl[(1-4-η)-5-(2-amino-4-hydroxymethyl-3-methoxyphenyl)-1,3-cyclohexadiene]iron (8)
A 1 M solution of DIBAL in hexane (0.58 ml, 0.58 mmol) was added to a solution of the iron complex **3** (77 mg, 0.19 mmol) in tetrahydrofuran (5 ml) at -78°C. The reaction mixture was warmed to room temperature over a period of 19 h. Methanol (0.5 ml), water (0.5 ml), and diethyl ether (3 ml) were added and the mixture was stirred for 30 min at room temperature. The mixture was filtered through a short path of Celite which was subsequently washed with diethyl ether. The organic layer of the filtrate was separated, washed with water and dried over magnesium sulfate. Evaporation of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:2) of the residue on silica gel provided 44 mg (62%) of the iron complex **8** as light yellow crystals. IR (KBr): ν 3403, 3310, 2934, 2857, 2040, 1997, 1985, 1962, 1946, 1490, 1465, 1292, 1159, 622, 563 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.73 (d, J = 1.4, 1 H), 6.70 (br s, 1 H), 5.51 (m, 2 H), 4.56 (s, 2 H), 3.84 (s, 3 H), 3.41 (dt, J = 11.1, 3.7, 1 H), 3.16 (m, 2 H), 2.39 (ddd, J = 15.1, 11.1, 4.0, 1 H), 1.60 (ddd, J = 15.1, 3.4, 2.3, 1H); MS (100°C): *m/z* 371 (M^+, 4), 343 (12), 315 (15), 287 (26), 269 (63), 267 (49), 252 (33), 166 (100); HRMS calcd for $C_{17}H_{17}FeNO_5$ (M^+): 371.0456, found: 371.0457.

Tricarbonyl[(1-4-η)-5-(2-amino-3-methoxy-5-formylphenyl)-1,3-cyclohexadiene]iron (6)
Very active manganese dioxide[15] (125 mg) was added to a solution of the iron complex **8** (25 mg, 0.07 mmol) in toluene (5 ml) and the reaction mixture was stirred for 22 h at room temperature. Removal of the oxidizing reagent by filtration through a short path of Celite, evaporation of the solvent *in vacuo*, and flash chromatography (ethyl acetate/light petroleum, 1:4) of the residue on silica gel afforded 12 mg (48%) of the iron complex **6** as yellow crystals; spectral data, see above.

1-Methoxy-9*H*-carbazole-3-carbaldehyde (Murrayanine)
Very active manganese dioxide[15] (220 mg) was added to a solution of the iron complex **8** (44 mg, 0.12 mmol) in toluene (5 ml). The heterogeneous reaction mixture was stirred at room temperature for 30 h and further very active manganese dioxide (220 mg) was added. The entire reaction time was 3 days, after which the oxidizing reagent was removed by filtration through a short path of Celite. Removal of the solvent *in vacuo* and flash chromatography (ethyl acetate/light petroleum, 1:3) of the residue on silica gel provided 7 mg (26%) of **murrayanine** as colorless crystals; spectral data, see above.

Tricarbonyl[(1-4-η)-5-(2-amino-3,5-dimethoxyphenyl)-1,3-cyclohexadiene]iron (10)

A solution of the complex salt **2** (3.06 g, 10.0 mmol) in acetonitrile (60 ml) was added to a solution of 2,4-dimethoxyaniline **9** (3.37 g, 22.0 mmol) in acetonitrile (60 ml). The reaction mixture was stirred at room temperature for 24 h and subsequently heated at 75°C for 75 min. Removal of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:3) of the residue on silica gel afforded 2.27 g (61%) of the iron complex **10** as light yellow crystals, m.p. 153-154°C. UV (MeOH): λ 299 nm; IR (KBr): ν 3422, 3352, 2044, 1959, 1590, 1488, 1456, 1320, 1158, 614, 563 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.33 (s, 2 H), 5.51 (m, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.58 (s, 2 H), 3.46 (dt, *J* = 11.1, 3.6, 1 H), 3.20 (m, 1 H), 3.14 (m, 1 H), 2.40 (ddd, *J* = 15.2, 11.1, 3.9, 1 H), 1.61 (dt, *J* = 15.2, 3.2, 1 H); ^{13}C-NMR and DEPT (100 MHz, $CDCl_3$): δ 211.9 (CO), 152.6 (C), 148.5 (C), 132.0 (C), 126.7 (C), 103.2 (CH), 96.5 (CH), 85.8 (CH), 84.8 (CH), 64.7 (CH), 60.4 (CH), 55.72 (CH_3), 55.71 (CH_3), 38.8 (CH), 31.4 (CH_2); MS (110°C): *m/z* 371 (M^+, 16), 343 (6), 314 (22), 287 (90), 285 (66), 270 (11), 269 (11), 254 (11), 230 (14), 229 (14), 214 (18), 209 (38), 193 (100), 153 (25); HRMS calcd for $C_{17}H_{17}FeNO_5$ (M^+): 371.0456, found: 371.0457.

Tricarbonyl[(1-4-η)-5-(6-imino-5-methoxycyclohexa-1,4-dien-3-onyl)-1,3-cyclohexadiene]iron (11)

Commercial manganese dioxide[17] (8.38 g) was added to a solution of the iron complex **10** (1.68 g, 4.51 mmol) in dichloromethane (90 ml) and the heterogeneous reaction mixture was stirred at room temperature for 100 min. Removal of the oxidizing reagent by filtration through a short path of Celite, evaporation of the solvent *in vacuo*, and flash chromatography (ethyl acetate/light petroleum, 1:3) of the residue on silica gel provided 1.24 g (77%) of the non-cyclized iminoquinone **11** as yellow crystals, m.p. 53-55°C. UV (MeOH): λ 262 nm; IR (KBr): ν 2045, 1967, 1650, 1631, 1597, 1329, 1228, 623, 564 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.46 (br s, 1 H), 6.39 (s, 1 H), 5.63 (s, 1 H), 5.51 (m, 1 H), 5.46 (m, 1 H), 3.90-3.80 (m, 1 H), 3.82 (s, 3 H), 3.15 (m, 1 H), 3.03 (m, 1 H), 2.39 (ddd, *J* = 15.5, 11.4, 3.7, 1 H), 1.45 (br d, *J* = 15.5, 1 H); ^{13}C-NMR and DEPT (100 MHz, $CDCl_3$): δ 211.5 (CO), 187.9 (C=O), 161.4 (C), 156.3 (C), 154.4 (C), 127.0 (CH), 103.2 (CH), 86.2 (CH), 84.7 (CH), 62.4 (CH), 60.3 (CH), 56.3 (CH_3), 36.6 (CH), 32.4 (CH_2); MS (130°C): *m/z* 355 (M^+, 9), 327 (19), 300 (12), 299 (39), 271 (80), 269 (100), 254 (37), 215 (9), 176 (13); HRMS calcd for $C_{16}H_{13}FeNO_5$ (M^+): 355.0143, found: 355.0144.

Tricarbonyl[(5-8-η)-4b,8a-dihydro-1-methoxycarbazol-3-one]iron (12)

Sodium bicarbonate (324 mg, 3.86 mmol) and then thallium(III) trifluoroacetate (1.34 g, 2.46 mmol) were added to a solution of the iminoquinone **11** (416 mg, 1.17 mmol) in methanol (20 ml) at 0°C and the reaction mixture was stirred for 30 min at 0°C. Subsequently a saturated aqueous solution of sodium carbonate was added, the mixture was stirred for 5 min at room temperature, filtered through a short path of Celite, and the Celite was washed with ethyl acetate. The combined filtrates were poured into a saturated aqueous solution of sodium bicarbonate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated *in vacuo*. Flash chromatography (diethyl ether) of the residue on silica gel provided 164 mg (40%) of the cyclized iminoquinone **12** as yellow crystals, m.p. 185°C (dec.). UV (MeOH): λ 279 nm; IR (KBr): ν 2050, 1973, 1653, 1626, 1601, 1558, 1229, 1069, 618, 564 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1 H), 5.75 (d, *J* = 0.7, 1 H), 5.43 (m, 2 H), 4.99 (dd, *J* = 6.3, 4.3, 1 H), 3.84 (s, 3 H), 3.53 (m, 1 H), 3.45 (m, 1 H), 3.11 (m, 1 H); ^{13}C-NMR and DEPT (100 MHz, $CDCl_3$): δ 210.2 (CO), 188.6 (C=O), 159.55 (C), 159.49 (C), 154.1 (C), 122.1 (CH), 107.2 (CH), 86.3 (CH), 85.3 (CH), 78.9 (CH), 58.4 (CH), 56.8 (CH), 56.1

(CH_3), 44.6 (CH); MS (160°C): *m/z* 353 (M^+, 14), 326 (18), 324 (100), 297 (36), 269 (99), 254 (60), 252 (48), 213 (7), 191 (25); HRMS calcd for $C_{16}H_{11}FeNO_5$ (M^+): 352.9987, found: 352.9987.

Tricarbonyl[(5-8-η)-4b,8a-dihydro-3-hydroxy-1-methoxy-3-methyl-3*H*-carbazole]iron (13)

A 1.6 M solution of methyllithium in diethyl ether (115 µl, 0.18 mmol) was added to a solution of the iminoquinone **12** (54 mg, 0.15 mmol) in tetrahydrofuran (3 ml) at -40°C. The reaction mixture was stirred for 1 h at -40°C and poured into a saturated solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layers were subsequently dried over magnesium sulfate. Removal of the solvent and flash chromatography (ethyl acetate) of the residue on silica gel afforded 23 mg (40%) of the iron complex **13** as a red oil (1:1 mixture of diastereoisomers). IR ($CHCl_3$): ν 2930, 2052, 1983, 1631, 1587, 1131, 1101, 1073, 620, 565 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.88 (m, 1 H), 5.37 (m, 3 H), 4.77 (m, 1 H), 3.70 (s, 3 H), 3.48 (m, 1 H), 3.31 (m, 1 H), 3.17 (m, 1 H), 2.18 (br s, 1 H), 1.46/1.42 (s, 3 H); MS (140°C): *m/z* 369 (M^+, 11), 353 (45), 340 (57), 312 (24), 296 (23), 284 (35), 267 (91), 252 (48), 211 (100); HRMS calcd for $C_{17}H_{15}FeNO_5$ (M^+): 369.0300, found: 369.0300.

1-Methoxy-3-methyl-9*H*-carbazole (Murrayafoline A) and
Tricarbonyl[(1-4-η)-4a,9a-dihydro-8-methoxy-6-methyl-9*H*-carbazole]iron (14)

The iron complex **13** (180 mg, 0.49 mmol) was dissolved in benzene (15 ml), *p*-toluenesulfonic acid (6 mg) was added, and the resulting solution was heated at reflux for 24 h. Removal of the solvent and flash chromatography (ethyl acetate/light petroleum, 1:6) of the residue on silica gel provided **murrayafoline A** as the less polar fraction and the dihydrocarbazole derivative **14** as the more polar fraction.

Murrayafoline A: Yield 4 mg (4%), light brown crystals. UV (MeOH): λ 221, 240, 249 (sh), 258 (sh), 282 (sh), 290, 327, 340 nm; IR ($CHCl_3$): ν 3474, 3013, 3009, 2925, 1636, 1590, 1505, 1466, 1455, 1393, 1306, 1230, 1137, 1107, 1040, 831, 750 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.15 (br s, 1 H), 8.02 (br d, J = 7.7, 1 H), 7.48 (br s, 1 H), 7.46-7.15 (m, 3 H), 6.74 (br s, 1 H), 4.00 (s, 3 H), 2.53 (s, 3 H); MS (70 °C): *m/z* 211 (M^+, 100), 196 (67), 180 (16), 168 (51), 167 (48); HRMS calcd for $C_{14}H_{13}NO$ (M^+): 211.0997, found: 211.0998.

14: Yield 18 mg (10%), light brown crystals, m.p. 172-174°C. IR (KBr): ν 2041, 1963, 1600, 1499, 1306, 1143, 1078, 614, 565 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.45 (d, J = 0.6, 1 H), 6.43 (s, 1 H), 5.37 (m, 2 H), 4.37 (ddd, J = 10.7, 3.0, 0.9, 1 H), 3.83 (dd, J = 10.7, 4.4, 1 H), 3.76 (s, 3 H), 3.47 (m, 1 H), 3.22 (m, 1 H), 2.26 (s, 3 H); MS (150°C): *m/z* 353 (M^+, 45), 296 (23), 269 (33), 267 (100), 251 (18), 211 (47), 191 (54); HRMS calcd for $C_{17}H_{15}FeNO_4$ (M^+): 353.0350, found: 353.0351.

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16. Note that previous examples which have been reported for iron-mediated arylamine cyclizations led to 3-oxygenated and 3,4-dioxygenated carbazoles in 25-46% yield.[11,12b]
17. Manganese dioxide (precipitated active) from Merck-Schuchardt (art. 805958).
18. The aromatization/demetalation of tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazoles using very active manganese dioxide[15] was previously applied to alkaloid synthesis.[11a,c,d]
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