Iron-Mediated Synthesis of Heterocyclic Ring Systems and Applications in Alkaloid Chemistry

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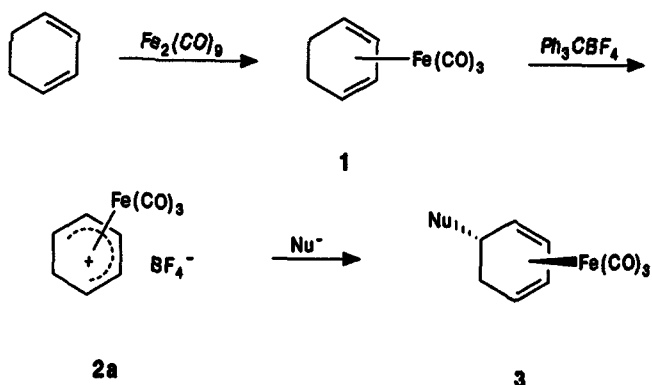
Abstract: The reaction of tricarbonyliron-complexed cyclohexadienylium cations with arylamines allows regio- and stereoselective formation of carbon–carbon and carbon–nitrogen bonds, and gives easy access to nitrogen heterocyclic ring systems. Electrophilic aromatic substitution and subsequent oxidative cyclization provides a convergent route to biologically active carbazole alkaloids. Cyclization by nucleophilic substitution of a leaving group in the side chain of the cyclohexadiene ring opens up a versatile synthesis of 3-aza- and 1-azaspiro[5.5]undecanes.

1. Introduction

In 1930, Rheilen and co-workers prepared tricarbonyl(η^4-butadiene)iron, the first iron–diene complex.[2] The first complex of a cyclic diene, tricarbonyl(η^4-cyclohexadiene)iron (1) was synthesized by Pauson and his group in 1958.[3] Hydride abstraction from complex 1 using trityl tetrafluoroborate yields quantitatively tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (2a).[4] This discovery by E. O. Fischer in 1960 was the breakthrough for these transition metal complexes for applications in synthetic organic chemistry. The groups of Lewis,[5] Birch,[6–8] and Pearson[9–13] have demonstrated the utility of iron-complexed η^5-cyclohexadienylium cations[14] for regio- and stereoselective formation of C–C and C–heteroatom bonds by reaction with nucleophiles to provide 5-anti substituted tricarbonyl(η^4-cyclohexadiene)iron complexes 3 (Scheme 1).

2a   **3**

Scheme 1

In this chemistry, the tricarbonyliron moiety serves as a multifunctional auxiliary group. Complexation of the diene by the transition-metal unit opens up the possibility of hydride abstraction to the stable, metal-complexed η^5-cyclohexadienylium cation and sets the basis for bond formation upon reaction with nucleophiles. Nucleophilic attack on the η^5-cyclohexadienylium cation in most cases is highly regioselective and takes place exclusively at one of the termini of the π system. This observation is rationalized by the Davies–Green–Mingos rules.[15,16] The bulky tricarbonyliron moiety also acts as a stereodirecting group and enforces the incoming nucleophile on the face opposite to the iron (anti selectivity). Moreover, labile diene systems can be protected by complexation to the tricarbonyliron group because of the pronounced modification of reactivity of the organic ligand in the coordination sphere of the transition metal. These features render tricarbonyliron complexes extremely useful and versatile tools for synthetic organic chemistry.

We are engaged in a program to explore the utility of these complexes for the total synthesis of biologically active alkaloids via a methodology of consecutive iron-induced C–C and C–N bond formation. The present article[1] demonstrates that this strategy opens up short and direct access to the desired synthetic targets and emphasizes the utility of transition metal chemistry in the total synthesis of heterocyclic natural products.

2. Regio- and Stereoselective Electrophilic Substitutions of Arylamines by Iron-Complexed Cations

Usually C–C bond formation using iron-complexed cations has been achieved by the regio- and stereoselective attack of classical carbanions. Kane-Maguire was the first to show

that nucleophilic attack on the cation 2a can be accomplished with electron-rich heteroaromatic systems such as indole, pyrrole, imidazole, furan, and thiophene[17] as well as with donor-substituted aryl derivatives.[18] Based on this reactivity cation 2a may be considered as a mild electrophile for aromatic substitution. Our expectation was that even with highly donor-substituted arylamines, where alternative procedures often fail, C–C bond formation should be possible under very mild reaction conditions. This would provide a method complementary to classical electrophilic aromatic substitution.

First we investigated the regioselectivity of electrophilic aromatic substitutions of donor-substituted arylamines with tricarbonyliron-complexed η^5-cyclohexadienylium cations.

The reaction of *p*-anisidine with the iron-complexed cyclohexadienylium cations 2 provided regio- and stereoselectively the iron complexes 4 by a modified literature procedure[18] (Scheme 2).
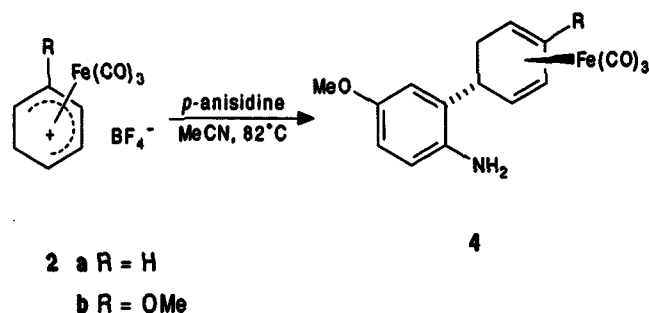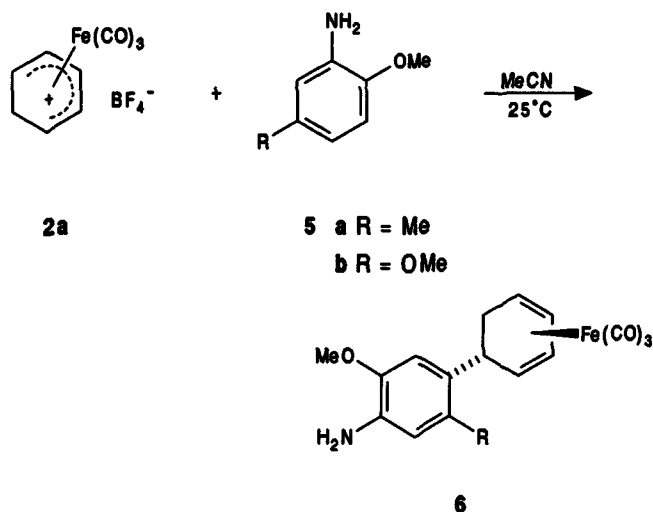
Scheme 2

Even under optimized reaction conditions (slow addition of the cation 2a to the refluxing solution of *p*-anisidine in acetonitrile) a nonpolar by-product, resulting from double attack of the electrophile 2a at both *ortho*-amino positions of the arylamine, was formed. The reaction of *p*-anisidine with the 2-methoxy substituted cation 2b is sluggish and decomposition occurs to a large extent.[19] It had already been demonstrated by kinetic studies that the 2-methoxy substituted cation 2b is much less reactive towards nucleophiles than the parent compound 2a.[18c,20] Therefore, even more electron-rich arylamines would be required in the reaction with cation 2b.

Further investigations have shown that the iron-complexed cation 2a is especially useful for regioselective electrophilic substitutions of highly donor-substituted arylamines. It is known that 3-methoxyaniline, because of its increased nucleophilicity, reacts twice with cation 2a even at room temperature to afford exclusively the 4,6-disubstituted 3-methoxyaniline derivative.[18d,e] The second electrophilic substitution can be avoided by having an additional methoxy group (5b) in the 2-position of the arylamine.[19] However, reactions of the arylamines 5 with the cation 2a at room temperature take place exclusively in the position *para* to the amino group to yield the iron complexes 6 which are unsuitable for cyclization (Scheme 3).

Obviously the only available free *ortho* amino position is too hindered for the sterically demanding tricarbonyl(η^5-cyclohexadienylium)iron cation because of two adjacent substi-
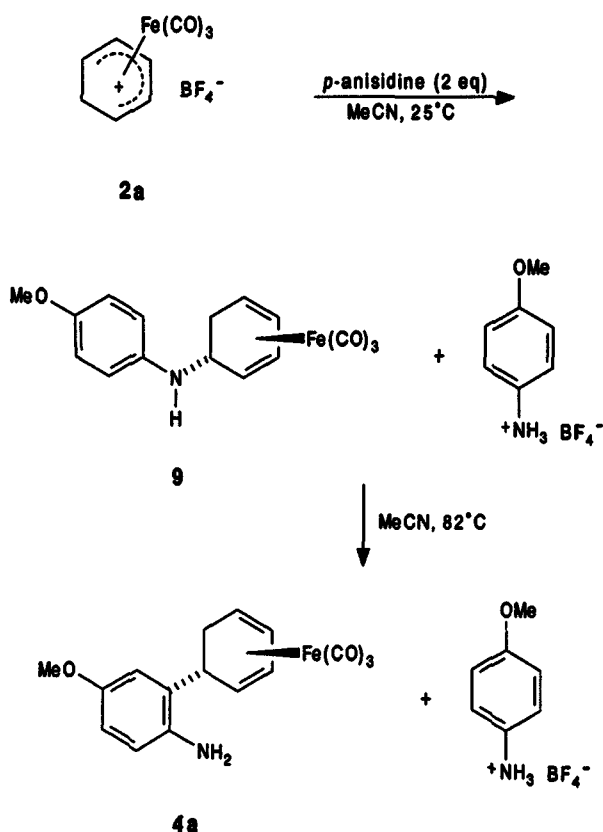
Scheme 3

tuents.[18e] With the arylamine 7, where the *para* amino position is blocked by a methyl group, electrophilic substitution using cation 2a again takes place at room temperature regioselectively in the 2-position to provide iron-complex 8[19] (Scheme 4). It is important to note that electrophilic substitution of aryl derivatives bearing a free hydroxy and a free amino group is possible by using iron-complexed cations.
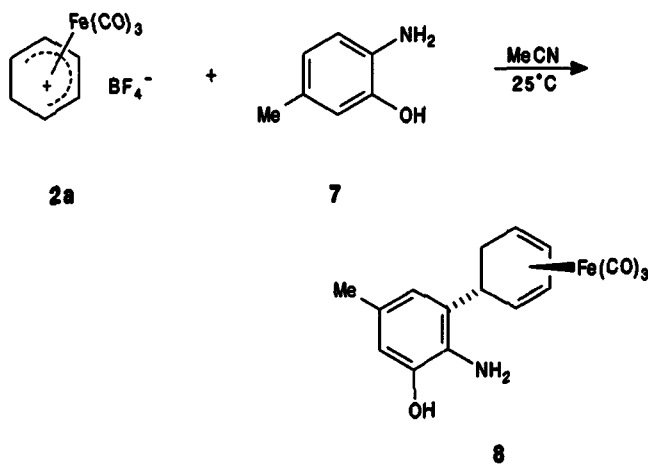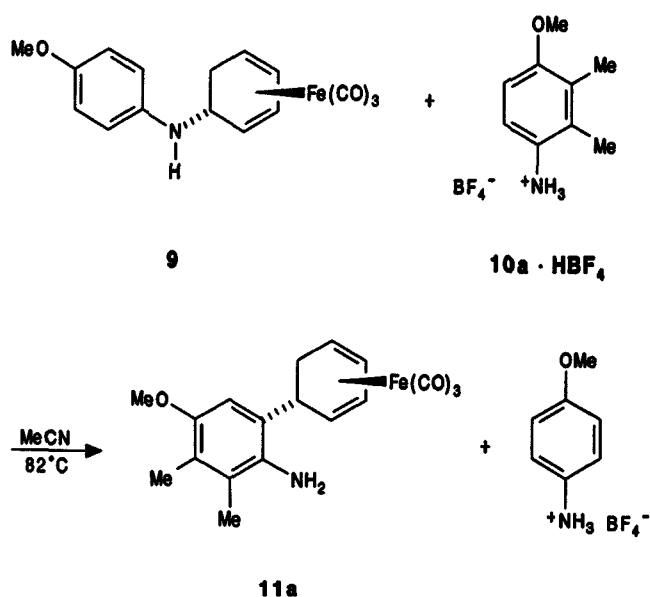
Scheme 4

Treatment of less donor-substituted arylamines, e. g., aniline or *p*-anisidine, with cation 2a in acetonitrile at room temperature provides the *N*-alkylated amines as the kinetic products.[18d,e,21] When the reactions are carried out at reflux temperature, the initially formed kinetic products (*N*-alkylated arylamines) rearrange to the thermodynamic products (products of electrophilic aromatic substitution by C–C bond formation, e. g., 4a).[18d,e,22] When cation 2a is treated with two equivalents of *p*-anisidine, the second equivalent is used as a base to trap the hydrotetrafluoroboric acid which drives the reaction to completion. We have found that the *p*-anisidine hydrotetrafluoroborate which is formed in the initial step is crucial for the complete intermolecular rearrangement of 9 to 4a at reflux temperature. The rearrangement of the isolated, pure compound 9 on heating with acid is achieved only when additional *p*-anisidine is present as a nucleophile.[23]

2a

p-anisidine (2 eq)
MeCN, 25°C

9

MeCN, 82°C

4a

Scheme 5

A sequence of transprotonation, regeneration of cation **2a**, and attack by the second equivalent of p-anisidine to afford **4a**, is involved in this conversion. The intermolecular character of the rearrangement has been confirmed by a crossover experiment between the N-substituted product **9** and the hydrotetrafluoroborate of the 4-methoxy-2,3-dimethylaniline (**10a**). Heating the reaction mixture at reflux provided exclusively the iron complex **11a** (63% yield of isolated product).[23] This experiment mimics the reaction of p-anisidine with cation **2a** at reflux in which the kinetic product **9** reacts with one equivalent of p-anisidine hydrotetrafluoroborate.

9

**10a · HBF₄**

MeCN
82°C

11a

Scheme 6

3. Iron-Mediated Oxidative Cyclizations to Oxygenated Carbazoles

The oxidative cyclization of tricarbonyl(η^4-cyclohexadiene)iron complexes having an enolizable carbonyl group (β-diketone or β-ketoester) on a side chain provides a direct access to annulated heterocyclic ring systems. This reaction, discovered by Birch in 1973, is usually achieved at elevated temperature (80°C) with manganese dioxide or lead dioxide and has been applied to the synthesis of iron-complexed cis-4a,7a-dihydrobenzofurans (e.g., **12**, Scheme 7).[24]

MnO₂
benzene, 80°C

12
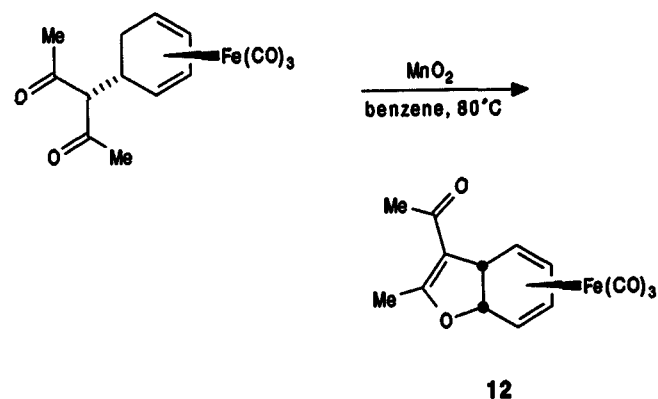
Scheme 7

Pearson utilized this method for cyclization of a wide range of hydroxyalkyl-substituted iron-diene complexes.[25] An intermolecular variant (a Tl^{3+}-induced addition of ethanol to tricarbonyliron-complexed cyclohexadiene) had been reported by Lewis.[26] However, there was only one report of an oxidative cyclization involving an amino group to yield an azacyclic product.[18d] We felt that exploitation of such a reaction would provide access to nitrogen heterocyclic ring systems with diverse potential in alkaloid synthesis. In order to explore the utility of such oxidative cyclizations for the synthesis of naturally occurring oxygenated carbazole alkaloids, we investigated the oxidation of appropriate precursors, such as **4** and **8**.[19,23] However, the previously described procedure (reaction with iodine in pyridine at 90°C for 1 h)[8] was ineffective in our hands and, instead of cyclization, led mainly to demetalation of the iron-diene complexes (yield of **13b**: 10%).[23]

A) I₂, pyridine, 90°C

B) γ-MnO₂, C₆H₆, 25°C

4   **a** R = H
     b R = OMe

13
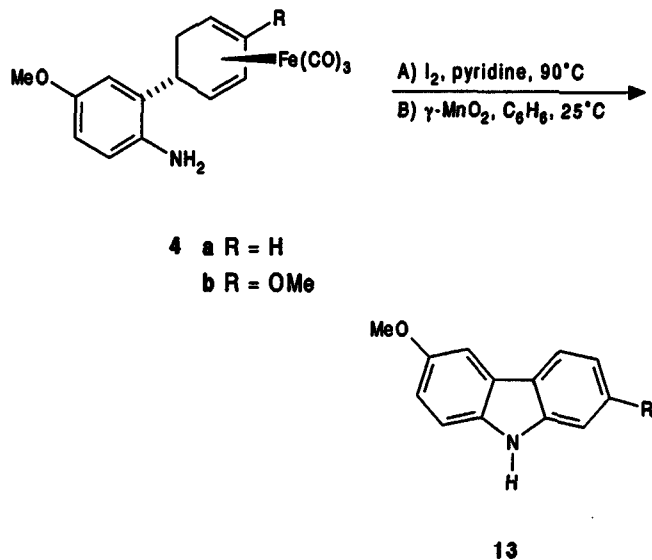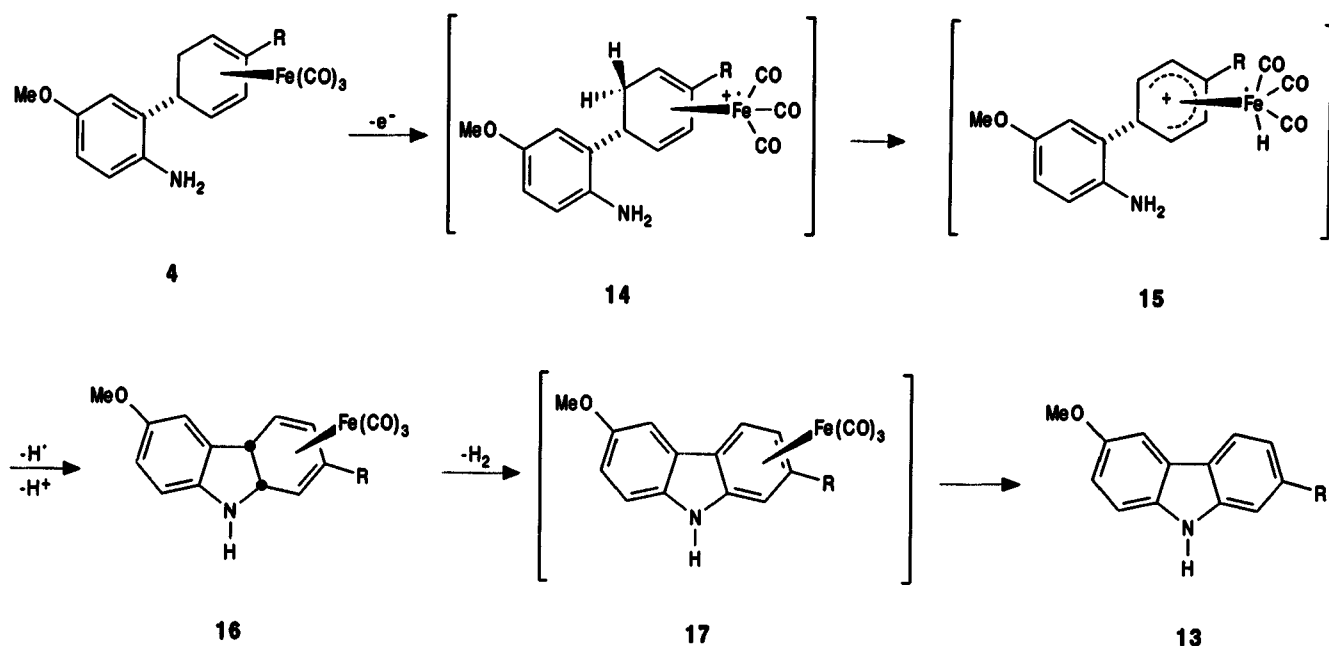
Scheme 8

Scheme 9

Other oxidizing agents including manganese dioxide had been used before for the oxidative cyclization of hydroxyalkyl-substituted tricarbonyliron-cyclohexadiene complexes.[24,25] However, attempts to achieve an oxidative cyclization using commercial activated manganese dioxide led only to decomposition of the iron complexes 4 even with variation of temperature and solvent. Use of milder reaction conditions (oxidative cyclization at room temperature) becomes possible by using especially activated manganese dioxides such as those reported by Fatiadi.[27] Cyclization of 4a with freshly prepared activated γ-manganese dioxide in benzene at room temperature provided 3-methoxycarbazole (13a) in 29% yield (Scheme 8).[19,23] Attempts to achieve cyclization of the iron complex 8 led only to decomposition under various reaction conditions, which indicates that oxidative cyclizations to carbazoles are not possible with iron complexes having free hydroxy groups.

The one-pot transformation of the iron complexes 4 to the carbazoles 13 proceeds directly and no intermediates of this cyclization could be isolated under the conditions used. We proposed the following mechanism for this reaction, which involves, in sequence, cyclizing dehydrogenation, aromatizing dehydrogenation, and demetalation (Scheme 9).[23]

The cyclizing dehydrogenation of the 18-electron complex 4 is initiated by a single-electron transfer (SET) oxidation, which generates the radical cation 14, a 17-electron species. An intramolecular syn-stereospecific hydrogen transfer[24] leads to 15, which cyclizes to the 4a,9a-dihydro-9H-carbazole 16, a potentially stable 18-electron complex. Aromatization of 16 under the oxidizing reaction conditions affords the tricarbonyl(η^6-arene)iron complex 17. This 20-electron complex finally demetalates instantaneously to the carbazole 13.

These early results indicated that the described methodology of consecutive iron-induced C–C and C–N bond formation opens up the way to a direct synthesis of many naturally occurring, biologically active, oxygenated carbazole alkaloids.[28,29]

4. Total Synthesis of the Carbazomycins

In 1980 Nakamura and co-workers described the isolation and structure elucidation of the carbazomycins A and B, produced by microorganisms of the strain Streptoverticillium ehimense H 1051-MY 10.[30] These structurally unique alkaloids, biogenetically derived from tryptophan,[31] are the first antibiotics with a carbazole framework. Carbazomycinal (carbazomycin E) has been isolated by Marumo from Streptoverticillium KCC-U-0166.[32] Subsequently this alkaloid, along with further novel members of the carbazomycin family, has been isolated by Nakamura from Streptoverticillium ehimense.[33] The unusual substitution pattern and the useful biological activities of these alkaloids prompted several groups to develop strategies for the total synthesis of the carbazomycins.[34–37] The arrangement of four donor substituents at four adjacent carbon atoms of a carbazole is difficult to achieve by classical procedures.[38]

Retrosynthetic analysis of the carbazomycins based on the iron-mediated construction of the carbazole ring system suggests cyclohexadiene and the corresponding arylamine 10 as starting materials (Scheme 10). Our intention was to use this approach for a highly convergent synthesis of these alkaloids where all the substituents are already present in the arylamine moiety. The required arylamines can be prepared in only a few simple steps. At the final stage of the synthesis, both building blocks would be combined by a consecutive iron-induced C–C and C–N bond formation involving a sequence of electrophilic aromatic substitution of 10 by the iron-complexed cation 2a and subsequent oxidative cyclization to the carbazole derivative.

4.1. Synthesis of 4-Deoxycarbazomycin B via Iron-Mediated Arylamine Cyclization

We investigated the applicability of the iron-mediated carbazole construction in the synthesis of the carbazomycins by focussing first on 4-deoxycarbazomycin B.[39,40] This degradation product of the main antibiotic carbazomycin B has been described by Nakamura and his group.[30]
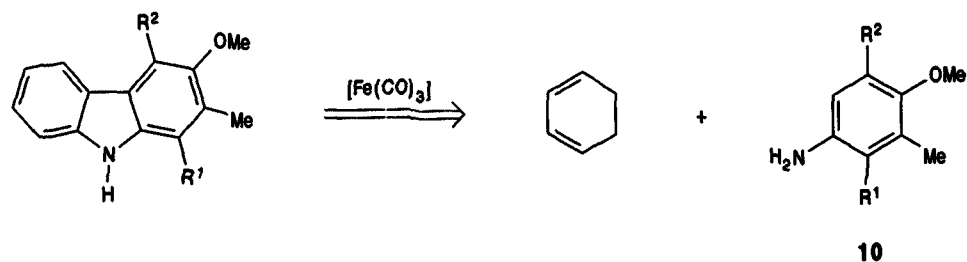
	R¹	R²	
4-Deoxycarbazomycin B	R¹ = Me	R² = H	10a
Carbazomycin A	*R¹ = Me*	*R² = OMe*	*10b*
Carbazomycin B	R¹ = Me	R² = OH	10c
Carbazomycinal (Carbazomycin E)	R¹ = CHO	R² = OH	10d

Scheme 10
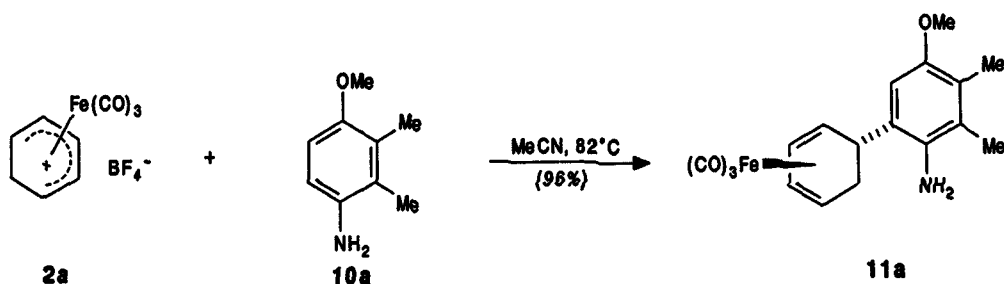
Scheme 11
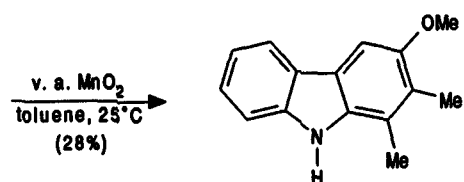
4-Deoxycarbazomycin B

Scheme 12

19
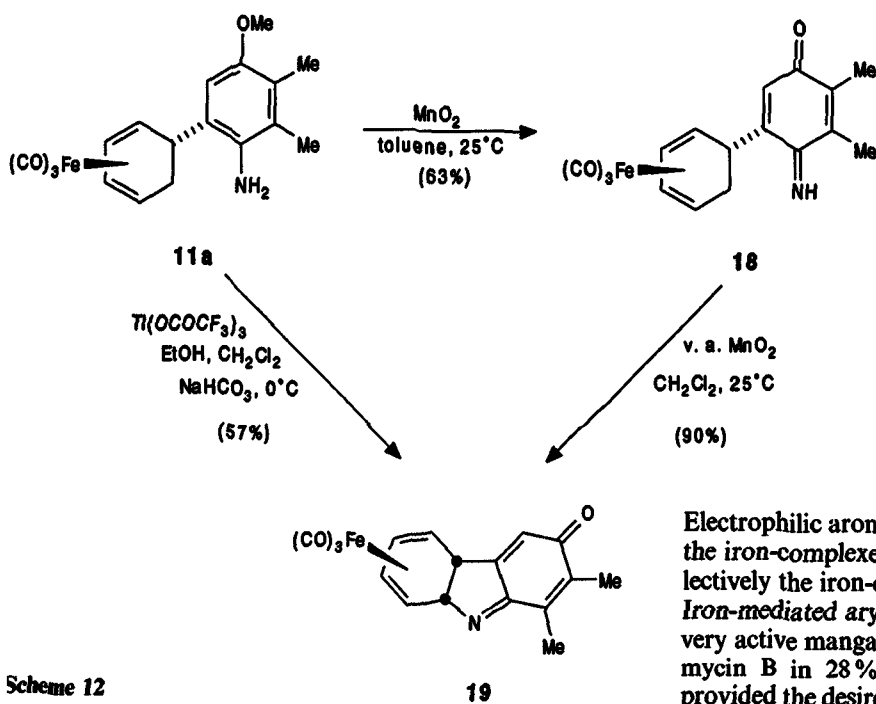
Electrophilic aromatic substitution of the arylamine 10a by the iron-complexed cation 2a afforded regio- and stereoselectively the iron-complex 11a in almost quantitative yield. Iron-mediated arylamine cyclization of 11a using Fatiadi's very active manganese dioxide[27] provided 4-deoxycarbazomycin B in 28% yield (Scheme 11).[39,40] This synthesis provided the desired carbazole alkaloid by a simple two-step

process. Our goal was to improve the overall yield of the sequence cyclization/aromatization/demetalation by the application of more selective oxidizing reagents including techniques that would achieve cyclization in two steps with higher chemoselectivity. We selected the readily available complex 11a as an appropriate substrate for an optimization study.

4.2 Chemoselective Oxidations of Iron-Cyclohexadiene Complexes

We first tested several differently activated manganese dioxides.[40] A completely chemoselective oxidation of the aromatic nucleus of 11a to the iminoquinone 18 was achieved using commercial activated manganese dioxide.[41] This is the first example of oxidation of an aromatic ring in presence of a tricarbonyliron-diene unit. Cyclization of the iminoquinone 18 with very active manganese dioxide[27] provided stereoselectively the novel iron-complexed 4b,8a-dihydrocarbazol-3-one 19.[39,40]

Oxidation of 11a with thallium trifluoroacetate[42] in buffered ethanol/dichloromethane (2:1) afforded the 4b,8a-dihydrocarbazol-3-one 19 in a one-pot reaction (57% yield).[43] The stereospecificities of the consecutive iron-induced C–C and C–N bond formations (anti to the tricarbonyliron group) have been confirmed by an X-ray analysis of the iron complex 19 (Figure 1).[40]
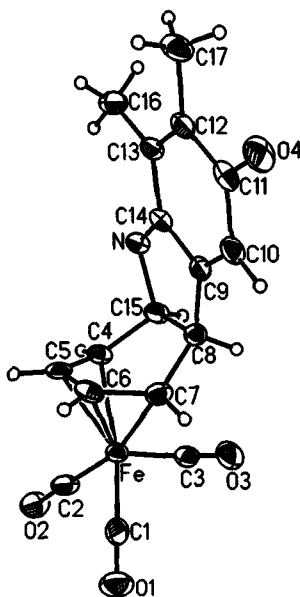

Figure 1. Molecular structure of 19 in the crystal. Selected bond lengths [Å]: Fe–C4 2.109(4), Fe–C5 2.053(5), Fe–C6 2.074(5), Fe–C7 2.106(4)

Iron complex 19 is the first example of a compound with a dihydrobenzene ring adjacent to an oxidized benzene ring. The 4b,8a-dihydrocarbazol-3-one ring system is stabilized by complexation with the transition metal. In this context one has to recall the early work of Harley-Mason in his study of the biogenesis of melanin.[44] He reported that 2,3-dihydroindol-5-one (21), obtained by oxidation of 2-(2,5-dihydroxyphenyl)ethylamine (20), undergoes a spontaneous isomerization to 5-hydroxyindole (22) (Scheme 13).
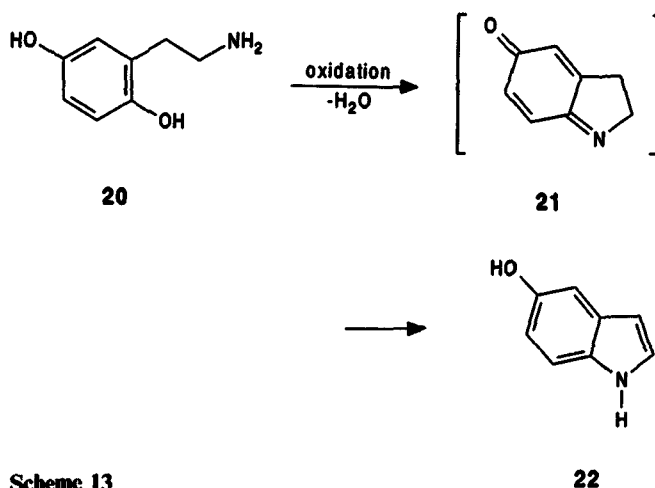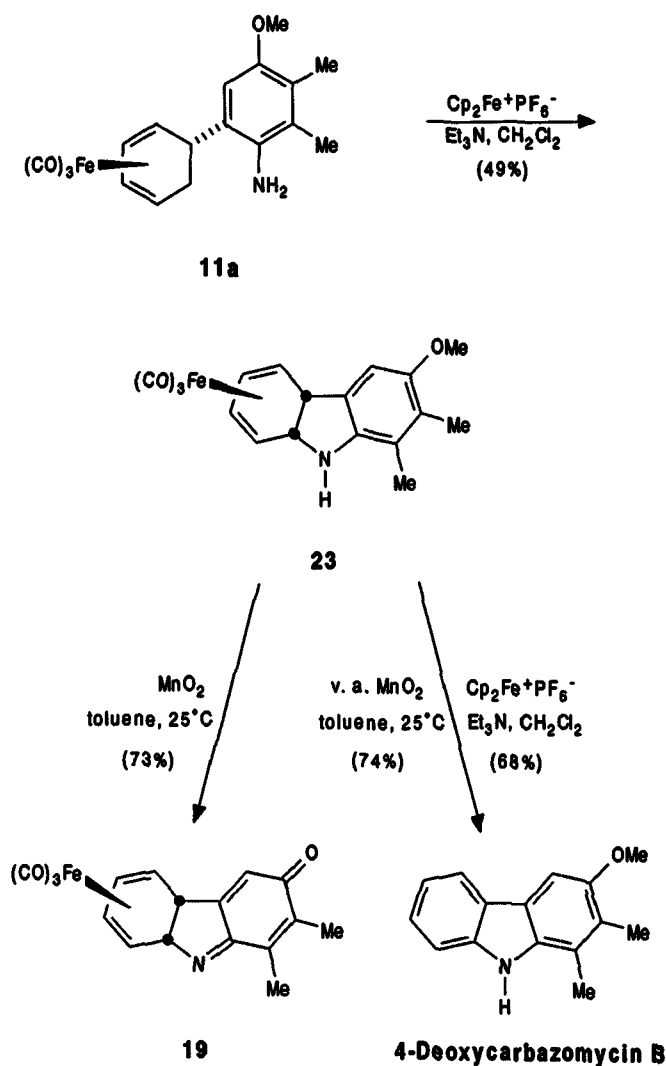

Scheme 13

Hydroxyindoles formed by isomerization of indole iminoquinones such as 21 are intermediates in the biogenesis of melanin pigments. The intermediate 21 could not be isolated in this study because of the rapid aromatization process. The carbazole iminoquinone 19, which contains the same structural features as 21, is surprisingly stable in air (decomposition above 198 °C). The driving force for isomerization of 19 should be much greater, since two complete 6π systems would be generated. Obviously, complexation by the transition metal avoids this process. Exploitation of such an isomerization by demetalation of the complex holds promise for improved access to 3-oxygenated carbazoles because of the cleaner course of the iminoquinone cyclization.

We propose that the iron-mediated arylamine cyclization is initiated by a single-electron transfer oxidation (see Scheme 9). The radical cation thus formed could cyclize to a 4a,9a-dihydro-9H-carbazole, e.g., 16. By application of oxidizing agents having an appropriate potential it should be possible to avoid further dehydrogenation to the aromatized carbazole derivative provided that the oxidation potential of the second (aromatizing) dehydrogenation is higher than the first (cyclizing) dehydrogenation. SET oxidizing reagents such as the ferricenium cation should be appropriate for the selective generation of the postulated 17-electron radical cation intermediate which then could cyclize to the 18-electron 4a,9a-dihydro-9H-carbazole complex. The 17-electron ferricenium cation is easily available as its hexafluorophosphate,[45] has a well-defined potential[46] and generates the stable 18-electron complex ferrocene in oxidation reactions. It is a useful reagent for the conversion of 18-electron organometallic complexes to the corresponding 17-electron species.[47]

In fact, treatment of complex 11a with ferricenium hexafluorophosphate provided in a chemoselective oxidation the iron-complexed 4a,9a-dihydro-9H-carbazole 23 (Scheme 14).[23] The structural assignment for the complex 23 has been confirmed by an X-ray analysis (Figure 2).[40] This strategy opens up a direct access to compounds with the interesting 4a,9a-dihydro-9H-carbazole ring system.[48] The iron complex 23 is of further interest because of its remarkable physical properties. Single crystals of 23 exhibit optical anisotropism.

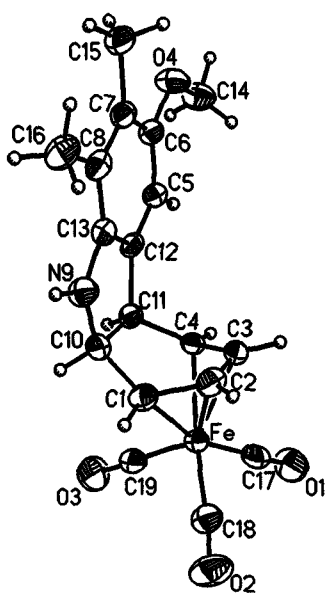The smooth conversion of complex 23 into 4-deoxycarbazo-mycin B with very active manganese dioxide (Scheme 14) provides support for our proposed mechanism (Scheme 9).[40] The fact that this transformation can be achieved using ferricenium hexafluorophosphate indicates that the aromatizing dehydrogenation, like the cyclizing dehydrogenation, takes place via the iron and is initiated by a single-electron transfer. Chemoselective oxidation of the aromatic nucleus to the iminoquinone in the presence of the tricarbonyliron diene moiety is also possible following the cyclizing dehydrogenation. Treatment of 4a,9a-dihydro-9H-carbazole 23 with commercial activated manganese dioxide[41] again provided 4b,8a-dihydrocarbazol-3-one 19.[49] The results presented in Schemes 12 and 14 emphasize the high selectivity which we have been able to realize by fine tuning of the reaction conditions. Using the more selective ferricenium cation as the oxidizing reagent for the cyclizing dehydrogenation increased the overall yield to 4-deoxycarbazomycin B to 35% (based on the three steps from the iron complex salt 2a).

4.3. Synthesis of 4-Deoxycarbazomycin B via Iron-Mediated Iminoquinone Cyclization

The much higher yield of the iron-mediated iminoquinone cyclization led us to investigate its use in the synthesis of 4-deoxycarbazomycin B. Demetalation of iron-complexed 4b,8a-dihydrocarbazol-3-one 19 using trimethylamine N-oxide[50] provided directly the 3-hydroxycarbazole 24 (Scheme 15).
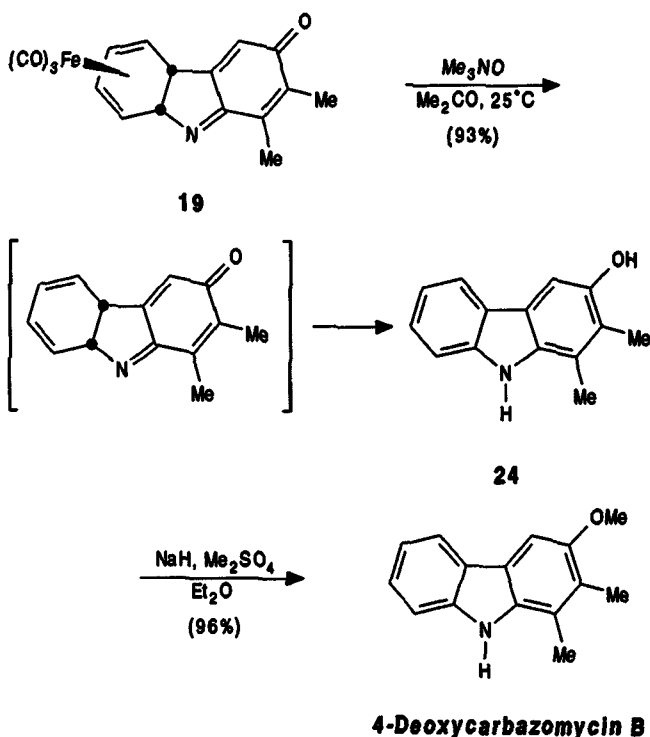
Scheme 14

Scheme 15

The free ligand instantaneously isomerized to the aromatized carbazole 24. Methylation of the carbinol 24 led to 4-deoxycarbazomycin B.[39,40] By this improved route, 4-deoxycarbazomycin B is available in four steps and 49% overall yield (based on the iron complex salt 2a). A comparison with the iron-mediated arylamine cyclization (two steps and 27% overall yield based on 2a) demonstrates the advantage of the iminoquinone cyclization.

Figure 2. Molecular structure of 23 in the crystal. Selected bond lengths [Å]: Fe–C1 2.106(3), Fe–C2 2.060(3), Fe–C3 2.063(2), Fe–C4 2.111(2)

4.4. Total Syntheses of Carbazomycin A, Carbazomycin B, and Carbazomycinal

The arylamine 10b, required for the synthesis of carbazomycin A, was prepared in multigram quantities in eight simple steps from 2,3-dimethylphenol (29% overall yield).[23,40] Upon treatment with 2a electrophilic aromatic substitution of 10b occurred at room temperature to generate the hexasubstituted aromatic compound 11b in 85% yield. This result emphasizes the efficiency of the iron-complexed cations as mild electrophiles for highly donor-substituted and, therefore, oxidation-sensitive aromatic rings.

2a   **10b**

11b
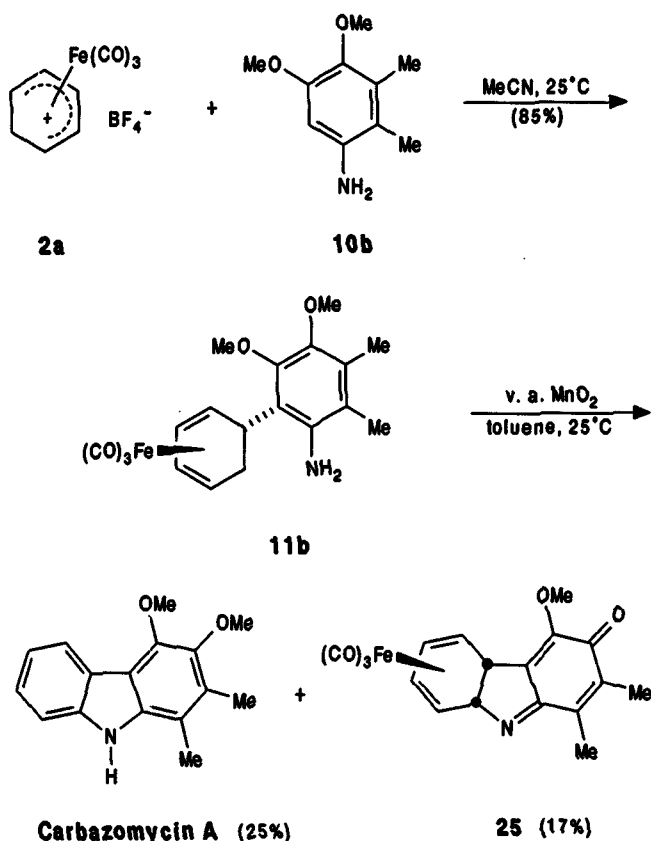
Carbazomycin A (25%)   **25** (17%)
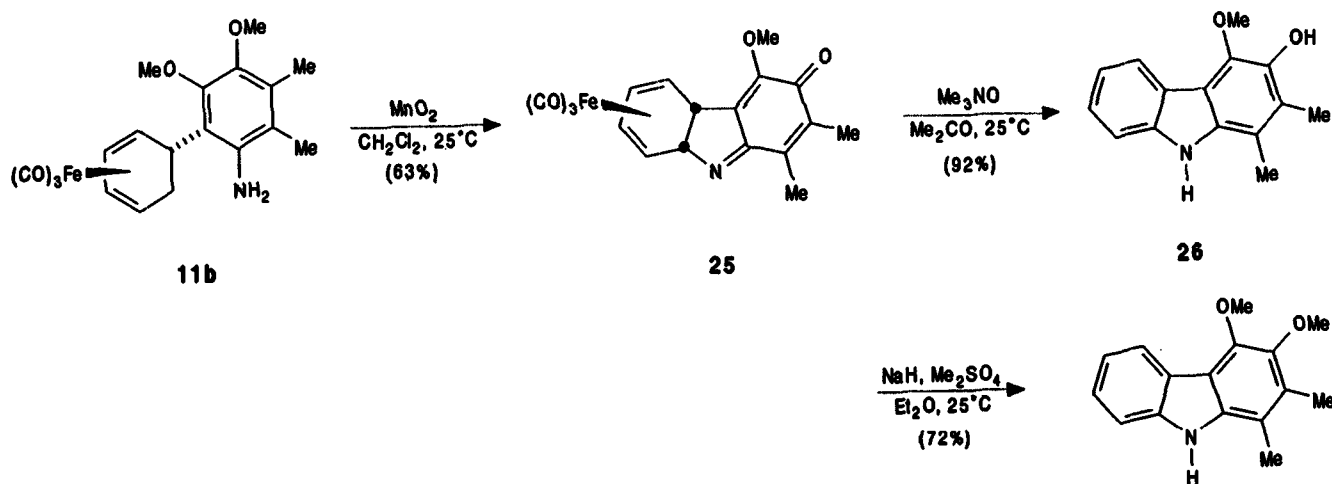
Scheme 16

We completed the first total synthesis of carbazomycin A by the iron-mediated arylamine cyclization of complex 11b using very active manganese dioxide.[27] This procedure afforded 25% of the natural product along with 17% of the 4b,8a-dihydrocarbazol-3-one 25 (Scheme 16).[39,40]

The isolation of the cyclized iron-complexed iminoquinone 25 as a by-product of this reaction indicated that the iron-mediated iminoquinone cyclization could be used to improve the sequence. Treatment of the iron complex 11b with commercial ac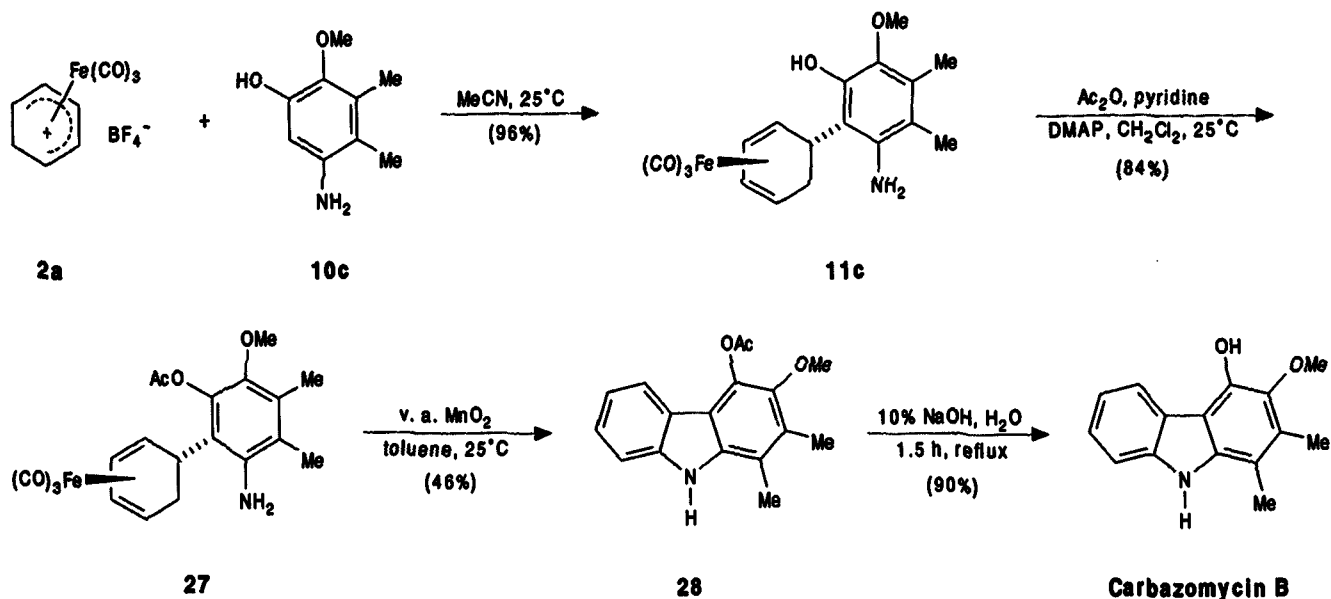tivated manganese dioxide[41] provided, in a direct iminoquinone cyclization, the 4b,8a-dihydrocarbazol-3-one 25. This surprising result contrasts with analogous oxidations in the deoxy-series (Scheme 12). Apparently the cyclizing dehydrogenation step is influenced by the substituents on the intermediate iminoquinone moiety. Obviously fine-tuning of these oxidative cyclizations is necessary in order to come to the optimized reaction conditions for each system. Demetalation of the iron complex 25 with trimethylamine N-oxide[50] and concomitant dihydrocarbazolone–hydroxycarbazole isomerization provided the non-natural isocarbazomycin B (26). Methylation of 26 gave carbazomycin A (Scheme 17).[51]

The route via the iron-mediated iminoquinone cyclization leads to carbazomycin A in four steps and 35% overall yield (based on complex salt 2a). This synthesis shows again the advantage of the iminoquinone cyclization over the arylamine cyclization (two steps and 21% overall yield based on 2a).

Starting with the arylamine 10c (prepared in seven steps and 30% overall yield from 2,3-dimethylphenol) we accomplished the total synthesis of carbazomycin B by the iron-mediated arylamine cyclization (Scheme 18).[51] Treatment of 10c with 2a (2 h at room temperature) afforded the iron complex 11c in 96% yield. Several attempts to achieve an oxidative cyclization of 11c having the free hydroxy group failed and led only to decomposition of the starting material. The example of iron complex 8 had already alerted us that unprotected hydroxy groups cause problems in these cyclizations. However, acetylation to the complex 27 followed by cyclization with very active manganese dioxide provided O-acetylcarbazomycin B (28) (a known derivative[30b] of the natural product). Cleavage of the ester gave carbazomycin B which proved to have spectral data identical with that of an authentic sample of the natural product,[30]
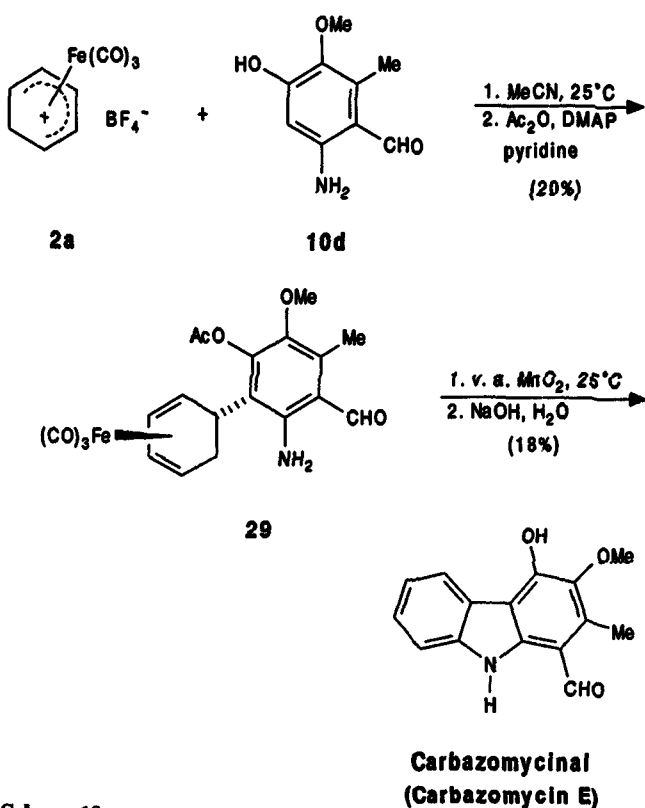

11b   **25**   **26**

Carbazomycin A

Scheme 17

Scheme 18

Compounds: 2a, 10c, 11c, 27, 28, Carbazomycin B

Reagents: MeCN, 25°C (96%); Ac₂O, pyridine, DMAP, CH₂Cl₂, 25°C (84%); v. a. MnO₂, toluene, 25°C (46%); 10% NaOH, H₂O, 1.5 h, reflux (90%)

kindly provided by Professor S. Nakamura (Institute of Pharmaceutical Sciences, Hiroshima University).

The decribed route provides carbazomycin B in four steps and 33% overall yield (based on complex salt 2a). The total syntheses of carbazomycin A and B emphasize the efficiency of the iron-mediated construction of 3,4-dioxygenated carbazole alkaloids. In alternative syntheses[34,36] of these natural products, the oxy substituents were introduced by a linear multistep sequence.

Recently we have realized the first total synthesis of carbazomycinal (carbazomycin E),[52] an even more challenging target having four different substituents in one benzo ring (Scheme 19).
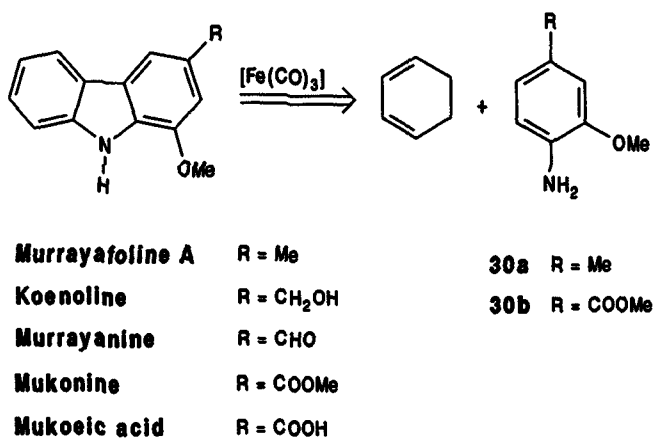
Compounds: 2a, 10d, 29, Carbazomycinal (Carbazomycin E)

Reagents: 1. MeCN, 25°C; 2. Ac₂O, DMAP, pyridine (20%); 1. v. a. MnO₂, 25°C; 2. NaOH, H₂O (18%)

Scheme 19

Arylamine 10d (available in seven steps from vanillyl alcohol) when treated with cation 2a followed by acetylation afforded the iron complex 29. Finally iron-mediated arylamine cyclization and ester cleavage provided the natural product.

5. Total Synthesis of 1-Methoxycarbazole Alkaloids

The plants of the genus *Murraya* (*Rutaceae* family) represent the major natural source of 1-methoxycarbazole alkaloids.[29] Extracts of leaves and bark of this tree have been used as folk medicine. Among the various carbazole alkaloids isolated from the bark and roots of different *Murraya* species are murrayafoline A,[53] koenoline,[54] murrayanine,[55] mukonine,[29a] and mukoeic acid.[56] The co-occurence of several of these alkaloids indicates that they are biosynthesized by oxidation of murrayafoline A.[29,54,56] We envisaged a brief and convergent synthesis of these alkaloids by the iron-mediated construction of the carbazole ring system as outlined in Scheme 20.

	R			R
Murrayafoline A	R = Me		30a	R = Me
Koenoline	R = CH₂OH		30b	R = COOMe
Murrayanine	R = CHO			
Mukonine	R = COOMe			
Mukoeic acid	R = COOH			

Scheme 20

Treatment of the arylamine 30a with cation 2a provided complex 31a (Scheme 21). The cyclization of the latter proceeded with concomitant oxidation of the methyl group

and provided directly murrayanine. Borohydride reduction of murrayanine gave the cytotoxic carbazole alkaloid koenoline (14% overall yield).[57]

2a   **30a**

31a

Murrayanine   **Koenoline**

Scheme 21

2a   **30b**

31b

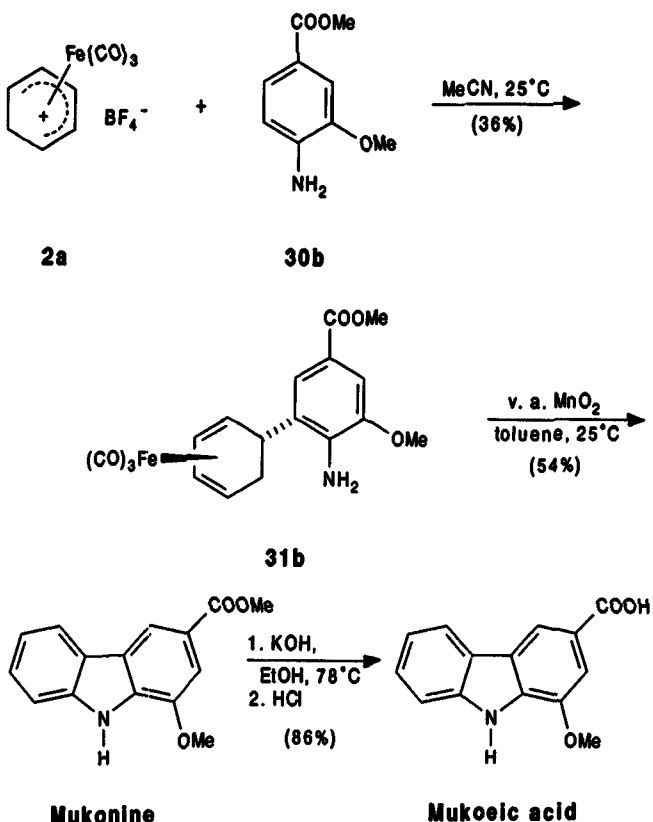**Mukonine**   **Mukoeic acid**
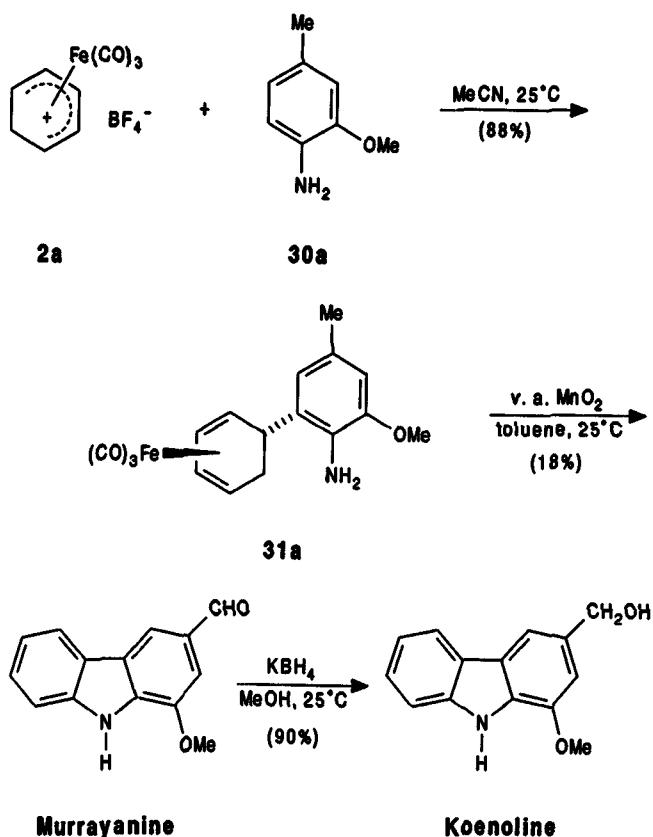
Scheme 22

Electrophilic substitution of the arylamine **30b** by the cation **2a** proceeded in lower yield due to the decreased nucleophilicity of the aromatic ring (Scheme 22). Cyclization of complex **31b** with very active manganese dioxide led to mukonine, ester cleavage of which afforded mukoeic acid (17% overall yield).[57]

A related procedure of consecutive iron-induced C–C and C–N bond formation has recently been applied to the synthesis of murrayafoline A.[58] The scope of the iron-mediated construction of carbazoles has been demonstrated by the fact that a broad variety of derivatives oxygenated at different positions of the heterocycle becomes available by this method.

**6. Regio- and Stereoselective Reactions of Iron-Complexed 4b,8a-Dihydrocarbazol-3-ones**

The hitherto unprecedented iron-complexed 4b,8a-dihydrocarbazol-3-one represents an intriguing example of a ring system which is stabilized by transition metal complexation (cf., cyclopentadienone,[59] cyclobutadiene,[60] o-quinodimethane,[61] cyclohexa-2,4-dien-1-one,[5] and norbornadien-7-one[62]). The remarkably high stability of these iron complexes prompted us to investigate the reactivity of this novel ring system by taking advantage of the tricarbonyliron moiety as a protecting group.

Reduction of the iron complex **19** by sodium borohydride provided the iron-complexed 4a,9a-dihydro-9H-carbazole **32** which is transformed to its N,O-dimethyl derivative **33** (Scheme 23).[43]

Because of the synthetic scope of the iron-mediated iminoquinone cyclization, this method represents a general access to the 4a,9a-dihydro-9H-carbazoles. Demetalation of complex **33** with trimethylamine N-oxide[50] provided the free ligand **34** which was aromatized by 10% Pd/C in boiling p-xylene.[43,49] The liberated cyclohexadiene unit in **34** underwent a stereoselective Diels–Alder cycloaddition when exposed to N-phenyltriazoline-2,4-dione to afford compound **35**.[48,49]

The iminoquinone moiety of the iron-complexed 4b,8a-dihydrocarbazol-3-one should be amenable to nucleophilic conjugate additions. Of special interest are those transformations which enable the regio- and stereoselective introduction of a functionalized carbon side chain at C4a since this would afford potential aspidosperma and strychnos alkaloid precursors. For this purpose, we prepared the iron complex **38** by electrophilic substitution of the arylamine **36** using the cation **2a** and subsequent iron-mediated iminoquinone cyclization of complex **37** (62% overall yield).[43] The Sakurai reaction[63] of the iron-complexed 4b,8a-dihydrocarbazol-3-one **38** using allyltrimethylsilane and titanium tetrachloride results in a chemo-, regio-, and stereoselective introduction of the allyl group at C4a of the carbazole nucleus to provide the iron complex **39** in 65% yield (Scheme 24).[43]

Noteworthy is that we obtained the trimethylsilylcyclopentane **40** as a silicon-containing by-product of this reaction. The structure of this tetracyclic carbazole derivative, which is obtained as a single diastereoisomer, was unequivocally confirmed by X-ray crystallography (Figure 3).[43]
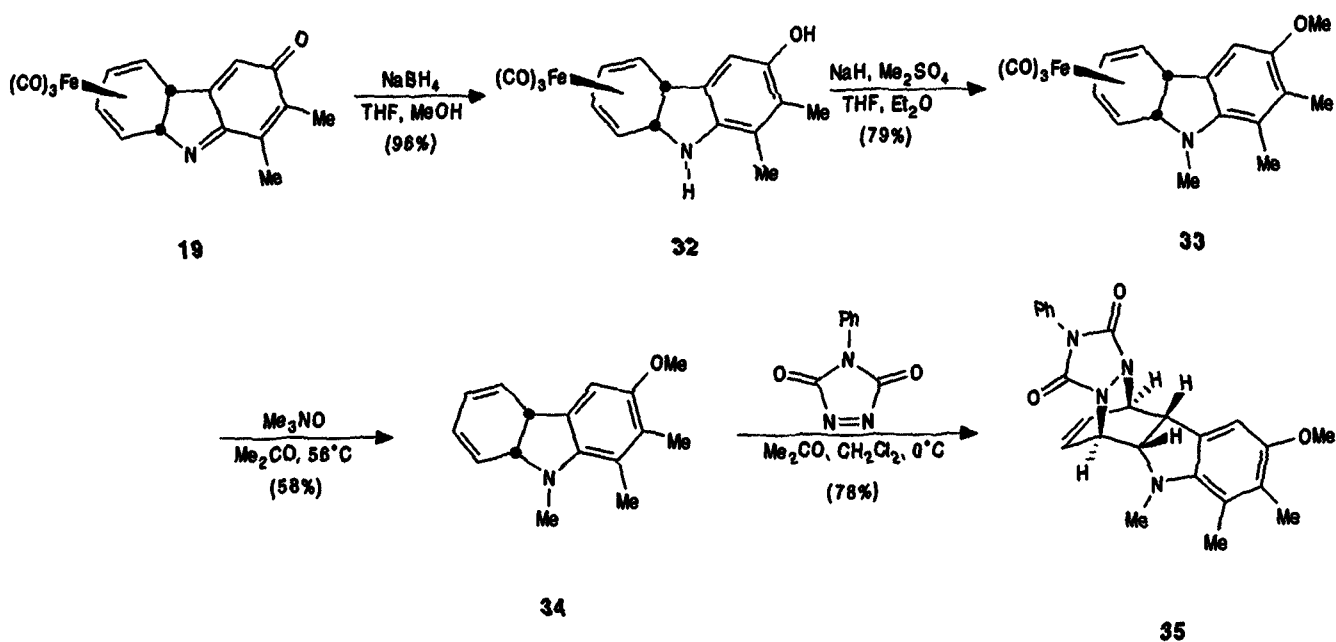
Scheme 23
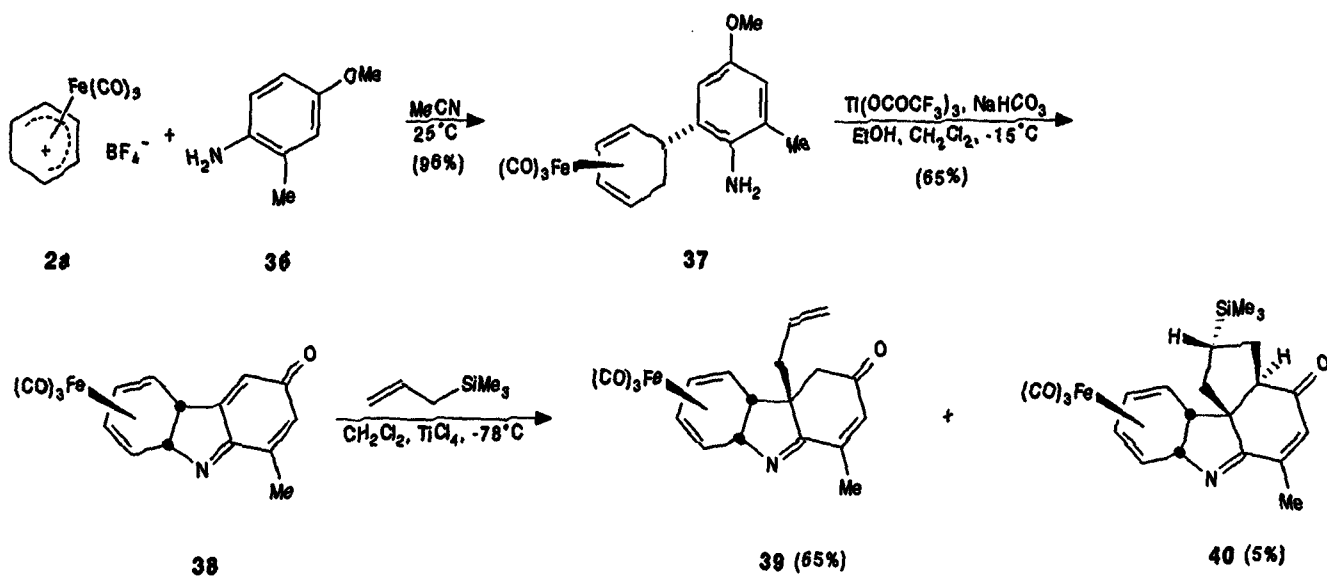
Scheme 24

The formation of this by-product is explained by a sequence of conjugate addition of the allylsilane and subsequent β-silyl-cation-induced, sila-Wagner–Meerwein rearrangement. We suggested a bridged non-classical pentavalent silicon cation as the key intermediate which cyclizes by the titanium enolate resulting in a stereospecific 1,2-silyl shift.[64] A stereoselective annulation of a trimethylsilylcyclopentane in the course of a Sakurai reaction was hitherto unprecedented.[65-67] Several trimethylsilylmethylcyclobutanes which have been reported as by-products of the Sakurai reaction have to be reassigned in view of our findings.[64,68] We recently found that this novel trimethylsilylcyclopentane annulation becomes the main reaction by appropriate fine-tuning of the conditions.[69]

Demetalation of the iron-complexed 4a-allyl derivative 39 using trimethylamine N-oxide[50] affords the free ligand 41 which is stable with respect to aromatization. Dehydrogenation of the cyclohexadiene 41 to the carbazole derivative 42 is achieved upon refluxing in toluene with palladium on charcoal (Scheme 25).[43]

Reaction of complex 39 with ethylmagnesium chloride results in the stereoselective introduction (syn relative to the tricarbonyliron unit) of an ethyl group at C3 of the carbazole nucleus.[43] The chemistry of iron-complexed 4b,8a-dihydrocarbazol-3-ones with respect to applications to alkaloid synthesis is under further investigation.
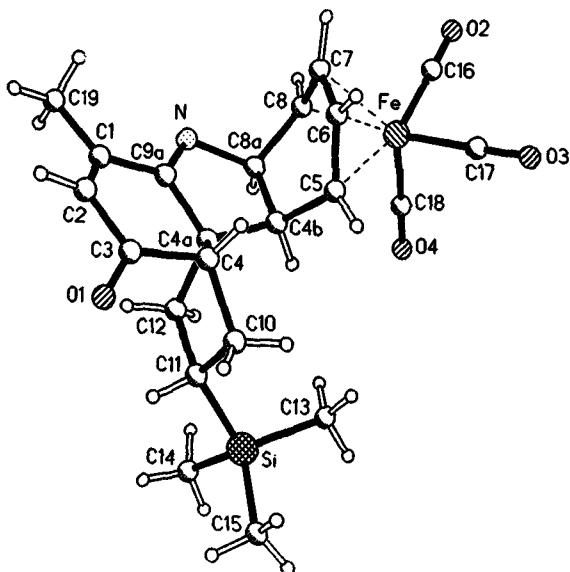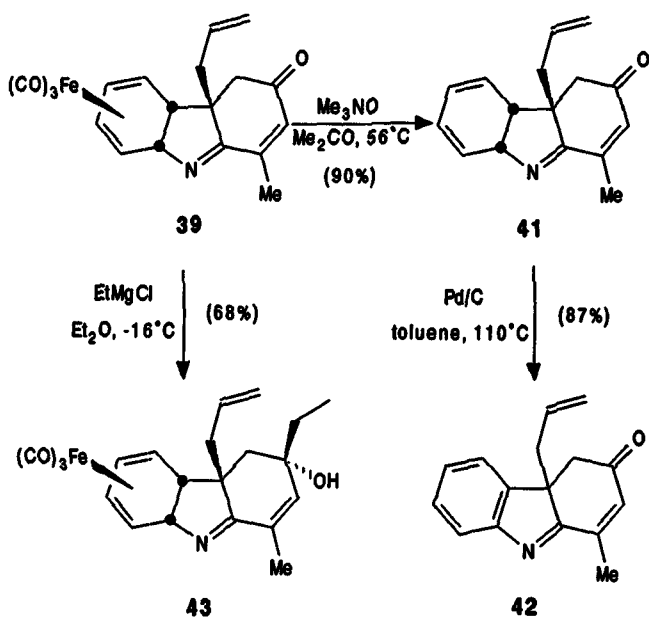
Figure 3. Molecular structure of 40 in the crystal. Selected bond lengths [Å]: Fe–C5 2.110(2), Fe–C6 2.063(3), Fe–C7 2.047(2), Fe–C8 2.092(2), Si–C11 1.875(2)

Scheme 25

7. Diastereoselective Iron-Mediated Spiroannulations

A broad variety of spirocyclic alkaloids with challenging structures and useful pharmacological properties has been isolated from nature. The 3-azaspiro[5.5]undecanes, as represented by the discorhabdins[70] or prianosins,[71] and the 1-azaspiro[5.5]undecanes, as represented by the histrio-nicotoxins[72] and erythrina alkaloids,[73] are important members of this group of natural products. We provided a diastereoselective access to both ring systems by an iron-mediated spiroannulation of arylamines.

Pearson has demonstrated that nucleophilic additions to tricarbonyl(η^5-1-alkyl-4-methoxycyclohexadienylium)iron cations provide a stereoselective access to quaternary carbon centers.[74] The selectivity of these reactions is controlled by the stereodirecting effect of the tricarbonyliron group (anti selectivity) and by the regiodirecting effect of the methoxy group which enforces the incoming nucleophile on the carbon atom *para* relative to the methoxy group. An iron-complexed cyclohexadienylium cation, containing a side chain at C1 with a leaving group at an appropriate distance from the ring system, may be regarded as a double acceptor. The addition of arylamines as double nucleophiles to these cations should allow C–C and C–N bond formation in a one-pot reaction, thus giving rise to the diastereoselective formation of spirocyclic quinolines.

7.1. Cyclization to 3-Azaspiro[5.5]undecanes

Transformation of *p*-methoxyphenylacetic acid (44) to the iron complex 45 is achieved by a simple four-step procedure.[75] Benzoylation with *p*-nitrobenzoyl chloride and subsequent regioselective hydride abstraction using triphenylcarbenium tetrafluoroborate generated the iron complex salt 46 (Scheme 26).[76] By this sequence, the complex salt 46 was available in multigram quantities and 50–60% overall yield based on 44.
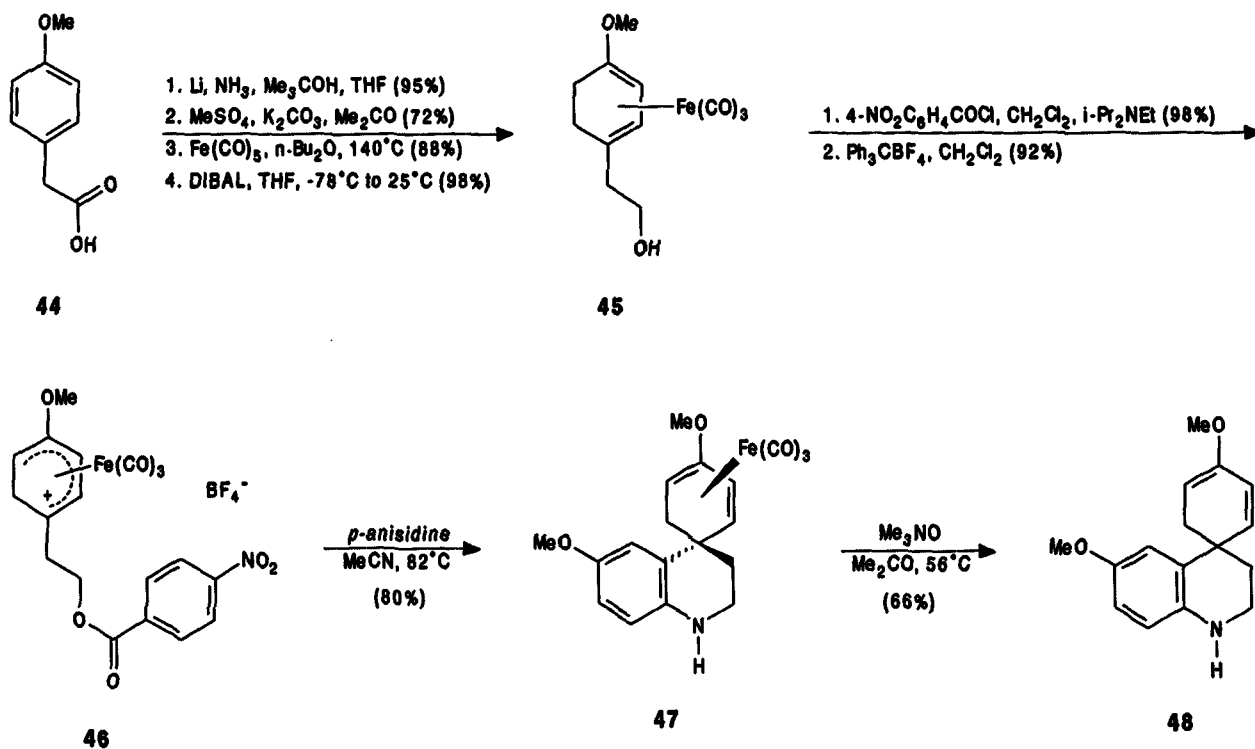
Reaction of *p*-anisidine with the complex salt 46 in acetonitrile at reflux leads regio- and diastereoselectively in 80% yield to the spiroquinoline 47 involving a sequence of electrophilic aromatic substitution and in situ nucleophilic substitution of the leaving group in the side chain.[76] This reaction represents the first example of the generation of a quaternary carbon by electrophilic substitution of an aromatic system with an iron-complexed cation. A further diastereoselective approach to 5-aryl substituted 5-alkylcyclohexadienes using organoiron chemistry has been described more recently by Stephenson and co-workers.[77]

The structural assignment of the iron complex 47 is based on spectroscopic data (^{1}H and ^{13}C NMR) and an X-ray crystal structure determination which confirms the anti orientation of the aryl ring relative to the tricarbonyliron group referred to the cyclohexadiene ring plane (Figure 4).[76]

Demetalation of 47 with trimethylamine *N*-oxide[50] provides the free ligand 48. Reactions at the 2-methoxydiene moiety of 48, e. g. cycloadditions, should occur stereoselectively anti relative to the aryl ring. This has been suggested by stereoselective recomplexation of 48 to the original complex 47.[76]

7.2. Cyclization to 1-Azaspiro[5.5]undecanes

The spiroannulations of *p*-anisidine, 3,4-dimethylaniline, *p*-toluidine, and aniline with cation 46 result regioselectively in a cyclization to 3-azaspiro[5.5]undecanes.[76] An extensive investigation of the iron-mediated spiroannulation revealed that highly donor-substituted arylamines provide increasing amounts of 1-azaspiro[5.5]undecanes with increasing donor ability of the substituents. The diastereoselectivity of the spiroannulation process which is directed by the tricarbonyliron group is maintained. An almost complete reversal of the regioselectivity of the iron-mediated spiroannulation has been achieved with 1-amino-4-methoxynaphthalene (49). Reaction of the complex salt 46 with amine 49 provided in 71% yield the 1-azaspiro[5.5]undecane 50 in a 9:1 ratio

1. Li, NH₃, Me₃COH, THF (95%)
2. MeSO₄, K₂CO₃, Me₂CO (72%)
3. Fe(CO)₅, n-Bu₂O, 140°C (88%)
4. DIBAL, THF, -78°C to 25°C (98%)

1. 4-NO₂C₆H₄COCl, CH₂Cl₂, i-Pr₂NEt (98%)
2. Ph₃CBF₄, CH₂Cl₂ (92%)

44

45

p-anisidine
MeCN, 82°C
(80%)

Me₃NO
Me₂CO, 56°C
(66%)

46

47

48
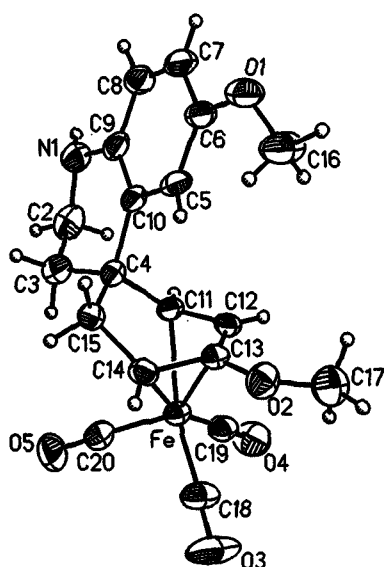
Scheme 26

Figure 4. Molecular structure of 47 in the crystal. Selected bond lengths [Å]: Fe–C11 2.096(3), Fe–C12 2.054(4), Fe–C13 2.099(3), Fe–C14 2.116(4)

MeCN
82°C
(71%)

46

49

together with the 3-azaspiro[5.5]undecane 51 (Scheme 27).[78] The *regioisomer 50 was obtained as a pure compound by simple crystallization.*

The structure assignment for the tetracyclic iron complex 50 is based on comparison of the ¹H and ¹³C NMR data with those of 47 and has been confirmed by X-ray analysis. The two opposite enantiomers of 50 adopt different conformations in the crystal due to crystal packing forces (Figure 5).[78]

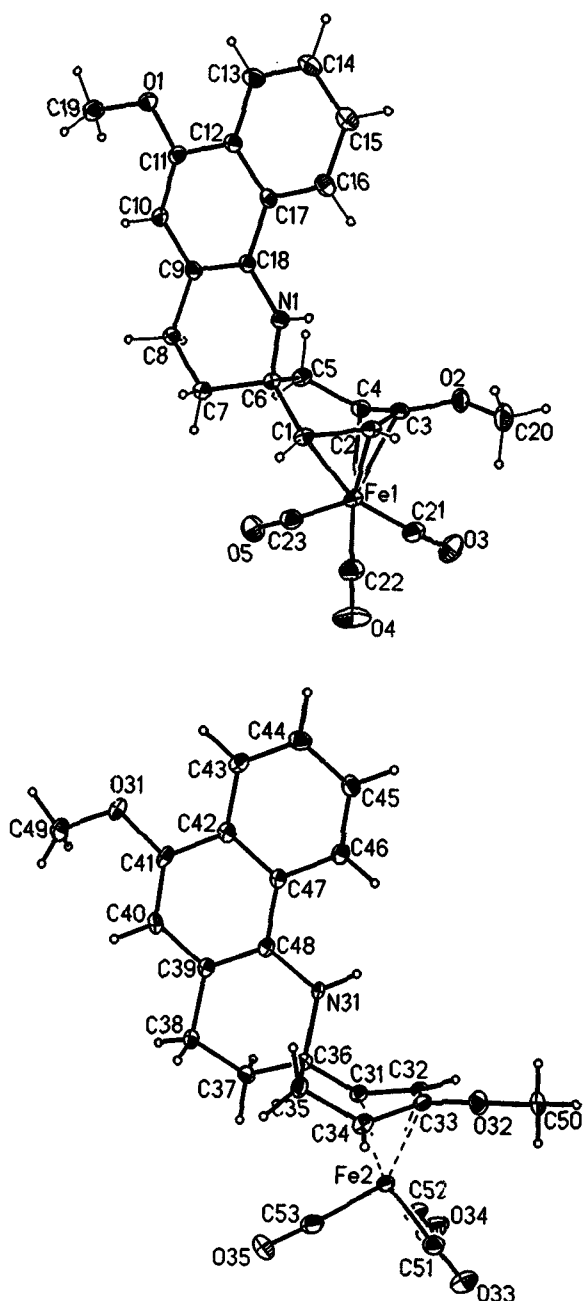**50**   **51**

ratio   9   :   1
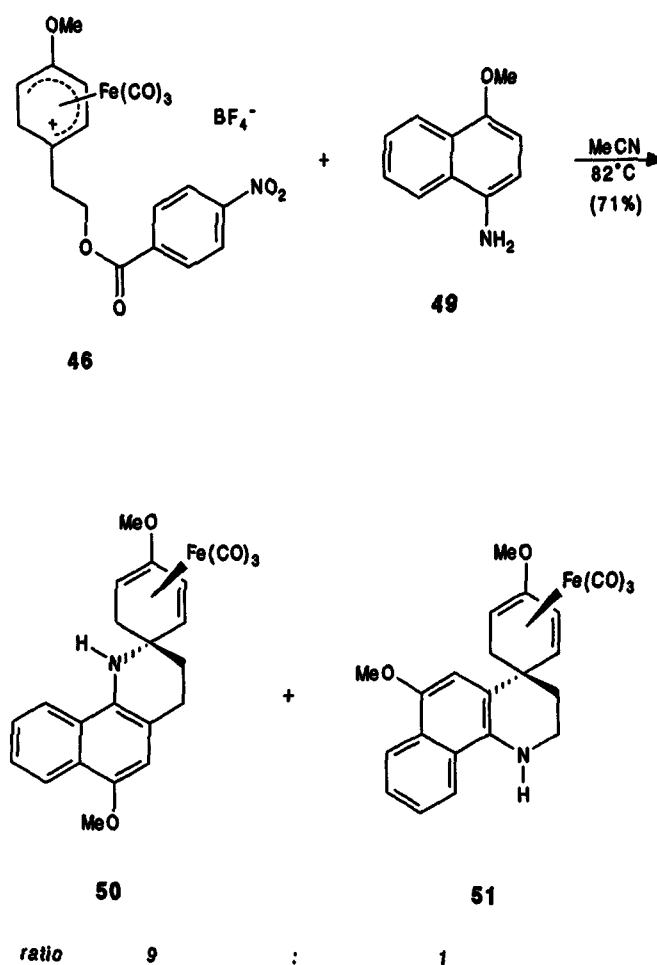
Scheme 27

Figure 5 Molecular structure of 50 in the crystal. Selected bond lengths [Å]: Fe1–C1 2.077(2), Fe1–C2 2.049(2), Fe1–C3 2.107(2), Fe1–C4 2.106(3); Fe2–C31 2.081(2), Fe2–C32 2.052(3), Fe2–C33 2.113(3), Fe2–C34 2.116(3)

This novel mode of iron-mediated spiroannulation results from nucleophilic attack of the amino group on the iron-complexed cation and subsequent cyclization to a 1-azaspiro[5.5]undecane[79] by a proton-catalyzed Friedel–Crafts reaction. The reaction rate of the N-alkylation of the arylamine by the iron-complexed cation is dependent on the basicity of the amine.[80] The dual reactivity of iron-complexed cations in N- versus C-substitutions of arylamines has already been discussed in Part 2 of the account. We have demonstrated by using a series of arylamines that the nucleophilicity of the ortho amino position is a determining factor for the regiochemical outcome of this reaction. Moreover, the regioselectivity of the iron-mediated spiroannulation of arylamines is influenced by the reaction temperature. At low temperature, cyclization to the 3-azaspi-

ro[5.5]undecanes is favored. However, the electronic effect, as determined by the substituents of the arylamine, is overriding.[78]

It is possible to govern the regioselectivity of the iron-mediated spiroannulation by the substituents of the arylamine and, to a smaller extent, by the reaction temperature. The flexibility described above promises a versatile synthetic potential for this reaction with future applications directed towards the total synthesis of spiroheterocyclic natural products.
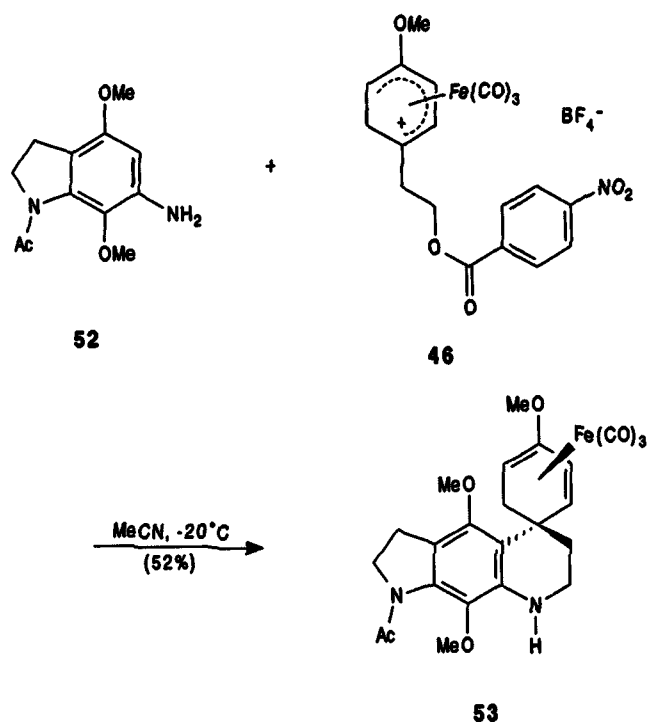
7.3. Synthetic Approach to the Discorhabdin and Prianosin Alkaloids

The discorhabdins, a novel class of spirocyclic alkaloids, have been isolated as the major cytoxic pigments from New Zealand sponges of the genus Latrunculia.[70] Their unique structural features involve a hitherto unprecedented pyrrolo[1,7]phenanthroline framework with a spiroannulated cyclohexenone and an additional sulfur bridge (which is not present in discorhabdin C). Compounds of the same class with some new structural featurs, e.g., prianosin B, have been isolated from the Okinawan marine sponge Prianos melanos.[71] The discorhabdins and prianosins are distinguished by their strong cytotoxic and antimicrobial activity. Discorhabin D (prianosin D) exhibits significant in vivo antitumor activity.

Discorhabdin A
(Prianosin A)

Prianosin B

Discorhabdin C

Discorhabdin D
(Prianosin D)
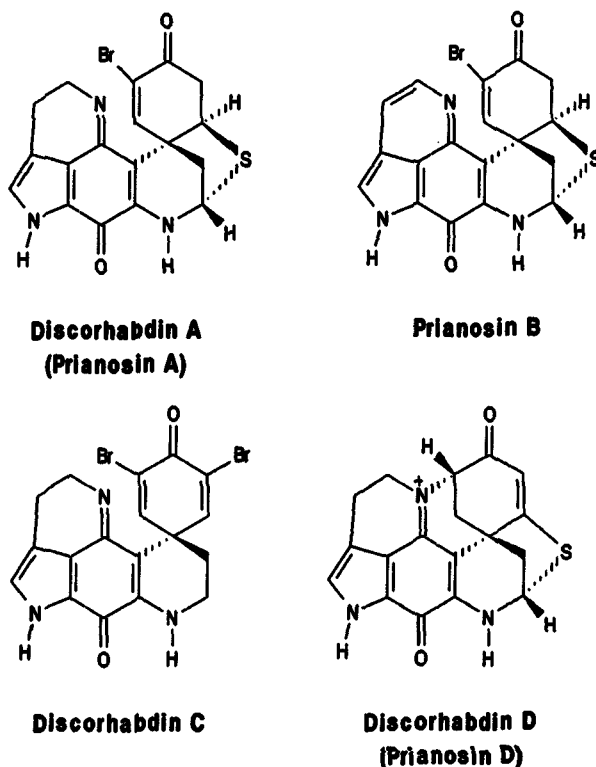
We had already achieved diastereoselective access to a simple tricyclic subunit of these alkaloids by iron-mediated spiroannulation of p-anisidine with cation 46 (Scheme 26).[76] Several other approaches have been reported in the meantime.[81–85] Application of our iron-mediated spiroannulation in a convergent approach to the discorhabdins and prianosins is outlined in Scheme 28.

Reaction of the 6-aminoindoline 52 (prepared in three steps from 4,7-dimethoxyindole[86], 61 % overall yield) with cation 46 in acetonitrile at − 20 °C provided the desired iron

OMe

OMe

NH$_2$

Ac   OMe

52

+

OMe

Fe(CO)$_3$

BF$_4^-$

NO$_2$

O

O

46

MeO

Fe(CO)$_3$

MeO

MeO

$\xrightarrow[\text{(52\%)}]{\text{MeCN, -20°C}}$

N
Ac   MeO   N   H

53

Scheme 28

complex **53** in 52% yield.[87] The regioisomer resulting from cyclization to a 1-azaspiro[5.5]undecane (34% yield) was separated by flash chromatography. Complex **53** contains the complete ABCD ring system of the natural products. The spiroannulation as well as the diastereoselectivity of this process are induced by the transition metal unit. Further elaboration of this chemistry should allow a convergent and diastereoselective access to the discorhabdins and prianosins.

8. Conclusion

We have demonstrated that the use of tricarbonyl-iron-complexed cyclohexadienylium cations as electrophiles in the substitution of arylamines opens ample opportunities for the total synthesis of biologically active alkaloids. The oxidative cyclization of these products can be used for the synthesis of the antibiotic carbazomycins as well as the cytotoxic carbazole koenoline and some related alkaloids. Further applications of this strategy are currently in progress. The novel iron-mediated iminoquinone cyclization led to the hitherto unprecedented 4b,8a-dihydrocarbazol-3-ones which exhibit promising reactivity. The iron-mediated one-pot spiroannulation provides 3-aza- as well as 1-azaspiro[5.5]undecanes. Regioselective control in this reaction is provided by the substituents of the arylamine and by the reaction temperature. We have demonstrated the feasibility of using this reaction for direct access to a tetracyclic fragment of the discorhabdin and prianosin alkaloids; further investigations towards the total synthesis of these cytotoxic natural products are under way.

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