Iron-mediated Total Synthesis of the Cytotoxic Carbazole Koenoline and Related Alkaloids[1]

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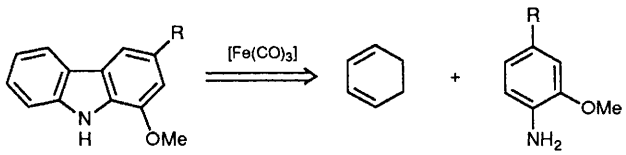
The total syntheses of the alkaloids mukonine, murrayanine, and koenoline are described using an iron-mediated arylamine cyclization as the key step.

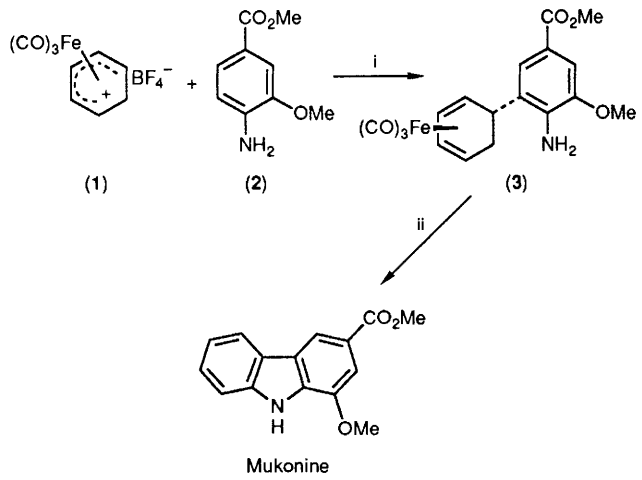
Recently we have shown the efficiency of various (η^5-cyclohexadienyl)tricarbonyliron cations as electrophiles for the substitution of arylamines.[1–3] Oxidative cyclizations of the products gave easy access to 3-oxygenated and 2,6-dioxygenated carbazoles.[2,3] Starting with the appropriately substituted iron-complexed cation allows the diastereoselective construction of spirocyclic quinolines by an *in situ* cyclization *via* nucleophilic substitution.[1] However, the iron-mediated iminoquinone cyclization, which proved to be very useful for the synthesis of 3-oxygenated carbazoles,[2,3] is not suitable for the 1-oxygenated derivatives. We now report for the first time an optimized iron-mediated arylamine cyclization providing a broad and general access to 1-oxygenated carbazole alkaloids.

A major natural source of 1-methoxycarbazole alkaloids are the trees of the genus *Murraya*, extracts of which have valuable biological activities. Murrayafoline A was isolated from *M. euchrestifolia* Hayata collected in Taiwan,[4] while the cytotoxic carbazole alkaloid koenoline[5] and its more highly oxidized derivatives murrayanine[6] and mukonine[7] were obtained from the Indian *M. koenigii*. The corresponding carbazole carboxylic acid, mukoeic acid, was also isolated from the same plant.[8] Because of the described lability of many oxygenated carbazoles mild procedures are required for their synthesis. A simple synthesis of murrayafoline A starting

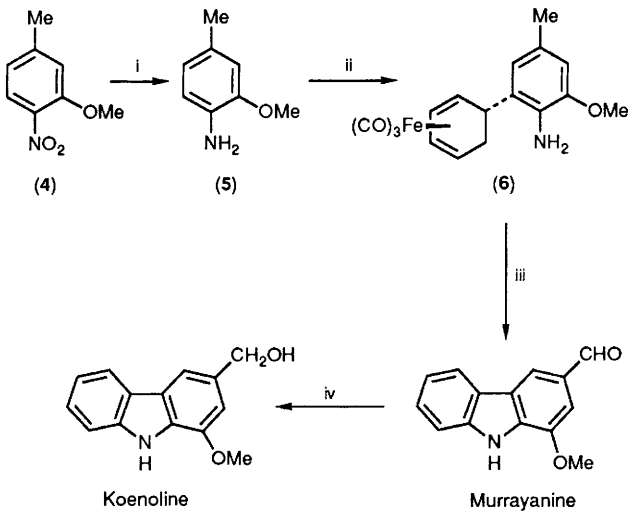


Murrayafoline A	R = Me
Koenoline	R = CH_2OH
Murrayanine	R = CHO
Mukonine	R = CO_2Me
Mukoeic acid	R = CO_2H

Scheme 1



Scheme 2. *Reagents and conditions*: i, MeCN, 25 °C; ii, very active MnO_2, toluene, 25 °C.



Scheme 3. *Reagents and conditions*: i, H_2, Pd/C, EtOH; ii, (**1**), MeCN, 25 °C; iii, very active MnO_2, toluene, 25 °C; iv, KBH_4, MeOH, 25 °C.

from methyl indole-2-carboxylate was reported recently by Moody *et al.*[9] We envisaged a short access to the 1-methoxycarbazole alkaloids based on the retrosynthesis outlined in Scheme 1. Electrophilic aromatic substitution of the corresponding precursor using the (η^5-cyclohexadienyl)tricarbonyliron cation and subsequent iron-mediated arylamine cyclization should lead directly to the natural products described above.

The electrophilic substitution of the acceptor-substituted arylamine (**2**) using the iron-complexed cation (**1**) proved to be less satisfactory (36% yield) than the cases investigated so far, all of which were highly donor-substituted.[2,3] However, the obtained iron complex (**3**) is transformed directly to mukonine† by the iron-mediated arylamine cyclization with very active manganese dioxide[10] in 54% yield (Scheme 2). This route provides the natural product in two steps and 20% overall yield based on the iron-complexed cation (**1**).

Hydrogenation of the nitroaryl derivative (**4**) affords the arylamine (**5**), which on subsequent reaction with the iron-complexed cation (**1**) provides the iron complex (**6**) in 88% yield† (Scheme 3). Compound (**6**) is converted directly with concomitant oxidation of the methyl group to murrayanine again using very active manganese dioxide. This outcome of the oxidative cyclization of (**6**) is rationalized by the following four-step process. (i) Oxidation of the methyl to the formyl group, (ii) cyclizing dehydrogenation to a 4a,9a-dihydro-9*H*-carbazole, (iii) aromatization to a 20-electron complex, and (iv) demetallation to murrayanine. The described reaction sequence derives support from two experimental results. First, the non-cyclized aldehyde formed in step 1 is isolated as a by-product upon incomplete oxidation of the complex (**6**). Second, we have already been successful in trapping an intermediate iron-complexed 4a,9a-dihydro-9*H*-carbazole from an oxidative cyclization leading to a 3-methoxycarbazole.[2] Borohydride reduction of murrayanine[6] affords the cytotoxic carbazole alkaloid koenoline.† By this synthesis koenoline is available in four steps and 14% overall yield based on the nitroaryl derivative (**4**).

Both syntheses demonstrate again the versatility of this iron-mediated carbazole construction, which is especially useful for the synthesis of more sensitive carbazole alkaloids.

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† All new compounds were fully characterized. The spectral data (UV, IR, MS, ^1H and ^{13}C NMR) of the obtained carbazole alkaloids are in full agreement with those reported for the natural products.

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