J. CHEM. SOC., CHEM. COMMUN., 1990

## Iron-mediated Total Synthesis of the Cytotoxic Carbazole Koenoline and Related Alkaloids<sup>1</sup>

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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.

Mukonine

Mukoeic acid

Recently we have shown the efficiency of various ( $\eta^{5}$ -cyclohexadienyl)tricarbonyliron cations as electrophiles for the substitution of arylamines.<sup>1-3</sup> Oxidative cyclizations of the products gave easy access to 3-oxygenated and 2,6dioxygenated carbazoles.<sup>2,3</sup> Starting with the appropriately substituted iron-complexed cation allows the diastereoselective construction of spirocyclic quinolines by an *in situ* cyclization *via* nucleophilic substitution.<sup>1</sup> However, the ironmediated iminoquinone cyclization, which proved to be very useful for the synthesis of 3-oxygenated carbazoles,<sup>2,3</sup> 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,<sup>4</sup> while the cytotoxic carbazole alkaloid koenoline<sup>5</sup> and its more highly oxidized derivatives murrayanine<sup>6</sup> and mukonine<sup>7</sup> were obtained from the Indian *M. koenigii*. The corresponding carbazole carboxylic acid, mukoeic acid, was also isolated from the same plant.<sup>8</sup> Because of the described lability of many oxygenated carbazoles mild procedures are required for their synthesis. A simple synthesis of murrayafoline A starting



Scheme 1

R = CO<sub>2</sub>Me

 $R = CO_2H$ 



Scheme 2. Reagents and conditions: i, MeCN, 25 °C; ii, very active MnO<sub>2</sub>, toluene, 25 °C.

from methyl indole-2-carboxylate was reported recently by Moody *et al.*<sup>9</sup> 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 ( $\eta^5$ -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.<sup>2,3</sup> However, the obtained iron complex (3) is transformed directly to mukonine† by the iron-mediated arylamine cyclization with very active manganese dioxide<sup>10</sup> 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 ironcomplexed cation (1) provides the iron complex (6) in 88% yield<sup>†</sup> (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-9Hcarbazole, (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-9H-carbazole from an oxidative cyclization leading to a 3-methoxycarbazole.<sup>2</sup> Borohydride reduction of murrayanine<sup>6</sup> affords the



Scheme 3. Reagents and conditions: i, H<sub>2</sub>, Pd/C, EtOH; ii, (1), MeCN, 25 °C; iii, very active MnO<sub>2</sub>, toluene, 25 °C; iv, KBH<sub>4</sub>, MeOH, 25 °C.

cytotoxic carbazole alkaloid koenoline.<sup>†</sup> 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.

This work was supported by the Deutsche Forschungsgemeinschaft. We thank Dr. K.-H. Geiß, BASF, Ludwigshafen/Rhein, for a generous gift of nonacarbonyldiiron, and Dr. V. Wray, Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig-Stöckheim, for the <sup>13</sup>C NMR spectra.

Received, 16th January 1990; Com. 0/00253D

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<sup>&</sup>lt;sup>†</sup> All new compounds were fully characterized. The spectral data (UV, IR, MS, <sup>1</sup>H and <sup>13</sup>C NMR) of the obtained carbazole alkaloids are in full agreement with those reported for the natural products.