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Transition Metal Complexes in Organic Synthesis, Part 33.[1]
Molybdenum-Mediated Total Synthesis of Girinimbine, Murrayacine, and Dihydroxygirinimbine

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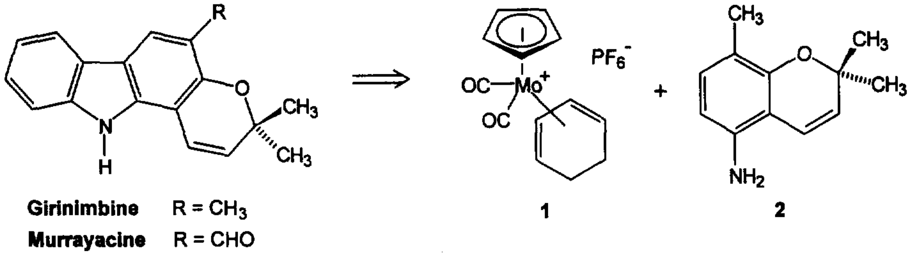
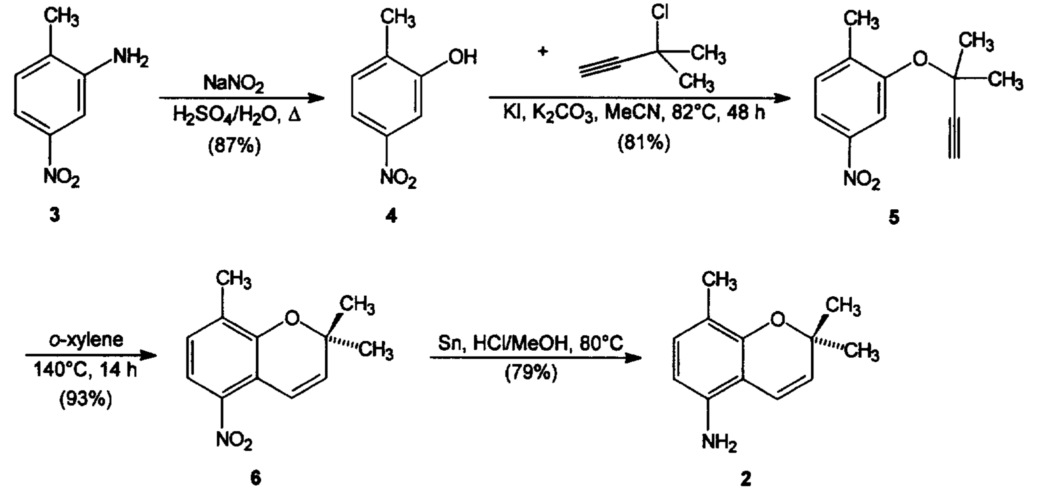
Abstract: A highly convergent total synthesis of the pyrano[3,2-*a*]carbazole alkaloids girinimbine, murrayacine, and dihydroxygirinimbine has been accomplished using a consecutive molybdenum-mediated C–C- and C–N-bond formation.

Most of the carbazole alkaloids were isolated from terrestrial plants.[2] Very efficient syntheses to these natural products have been elaborated over the past years, especially by transition metal-mediated reactions.[3] We developed an efficient methodology for the synthesis of highly oxygenated carbazoles by oxidative cyclization of appropriately functionalized tricarbonyl(η^4-1,3-cyclohexadiene)iron complexes.[4] This procedure was shown to have a broad scope,[5] however, the cyclization to 2-oxygenated carbazoles proceeded unsatisfactory.[6] More recently we have shown that the electrophilic aromatic substitution of 3-alkoxyarylamines by the cationic dicarbonyl(η^5-cyclopentadienyl)(η^4-1,3-cyclohexadiene)molybdenum complex **1** and subsequent oxidative cyclization of the resulting dicarbonyl(η^3-cyclohexenyl)(η^5-cyclopentadienyl)molybdenum complexes provides a novel method for the synthesis of 2-oxygenated carbazole alkaloids.[7] In this paper we report the application of this method to the total synthesis of the pyrano[3,2-*a*]carbazole alkaloids girinimbine,[8] murrayacine,[9] and dihydroxygirinimbine.[10]



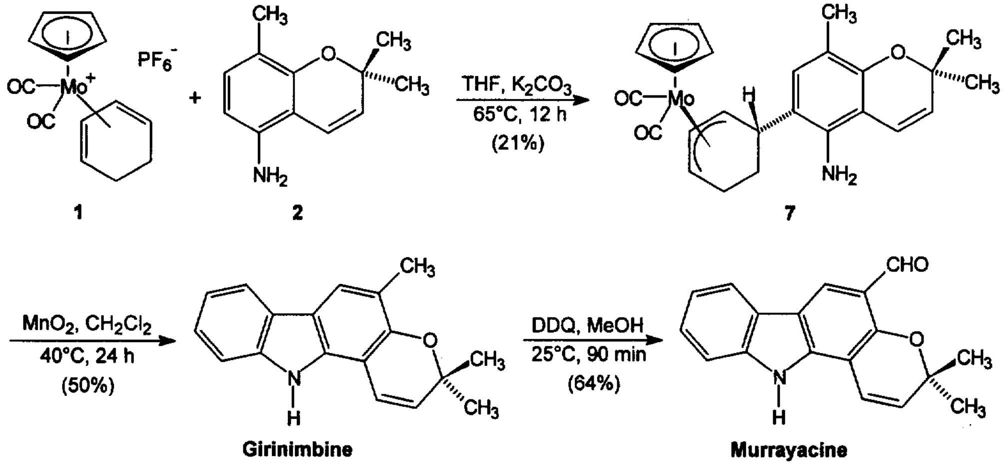
Scheme 1

Retrosynthesis of the pyrano[3,2-*a*]carbazole alkaloids based on the above-mentioned methodology provides the molybdenum complex salt **1** and and the 5-aminochromene **2** as potential synthetic precursors (Scheme 1). Complex **1** is easily prepared using the procedures reported by Faller[11] and Liebeskind[12] and exhibits useful reactivity towards nucleophiles.[11,13] The synthesis of the 5-amino-2,2,8-trimethylchromene **2** was achieved in four steps and 52% overall yield starting from commercially available 2-methyl-5-nitroaniline **3** (Scheme 2).



Scheme 2

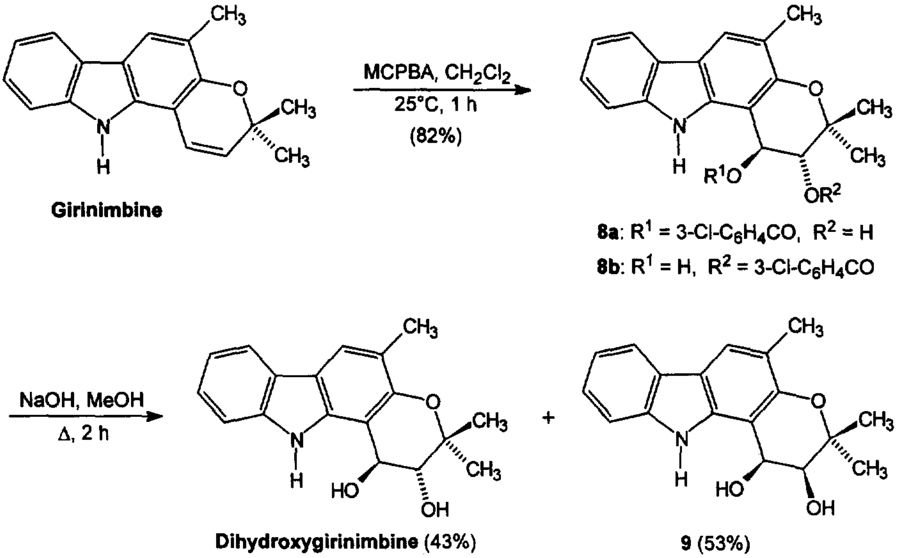
Treatment of **3** with nitrous acid afforded the phenol **4**,[14] which was alkylated by 3-chloro-3-methyl-1-butyne[15] to the aryl propargyl ether **5**. Refluxing of **5** in *o*-xylene for 14 h provided the 5-nitrochromene **6** by [3,3] sigmatropic rearrangement and subsequent cyclization.[16] Reduction of **6** with tin in methanolic hydrochloric acid afforded the 5-aminochromene **2**.



Scheme 3

Reaction of the 5-aminochromene **2** with the complex salt **1** provided regio- and diastereoselectively the molybdenum complex **7**.[17] Oxidative cyclization of complex **7** with concomitant aromatization using activated manganese dioxide[18] afforded directly girinimbine, m. p. 176°C (lit.[8]: 176°C). Oxidation of girinimbine with DDQ in methanol[19] gave murrayacine, m. p. 244°C (lit.[9]: 244-245°C). The spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS) of synthetic girinimbine and murrayacine are in full agreement with those reported for the natural products.[2,8,9]

In 1985 Furukawa reported the isolation of dihydroxygirinimbine from the roots of *Murraya euchrestifolia*.[10] The *trans*-1,2-diol substructure was assigned based on the ^{1}H-NMR data. This assignment was additionally confirmed by a partial synthesis of dihydroxygirinimbine from girinimbine. Epoxidation of girinimbine using *meta*-chloroperbenzoic acid (MCPBA) in benzene was described to afford two isomeric dihydroxy derivatives after chromatography on silica gel. The polar fraction was shown to be identical with the natural dihydroxygirinimbine, the less polar product was the *cis*-isomer. Due to the lability of the oxirane ring an epoxygirinimbine could not be isolated.[10]



Girinimbine

8a: R^1 = 3-Cl-C_6H_4CO, R^2 = H
8b: R^1 = H, R^2 = 3-Cl-C_6H_4CO

Dihydroxygirinimbine (43%)

9 (53%)

Scheme 4

We obtained on oxidation of girinimbine with MCPBA in dichloromethane a mixture of the two regioisomeric 3-chlorobenzoic acid esters **8a** and **8b** in 82% yield (ratio $\approx$ 1.5 : 1). Compound **8a** was obtained in pure form by flash chromatography on silica gel (hexane/ether, 1:1). The structure assignment for **8a** was confirmed in the ^{1}H-NMR spectrum (400 MHz) by the presence of 9 signals for aromatic protons, in the ^{13}C-NMR spectrum (100 MHz, acetone-D_6) by the presence of 6 additional signals for aromatic carbons (4 CH and 2 C) and 1 signal for the carbonyl C-atom (at δ = 166.34 ppm), and in the mass spectrum by the molecular ion of m/z = 435 and the base peak at m/z = 279 (M^+–$C_6H_4ClCOOH$). The hydrolysis of the isolated mixture of the 3-chlorobenzoates **8a** and **8b** with methanolic sodium hydroxide provided dihydroxygirinimbine in 43% yield and the corresponding *cis*-diol **9** in 53% yield (the ^{1}H-NMR spectrum and the R_f value of this product were compared with those reported by Furukawa for the *cis*-isomer[10]). The *cis*- and the *trans*-diol were easily distinguished in the ^{1}H-NMR spectrum (400 MHz, acetone-D_6 + D_2O) by the coupling constants between their methine protons which are J = 8.0 Hz for dihydroxygirinimbine (δ = 3.78 and 4.93 ppm) and J = 4.6 Hz for **9** (δ = 3.83 and 5.17 ppm). All physical data (UV, IR, ^{1}H-NMR, MS, R_f value) of synthetic dihydroxygirinimbine are in agreement with those described by Furukawa for the natural product.[10]

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References and Notes

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17. **7**: Yellow crystals, m.p. 93°C (dec.); IR (KBr): ν = 2929, 1932, 1850, 1638, 1617, 1591, 1464, 1359, 1258, 1213, 1131, 1097, 905 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.82 (m, 1 H), 0.98 (m, 1 H), 1.39 (s, 3 H), 1.40 (s, 3 H), 1.64 (m, 1 H), 2.05 (m, 1 H), 2.15 (s, 3 H), 3.02 (m, 1 H), 3.58 (m, 3 H), 3.83 (m, 1 H), 4.52 (t, J = 7.1, 1 H), 5.32 (s, 5 H), 5.59 (d, J = 9.9, 1 H), 6.38 (d, J = 9.9, 1 H), 7.28 (s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.39 (CH_3), 19.00 (CH_2), 23.86 (CH_2), 27.50 (CH_3), 27.67 (CH_3), 31.36 (CH), 55.41 (CH), 56.09 (CH), 58.22 (CH), 74.54 (C), 92.20 (Cp), 108.21 (C), 115.11 (C), 117.44 (CH), 123.52 (C), 128.75 (CH), 129.10 (CH), 136.77 (C), 149.52 (C), 235.28 (CO), 236.87 (CO).
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