Transition Metal Complexes in Organic Synthesis, Part 69.[1] Total Synthesis of the *Amaryllidaceae* Alkaloids Anhydrolycorinone and Hippadine Using Iron- and Palladium-Mediated Coupling Reactions

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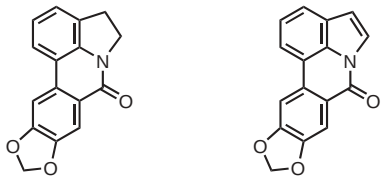
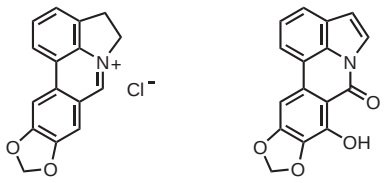
Abstract: A novel synthesis of the *Amaryllidaceae* alkaloids anhydrolycorinone and hippadine has been developed using an iron-mediated oxidative alkylamine cyclization and an intramolecular palladium-mediated biaryl coupling as the key steps.

Key words: alkaloids, cyclizations, dehydrogenations, iron, palladium

The lycorine alkaloids **1**–**4** isolated from *Amaryllidaceae* plants have a pyrrolo[3,2,1-*de*]phenanthridine skeleton and show interesting biological activities (Figure 1). Hippadine (**2**) reversibly inhibits the fertility in male rats.[2] Anhydrolycorinium chloride (**3**) and kalbretorine (**4**) show antitumor activity.[3,4] Anhydrolycorinone (**1**) represents a precursor for the synthesis of the biologically active natural products **2** and **3**.[2a]



1 Anhydrolycorinone **2** Hippadine

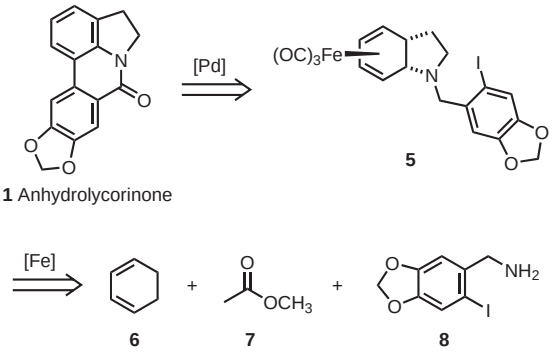


3 Anhydrolycorinium chloride **4** Kalbretorine

Figure 1 Pyrrolophenanthridine alkaloids

The potent biological activities found for many pyrrolophenanthridine alkaloids induced the development of diverse synthetic approaches.[5] Herein, we report a novel synthesis based on an iron-mediated indole annulation followed by an intramolecular palladium-mediated biaryl coupling with concomitant oxidation (Scheme 1).

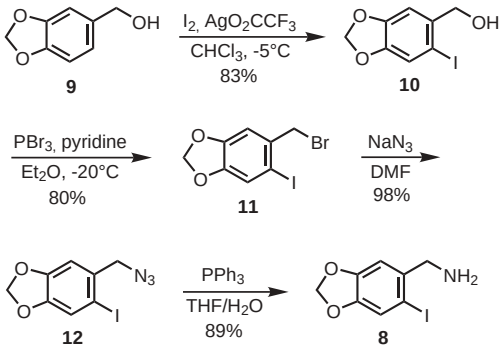
Using various methods for the oxidative cyclization,[6] the iron-mediated oxidative coupling of arylamines and cyclohexa-1,3-diene was applied to the total synthesis of a wide range of biologically active carbazole alkaloids.[7] Moreover, the oxidative cyclization of tricarbonyl[η⁴-cyclohexa-1,3-diene]iron complexes with an appropriate alkylamine side chain afforded 2,3,3a,7a-tetrahydroindoles.[8] The implementation of this iron-mediated alkylamine cyclization is the characteristic feature of our present synthesis of pyrrolophenanthridine alkaloids.



1 Anhydrolycorinone **5** **6** **7** **8**

Scheme 1 Retrosynthetic analysis of anhydrolycorinone (**1**)

An iron-mediated oxidative coupling of cyclohexa-1,3-diene (**6**) with methyl acetate (**7**) and iodopiperonylamine **8** to the iron-complexed tetrahydroindole **5** followed by a sequence of aromatization, intramolecular palladium-mediated biaryl coupling, and oxidation at the benzylic position should provide anhydrolycorinone (**1**).



9 **10** **11** **12** **8**

Scheme 2 Synthesis of the iodopiperonylamine **8**

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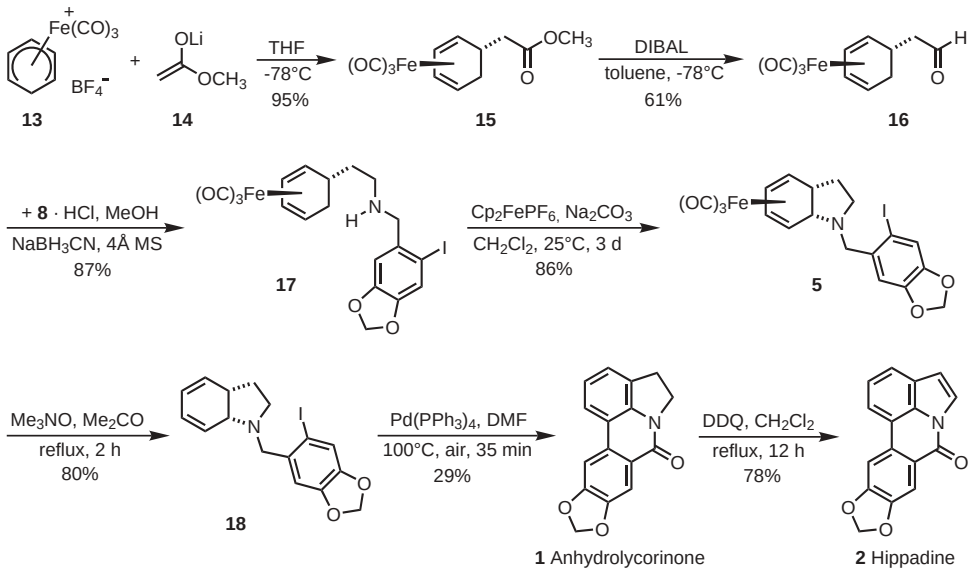

Scheme 3 Iron- and palladium-mediated total synthesis of anhydrolycorinone (**1**) and hippadine (**2**)

Iodopiperonylamine **8** is readily prepared on large scale in four steps and 58% overall yield from commercially available piperonyl alcohol **9** (Scheme 2).[9] The silver trifluoroacetate promoted iodination of **9** afforded iodopiperonyl alcohol **10**. Consecutive treatment with phosphorus tribromide to iodopiperonyl bromide **11** and then with sodium azide led to iodopiperonyl azide **12**. Subsequent Staudinger reduction provided iodopiperonylamine **8**.

Using three transition metal-mediated bond formations, we elaborated a concise synthesis of the *Amaryllidaceae* alkaloids anhydrolycorinone (**1**) and hippadine (**2**) (Scheme 3). Cyclohexa-1,3-diene (**6**) was almost quantitatively transformed to the complex salt **13** by azadiene-catalyzed complexation with pentacarbonyliron[10] and subsequent hydride abstraction using trityl tetrafluoroborate.[11] The introduction of the side chain was achieved by nucleophilic addition of the lithium ester enolate **14** [prepared by deprotonation of methyl acetate (**7**) with LDA] to the complex salt **13**.[12] Our modified procedure (reaction at –78 °C for 2 h) afforded complex **15** in 95% yield.[8] Using the low temperature reduction with DIBAL,[13] ester **15** was converted into aldehyde **16**. The two building blocks were then combined to alkylamine-substituted iron complex **17** by a reductive amination of aldehyde **16** with the hydrochloride of iodopiperonylamine **8** using sodium cyanoborohydride as the reducing agent.[14] Oxidative cyclization of complex **17** with ferricenium hexafluorophosphate in the presence of sodium carbonate afforded the tetrahydroindole complex **5**.[14,15] The SET reagent has been applied previously to the iron-mediated oxidative cyclization of alkylamines[8] and arylamines.[16] Demetalation of complex **5** with anhydrous trimethylamine *N*-oxide[17] led to tetrahydroindole **18**.[14]

We envisaged to achieve the final intramolecular biaryl coupling by a Heck-type reaction.[18] Miki et al. synthesized pyrrolophenanthridines by a Heck coupling in a related system with an aromatized indole.[5b] After variation of several reaction parameters, we found a biaryl coupling procedure that proceeded with concomitant aromatization of the cyclohexadiene ring and oxidation at the benzylic position to the lactam. Treatment of compound **18** with a stoichiometric amount of tetrakis[triphenylphosphine]palladium in DMF at 100 °C under air for 35 min gave anhydrolycorinone (**1**) (mp 226–228 °C). The oxidation of anhydrolycorinone (**1**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided hippadine (**2**) (mp 207–208 °C).[2] The spectral data of both alkaloids were in good agreement with those reported for the natural products.[2,14]

In conclusion, we developed a novel approach to the pyrrolophenanthridine alkaloids anhydrolycorinone (**1**) and hippadine (**2**). Iron-mediated C–C and C–N bond formations are applied to construct the indole nucleus. Thus, this route features the first application of the iron-mediated alkylamine cyclization in natural product synthesis. The palladium-mediated intramolecular Heck coupling with concomitant aromatization and oxidation to the lactam provides directly anhydrolycorinone (**1**). The synthesis affords the biologically active *Amaryllidaceae* alkaloid hippadine (**2**) in seven steps and 8% overall yield based on the complex salt **13**. Further applications of this methodology in natural product synthesis are in progress.

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(14) All new compounds have been fully characterized (IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis or HRMS). ^{13}C NMR and DEPT spectral data (125 MHz, $CDCl_3$) of representative compounds. **17**: δ = 30.75 (CH_2), 35.90 (CH), 40.27 (CH_2), 47.66 (CH_2), 57.97 (CH_2), 59.76 (CH), 66.57 (CH), 84.39 (CH), 85.53 (CH), 86.99 (C), 101.53 (CH_2), 109.71 (CH), 118.46 (CH), 135.61 (C), 147.35 (C), 148.34 (C), 212.06 (3 CO). **5**: δ = 34.64 (CH_2), 43.22 (CH), 54.31 (CH_2), 60.16 (CH), 60.85 (CH_2), 63.78 (CH), 66.32 (CH), 85.85 (CH), 86.70 (CH), 87.25 (C), 101.53 (CH_2), 110.19 (CH), 118.45 (CH), 135.01 (C), 147.36 (C), 148.44 (C), 211.75 (3 CO). **18**: δ = 32.95 (CH_2), 36.46 (CH), 49.25 (CH_2), 59.56 (CH), 62.43 (CH_2), 87.26 (C), 101.50 (CH_2), 110.51 (CH), 118.25 (CH), 119.80 (CH), 122.92 (CH), 124.79 (CH), 130.31 (CH), 135.29 (C), 147.33 (C), 148.43 (C). Anhydrolycorinone (**1**): δ = 27.45 (CH_2), 46.52 (CH_2), 100.89 (CH), 102.05 (CH_2), 106.83 (CH), 116.79 (C), 119.46 (CH), 123.10 (C), 123.27 (CH), 123.82 (CH), 130.66 (C), 130.87 (C), 139.39 (C), 148.43 (C), 151.85 (C), 159.52 (C=O). Hippadine (**2**): δ = 101.75 (CH), 102.29 (CH_2), 108.05 (CH), 110.82 (CH), 116.71 (C), 118.38 (CH), 122.51 (C), 122.63 (CH), 123.55 (CH), 124.00 (CH), 128.42 (C), 130.97 (C), 131.66 (C), 148.54 (C), 152.60 (C), 158.19 (C=O).

(15) Iron-mediated oxidative alkylamine cyclization of **17** to **5**: Ferricenium hexafluorophosphate (291 mg, 0.88 mmol) and anhyd. Na_2CO_3 (374 mg, 3.53 mmol) were added to a solution of complex **17** (185 mg, 0.354 mmol) in degassed anhyd CH_2Cl_2 (15 mL) under an argon atmosphere. The resulting dark green suspension was stirred at r.t. for 3 d. During this time the color turned to orange (formation of ferrocene). The reaction mixture was filtered through a short path of Celite which was subsequently washed with CH_2Cl_2. Removal of the solvent from the combined filtrates and flash chromatography (hexane–EtOAc, 9:1) of the residue on silica gel provided complex **5** as light yellow crystals, yield: 158 mg (86%), mp 122 °C.

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