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Transition metal complexes in organic synthesis. Part 62:[1] Total synthesis of (±)-demethoxycarbonyldihydrogambirtannine and norketoyobyrine by an iron-mediated [2+2+1] cycloaddition

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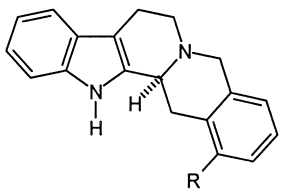
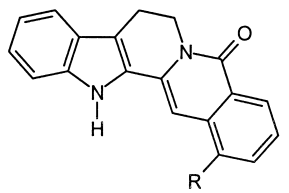
Abstract

(±)-Demethoxycarbonyldihydrogambirtannine was obtained in six steps and 49% overall yield from 3,4-dihydro-β-carboline using an iron-mediated [2+2+1] cycloaddition as the key-step. Oxidation of (±)-demethoxycarbonyldihydrogambirtannine led to norketoyobyrine.

Gambirtannine and (–)-dihydrogambirtannine **1a** are aromatized yohimbane alkaloids isolated from extracts of the leaves and stems of the Rubiacea *Uncaria gambier* (*Ourouparia gambir*), a tree growing in Southeast Asia.[2] The (–)-demethoxycarbonyldihydrogambirtannine **1b** was isolated first from the leaves of *Ochrosia lifuana* and *Ochrosia miana* (Apocynaceae).[3] Subsequently it was found that **1b** represents the main alkaloid of the fruits of *Strychnos usambarensis*, a plant of the family Loganiaceae found in Africa.[4] The consumption of these fruits was reported to cause poisoning.



1a R = COOMe
1b R = H



2a R = Me
2b R = H

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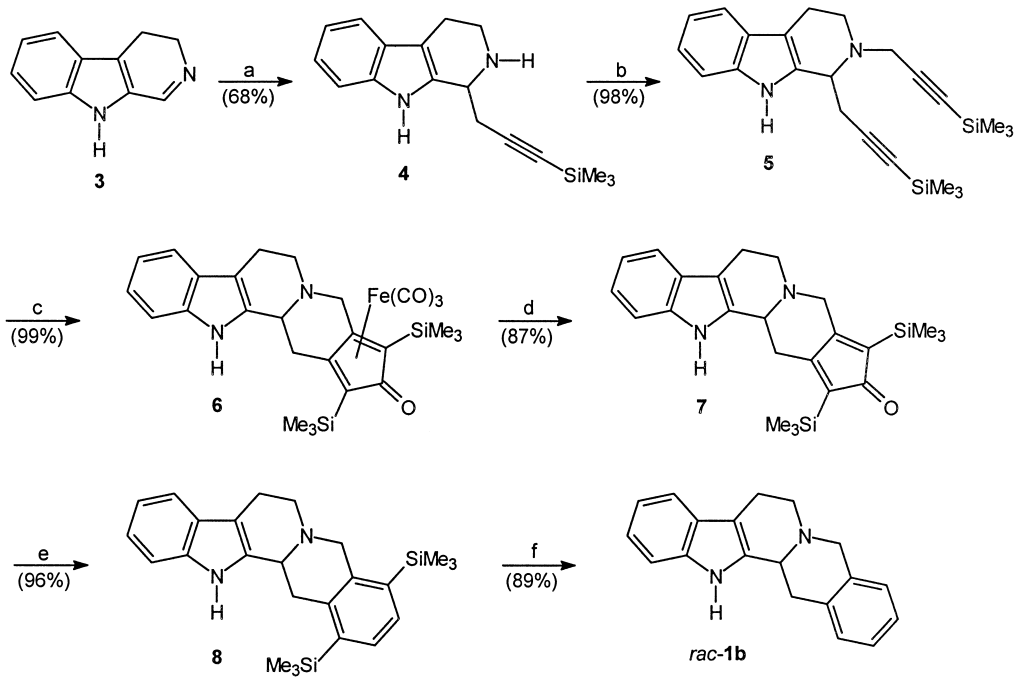
Structurally related to these natural products are ketoyobyrine **2a**, a degradation product of yohimbine, and the norketoyobyrine **2b**.[5] The aromatized yohimbanes **1** and **2** have been the target of various synthetic approaches.[6] We have a continuous program directed towards the development of novel methodologies for organic synthesis using tricarbonyliron–diene complexes.[7] In this context we envisaged a short synthetic route to the aromatized yohimbanes by an iron-mediated [2+2+1] cycloaddition of a 1,2-dipropargyl-substituted 1,2,3,4-tetrahydro-β-carboline derivative. The iron-mediated [2+2+1] cycloaddition of diynes and carbon monoxide is a very efficient method for the synthesis of cyclopentadienones.[8,9] In this respect, we have previously investigated the transformation of bis(trimethylsilyl)-substituted terminal diynes to tricarbonyliron-complexed annulated cyclopentadienones and developed for the first time efficient methods for their selective demetalation to the corresponding free ligands.[9–12] The annulated 2,5-bis(trimethylsilyl)cyclopentadienones are stable towards dimerization for steric reasons, but undergo a Diels–Alder reaction in the presence of appropriate dienophiles.[13,14] This reactivity was recently utilized for a highly efficient synthesis of corannulene.[15]

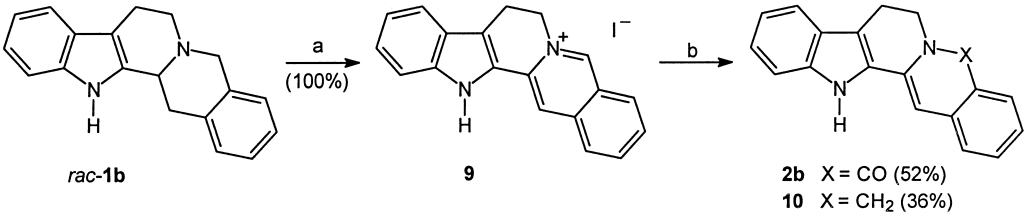
The alkylation of 3,4-dihydro-β-carboline **3** [16] with trimethylsilylpropargylmagnesium bromide was achieved by using the procedure of Nakagawa.[17] Addition of the Grignard reagent to the preformed BF_3–iminium salt gave the 1-(trimethylsilylpropargyl)-1,2,3,4-tetrahydro-β-carboline **4** (Scheme 1). Subsequent *N*-alkylation of **4** led to the 1,2-bis(trimethylsilylpropargyl)-1,2,3,4-tetrahydro-β-carboline **5** (67% yield over both steps). Heating of the diyne **5** with 2 equivalents of pentacarbonyliron in dimethoxyethane at 140°C for 20 h in a sealed tube afforded quantitatively the tricarbonyliron-complexed cyclopentadienone **6** as a mixture of two diastereoisomers in a ratio of 2:1. This result emphasized that using our optimized reaction conditions the iron-mediated [2+2+1] cycloaddition of diynes and carbon monoxide is a very efficient process. Demetalation of complex **6** with trimethylamine *N*-oxide dihydrate (4 equivalents, acetone, 25°C, 1 h)[9,10] resulted in complete decomposition. We recently described two novel procedures for the demetalation of tricarbonyl(η^4-cyclopentadienone)iron complexes.[11,12] Exchange of a carbon monoxide ligand by an hydrido ligand using NaOH and then by an iodo ligand with iodopentane provides by addition of phosphoric acid the corresponding dicarbonyl(η^5-hydroxycyclopentadienyl)iodoiron complex, which is demetalated by contact with air in the presence of daylight.[12] This demetalation procedure was successfully used in the course of our corannulene synthesis.[15] Application to the demetalation of complex **6** afforded the desired free ligand **7** in 57% yield. Finally, the best result for the conversion of complex **6** to the cyclopentadienone **7** was achieved by a photolytically induced ligand exchange reaction to the intermediate triacetonitrile(η^4-cyclopentadienone)iron complex and subsequent demetalation in the air.[11] Using our original procedure (ligand exchange and demetalation at –30°C) the yield of **7** was 68%. Lowering of the reaction temperature to –40°C increased the yield of **7** to 87%. A *trans* conformation of the indolo[2,3-*a*]quinolizidine ring system was confirmed by the presence of Bohlmann bands in the IR spectrum[18] and by the chemical shift of the angular proton at a field higher than 3.8 ppm in the ^{1}H NMR spectrum.[19] The Diels–Alder cycloaddition of the cyclopentadienone **7** and norbornadiene in toluene at reflux with concomitant extrusion of carbon monoxide and cyclopentadiene afforded the 16,19-bis(trimethylsilyl)-15,16,17,18,19,20-hexadehydroyohimbane **8** in 96% yield. Double protodesilylation of **8** using trifluoroacetic acid at reflux provided (±)-demethoxycarbonyldihydrogambirtannine *rac*-**1b** in 89% yield. The spectral data of our *rac*-**1b** [20] are in good agreement with those of the natural product.[3,4]

We next investigated the conversion of *rac*-**1b** to norketoyobyrine **2b** (Scheme 2). Dehydrogenation of *rac*-**1b** with iodine gave the demethoxycarbonylourouparine iodide **9** (mp 335°C),



Scheme 1. Reagents and conditions: (a) (1) $BF_3{\cdot}OEt_2$ (0.97 equiv.), THF, –23°C, 10 min, (2) $Me_3SiC{\equiv}CCH_2MgBr$ (2.9 equiv.), Et_2O, –23°C, 15 h; (b) $Me_3SiC{\equiv}CCH_2I$ (1.3 equiv.), THF, Na_2CO_3, 25°C, 20 h; (c) $Fe(CO)_5$ (2.0 equiv.), DME, 140°C, 20 h (sealed tube); (d) (1) hν, MeCN, –40°C, 2.5 h, (2) air, –40°C, 20 min; (e) norbornadiene (70 equiv.), toluene, 110°C, 12 h; (f) CF_3COOH, 72°C, 1 h

which was subsequently treated with alkaline hydrogen peroxide to afford norketoyobyrine **2b** (52% yield, mp 304°C) along with the demethoxycarbonylgambirtannine **10** (36% yield, mp 184–186°C). The spectral data and the melting points of the compounds **9**, **2b**, and **10** are in agreement with those reported in the literature.[5,6]



Scheme 2. Reagents and conditions: (a) Iodine (6 equiv.), KOAc, EtOH, 78°C, 15 min; (b) $NaOH/H_2O_2$ (excess), reflux, 6 h

In conclusion, we have developed a highly efficient synthesis of (±)-demethoxycarbonyldihydrogambirtannine in six steps and 49% overall yield based on 3,4-dihydro-β-carboline. The chemistry described demonstrates for the first time that the iron-mediated [2+2+1] cycloaddition of diynes can be applied to the construction of polyheterocyclic frameworks and the total synthesis of biologically active alkaloids.

Acknowledgements

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20. (±)-Demethoxycarbonyldihydrogambirtannine (*rac*-**1b**): colorless crystals; mp 196–197°C (lit.[5a]: 196–197°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.75$ (dt, $J = 4.0$, 11.3 Hz, 1H), 2.83 (m, 1H), 3.01–3.12 (m, 2H), 3.19 (dd, $J = 15.7$, 3.8 Hz, 1H), 3.31 (dd, $J = 11.3$, 4.7 Hz, 1H), 3.70 (br d, $J = 11.5$ Hz, 1H), 3.80 (d, $J = 14.9$ Hz, 1H), 4.12 (d, $J = 14.9$ Hz, 1H), 7.11–7.21 (m, 6H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.83 (br s, 1H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): $\delta = 21.52$ (CH_2), 34.81 (CH_2), 52.40 (CH_2), 56.32 (CH), 57.82 (CH_2), 108.77 (C), 110.83 (CH), 118.27 (CH), 119.54 (CH), 121.62 (CH), 126.12 (CH), 126.36 (CH), 126.45 (CH), 127.18 (C), 128.65 (CH), 133.19 (C), 134.42 (C), 134.58 (C), 136.31 (C); MS (120°C): m/z (%) = 274 (M^+, 100), 273 (89), 272 (5), 271 (8), 245 (6), 244 (14), 230 (7), 170 (8), 169 (34), 144 (7), 143 (5), 130 (6), 115 (5), 105 (9), 104 (14); HRMS: calcd for $C_{19}H_{18}N_2$ (M^+): 274.1470, found: 274.1478. Anal. calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21; found: C, 83.00; H, 6.57; N, 10.42.