Transition Metal Complexes in Organic Synthesis, Part 71:[1] First Total Synthesis of Furoclausine-A

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Abstract: The first total synthesis of the furo[3,2-*a*]carbazole alkaloid furoclausine-A is described using an iron-mediated construction of the carbazole framework and an acid-catalyzed annulation of the furan ring as key steps.

Key words: alkaloids, cyclizations, furans, iron, oxidations

Until now only four members of the relatively young class of furocarbazole alkaloids (**1**–**4**) have been discovered (Figure 1).[1–5] In 1990, Furukawa described the isolation and structural elucidation of furostifoline (**1**) and eustifoline-D (**2**).[6] Both alkaloids were obtained from the root bark of *Murraya euchrestifolia*, a shrub growing in Taiwan. Seven years later, Wu isolated furoclausine-A (**3**) and furoclausine-B (**4**) from the acetone extract of the root bark of *Clausena excavata*.[7]

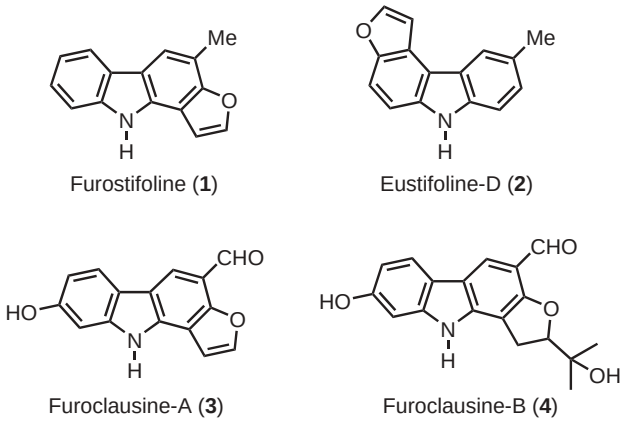

Figure 1 Furocarbazole alkaloids

The extracts of the plant *Clausena excavata* are used in traditional folk medicine in China for the treatment of various infections and poisonous snakebites (Figure 2). Because of their pharmacological potential the furocarbazole alkaloids have attracted a lot of interest among synthetic chemists.[8–12] The first total synthesis of furostifoline (**1**) was described by us in 1996, by an iron-mediated construction of the carbazole framework.[8] Two years later, Hibino and Beccalli reported two further total syntheses using an electrocyclic ring closure reaction as key step.[9,10] In 1999, Timári developed a novel route to furostifoline (**1**) based on a palladium-catalyzed cross-coupling and subsequent regioselective insertion of a nitrene.[11] More recently, Yasuhara has described the fifth approach via an oxidative photocyclization of 3-(indol-2-yl)-2-(isopropenyl)furan.[12] Total syntheses of the other furocarbazole alkaloids have not been reported yet.

Figure 2 *Clausena excavata* (courtesy of Professor Pei-Fen Lee, National Taiwan University, Taipei, Nature Conservation Network)

In the present paper, we describe the first total synthesis of furoclausine-A (**3**). Using the iron-mediated oxidative coupling of arylamines and cyclohexadienes a wide range of biologically active carbazole alkaloids has been synthesized previously.[13] However, this method was not utilized for the total synthesis of a 7-oxygenated carbazole natural product, as present in furoclausine-A (**3**). Such a substitution pattern requires a 2-methoxy-substituted tricarbonyl(η^5-cyclohexadienyl)iron cation as a building block. Our approach to furoclausine-A (**3**) envisaged the iron-mediated formation of the carbazole skeleton followed by an acid-catalyzed annulation of the furan ring as key steps. The retrosynthetic analysis of furoclausine-A (**3**) based on this strategy leads to 1-methoxycyclohexa-1,4-diene (**5**) and the arylamine **6** as precursors (Scheme 1).

Alkylation of commercial 2-methyl-5-nitrophenol (**7**) with 2-bromo-1,1-diethoxyethane to compound **8** and subsequent catalytic hydrogenation using palladium on activated carbon afforded the arylamine **6** (Scheme 2).

Tricarbonyl(η^5-2-methoxycyclohexadienylium)iron tetrafluoroborate (**9**) is readily prepared on a large scale by the azadiene-catalyzed complexation of 1-methoxycyclohexa-1,4-diene (**5**),[14] followed by hydride abstraction and hydrolytic separation of the 1-methoxy and 2-methoxy re-

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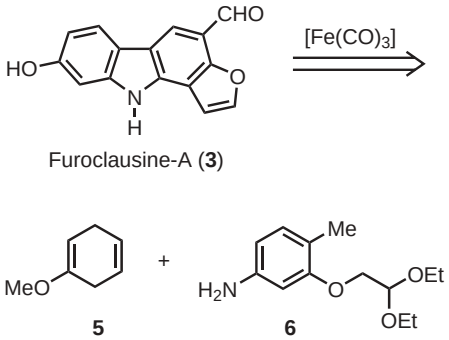
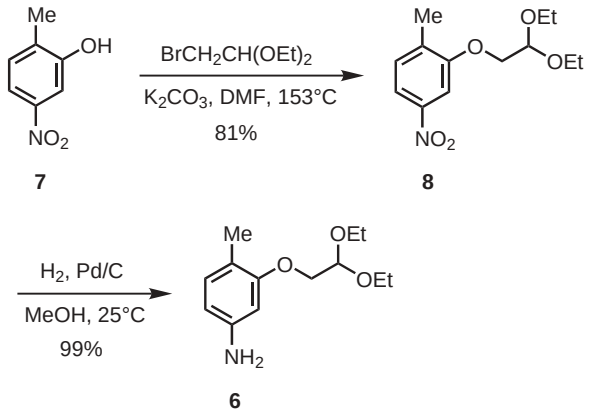


Scheme 1 Retrosynthetic analysis of furoclausine-A (**3**)



Scheme 2 Synthesis of the arylamine **6**

gioisomers.[15] Electrophilic substitution of the arylamine **6** by reaction with the iron complex salt **9** led regioselectively to the iron complex **10**.[16] Oxidative cyclization of complex **10** using iodine in pyridine provided the carbazole **11**.[16,17] The annulation of the furan ring, by heating the carbazole **11** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C,[18,19] afforded 8-methoxy-4-methyl-10*H*-furo[3,2-*a*]carbazole (**12**).[16] Oxidation of **12** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave *O*-methylfuroclausine-A (**13**).[16] Finally, cleavage of the methyl ether using BBr_3 provided furoclausine-A (**3**) (Scheme 3).[20]

In conclusion, a convergent five-step synthesis leading to furoclausine-A (**3**) in 9% overall yield has been developed. We obtained furoclausine-A (**3**) as crystals (decomposition 110 °C),[20] whereas the natural product was described as an oil.[7] All spectral data (UV, IR, ^{1}H NMR, ^{13}C NMR, and MS) of our synthetic furoclausine-A (**3**)[20] are in good agreement with those reported for the natural product.[7] The method described above can be used to provide access to furoclausine-A and a variety of structural analogues in sufficient quantities for biological screening.

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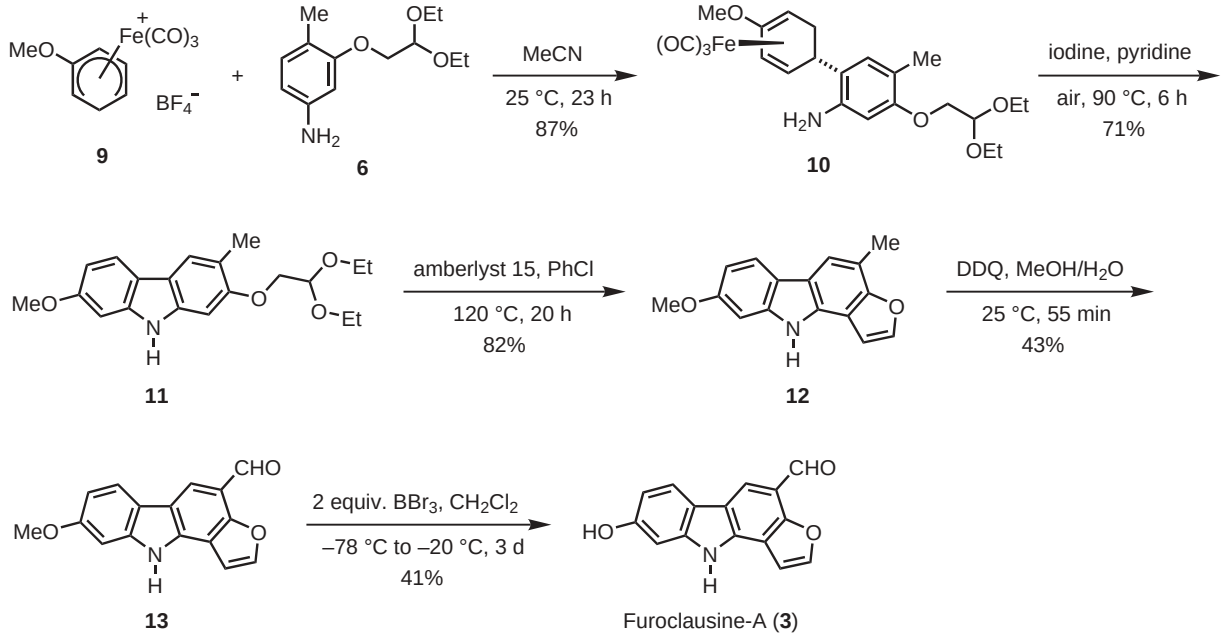

Scheme 3 Iron-mediated total synthesis of furoclausine-A (**3**)

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(16) All new compounds have been fully characterized (UV, IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis). ^{13}C NMR and DEPT spectral data, and elemental analyses. **10**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.34 (2 × CH_3), 15.57 (CH_3), 32.62 (CH_2), 37.58 (CH), 53.10 (CH), 54.01 (CH), 54.39 (CH_3), 62.70 (2 × CH_2), 66.98 (CH), 68.99 (CH_2), 100.14 (CH), 100.73 (CH), 116.93 (C), 122.74 (C), 128.50 (CH), 139.93 (C), 142.10 (C), 155.53 (C), 211.25 (3 × CO). Anal. Calcd for $C_{23}H_{29}FeNO_7$: C, 56.69; H, 6.00; N, 2.87. Found: C, 56.77; H, 6.12; N, 2.91. **11**: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.39 (2 × CH_3), 16.68 (CH_3), 55.64 (CH_3), 62.92 (2 × CH_2), 69.36 (CH_2), 93.81 (CH), 94.90 (CH), 100.90 (CH), 107.68 (CH), 116.75 (C), 117.41 (C), 119.37 (C), 119.98 (CH), 120.82 (CH), 138.89 (C), 140.56 (C), 155.33 (C), 157.95 (C). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.03; H, 7.48; N, 4.15. **12**: ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.42 (CH_3), 55.67 (CH_3), 95.18 (CH), 103.54 (CH), 108.12 (CH), 111.37 (C), 114.11 (C), 116.06 (CH), 117.94 (C), 118.00 (C), 120.16 (CH), 130.69 (C), 140.01 (C), 143.72 (CH), 153.35 (C), 157.96 (C). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.27; H, 5.31; N, 5.74. *O*-Methylfuroclausine-A (**13**): ^{13}C NMR (125 MHz, acetone-d_6): δ = 55.82 (CH_3), 96.40 (CH), 104.73 (CH), 110.14 (CH), 113.56 (C), 116.30 (C), 118.31 (C), 119.11 (C), 120.11 (CH), 121.58 (CH), 137.80 (C), 142.31 (C), 146.06 (CH), 154.11 (C), 159.99 (C), 187.79 (CHO). Anal. Calcd for $C_{16}H_{11}NO_3$: 72.45; H, 4.18; N, 5.28. Found: C, 72.31; H, 4.20; N, 5.49.
(17) **Experimental Procedure for the Oxidative Cyclization to the Carbazole 11**: Iodine (1.18 g, 4.65 mmol) was added to a solution of the iron complex **10** (713 mg, 1.46 mmol) in anhyd pyridine (20 mL) at 90 °C. After stirring for 6 h at 90 °C in the air, the reaction mixture was cooled to r.t., a solution of sodium thiosulfate (2.4 g) and citric acid (1.3 g) in water (24 mL) was added, and the resulting mixture was extracted with Et_2O several times. The combined organic layers were washed with water (3 × 30 mL) and dried over $MgSO_4$. Removal of the solvent and purification of the residue by flash chromatography (EtOAc–hexane, 1:1) on silica gel provided the carbazole **11** as colorless crystals; yield: 356 mg (71%); mp: 195–196 °C.
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(19) Amberlyst 15 from Fluka (art. 06423).
(20) Furoclausine-A (**3**): Light yellow crystals; mp: 110 °C (dec.). IR (ATR): ν = 3302, 1703, 1670, 1619, 1590, 1444, 1350, 1325, 1302, 1276, 1258, 1228, 1165, 1149, 1114, 1070, 1040, 993, 956, 856, 830, 810, 799, 775, 750, 730, 686, 629, 591, 549 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ = 6.92 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.09 (d, *J* = 2.1 Hz, 1 H), 7.32 (d, *J* = 2.2 Hz, 1 H), 8.05 (d, *J* = 2.2 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 8.51 (s, 1 H), 8.54 (s, 1 H), 10.47 (s, 1 H), 11.16 (br s, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 98.22 (CH), 104.67 (CH), 110.73 (CH), 113.43 (C), 116.16 (C), 117.64 (C), 119.36 (C), 119.85 (CH), 121.62 (CH), 137.75 (C), 142.57 (C), 146.02 (CH), 154.09 (C), 157.49 (C), 187.75 (CHO). UV (MeOH): λ = 220, 235, 287(sh), 300, 345 nm. MS (150 °C): *m/z* (%) = 251(100) [M$^+$], 250 (74), 222 (26), 194 (11), 139 (3). HRMS: *m/z* [M$^+$] calcd for $C_{15}H_9NO_3$: 251.0582; found: 251.0568.