COMMUNICATION

First total synthesis of carbazomycin C and D [1]

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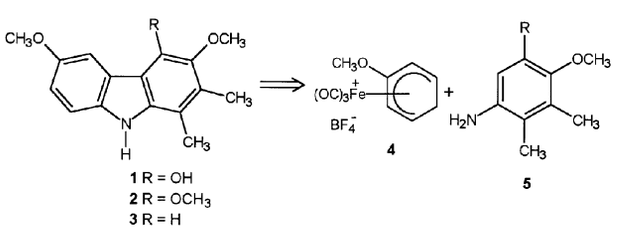
The first total synthesis of the antibiotic carbazomycins C and D using a convergent iron-mediated construction of the carbazole framework is described.

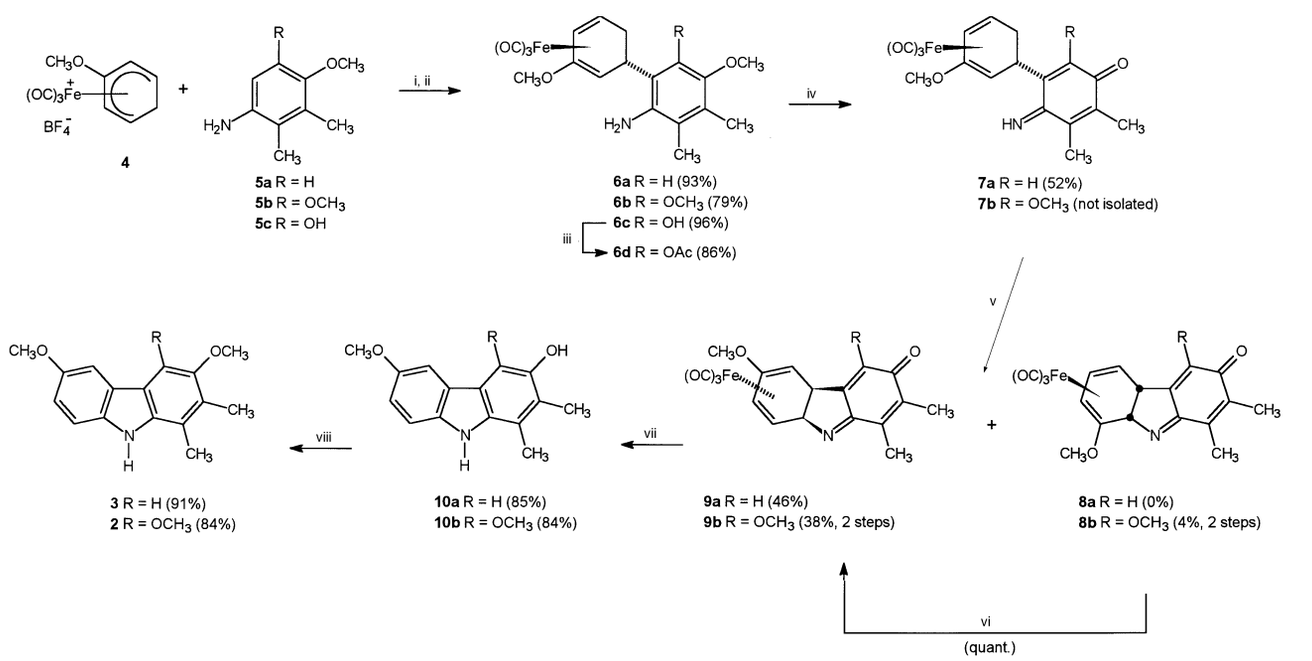
The carbazomycins isolated from *Streptoverticillium ehimense* were the first antibiotics to contain a carbazole framework.[2] Moreover, the carbazomycins B and C were shown to inhibit 5-lipoxygenase.[2h] The biological activity and unusual structure of the carbazomycins stimulated the development of diverse strategies directed towards their total synthesis.[3] We reported a novel methodology, *via* iron-mediated consecutive C–C and C–N bond formation, for the coupling of cyclohexa-1,3-diene and the corresponding arylamine, which was applied to the total synthesis of carbazomycin A, B and E.[4] Here we describe an extension of our method which is used for the first total synthesis of carbazomycin C **1**,[2f] carbazomycin D **2**[2f] and the non-natural 4-deoxycarbazomycin C **3**. Retrosynthetic analysis of the carbazomycins **1**–**3** based on the iron-mediated construction of the carbazole framework leads to tricarbonyl-[3-methoxy-(1,2,3,4,5-η)-cyclohexadienyl]iron tetrafluoroborate **4** and the arylamines **5** (Scheme 1). Complex **4** is readily available in 3 steps from 1,3-dimethoxybenzene.[5] The arylamines **5** have been described by us in our previous studies.[6,7]



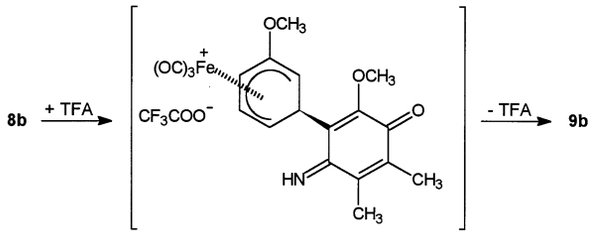
Scheme 1

The synthesis of the alkaloids **2** and **3** was achieved by the iron-mediated quinone imine cyclization (Scheme 2). Electrophilic substitution of the arylamines **5a** and **5b** with **4** provided the complexes **6a** and **6b**. Chemoselective oxidation of the aromatic nucleus to afford **7a** and **7b** was achieved with commercial manganese dioxide.† Oxidative cyclization of the quinone imines using very active manganese dioxide[8] provided the stable tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-ones **8** and **9**. In the case of **7a** the desired 6-methoxy substituted regioisomer **9a** was exclusively isolated (46% yield), while **7b** gave minor quantities (4%) of the 8-methoxy isomer **8b** along with 38% of the 6-methoxy isomer **9b**. The regioselectivity of these cyclizations can be rationalized by the results previously obtained in our deuterium labelling studies.[9] Cyclizations with two-electron oxidants, such as manganese dioxide, initially lead to the product resulting from exclusive attack at C-4 of the cyclohexadiene ligand, which is represented by isomer **8** in the present case. However, a subsequent proton-catalysed isomerization of the kinetic product may occur. The isomerization of **8** to **9** is overriding due to the well-established regio-directing effect[10] of the 2-methoxy substituent of the intermediate cyclohexadienylium cation **11**, which forces the nucleophile to attack at the 5-position (Scheme 3). Consequently, the proton-catalysed isomerization of **8b** results in smooth conversion to

† Manganese dioxide (precipitated active) from Merck-Schuchardt (art. 805958).



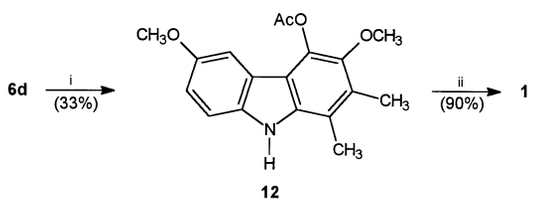
Scheme 2 *Reagents and conditions:* i, MeCN, 25 °C; ii, dil. aq. NaOH; iii, Ac_2O, CH_2Cl_2, pyridine, DMAP, 25 °C; iv, MnO_2, CH_2Cl_2, 25 °C; v, very active MnO_2, CH_2Cl_2, 25 °C; vi, cat. CF_3CO_2H, CH_2Cl_2, 25 °C; vii, $Me_3NO{\cdot}2\,H_2O$, Me_2CO, 25–40 °C; viii, MeI, K_2CO_3, Me_2CO, 56 °C



Scheme 3

the desired 6-methoxy isomer **9b**. The tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-ones are useful synthetic precursors for 3-hydroxy-9*H*-carbazole alkaloids.[11] Thus, demetallation of the complexes **9a** and **9b** using trimethylamine *N*-oxide[12] afforded the 3-hydroxycarbazole derivatives **10a** and **10b**, which after *O*-methylation gave 4-deoxycarbazomycin C **3** and carbazomycin D **2**.‡

Carbazomycin C **1** was obtained *via* the iron-mediated arylamine cyclization. Electrophilic substitution of the aminophenol **5c** by **4** afforded the complex **6c** which was transformed into the acetate **6d** (Scheme 2). Oxidative cyclization of **6d** using very active manganese dioxide[8] to give the carbazole **12** followed by saponification of the ester provided carbazomycin C **1** (Scheme 4).§



Scheme 4 *Reagents and conditions:* i, very active MnO_2, CH_2Cl_2, 25 °C; ii, NaOH, H_2O, reflux

‡ This synthesis affords carbazomycin D **2** in 5 steps and 23% overall yield based on **4** as pale yellow needles, mp 125 °C (from cyclohexane) (lit.,[2f] mp 129.5–130 °C, colourless needles from hexane–dichloromethane). All spectral data (UV, IR, ^{1}H and ^{13}C NMR, MS) are in full agreement with those reported for the natural product.

§ Carbazomycin C **1** was obtained in 4 steps and 25% overall yield based on **4** as colourless crystals, mp 190–191 °C (from hexane–ethyl acetate) (lit.,[2f] mp 198–198.5 °C, pale yellow prisms from hexane–ethyl acetate). All spectral data (UV, IR, ^{1}H and ^{13}C NMR, MS) are in full agreement with those reported for the natural product.

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