The Total Synthesis of the Carbazole Antibiotic Carbazomycin B and an Improved Route to Carbazomycin A[1b]

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Using a methodology involving consecutive iron-induced C–C and C–N bond formation we have completed the total synthesis of the antibiotic carbazomycin B; application of a novel iron-mediated direct iminoquinone cyclization provides carbazomycin A in an improved high yield sequence.

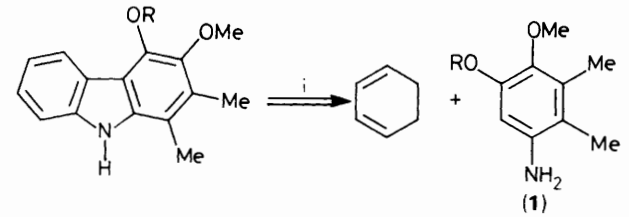
The carbazomycins A and B, which are produced by micro-organisms assigned as *Streptoverticillium ehimense* H 1051-MY 10, inhibit the growth of phytopathogenic fungi and have weak anti-bacterial and anti-yeast activities. Their isolation,[2] structural elucidation,[3,4] and biogenesis[5] have been reported by Nakamura *et al.* The carbazomycins represent the first antibiotics with a carbazole framework. This fact and the unusual congestion of donor substituents have made them attractive as synthetic targets.[6,7,8]

We recently reported a procedure leading to various highly substituted dihydrocarbazole and aromatic carbazole derivatives by electrophilic aromatic substitution of arylamines using tricarbonyl(η^5-cyclohexadienyl)iron cations and subsequent oxidative cyclization with activated manganese dioxide.[1]

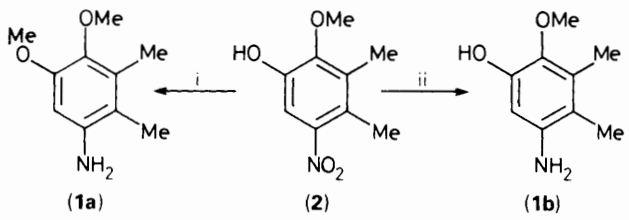
Retrosynthesis of the carbazomycins based on this strategy leads to cyclohexa-1,3-diene and the corresponding amine (**1**) (Scheme 1), which are transformed to the carbazole alkaloids *via* consecutive iron-induced C–C and C–N bond formation. This reaction sequence has been applied to the first total synthesis of carbazomycin A.[1] Herein we describe the synthesis of carbazomycin B, the main antibiotic produced by *S. ehimense*, and an improved route to carbazomycin A.

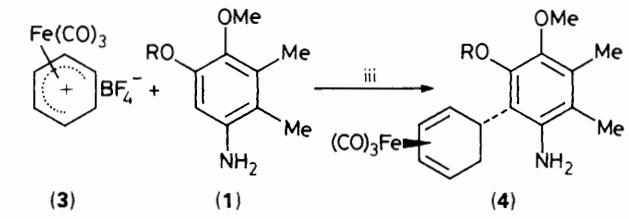
The nitroaryl derivative (**2**) is prepared in six steps starting from 2,3-dimethylphenol (overall yield 33%) and transformed to (**1a**) in 87% yield as reported in our carbazomycin A synthesis.[1] Hydrogenation of (**2**) provides the desired amine (**1b**) in 90% yield (Scheme 2).

Electrophilic aromatic substitution of the amines (**1**) by the iron-complexed cation (**3**) at room temperature provides the iron complex (**4a**) in 85% yield after 3 days, while the carbazomycin B precursor (**4b**) is obtained in 94% yield after 2 h (Scheme 2). These conversions demonstrate again the usefulness of such cations as mild electrophiles for highly donor-substituted and thus oxidation sensitive aromatic rings. Several attempts to achieve oxidative cyclization of (**4b**) having the free hydroxy group failed. However, its acetyl derivative (**5**) (84% yield) is cyclized in the usual way,[1] again using very active manganese dioxide,[9] in 46% yield to *O*-acetylcarbazomycin B (**6**) (Scheme 3), a known derivative of the natural product.[3] Cleavage of the ester generates



Scheme 1. *Reagent:* i, $[Fe(CO)_3]$.



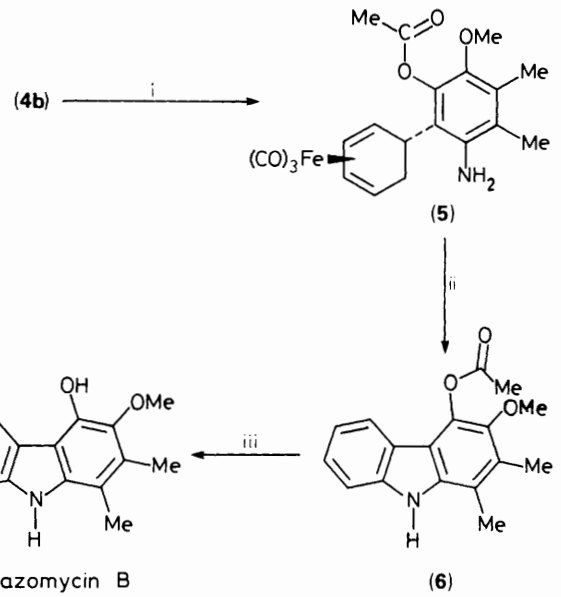


Scheme 2. *Reagents and conditions:* i, CH_2N_2 then H_2, Pd/C; ii, H_2 Pd/C; iii, MeCN, room temp.

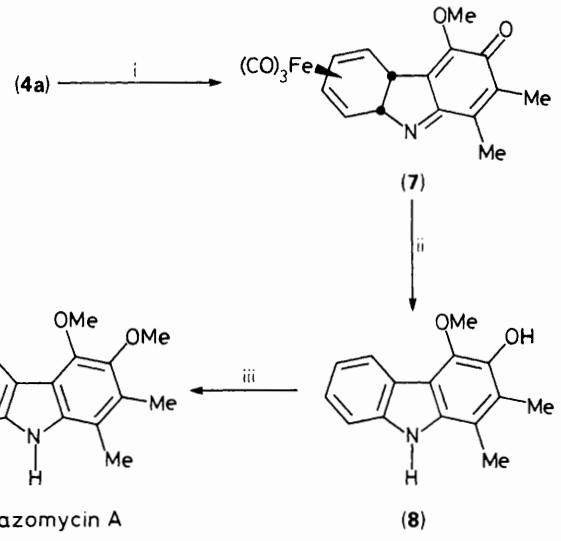
carbazomycin B,† identical in all spectral data (u.v., i.r., m.s., ^1H and ^{13}C n.m.r.)[2,3,4] and by t.l.c. comparison with an authentic sample, kindly provided by Professor S. Nakamura. By this synthesis carbazomycin B is available in four steps and 33% overall yield based on the iron-complexed cation (**3**).

In the course of our synthesis of 4-deoxycarbazomycin B we discovered a novel iron-mediated iminoquinone cyclization providing much better access to the carbazole nucleus than the direct oxidative cyclization with concomitant aromatization.[1] This method has now been applied to an improved synthesis of carbazomycin A. However, selective oxidation of the iron complex (**4a**) using commercial manganese dioxide‡ provides directly the 4b, 8a-dihydrocarbazol-3-one (**7**) in 63% yield (Scheme 4). This result contrasts with the analogous oxidations in the deoxy-series giving the non-cyclized iminoquinones, which have to be cyclized in a second step with very active managanese dioxide.[1] The observed direct iminoquinone cyclization, which is very useful with respect to the synthesis of the envisaged natural product, may be explained by the different oxidation potential of this complex. Demetallation of (**7**) with trimethylamine *N*-oxide[10] affords, *via* the expected rearrangement,[1] the 3-hydroxycarbazole (**8**) (92% yield). Methylation of the hydroxy derivative (**8**) gives in 72% yield carbazomycin A,§ the spectral data of which are in full agreement with those reported by Nakamura *et al.*[2,3,4] for the natural product. The described synthesis *via* the iron-mediated iminoquinone cyclization provides carbazomycin A in four steps and 35% overall yield based on the iron-complexed cation (**3**).

Both syntheses demonstrate the superiority of this iron-mediated carbazole construction over those procedures suffer-



Scheme 3. *Reagents and conditions:* Ac_2O, C_5H_5N, 4-*N*, *N*-dimethylaminopyridine, CH_2Cl_2, room temp.; ii, very active MnO_2, PhMe, room temp., 24 h; iii, 10% NaOH, H_2O, 1.5 h, reflux.



Scheme 4. *Reagents and conditions:* i, MnO_2, CH_2Cl_2, room temp.; ii, Me_3NO, Me_2CO, room temp.; iii, NaH, Et_2O, Me_2SO_4, room temp.

† Carbazomycin B was obtained as pale yellow crystals, m.p. 165—166 °C (from light petroleum/ethyl acetate); lit.[2] m.p. 158.5—160 °C (pale yellow prisms from n-hexane/ethyl acetate).

‡ Manganese dioxide (precipitated active) from Merck–Schuchardt, (art. 805958).

§ The m.p. we found for carbazomycin A was 138—139 °C (colourless plates from light petroleum/ethyl acetate), which closely matches a report of Moody *et al.*[8] (colourless plates, m.p. 143—146 °C from dichloromethane/hexane), but is in contrast to the original literature[2,4] (pale yellow needles, m.p. 51—52.5 °C from n-hexane/ethyl acetate).

ing from the drawback that the oxy-substituents have to be introduced by classical long-step sequences.[6,7,8]

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