Pergamon

Tetrahedron Letters, Vol. 38, No. 23, pp. 4051-4054, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00826-5

Transition Metal Complexes in Organic Synthesis, Part 38.[1]
First Total Synthesis of Carbazomycin G and H

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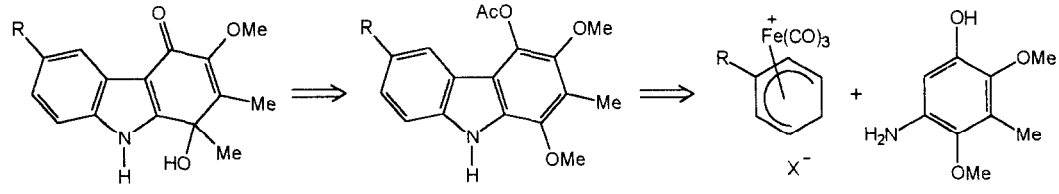
Abstract: The first total synthesis of the carbazole quinol alkaloids carbazomycin G and H has been achieved by a highly convergent synthesis using an iron-mediated construction of the carbazole nucleus as key-step. © 1997 Elsevier Science Ltd.

The carbazomycins A to H were isolated by Nakamura and co-workers from *Streptoverticillium ehimense*.[2] Because of their useful biological activities and the unusual substitution pattern the carbazomycins became attractive synthetic targets for several groups.[3,4] We developed a convergent synthesis for highly substituted carbazole alkaloids which furnishes the heterocyclic framework by a consecutive iron-mediated C–C and C–N bond formation.[5,6] This method was applied to the total synthesis of carbazomycin A,[7,8] B,[8] C,[9] D,[9] and E.[10] In this paper we report the first total synthesis of the carbazomycins G and H, which are structurally unique due to their quinol substructure.[2g] Retrosynthetic analysis of these alkaloids suggests the carbazoles **1** as synthetic precursors, which based on the iron-mediated synthesis on the carbazole ring system, should derive from the iron complex salts **2** and the arylamine **3** (Scheme 1).



Carbazomycin G R = H
Carbazomycin H R = OMe

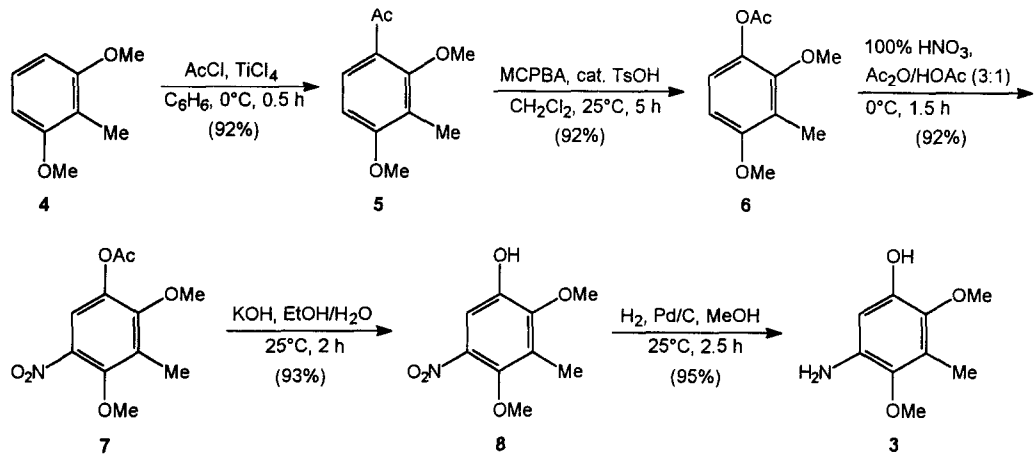
1a R = H
1b R = OMe

2a R = H, X = BF_4
2b R = OMe, X = PF_6

3

Scheme 1

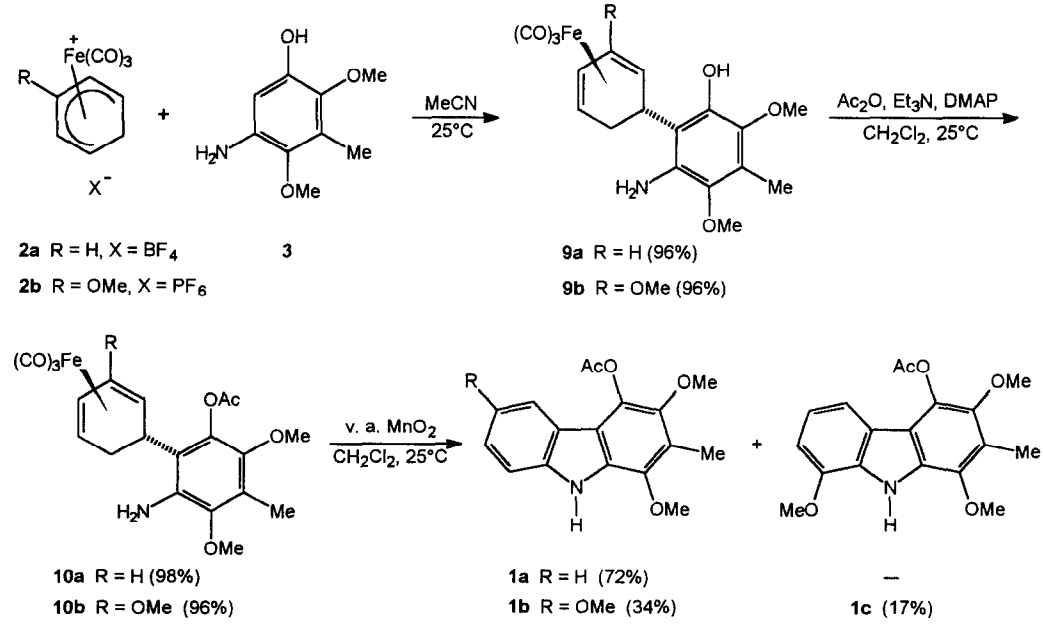
The required arylamine **3** was readily prepared starting with commercial 2,6-dimethoxytoluene **4** (Scheme 2). Titanium tetrachloride promoted Friedel-Crafts acylation[11] afforded the acetophenone **5** which was transformed into the acetate **6** by a proton-catalyzed Baeyer-Villiger oxidation. Nitration of **6** with fuming nitric acid in a mixture of acetic anhydride and glacial acetic acid (3:1) provided regioselectively the nitro derivative **7**. Finally, ester cleavage to the phenol **8** and hydrogenation at palladium on activated carbon gave the required arylamine **3**.[12] The sequence depicted in Scheme 2 provides compound **3** in five steps and 69% overall yield on a multigram scale.



Scheme 2

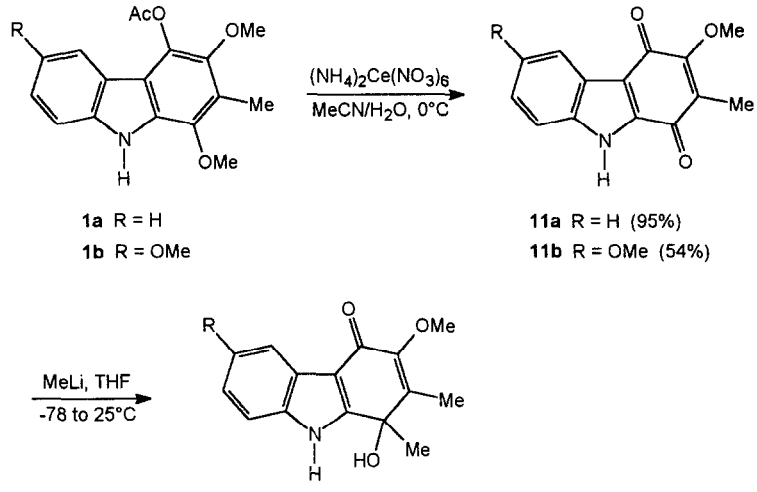
Reaction of the iron complex salts **2a** and **2b**[13] with the arylamine **3** afforded the iron complexes **9a** and **9b** (Scheme 3). Subsequent *O*-acetylation provided the acetates **10a** and **10b** which represent the synthetic precursors of carbazomycin G and H respectively. It was shown earlier that hydroxyanilines provide high yields in the electrophilic aromatic substitution with tricarbonyliron-complexed cyclohexadienylium cations, but that the free hydroxy groups have to be protected prior to oxidative cyclization with manganese dioxide.[8,14]

The iron-mediated arylamine cyclization of complex **10a** with very active manganese dioxide[15] provided the carbazole **1a** in 72% yield. Oxidation of **1a** with ceric ammonium nitrate[16] afforded the carbazolequinone **11a**, which by addition of methyl lithium gave carbazomycin G (Scheme 4).



Scheme 3

To complete the total synthesis of carbazomycin H, the iron complex **10b** containing a 3-methoxy-substituted cyclohexadiene ligand has to be cyclized regioselectively. Previous studies using deuterium-labelled cyclohexadiene ligands have demonstrated that cyclizations by two-electron oxidants, such as manganese dioxide, initially give rise to the product resulting from exclusive attack at C-4 of the cyclohexadiene ligand.[16] In the present case this regiochemistry is represented by the 8-methoxy-substituted carbazole **1c**, the undesired regioisomer. However, a subsequent proton-catalyzed rearrangement of the kinetic product to a 6-methoxy-substituted carbazole derivative may occur at the stage of the tricarbonyliron-complexed dihydrocarbazole.[9,17] The driving force behind this isomerization is the well-established regio-directing effect[18] of the 2-methoxy substituent of the intermediate iron-complexed cyclohexadienyl cation, which directs the amino group to the 5-position of the ligand. Dehydrogenation by manganese dioxide of the thermodynamic product, the 6-methoxy-substituted tricarbonyliron-complexed 4a,9a-dihydrocarbazole, provides the desired isomer **1b**.[19] Obviously, the proton-catalyzed rearrangement can compete with the dehydrogenation to **1c** at the stage of the kinetic product, as deduced from the 2 : 1 ratio of **1b** and **1c** (Scheme 3). Oxidation of **1b** with ceric ammonium nitrate to **11b** followed by addition of methyl lithium afforded carbazomycin H (Scheme 4).



1a R = H
1b R = OMe

11a R = H (95%)
11b R = OMe (54%)

Carbazomycin G R = H (71%)
Carbazomycin H R = OMe (41%)

Scheme 4

The present synthesis provides carbazomycin G and H in five steps based on the iron complex salts **2a** and **2b** respectively (overall yield for carbazomycin G: 46%, and for carbazomycin H: 7%). The spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR) of our synthetic carbazomycins G and H (G: m.p. 266-268°C, dec.; H: m.p. 208-209°C, dec.) are in good agreement with those reported by Nakamura and co-workers for the natural products (carbazomycin G: m.p. 241-243°C; carbazomycin H: m.p. 228-230°C).[2g]

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft (Gerhard-Hess Award) and the Fonds der Chemischen Industrie. We are grateful to the BASF AG, Ludwigshafen, for a generous gift of pentacarbonyliron.

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(*Received in Germany* 11 *April* 1997; *accepted* 22 *April* 1997)