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Improved Total Syntheses of the Antibiotic Alkaloids Carbazomycin A and B

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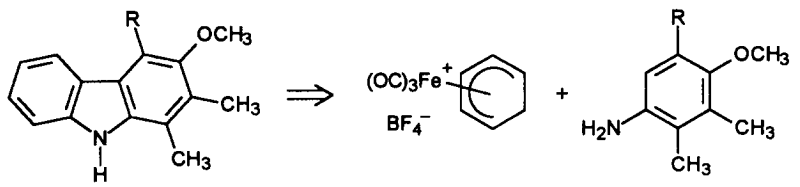
Abstract: Considerably improved total syntheses of the carbazole antibiotics carbazomycin A and B are reported using a convergent iron-mediated one-pot construction of the carbazole framework by oxidative cyclization in the air.

The carbazomycins are an unprecedented class of antibiotics with a carbazole framework and were isolated by Nakamura and coworkers from *Streptoverticillium ehimense* H 1051-MY 10.[2] The two parent compounds are carbazomycin A and B. They inhibit the growth of phytopathogenic fungi and have antibacterial and antiyeast activities. Moreover, carbazomycin B inhibits 5-lipoxygenase.[3] The unusual structure and the broad spectrum of biological activities led several groups to develop total syntheses of carbazomycin A and B.[4-6] We reported a total synthesis based on an iron-mediated construction of the carbazole skeleton.[4] The key steps are a C–C bond formation by electrophilic aromatic substitution at the fully functionalized arylamine **2** with the tricarbonyliron-complexed cyclohexadienyl cation **1** and a subsequent C–N bond formation by oxidative cyclization of the intermediate tricarbonyliron–cyclohexadiene complexes with especially activated manganese dioxide (Scheme 1).



Carbazomycin A R = OCH_3 **1** **2a** R = OCH_3
Carbazomycin B R = OH **2b** R = OAc

Scheme 1

We now describe a highly efficient synthetic route to the arylamine **2a**, which represents the precursor for carbazomycin A, and the application of a one-pot C–C and C–N bond formation to the synthesis of both alkaloids. This one-pot construction of the carbazole framework is achieved by electrophilic attack of **1** at the arylamines **2** followed by subsequent oxidative cyclization with air and was previously applied to the total syntheses of carbazoquinocin C, (±)-carquinostatin A, (±)-lavanduquinocin, and (±)-neocarazostatin B.[7]

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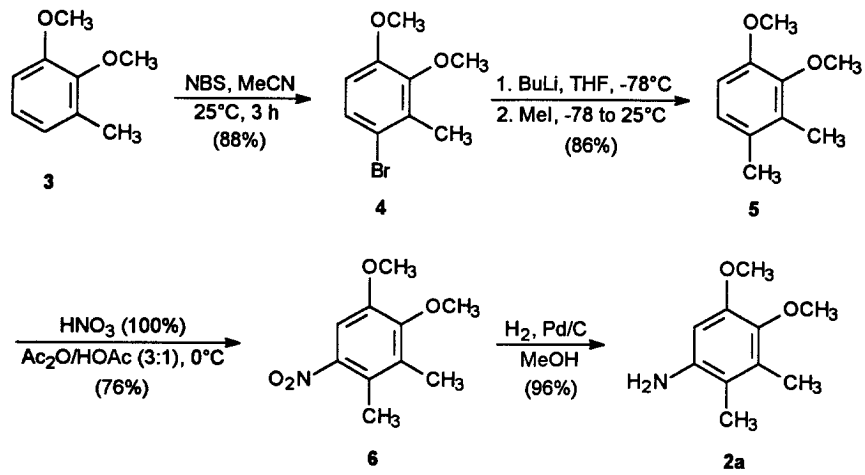
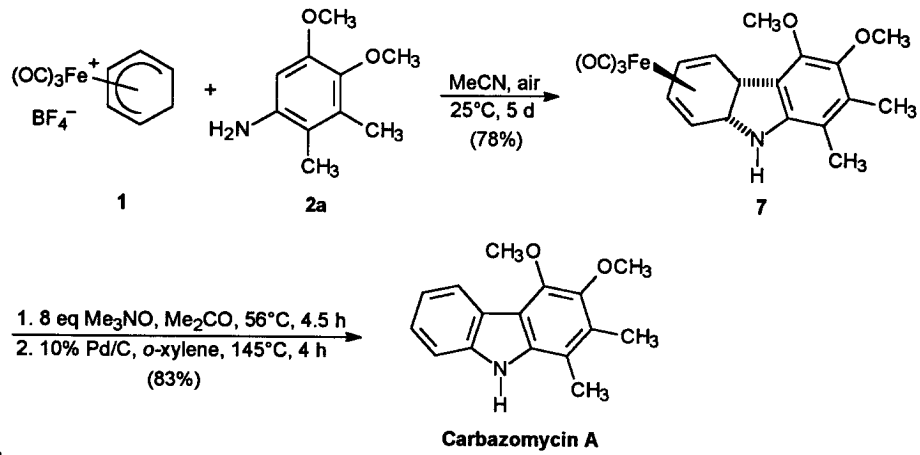


Scheme 2

Electrophilic bromination of 3-methylveratrole **3** provided 4-bromo-3-methylveratrole **4** (Scheme 2).[8] Halogen-metal exchange using *n*-butyllithium in tetrahydrofuran followed by alkylation with iodomethane afforded 3,4-dimethylveratrole **5**. Regioselective nitration of **5** with fuming nitric acid in a 3:1 mixture of acetic anhydride and glacial acetic acid led to the nitro derivative **6**. The regioselectivity of the nitration could be confirmed, since 1,2-dimethoxy-3,4-dimethyl-5-nitrobenzene was already obtained as intermediate of our previous synthesis of **2a** and comparison of the spectral data proved the identity.[4] Finally, catalytic hydrogenation of **6** over 10% palladium on activated carbon gave the arylamine **2a**.

The present route provides the arylamine **2a** in only four steps and 55% overall yield from commercial 3-methylveratrole **3** (previous route: 8 steps and 31% overall yield from commercial *o*-xylenol).[4c]



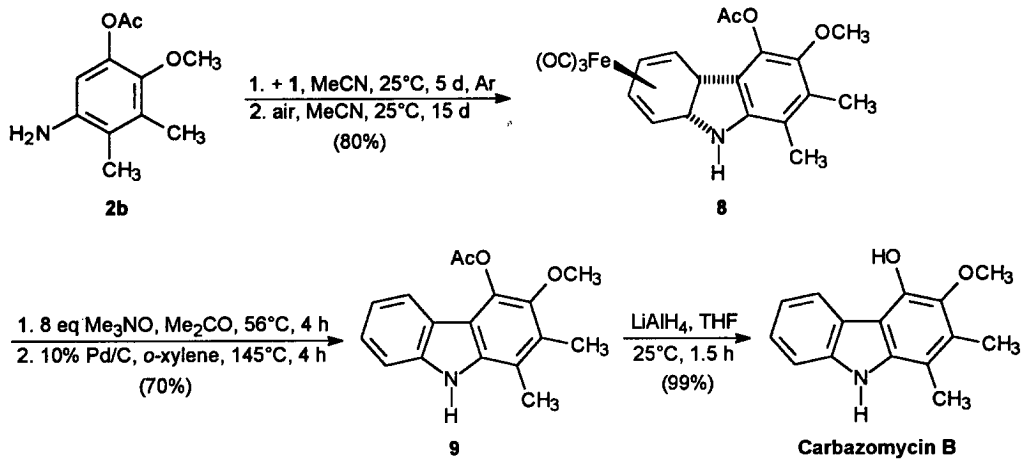
Scheme 3

We have shown previously that arylamine-substituted tricarbonyliron-cyclohexadiene complexes are selectively cyclized to the tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazoles by oxidation with air in acidic medium.[9] The one-pot C–C and C–N bond formation by reaction of the iron complex salt **1** with the corresponding

arylamine in the air was already applied to the total synthesis of several 3,4-dioxygenated carbazole alkaloids.[7] Based on the previous applications we expected a substantial improvement of our original syntheses of the carbazomycins A and B by using this third generation of iron-mediated oxidative cyclization.[10]

A solution of the iron complex salt **1** and two equivalents of the arylamine **2a** in acetonitrile was allowed to stay in the air at room temperature for 5 days, thus providing the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **7** in 78% yield (Scheme 3). Demetalation of complex **7** using trimethylamine *N*-oxide[11] in acetone at reflux and subsequent dehydrogenation of the crude product with 10% palladium on activated carbon in *o*-xylene at reflux afforded carbazomycin A, which is identical with the natural product in all spectral data.[2a-c]

The present synthesis provides carbazomycin A in three steps and 65% overall yield based on **1** (previous routes: two steps and 21% overall yield, four steps and 35% overall yield based on **1** in each case).[4]



Scheme 4

Reaction of the complex salt **1** with two equivalents of the arylamine **2b**[4c] in acetonitrile at room temperature for 5 days under argon and then for 15 days in the air provided the iron complex **8** in 80% yield (Scheme 4).[12] The reactivity of these tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complexes and their conversion to the aromatized 9*H*-carbazoles was already investigated in an earlier study.[13] Demetalation of complex **8** with trimethylamine *N*-oxide at reflux afforded a mixture of the corresponding 4a,9a-dihydro-9*H*-carbazole and the aromatized compound **9** (ratio about 4:1). A completion of the aromatization of the dihydrocarbazole/carbazole mixture can be achieved by catalytic dehydrogenation, as shown in the previous applications of this cyclization method.[7] Thus, *O*-acetylcarbazomycin B **9** was obtained in 70% overall yield. A selective transformation of complex **8** to the corresponding 4a,9a-dihydro-9*H*-carbazole was recently achieved by a photolytically induced ligand exchange reaction with acetonitrile and subsequent demetalation in the air.[14] Finally, a removal of the acetyl group by reduction of **9** with lithium aluminum hydride provided quantitatively carbazomycin B.[2a-c]

The present synthesis provides carbazomycin B in four steps and 55% overall yield based on **1** (previous route: four steps and 33% overall yield based on **1**).[4]

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References and Notes

1. Part 53: H.-J. Knölker, E. Baum, T. Hopfmann, *Tetrahedron* **1999**, *55*, 10391.
2. a) K. Sakano, K. Ishimaru, S. Nakamura, *J. Antibiot.* **1980**, *33*, 683. b) K. Sakano, S. Nakamura, *J. Antibiot.* **1980**, *33*, 961. c) M. Kaneda, K. Sakano, S. Nakamura, Y. Kushi, Y. Iitaka, *Heterocycles* **1981**, *15*, 993. d) K. Yamasaki, M. Kaneda, K. Watanabe, Y. Ueki, K. Ishimaru, S. Nakamura, R. Nomi, N. Yoshida, T. Nakajima, *J. Antibiot.* **1983**, *36*, 552. e) S. Kondo, M. Katayama, S. Marumo, *J. Antibiot.* **1986**, *39*, 727. f) T. Naid, T. Kitahara, M. Kaneda, S. Nakamura, *J. Antibiot.* **1987**, *40*, 157. g) M. Kaneda, T. Naid, T. Kitahara, S. Nakamura, T. Hirata, T. Suga, *J. Antibiot.* **1988**, *41*, 602.
3. D. J. Hook, J. J. Yacobucci, S. O'Connor, M. Lee, E. Kerns, B. Krishnan, J. Matson, G. Hesler, *J. Antibiot.* **1990**, *43*, 1347.
4. a) H.-J. Knölker, M. Bauermeister, D. Bläser, R. Boese, J.-B. Pannek, *Angew. Chem.* **1989**, *101*, 225; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 223. b) H.-J. Knölker, M. Bauermeister, *J. Chem. Soc. Chem. Commun.* **1989**, 1468. c) H.-J. Knölker, M. Bauermeister, *Helv. Chim. Acta* **1993**, *76*, 2500.
5. Reviews: H.-J. Knölker, *Synlett* **1992**, 371. D. P. Chakraborty in *The Alkaloids*; G. A. Cordell, Ed.; Academic Press: New York, **1993**; Vol. 44; p. 257. C. J. Moody, *Synlett* **1994**, 681. H.-J. Knölker in *Advances in Nitrogen Heterocycles*; C. J. Moody, Ed.; JAI Press: Greenwich, CT (USA), **1995**; Vol.1; p. 173.
6. C. J. Moody, P. Shah, *J. Chem. Soc. Perkin Trans. 1* **1989**, 2463. D. L. J. Clive, N. Etkin, T. Joseph, J. W. Lown, *J. Org. Chem.* **1993**, *58*, 2442. E. M. Beccalli, A. Marchesini, T. Pilati, *Tetrahedron* **1996**, *52*, 3029.
7. H.-J. Knölker, W. Fröhner, *Tetrahedron Lett.* **1997**, *38*, 1535. H.-J. Knölker, W. Fröhner, *Synlett* **1997**, 1108. H.-J. Knölker, W. Fröhner, *Tetrahedron Lett.* **1998**, *39*, 2537. H.-J. Knölker, W. Fröhner, A. Wagner, *Tetrahedron Lett.* **1998**, *39*, 2947.
8. M. Albrecht, *Synthesis* **1996**, 230.
9. H.-J. Knölker, M. Wolpert, *Tetrahedron Lett.* **1997**, *38*, 533.
10. H.-J. Knölker in *Transition Metals for Organic Synthesis*; M. Beller, C. Bolm, Eds.; Wiley-VCH: Weinheim, **1998**; Vol. 1; Chap. 3.13; p. 534. H.-J. Knölker, *Chem. Soc. Rev.* **1999**, *28*, 151.
11. Y. Shvo, E. Hazum, *J. Chem. Soc. Chem. Commun.* **1974**, 336.
12. **8**: A solution of the arylamine **2b** (2.80 g, 13.4 mmol) and the iron complex salt **1** (2.05 g, 6.70 mmol) in degassed acetonitrile (15 ml) was allowed to stay at room temperature to the exclusion of light first for 5 d under argon and then for 15 d in the air. During the oxidation complex **8** partly crystallizes from acetonitrile. The crystals were separated and washed with ether. The brown reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (80 ml), the aqueous layer was separated and extracted twice with ether (60 ml). The combined organic layers were dried over sodium sulfate, the solvent was evaporated, and the residue was recrystallized from chloroform to afford additional product. The combined crystals were powdered and dried overnight in vacuum at 100°C to provide the pure complex **8** as a light yellow solid, yield: 2.27 g (80%), m.p. 209-211°C. IR (drift): $\tilde{\nu}$ = 3366, 3348, 2935, 2043, 1969, 1949, 1747 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.91 (s, 3 H), 2.12 (s, 3 H), 2.36 (s, 3 H), 3.19 (ddd, *J* = 6.0, 3.8, 1.3 Hz, 1 H), 3.31 (m, 1 H), 3.38 (br s, 1 H), 3.63 (s, 3 H), 3.85 (dd, *J* = 10.8, 4.2 Hz, 1 H), 4.33 (dd, *J* = 10.8, 3.2 Hz, 1 H), 5.37 (m, 1 H), 5.41 (m, 1 H). ^{13}C-NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.49 (CH_3), 13.48 (CH_3), 20.81 (CH_3), 44.94 (CH), 60.92 (CH_3), 61.05 (CH), 61.84 (CH), 63.19 (CH), 85.73 (CH), 86.71 (CH), 116.27 (C), 121.86 (C), 130.51 (C), 137.97 (C), 142.69 (C), 144.70 (C), 169.09 (C=O), 211.12 (3 CO). Anal. calcd. for $C_{20}H_{19}FeNO_6$: C 56.49, H 4.50, N 3.29; found: C, 56.60, H 4.68, N 2.89.
13. H.-J. Knölker, G. Baum, J.-B. Pannek, *Tetrahedron* **1996**, *52*, 7345.
14. H.-J. Knölker, H. Goesmann, R. Klauss, *Angew. Chem. Int. Ed.* **1999**, *38*, 702.