Transition Metal Complexes in Organic Synthesis, Part 39.[1] First Total Synthesis of the Potent Neuronal Cell Protecting Substance (±)-Carquinostatin A *via* Iron- and Nickel-Mediated Coupling Reactions

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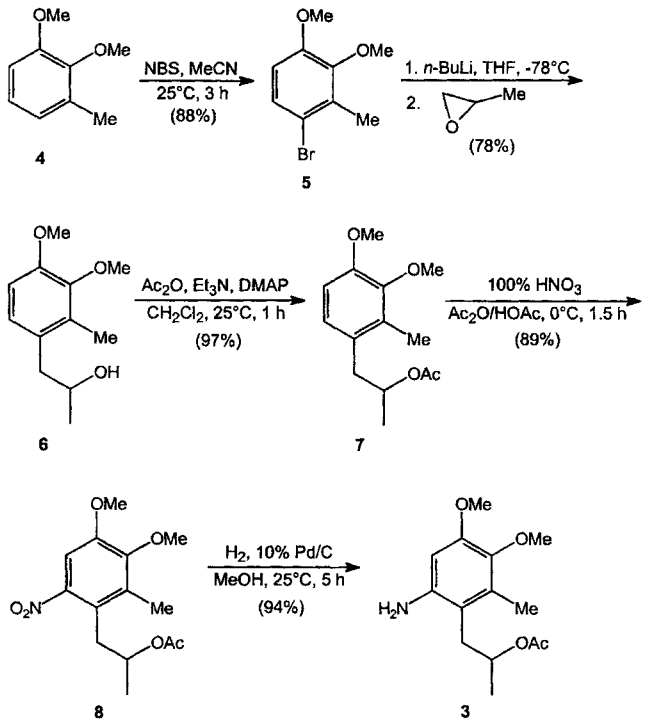
Abstract: The first total synthesis of the potent neuronal cell protecting carbazole alkaloid (±)-carquinostatin A was achieved by using an iron-mediated construction of the carbazole framework and a regioselective nickel-mediated prenylation as the key-steps.

The isolation and total synthesis of novel biologically active carbazole alkaloids has been an active area of research over the past 20 years.[2,3] Recently, Seto and coworkers on their screening for substances with neuronal cell protecting activities isolated carquinostatin A from *Streptomyces exfoliatus* 2419-SVT2.[4] Carquinostatin A also proved to be a free radical scavenger.

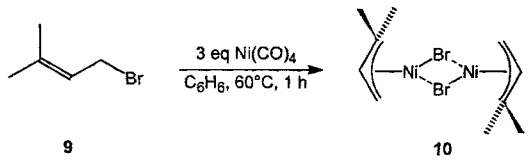
In the course of our investigations directed towards the iron-mediated total synthesis of carbazole alkaloids[3] we recently described a novel oxidative cyclization of tricarbonyliron-cyclohexadiene complexes to iron-complexed 4a,9a-dihydro-9*H*-carbazoles which is achieved by air in protic medium.[5] An extension of this procedure, the formation of the carbazole nucleus by a one-pot C–C and C–N bond formation on reaction of the tricarbonyliron-complexed cyclohexadienyl cation with the appropriate arylamine in the air, was applied to the total synthesis of the potent lipid peroxidation inhibitor carbazoquinocin C.[6] This novel method of carbazole construction and a nickel-mediated prenylation were envisaged as key-steps for the total synthesis of carquinostatin A. Based on these considerations, carquinostatin A should derive from regioselective prenylation of the carbazole **1**, which is obtained by coupling of the complex salt **2** and the corresponding arylamine **3** (Scheme 1).

The required arylamine **3** was prepared in five steps and 54% overall yield starting from commercial 3-methylveratrole **4** (Scheme 2). Regioselective bromination of **4** gave the bromo derivative **5**,[6,7] which on halogen-metal exchange with *n*-butyllithium in THF and subsequent treatment with propylene oxide provided the carbinol **6**. Acetylation of **6** to the acetate **7** followed by regioselective nitration led to the nitro aryl derivative **8**. The assignment of the regioselectivity of the nitration was based on previous examples.[6] Catalytic hydrogenation of **8** afforded the arylamine **3**.

The third component for the synthesis of carquinostatin A *via* the projected sequence of transition metal-mediated reactions is the bis[(μ-bromo(η^3-1,1-dimethylallyl)nickel] **10**. Complex **10** is readily prepared by treatment of prenyl bromide **9** with 3 equivalents of tetracarbonylnickel in benzene at 60°C (Scheme 3) and represents a useful reagent for the introduction of prenyl groups on reaction with organic halides.[8]

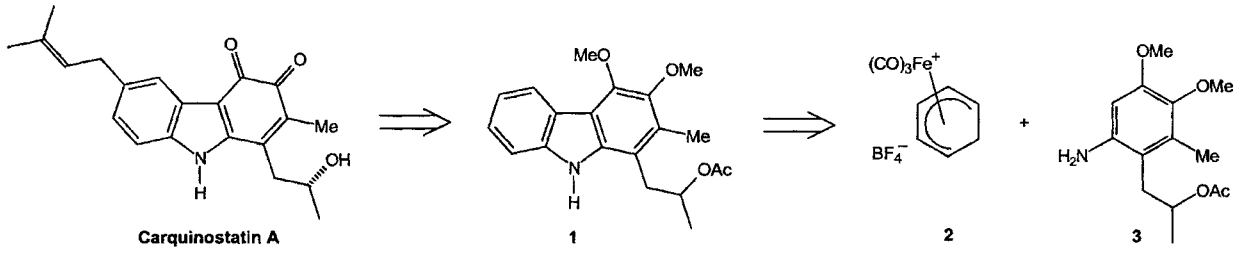


Scheme 2

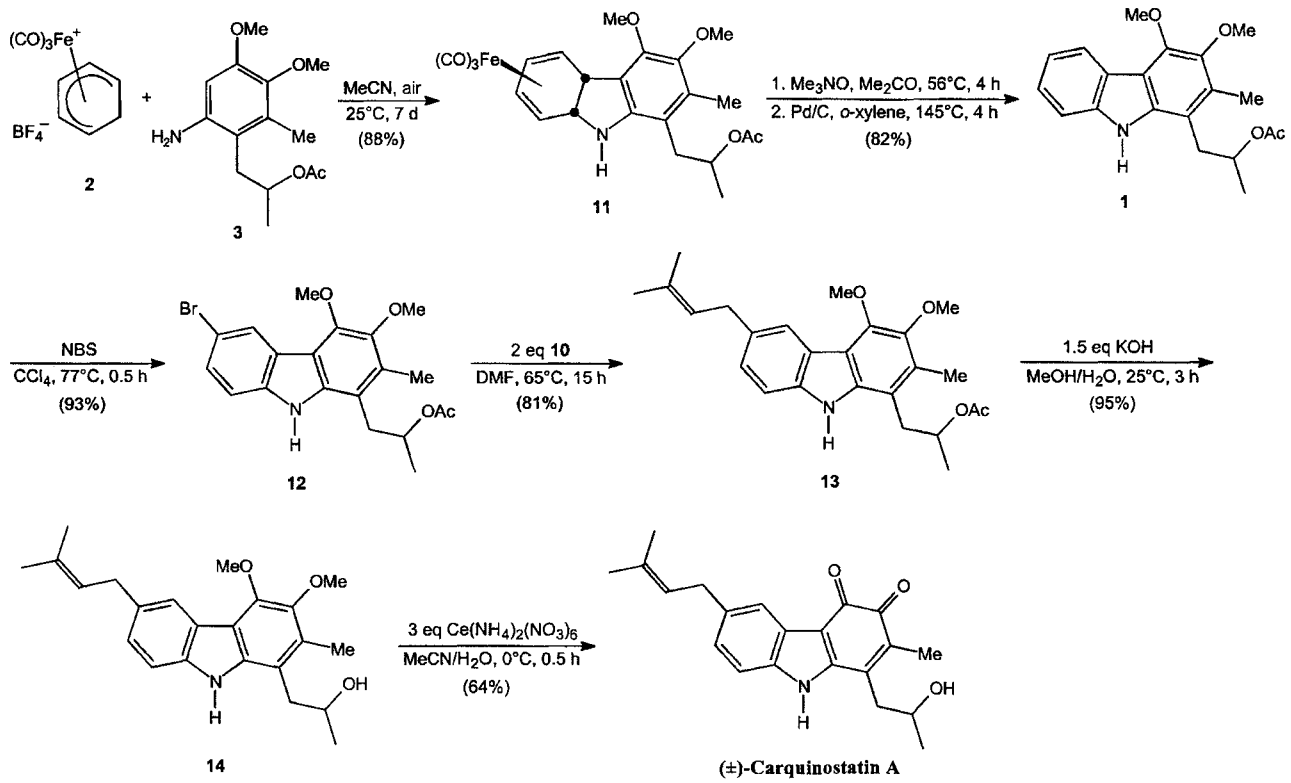


Scheme 3

The iron-mediated coupling of the arylamine **3** was achieved using the conditions previously optimized.[6] Reaction of the iron complex salt **2** with two equivalents of the arylamine **3** in acetonitrile at room temperature afforded after 7 days in the air the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron **11** in 88% yield (Scheme 4). Demetalation of the iron complex **11** with trimethylamine *N*-oxide in acetone at reflux[9] followed by dehydrogenation with 10% palladium on activated carbon in boiling *o*-xylene[10] provided the aromatized carbazole **1** in 82% yield.[11] Regioselective bromination *via* electrophilic substitution



Scheme 1



Scheme 4

of **1** with *N*-bromosuccinimide in tetrachloromethane led to the 6-bromocarbazole **12**. Coupling of the 6-bromocarbazole **12** with the dimeric prenylnickel bromide complex **10** in dimethylformamide at elevated temperature afforded the 6-prenylcarbazole **13** in 81% yield.[11] Ester cleavage of **13** to the carbinol **14** and subsequent oxidation with ceric ammonium nitrate[12] provided (±)-carquinostatin A.[11]

We achieved the first total synthesis of (±)-carquinostatin A using two transition metal-mediated coupling reactions as key-steps. Our route provides the novel neuronal cell protecting carbazole alkaloid in seven steps and 33% overall yield based on the iron complex salt **2**. All spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR)[11] of (±)-carquinostatin A are in good agreement with those described for the natural product, which was isolated in enantiomerically pure form. However, the melting point we found for our synthetic (±)-carquinostatin A (m.p. 203-204°C) was considerably higher than the one reported for the natural product (m.p. 144-145°C).

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(11) Selected spectral data of the carbazole derivatives **1**, **13** and of (±)-carquinostatin A.

1: ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.3, 3 H), 2.15 (s, 3 H), 2.41 (s, 3 H), 3.02 (dd, *J* = 13.8, 10.1, 1 H), 3.25 (dd, *J* = 13.8, 3.0, 1 H), 3.89 (s, 3 H), 4.12 (s, 3 H), 5.04 (m, 1 H), 7.20 (m, 1 H), 7.38 (m, 1 H), 7.49 (d, *J* = 8.1, 1 H), 8.23 (d, *J* = 7.8, 1 H), 9.62 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.81 (CH_3), 19.33 (CH_3), 21.49 (CH_3), 35.04 (CH_2), 60.42 (CH_3), 60.97 (CH_3), 71.96 (CH), 110.63 (CH), 113.38 (C), 114.60(C), 119.14 (CH), 122.30 (C), 122.38 (CH), 125.14 (CH), 128.62 (C), 137.18 (C), 139.63 (C), 144.18 (C), 146.90 (C), 172.52 (C=O).

13: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.3, 3 H), 1.77 (s, 3 H), 1.79 (s, 3 H), 2.15 (s, 3 H), 2.40 (s, 3 H), 3.00 (dd, *J* = 13.7, 10.0, 1 H), 3.24 (dd, *J* = 13.7, 3.0, 1 H), 3.51 (d, *J* = 7.3, 2 H), 3.88 (s, 3 H), 4.11 (s, 3 H), 5.03 (m, 1 H), 5.44 (br t, *J* = 7.3, 1 H), 7.21 (dd, *J* = 8.2, 1.6, 1 H), 7.40 (d, *J* = 8.2, 1 H), 8.01 (br s, 1 H), 9.49 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.82 (CH_3), 17.92 (CH_3), 19.35 (CH_3), 21.52 (CH_3), 25.84 (CH_3), 34.51 (CH_2), 35.04 (CH_2), 60.45 (CH_3), 61.00 (CH_3), 71.95 (CH), 110.46 (CH), 113.35 (C), 114.52 (C), 121.61 (CH), 122.46 (C), 124.57 (CH), 125.82 (CH), 128.40 (C), 131.64 (C), 132.60 (C), 137.53 (C), 138.09 (C), 144.04 (C), 146.81 (C), 172.49 (C=O).

(±)-Carquinostatin A: m.p. 203-204°C (recryst. from ethanol); UV (MeOH): λ (ε) = 231 (28800), 268 (26100), 426 (5300) nm; IR (KBr): ν = 3420 (br), 3222, 2972, 1654 (sh), 1639, 1621, 1600, 1587, 1475 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 1.23 (d, *J* = 6.1, 3 H), 1.70 (s, 6 H), 1.91 (s, 3 H), 2.70-2.77 (m, 2 H), 3.37 (d, *J* = 7.4, 2 H), 3.90-3.97 (m, 1 H), 4.85 (br s, 1 H), 5.31 (br t, *J* = 7.4, 1 H), 7.03 (dd, *J* = 8.3, 1.5, 1 H), 7.40 (d, *J* = 8.3, 1 H), 7.63 (br s, 1 H), 12.10 (br s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.18 (CH_3), 17.71 (CH_3), 23.75 (CH_3), 25.53 (CH_3), 33.87 (CH_2), 37.69 (CH_2), 65.88 (CH), 110.67 (C), 113.23 (CH), 119.25 (CH), 123.75 (CH), 124.92 (CH), 126.04 (C), 131.49 (C), 134.50 (C), 135.55 (C), 137.40 (C), 139.85 (C), 146.31 (C), 172.69 (C=O), 183.74 (C=O).

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