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First Total Synthesis of the Potent Neuronal Cell Protecting Substance (±)-Lavanduquinocin *via* Iron- and Nickel-Mediated Coupling Reactions

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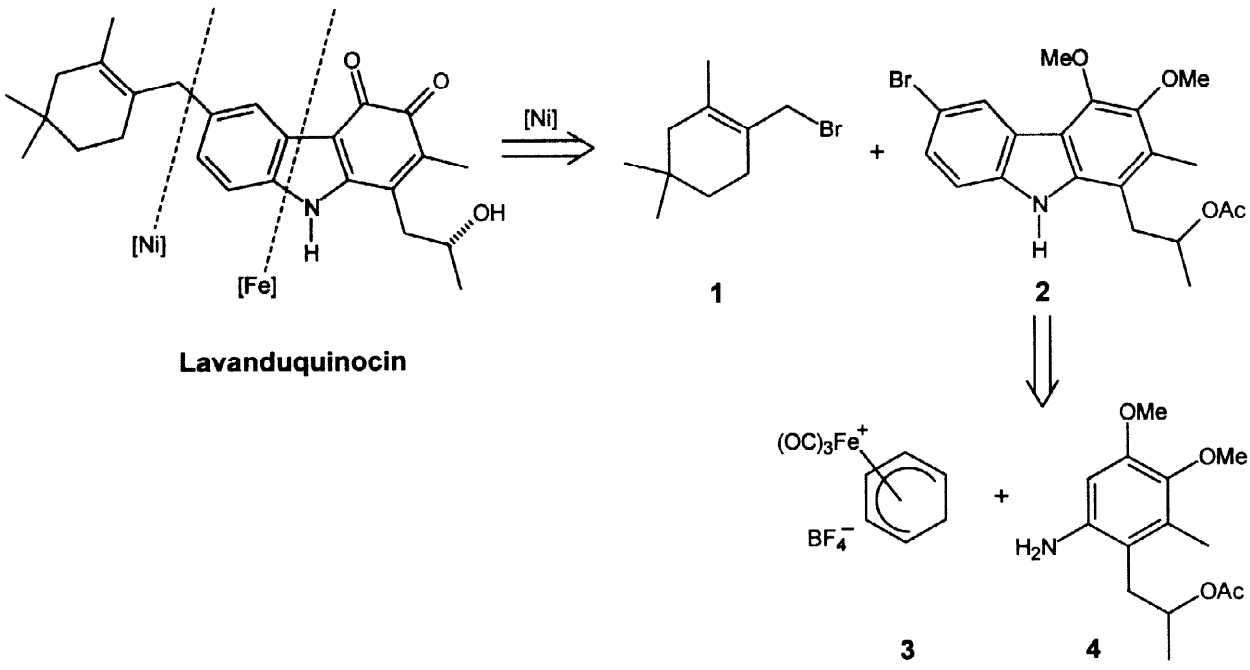
Abstract: The first total synthesis of the potent neuronal cell protecting alkaloid (±)-lavanduquinocin is described by using an iron-mediated construction of the carbazole skeleton and a nickel-mediated alkylation as the key-steps.

The chemistry of biologically active carbazole alkaloids which were isolated from *Streptomyces* was under strong investigation in the past years.[2] On their screening for substances with neuronal cell protecting activities Seto *et al.* recently isolated the carbazole alkaloid lavanduquinocin from *Streptomyces viridochromogenes* 2942-SVS3.[3] Lavanduquinocin proved to protect neuronal hybridoma N18-RE-105 cells from L-glutamate toxicity with EC_{50} value 15.5 nM. Apoptotic cell death of N18-RE-105 cells induced by buthionine sulfoximine due to the depletion of glutathione was also suppressed by lavanduquinocin which presumably acts as a reducing agent instead of glutathione. Therefore, the biological activity was proposed to depend on its antioxidative activity.[3] It is well known that oxygen-derived free radicals play a pivotal role in the initiation of a variety of diseases, for which free radical scavengers are thought to represent potential therapeutic agents.



Scheme 1

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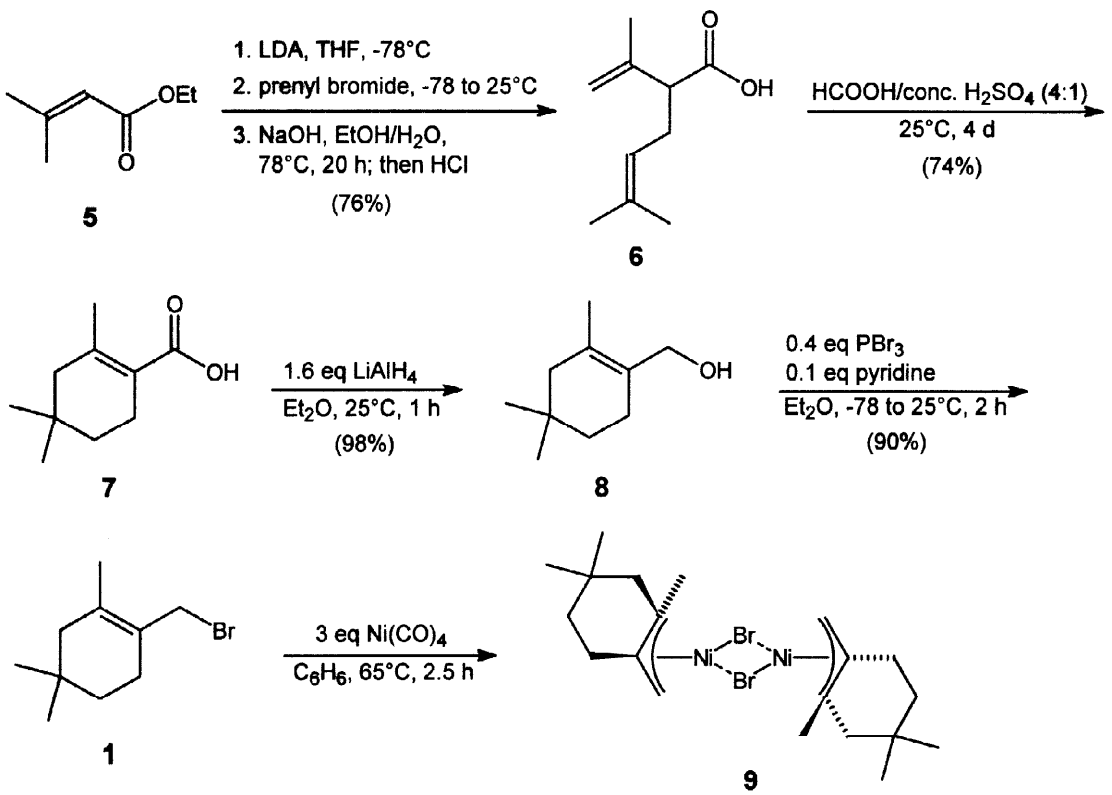
We developed an iron-mediated synthesis of carbazole alkaloids.[4] The crucial step, the formation of a C–N bond by an oxidative cyclization, can be achieved by oxidation with air in protic medium.[5] This method was extended to a direct construction of the carbazole nucleus by a one-pot C–C and C–N bond formation and applied to the total synthesis of carbazoquinocin C[6] and (±)-carquinostatin A.[7] Based on our previous work we envisaged for the total synthesis of lavanduquinocin a nickel-mediated introduction of the β-cyclolavandulyl residue. Thus, (±)-lavanduquinocin should derive from the β-cyclolavandulyl bromide **1** and the 6-bromo-carbazole **2**, which is prepared starting from the iron complex salt **3** and the arylamine **4** (Scheme 1).

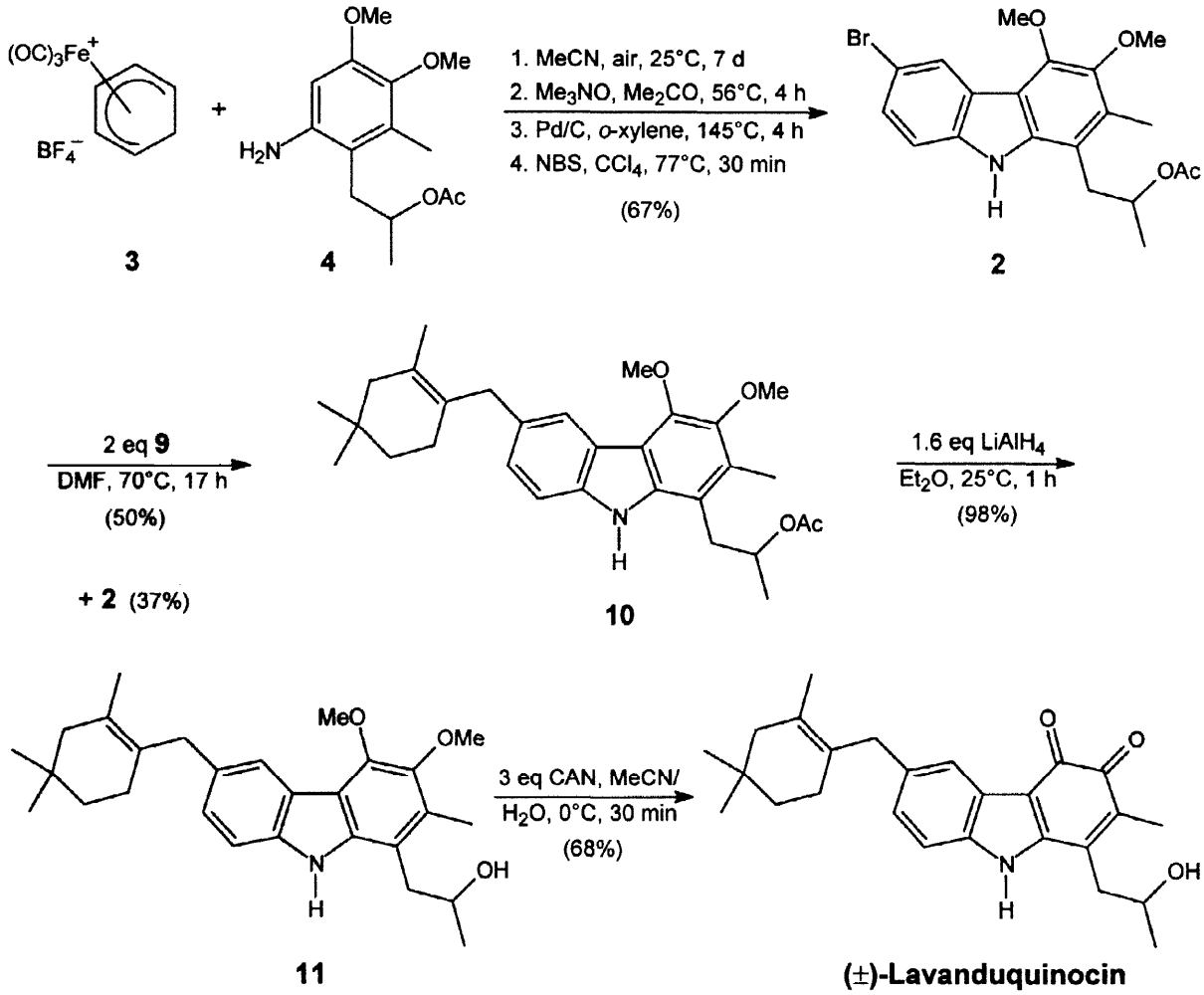


Scheme 2

A considerably improved synthesis of β-cyclolavandulyl bromide **1** was devised by adaptation of literature procedures (Scheme 2).[8-10] Deprotonation of commercial ethyl senecioate **5** with LDA followed by kinetic quenching with prenyl bromide leads to ethyl lavandulate,[8] which was transformed without further characterization into lavandulylic acid **6** by cleavage of the ester.[9] Proton-initiated cyclization of **6** using optimized reaction conditions provided the nicely crystallizing β-cyclolavandulylic acid **7** in 74% yield. Reduction of **7** using lithium aluminum hydride afforded β-cyclolavandulol **8**,[9] which on reaction with phosphorous tribromide led to the desired β-cyclolavandulyl bromide **1**.[10]

By the present route β-cyclolavandulyl bromide **1** is available in 5 steps and 50% overall yield based on ethyl senecioate **5**. The transformation to the dinuclear nickel complex **9** was achieved analogous to the preparation of the known dimeric π-prenylnickel bromide complex,[11] which was used previously for the total synthesis of (±)-carquinostatin A.[7] Treatment of β-cyclolavandulyl bromide **1** with 3 equivalents of tetracarbonylnickel in benzene at 65°C afforded after 2.5 h a red-brown solution indicating the formation of the nickel π-allyl system. The presumed complex **9** was not isolated and characterized, since this type of dimeric π-allylnickel bromide complexes are known to be very sensitive towards oxidation.[11] For the following cross coupling reaction it was sufficient to evaporate benzene and unreacted tetracarbonylnickel and to use the crude complex **9**.

The arylamine **4** was previously used as a precursor in our total synthesis of (±)-carquinostatin A.[7] Reaction of the iron complex salt **3** with the arylamine **4** in acetonitrile for 7 d in the air, demetalation using trimethylamine *N*-oxide in acetone at reflux,[12] aromatization with 10% palladium on activated carbon in boiling *o*-xylene,[13] and subsequent regioselective bromination of the 6-position using *N*-bromosuccinimide in tetrachloromethane at reflux provided the 6-bromocarbazole **2**.



Scheme 3

The cross coupling reaction of the dimeric π-allylnickel bromide complex **9** and the 6-bromocarbazole **2** was performed in dry and degassed *N,N*-dimethylformamide at 70°C to the strict exclusion of oxygen. This procedure provided the desired 6-β-cyclolavandulylcarbazole derivative **10** in 50% yield along with 37% of recovered starting material and 8% of the hydrodebrominated carbazole derivative. Removal of the acetyl protecting group in the side chain by reduction with lithium aluminum hydride afforded the carbazole derivative **11** almost quantitatively. Oxidation of **11** with ceric ammonium nitrate[14] in an acetonitrile/water mixture at 0°C provided (±)-lavanduquinocin. All spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR)[15] of our synthetic (±)-lavanduquinocin were in full agreement with those reported for the natural product.[3] However, the melting point of the racemic synthetic product (m.p. 221°C)[15] was considerably higher than the one reported for the natural enantiopure lavanduquinocin (m.p. 157-158°C).[3] The present synthesis affords (±)-lavanduquinocin in 7 steps and 22% overall yield based on the iron complex salt **3**.

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15. (±)-Lavanduquinocin: black crystals, m.p. 221°C; UV (MeOH): λ (ε) = 193 (20800), 211 (21500), 231 (25100), 268 (23100), 427 (4900) nm; IR (KBr): $\tilde{\nu}$ = 3532, 3438 (br), 3216, 2952, 2908, 2863, 1653, 1639, 1618, 1600, 1587, 1475 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 0.83 (s, 6 H), 1.22 (d, J = 6.0, 3 H), 1.23 (m, 2 H), 1.72 (s, 3 H), 1.77 (s, 2 H), 1.82 (m, 2 H), 1.90 (s, 3 H), 2.73 (m, 2 H), 3.40 (s, 2 H), 3.95 (m, 1 H), 4.86 (br s, 1 H), 6.99 (dd, J = 8.4, 1.5, 1 H), 7.40 (d, J = 8.4, 1 H), 7.63 (s, 1 H), 12.13 (br s, 1 H); ^{13}C-NMR and DEPT (125 MHz, DMSO-d_6): δ = 12.18 (CH_3), 19.60 (CH_3), 23.73 (CH_3), 26.82 (CH_2), 28.06 (CH_3), 28.09 (CH_3), 28.95 (C), 35.42 (CH_2), 37.70 (CH_2), 38.40 (CH_2), 45.59 (CH_2), 65.90 (CH), 110.68 (C), 113.23 (CH), 119.46 (CH), 124.66 (CH), 125.67 (C), 126.04 (C), 127.26 (C), 134.42 (C), 135.67 (C), 136.75 (C), 139.90 (C), 146.34 (C), 172.69 (C=O), 183.77 (C=O); MS (190°C): *m/z* (%) = 407 (M^+ +2, 100), 405 (M^+, 17), 403 (46), 389 (24), 388 (11), 387 (14), 363 (73), 362 (73), 361 (19), 280 (9), 240 (13), 239 (11), 238 (22), 226 (21); HRMS: calcd. for $C_{26}H_{31}NO_3$ (M^+): 405.2304, found: 405.2289.