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Transition metal mediated total synthesis of the potent neuronal cell protecting alkaloid (±)-lavanduquinocin

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Dedicated to Professor Rainer Beckert on the occasion of his 60th birthday

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Abstract
An efficient total synthesis of (±)-lavanduquinocin, a potent neuronal cell protecting alkaloid from Streptomyces viridochromogenes, is reported. Key-steps are an iron-mediated one-pot construction of the carbazole framework and a nickel-mediated coupling reaction.

Keywords: Alkaloids, cyclization, iron, nickel, quinones

Introduction

Over the past decades a wide variety of carbazole alkaloids with intriguing structures and useful biological activities has been isolated from diverse natural sources and a range of novel synthetic methodologies to these natural products has been developed.2 In 1983, Furukawa and co-workers reported the isolation of the first carbazole-1,4-quinone alkaloids from terrestrial plants.3 Ten years later, Seto and his group from Tokyo isolated the first carbazole-3,4-quinone alkaloids from Streptomyces (Figure 1).4-5 An example for this class of natural products is lavanduquinocin (I), which was isolated from Streptomyces viridochromogenes 2492-SVS3.5 Lavanduquinocin was shown to protect neuronal hybridoma N18-RE-105 cells from the L-glutamate toxicity with an EC50 value of 15.5 nM. The apoptotic cell death of N18-RE-105 cells, induced by buthionine sulfoximine (BSO) due to depletion of the endogenous reducing agent glutathione, was also suppressed by lavanduquinocin at concentrations higher than 12.5 nM. The toxicity of BSO is considered to involve oxygen-derived free radicals. Thus, the mode of action of lavanduquinocin is dependent on its antioxidative activity.5 It is well known that oxygen-derived free radicals play a pivotal role in the initiation of a variety of diseases, like myocardial and cerebral ischemia, arteriosclerosis, inflammation, rheumatism, senility, autoimmune diseases, and cancer.6
Therefore, free radical scavengers are thought to represent potential therapeutic agents for the treatment of these diseases.

The characteristic structural features of lavanduquinocin (1) are an ortho-benzoquinone moiety, an (R)-2-hydroxypropyl substituent at the 1-position of the carbazole nucleus and a monoterpenoidal \( \beta \)-cyclolavandulyl side chain at C-6.

\[ \text{Figure 1. Naturally occurring carbazole-3,4-quinone alkaloids.} \]

We have developed a highly efficient iron-mediated route for the synthesis of carbazole alkaloids.\(^7\) The crucial step of our synthesis is the formation of a C–N bond by an oxidative cyclization of a 5-(2-aminoaryl)-substituted cyclohexadiene–tricarbonyliron complex which can be achieved by oxidation with air in protic medium.\(^8\) Extension of this method led to a one-pot construction of the carbazole nucleus by a consecutive C–C and C–N bond formation. The utility of the one-pot procedure for natural product synthesis was demonstrated by the development of elegant routes to carbazoquinocin C (5),\(^9\) carquinostatin A (2),\(^10,11\) lavanduquinocin (1),\(^12,13\) neocarazostatin B,\(^14\) the carbazomycins A and B,\(^15\) and streptoverticillin.\(^16\) In the present paper, we describe our synthesis of (±)-lavanduquinocin \((\text{rac-1})\) in full detail.\(^12\)

**Results and Discussion**

For the total synthesis of (±)-lavanduquinocin \((\text{rac-1})\) we envisaged a nickel-mediated introduction of the \( \beta \)-cyclolavandulyl residue. Thus, (±)-lavanduquinocin \((\text{rac-1})\) should derive from \( \beta \)-cyclolavandulyl bromide (9) and the 6-bromocarbazole 10, which is prepared starting
from cyclohexa-1,3-diene (11) and the fully functionalized arylamine 12 as depicted in the retrosynthetic analysis (Scheme 1).

Scheme 1. Retrosynthetic analysis of (±)-lavanduquinocin (rac-1).

The iron complex salt 13 is quantitatively available on large scale by a 1-azabuta-1,3-diene-catalyzed complexation of cyclohexa-1,3-diene (11) with pentacarbonyliron17 followed by hydride abstraction using triphenylmethyl tetrafluoroborate.18 The second building block for the synthesis of (±)-lavanduquinocin (rac-1) is the arylamine 12. Compound 12 was previously used as precursor in our total synthesis of (±)-carquinostatin A (rac-2) and was obtained in five steps and 69% overall yield starting from commercial 3-methylveratrole.10

Scheme 2. Iron-mediated synthesis of the 6-bromocarbazole 10. Reagents and conditions: (a) MeCN, air, r.t., 7 d, 88%; (b) 1. Me₃NO, acetone, 56 °C, 4.5 h; 2. 10% Pd/C, o-xylene, 145 °C, 4 h, 82% over two steps; (c) NBS, CCl₄, 77 °C, 30 min, 93%.
Reaction of the iron complex salt 13 with two equivalents of the arylamine 12 in acetonitrile at room temperature for seven days in air, followed by demetalation using trimethylamine N-oxide\(^{19,20}\) and aromatization with 10% palladium on activated carbon in boiling \(\sigma\)-xylene\(^{21}\) provided the carbazole 14. Electrophilic bromination of 14 with N-bromosuccinimide (NBS) in tetrachloromethane at reflux afforded regioselectively the 6-bromocarbazole 10 (Scheme 2).

The third component for the synthesis of (\(\pm\))-lavandaquinocin (\(r-ac\)) is \(\beta\)-cyclolavandulyl bromide (9). Fine-tuning of the reaction conditions provided a considerably improved access to compound 9 as compared to the original synthesis described much earlier (Scheme 3).\(^{22-24}\) Thus, deprotonation of commercial ethyl senecioate (15) using lithium diisopropylamide (LDA) followed by kinetic quenching with prenyl bromide leads to ethyl lavandulate. Without further characterization this intermediate was subjected to alkaline hydrolysis to give lavandulic acid (16).\(^{22}\) Using optimized reaction conditions, proton-initiated cyclization of 16 afforded crystalline \(\beta\)-cyclolavandulic acid (17) in 78% yield. Reduction of 17 with lithium aluminum hydride provided \(\beta\)-cyclolavandulyl alcohol (18).\(^{23}\) Base-catalyzed allylic bromination of compound 18 with phosphorus tribromide afforded the desired \(\beta\)-cyclolavandulyl bromide (9).\(^{24}\) Using this route \(\beta\)-cyclolavandulyl bromide (9) is available in five steps and 62% overall yield based on ethyl senecioate (15) (Scheme 3).

\[\begin{array}{cccc}
\text{EtO}_2\text{C} & \xrightarrow{a} & \text{EtO}\text{C} & \text{OH} \\
15 & \xrightarrow{b} & 16 & \xrightarrow{c} 17 \\
\text{Br} & \xrightarrow{d} & \text{OH} & \xrightarrow{e} 9 \\
& & 18 & \\
\end{array}\]

**Scheme 3.** Improved synthesis of \(\beta\)-cyclolavandulyl bromide (9). *Reagents and conditions:* (a) 1. LDA, THF, –78 °C, 30 min; 2. prenyl bromide, –78 °C to r.t., 15 h; (b) NaOH, EtOH/H\(_2\)O, reflux, 48 h; then HCl, 87% over two steps; (c) HCOOH/H\(_2\)SO\(_4\) (5.3:1), r.t., 6.5 d, 78%; (d) LiAlH\(_4\), Et\(_2\)O, 0 °C, 3 h, 100%; (e) PBr\(_3\), pyridine, Et\(_2\)O, –78 °C to r.t., 1.5 h, 92%.

The dinuclear nickel complex 19 was prepared analogously to the known dimeric \(\pi\)-prenynickel bromide complex,\(^{25}\) which was used by us previously for the total synthesis of carquinostatin A (2)\(^{10,11}\) and neocarazostatin B.\(^{14}\) Reaction of \(\beta\)-cyclolavandulyl bromide (9) with an excess of tetracarbonylnickel in benzene at 60–65 °C afforded after 2.5 h a red-brown solution indicating the formation of the dimeric \(\pi\)-allylnickel bromide complex 19 (Scheme 4). The
presumed complex \(19\) was not isolated and characterized, since this type of dimeric \(\pi\)-allylnickel bromide complexes are known to be very sensitive towards oxidation.\(^{25}\) After evaporation of benzene and unreacted tetracarbonylnickel, the crude complex \(19\) could be used for the projected cross coupling reaction.

\[
\begin{align*}
\text{Scheme 4. Synthesis of the dimeric } \pi-(\beta\text{-cyclolavandulyl})\text{nickel bromide complex } 19. \\
\text{Reagents and conditions: (a) excess of Ni(CO)}_4, \text{benzene, 60–65 °C, 2.5–3.5 h.}
\end{align*}
\]

Initially, cross coupling of the dimeric \(\pi\)-allylnickel bromide \(19\) and the 6-bromocarbazole \(10\) was achieved by reaction of 6-bromocarbazole \(10\), \(\beta\text{-cyclolavandulyl} \)bromide \((9)\) and tetracarbonylnickel in a ratio of 1:2:6 (Scheme 5, Table 1). The mixture of \(\beta\text{-cyclolavandulyl} \)bromide \((9)\) and tetracarbonylnickel was heated at 60–65 °C in benzene for 2.5 h as described above. The crude complex \(19\) was then treated with 6-bromocarbazole \(10\) in dry and degassed \(N,\text{N}-\text{dimethylformamide (DMF) at 70 °C under the strict exclusion of oxygen. This procedure provided the desired 6-(\(\beta\text{-cyclolavandulyl})\text{carbazole } 20\) in 50% yield. Moreover, 37% of the starting material } 10, \text{ the carbazole } 14 (\text{formed by hydrodebromination of } 10, 8\% \text{ yield}) \text{ and the}
dimer 22 (resulting from homocoupling of β-cyclolavandulyl bromide (9), 34% yield) were isolated. The recovery of large amounts of starting material induced us to perform the coupling reaction using an even larger excess of tetracarbonylnickel (10 equivalents). These conditions afforded in addition to the compounds 20, 10, 14 and 22, the 6-acylcarbazole 21 in 13% yield. Obviously, compound 21 was formed by insertion of carbon monoxide resulting from excess tetracarbonylnickel. The 6-acylcarbazole 21 shows significant activity against *Mycobacterium tuberculosis* (H37Rv strain) with an MIC value of 4.0 μg mL⁻¹ (8 μM) and is relatively nontoxic for mammalian cells.²⁶

Table 1. Nickel-mediated coupling of β-cyclolavandulyl bromide (9) with bromocarbazole 10

<table>
<thead>
<tr>
<th>Stoichiometry 10 : 9 : Ni(CO)₄</th>
<th>Reaction Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 : 2 : 6</td>
<td>1. Ni(CO)₄, 9, C₆H₆, 60 °C, 1 h; 2. 65 °C, 1.5 h; 3. addition of 10, DMF, 70 °C, 17 h</td>
<td>50  37  8  34</td>
</tr>
<tr>
<td>1 : 2 : 10</td>
<td>1. Ni(CO)₄, 9, C₆H₆, 65 °C, 3.5 h; 2. addition of 10, DMF, 70 °C, 16 h</td>
<td>44  13  33  4  34</td>
</tr>
</tbody>
</table>

* The formation of dimer 22 (34% yield) results from the excess of compound 9 which is applied.

Removal of the acetyl protecting group at the side chain by reduction of the 6-(β-cyclolavandulyl)carbazole 20 with lithium aluminum hydride afforded almost quantitatively the carbinol 23. Finally, oxidation of 23 with ceric ammonium nitrate in an acetonitrile–water mixture at 0 °C provided (+)-lavanduquinocin (rac-1) in 68% yield (Scheme 6).

![Scheme 6. Synthesis of (+)-lavanduquinocin (rac-1). Reagents and conditions: (a) LiAlH₄, Et₂O, r.t., 1 h, 98%; (b) Ce(NH₄)₂(NO₃)₆, MeCN/H₂O (2:1), 0 °C, 30 min, 68%.](image-url)
Conclusions

The spectroscopic data of our synthetic (±)-lavanduquinocin (rac-1) are in good agreement with those reported for the natural product (UV, IR, 1H NMR, 13C NMR). Thus, the structural assignment of the natural product by Seto et al. has been confirmed by our total synthesis. The present route affords (±)-lavanduquinocin (rac-1) in seven steps and 22% overall yield based on the iron complex salt 13 and emphasizes the utility of our iron-mediated carbazole synthesis in paving the way for efficient routes to this class of natural products.

Experimental Section

General. All reactions were carried out using dry solvents under argon atmosphere unless stated otherwise. Flash chromatography: Merck silica gel (0.03–0.06 mm). Melting points: Büchi 535. UV spectra: Perkin–Elmer Lambda 2 (UV/VIS spectrometer). IR spectra: Bruker IFS 88 (FT–IR). 1H NMR and 13C NMR spectra: Bruker AC-250, Bruker AM-400, and Bruker DRX-500; internal standard: tetramethylsilane or the signal of the deuterated solvent; δ in ppm; coupling constants (J) in Hz. MS: Finnigan MAT-90; ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid.

1-[6-Bromo-3,4-dimethoxy-2-methyl-(9H-carbazol-1-yl)propan-2-yl acetate (10). Colorless crystals; mp: 130–131 °C. For the synthesis and spectral data, see ref. 10b

2-(1-Methylethenyl)-5-methyl-4-hexenoic acid (Lavandulic acid) (16). Neat ethyl senecioate (ethyl 3,3-dimethylacrylate) (15) (9.59 g, 10.4 mL, 74.8 mmol) was added dropwise over a period of 20 min to a solution of lithium diisopropylamide (LDA) [diisopropylamine (8.66 g, 12.0 mL, 85.6 mmol) and 1.6 M BuLi in hexane (80.0 mmol, 50.0 mL)] in tetrahydrofuran (50 mL) at −78 °C. After stirring for 30 min at the same temperature, prenyl bromide (11.9 g, 9.24 mL, 80.0 mmol) was added. The resulting yellow homogeneous reaction mixture was allowed to warm up to room temperature and stirring was continued for 15 h. The mixture was poured into a saturated aqueous solution of ammonium chloride (100 mL) and conc. HCl (9 mL). After separation of the organic layer, the aqueous layer was extracted with diethyl ether (5 × 25 mL). The combined organic layers were washed with water (2 × 25 mL) and dried over sodium sulfate. The solvent was evaporated to afford a yellowish red viscous liquid (14.2 g, 72.3 mmol, 97%). Without further purification, the crude product, ethyl 2-(1-methylethenyl)-5-methyl-4-hexenoate, was dissolved in ethanol (50 mL) and water (4 mL) followed by addition of NaOH (4.50 g, 112.5 mmol). The resulting dark red reaction mixture was heated at reflux for 48 h. After cooling to room temperature, the ethanol was removed to afford a dark red residue. Aqueous 10% KOH (50 mL) was added to the residue and the aqueous layer was washed with diethyl ether (50 mL). Conc. HCl was added to the aqueous solution (till pH < 1), which was then extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with water...
(2 × 50 mL) and dried over sodium sulfate. Removal of the solvent in vacuo and distillation at 76–78 °C (0.025 Torr) provided lavandulic acid (16), yield: 11.01 g (87%, two steps), as colorless oil; 1H NMR (250 MHz, CDCl3): δ = 1.63 (s, 3 H), 1.69 (s, 3 H), 1.79 (s, 3 H), 2.28 (m, 1 H), 2.53 (m, 1 H), 3.05 (t, J = 7.7 Hz, 1 H), 4.94 (s, 2 H), 5.05 (m, 1 H). For further spectral data, see ref. 22

**2,4,4-Trimethyl-1-cyclohexen-1-ylcarboxylic acid (β-Cyclolavandulic acid) (17).** Lavandulic acid (16) (8.58 g, 51.0 mmol) was added to a stirred solution of conc. formic acid (20 mL) and conc. sulfuric acid (3.8 mL) at room temperature. After stirring for 6.5 d at the same temperature, the reaction mixture was poured into water (40 mL). The precipitate was isolated by filtration over a period of 15 min to a solution of lithium aluminum hydride in tetrahydrofuran (1.0 M, 22.3 mL, 22.3 mmol) was added dropwise over a period of 15 min to a solution of β-cyclolavandulic acid (17) (2.50 g, 14.9 mmol) in diethyl ether (30 mL) at 0 °C. After stirring for 3 h at 0 °C, the mixture was carefully quenched with ice-cold water (40 mL) and conc. HCl (7.5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (5 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and dried over sodium sulfate. Removal of the solvent in vacuo afforded β-cyclolavandulic alcohol (18), yield: 2.29 g (100%). Light yellow oil; 1H NMR (250 MHz, CDCl3): δ = 0.89 (s, 6 H), 1.28 (br s, 1 H), 1.36 (t, J = 6.5 Hz, 2 H), 1.68 (s, 3 H), 1.75 (br s, 2 H), 2.13 (m, 2 H), 4.12 (s, 2 H). For further spectral data, see ref. 23

**1-(Bromomethyl)-2,4,4-trimethyl-1-cyclohexene (β-Cyclolavandulyl bromide) (9).** Phosphorus tribromide (0.80 g, 0.28 mL, 2.95 mmol) was added dropwise to a stirred solution of β-cyclolavandulyl alcohol (18) (1.01 g, 6.55 mmol) and pyridine (52 mg, 53 µL, 0.66 mmol) in diethyl ether (20 mL) at −78 °C. The resulting viscous liquid was allowed to warm to room temperature and stirring was continued for 1.5 h. The mixture was poured into water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (20 mL), then with water (20 mL), and dried over sodium sulfate. Removal of the solvent in vacuo and distillation at 93–95 °C (11 Torr) afforded β-cyclolavandulyl bromide (9), yield: 1.31 g (92%), as colorless oil; 1H NMR (250 MHz, CDCl3): δ = 0.89 (s, 6 H), 1.39 (t, J = 6.5 Hz, 2 H), 1.70 (s, 3 H), 1.77 (br s, 2 H), 2.16 (m, 2 H), 4.05 (s, 2 H). For further spectral data, see ref. 24

**1-[3,4-Dimethoxy-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylmethyl)-9H-carbazol-1-yl]propan-2-yl acetate (20), 1,2-Bis-(2,4,4-trimethyl-1-cyclohexen-1-yl)ethane (22) and 1-[3,4-Dimethoxy-2-methyl-9H-carbazol-1-yl]propan-2-yl acetate (14).** β-Cyclolavandulyl bromide (9) (1.17 g, 5.39 mmol) was added to a stirred solution of tetracarbonylnickel (2.10 mL, 2.77 g, 16.2 mmol) in degassed dry benzene (30 mL) at 60 °C. Stirring was continued for 1 h at
the same temperature under a slow stream of argon. After stirring at 65 °C for additional 1.5 h, all volatile components of the red solution were removed in vacuo to afford the red nickel complex 19. A solution of 6-bromocarbazole 10 (1.14 g, 2.71 mmol) in degassed dry DMF (15 mL) was added to the nickel complex 19. The resulting dark red solution was stirred at 70 °C for 17 h. After cooling to room temperature, the black reaction mixture was poured into water (60 mL) followed by addition of conc. HCl (1 mL) to dissolve the precipitate. The aqueous layer was extracted with diethyl ether (2 × 40 mL). The combined organic layers were subsequently washed with aqueous 5% HCl (30 mL), then with water (40 mL), and dried over sodium sulfate. Removal of the solvent and flash chromatography (hexane/ethyl acetate, 4:1) of the residue on silica gel provided the β-cyclolavandulyl dimer 22 (Rf = 0.70), 6-(β-cyclolavandulyl)carbazole 20 (Rf = 0.39), carbazole 14 (Rf = 0.31) and reisolated 6-bromocarbazole 10 (Rf = 0.28). Recrystallization of compound 20 from n-hexane afforded colorless crystals.

22. Yield: 250 mg (34%). Light yellow oil; 1H NMR (500 MHz, CDCl3): δ = 0.87 (s, 12 H), 1.31 (t, J = 6.5 Hz, 4 H), 1.59 (br s, 6 H), 1.69 (br s, 4 H), 1.98 (m, 4 H), 2.02 (s, 4 H); 13C NMR and DEPT (125 MHz, CDCl3): δ = 19.15 (2 CH3), 27.53 (2 CH2), 28.32 (4 CH3), 29.21 (2 C), 31.81 (2 CH2), 36.19 (2 CH2), 46.02 (2 CH3), 124.72 (2 C), 128.46 (2 C); MS (EI): m/z = 274 (29 [M•]), 259 (7), 189 (64), 138 (21), 137 (100), 136 (9), 95 (26), 81 (19); HRMS: m/z calc. for C20H34 [M•]: 274.2661, found: 274.2670.

20. Yield: 640 mg (50%). Colorless crystals; mp: 63–65 °C; UV (MeOH): λ = 226 (sh), 245, 255 (sh), 265, 288 (sh), 295, 331, 344 nm; IR (KBr): ν = 3314, 2929, 1723, 1613, 1503, 1447, 1398, 1369, 1253, 1108, 1056, 1011, 955, 806, 698, 617 cm−1; 1H NMR (500 MHz, CDCl3): δ = 0.892 (s, 3 H), 0.893 (s, 3 H), 1.28 (d, J = 6.3 Hz, 3 H), 1.30 (t, J = 6.5 Hz, 2 H), 1.80 (s, 3 H), 1.84 (s, 2 H), 1.96 (d, J = 6.2, 4.4 Hz, 2 H), 2.15 (s, 3 H), 2.40 (s, 3 H), 3.00 (dd, J = 13.7, 10.1 Hz, 1 H), 3.24 (dd, J = 13.7, 3.1 Hz, 1 H), 3.54 (s, 2 H), 3.88 (s, 3 H), 4.09 (s, 3 H), 5.03 (m, 1 H), 7.17 (dd, J = 8.3, 1.6 Hz, 1 H), 7.38 (d, J = 8.3 Hz, 1 H), 7.98 (s, 1 H), 9.45 (br s, 1 H); 13C NMR and DEPT (125 MHz, CDCl3): δ = 12.83 (CH3), 19.33 (CH3), 19.87 (CH3), 21.53 (CH3), 27.41 (CH2), 28.38 (CH3), 28.41 (CH3), 29.37 (C), 35.05 (CH2), 36.12 (CH2), 38.90 (CH2), 46.25 (CH2), 60.41 (CH3), 61.03 (CH3), 71.95 (CH), 110.33 (CH), 113.35 (C), 114.59 (C), 121.75 (CH), 122.38 (C), 125.88 (CH), 126.05 (C), 128.11 (C), 128.34 (C), 131.93 (C), 137.51 (C), 138.09 (C), 144.10 (C), 146.85 (C), 172.47 (C=O); MS (EI): m/z = 477 (100 [M•]), 462 (9), 402 (11), 390 (18); HRMS: m/z calc. for C30H39NO4 [M•]: 477.2879, found: 477.2869; Anal. calc. for C30H39NO4: C 74.54, H 8.23, N 2.93, found: C 75.27, H 8.50, N 3.16%.

14. Yield: 72 mg (8%). Light yellow crystals; mp: 91–93 °C. For spectral data, see ref.10b

10. Yield: 420 mg (37%). Colorless crystals; mp: 130–131 °C. For spectral data, see ref.10b

1-[3,4-Dimethoxy-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylmethyl)-9H-carbazol-1-yl]propan-2-yl acetate (20), 1-[3,4-Dimethoxy-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylacetyl)-9H-carbazol-1-yl]propan-2-yl acetate (21), 1,2-Bis-(2,4,4-trimethyl-1-cyclohexen-1-yl)ethane (22) and 1-[3,4-Dimethoxy-2-methyl-9H-carbazol-1-yl]propan-2-yl acetate (14).
tetracarboxylnickel (4.3 mL, 5.65 g, 33.1 mmol) in degassed dry benzene (30 mL) at 65 °C. Stirring was continued at the same temperature for 3.5 h under a slow stream of argon. All volatile components of the red solution were removed in vacuo to afford the red nickel complex 19. A solution of the 6-bromocarbazole 10 (1.39 g, 3.31 mmol) in degassed dry DMF (15 mL) was added to the nickel complex 19. The resulting dark red solution was stirred at 70 °C for 16 h. After cooling to room temperature, the black reaction mixture was poured into a solution of conc. HCl (2 mL) and water (60 mL). The aqueous layer was washed with diethyl ether (2 × 50 mL). The combined organic layers were dried over sodium sulfate. Removal of the solvent and flash chromatography (hexane/ethyl acetate, 4:1) of the residue on silica gel provided the β-cyclolavandulyl dimer 22 (Rf = 0.70), 6-((β-cyclolavandulyl)carbazole 20 (Rf = 0.39), carbazole 14 (Rf = 0.31), reisolated 6-bromocarbazole 10 (Rf = 0.28) and 6-acylcabazole 21 (Rf = 0.19).

22. Yield: 310 mg (34%). Light yellow oil. For spectral data, see above.

20. Yield: 695 mg (44%). Colorless crystals; mp: 63–65 °C. For spectral data, see above.

14. Yield: 45 mg (4%). Light yellow crystals; mp: 91–93 °C. For spectral data, see ref.10b

10. Yield: 460 mg (33%). Colorless crystals; mp: 130–131 °C. For spectral data, see ref.10b

21. Yield: 220 mg (13%). Colorless crystals; mp: 58–60 °C; UV (MeOH): λ = 216, 238, 249 (sh), 276, 288 (sh), 332 nm; IR (KBr): ν = 3321, 2946, 1738, 1713, 1674, 1660, 1507, 1472, 1447, 1396, 1373, 1310, 1259, 1111, 1057, 1008 cm–1; 1H NMR (500 MHz, CDCl3): δ = 0.87 (s, 6 H), 1.31 (d, J = 6.3 Hz, 3 H), 1.34 (t, J = 6.4 Hz, 2 H), 1.74 (s, 3 H), 1.82 (s, 2 H), 2.03 (m, 2 H), 2.18 (s, 3 H), 2.41 (s, 3 H), 3.03 (dd, J = 13.8, 10.2 Hz, 1 H), 3.25 (dd, J = 13.8, 2.6 Hz, 1 H), 3.84 (s, 2 H), 3.88 (s, 3 H), 4.14 (s, 3 H), 5.00 (m, 1 H), 7.48 (d, J = 8.5 Hz, 1 H), 8.08 (dd, J = 8.5, 1.6 Hz, 1 H), 8.88 (d, J = 1.6 Hz, 1 H), 10.04 (br s, 1 H); 13C NMR and DEPT (125 MHz, CDCl3): δ = 12.84 (CH3), 19.32 (CH3), 19.89 (CH3), 21.51 (CH3), 28.15 (CH2), 28.22 (2 CH3), 29.27 (C), 35.00 (CH2), 35.85 (CH2), 43.27 (CH2), 46.09 (CH2), 60.40 (CH3), 60.89 (CH3), 72.09 (CH), 110.37 (CH), 113.80 (C), 114.83 (C), 122.00 (C), 123.31 (C), 123.88 (CH), 125.78 (CH), 128.26 (C), 129.19 (C), 129.54 (C), 137.60 (C), 142.48 (C), 144.72 (C), 147.03 (C), 172.82 (C=O), 198.53 (C=O); MS (EI): m/z = 505 (15) [M⁺], 368 (100), 308 (9), 265 (8); HRMS: m/z calc. for C31H29NO5 [M⁺]: 505.2828, found: 505.2817; Anal. calc. for C31H39NO5: C 73.63, H 7.77, N 2.77, found: C 73.42, H 7.70, N 2.81%.

1-[3,4-Dimethoxy-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylmethyl)-(9H-carbazol-1-yl)propan-2-ol (23). A solution of lithium aluminum hydride in tetrahydrofuran (1.0 M, 1.21 mL, 1.21 mmol) was added dropwise to a solution of the 6-(β-cyclolavandulyl)carbazole 20 (362 mg, 0.76 mmol) in diethyl ether (15 mL) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was slowly hydrolyzed with water (25 mL) followed by addition of conc. HCl (0.5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (30 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed. Flash chromatography (hexane/ethyl acetate, 2:1) of the residue on silica gel provided the carbazole 23, yield: 324 mg (98%). Colorless solid; mp: 149–
150 °C; UV (MeOH): λ = 231 (sh), 245, 255 (sh), 265, 288 (sh), 296, 332, 345 nm; IR (KBr): ν = 3371 (br), 2907, 1611, 1500, 1458, 1396, 1306, 1205, 1112, 1059, 1007, 937, 809 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 0.89 (s, 6 H), 1.30 (t, J = 6.5 Hz, 2 H), 1.34 (d, J = 6.2 Hz, 3 H), 1.75 (br s, 1 H), 1.80 (s, 3 H), 1.83 (s, 2 H), 1.95 (m, 2 H), 2.37 (s, 3 H), 2.94 (dd, J = 14.6, 8.3 Hz, 1 H), 3.04 (dd, J = 14.6, 3.5 Hz, 1 H), 3.53 (s, 2 H), 3.88 (s, 3 H), 4.08 (s, 3 H), 4.17 (m, 1 H), 7.15 (dd, J = 8.3, 1.6 Hz, 1 H), 7.28 (d, J = 8.3 Hz, 1 H), 7.98 (s, 1 H), 8.45 (br s, 1 H); ¹³C NMR and DEPT (100 MHz, CDCl₃): δ = 12.70 (CH₃), 19.88 (CH₃), 23.51 (CH₃), 27.43 (CH₂), 28.41 (2 CH₃), 29.38 (C), 36.12 (CH₂), 38.02 (CH₂), 38.89 (CH₂), 46.24 (CH₂), 60.44 (CH₃), 61.06 (CH₃), 68.99 (CH), 110.31 (CH), 115.03 (C), 115.13 (C), 121.91 (CH), 122.89 (C), 125.86 (CH), 126.15 (C), 128.04 (C), 128.85 (C), 132.24 (C), 138.26 (C), 138.30 (C), 144.41 (C), 146.67 (C); MS (EI): m/z = 435 (100) [M⁺], 420 (19), 390 (40); HRMS: m/z calc. for C₂₈H₃₇NO₃ [M⁺]: 435.2773, found: 435.2787; Anal. calc. for C₂₈H₃₇NO₃: C 77.20, H 8.56, N 3.22, found: C 77.02, H 8.41, N 3.35%.

(±)-Lavanduquinocin [(±)-1-(2-Hydroxypropyl)-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylmethyl)-9H-carbazol-3,4-dione] (rac-1). A solution of ceric ammonium nitrate (356 mg, 0.65 mmol) in water (1.5 mL) was added slowly to a solution of the carbazole 23 (95 mg, 0.22 mmol) in acetonitrile (3 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min and then poured into ice-water (1.5 mL). The precipitate was isolated by filtration, washed with water and dried in vacuum to afford (±)-lavanduquinocin (rac-1) as a brown solid, which was recrystallized from chlorobenzene (35 mL), yield: 60 mg (68%). Black crystals; mp: 221 °C; UV (MeOH): λ = 231 (25100), 268 (23100), 427 (4900) nm; IR (KBr): ν = 3532, 3438 (br), 3216, 2952, 1653, 1639, 1618, 1600, 1587, 1475, 1383, 1370, 1351, 1284, 1252, 1205, 1164, 1119, 1101, 1084, 1048, 989 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ = 0.83 (s, 6 H), 1.22 (d, J = 6.0 Hz, 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), 3.93 (m, 1 H), 4.86 (br s, 1 H), 6.99 (dd, J = 8.4, 1.5 Hz, 1 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.63 (s, 1 H), 12.13 (br s, 1 H); ¹³C NMR and DEPT (125 MHz, DMSO-d₆): δ = 12.18 (CH₃), 19.60 (CH₃), 23.73 (CH₃), 26.82 (CH₂), 28.06 (CH₃), 28.09 (CH₃), 28.95 (C), 35.42 (CH₂), 37.70 (CH₂), 38.40 (CH₂), 45.59 (CH₂), 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 (EI): m/z = 407 (100) [M⁺ +2], 405 (17) [M⁺], 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: m/z calc. for C₂₈H₃₁NO₃ [M⁺]: 405.2304, found: 405.2289.

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References