Transition metals in organic synthesis, Part 98.[1]
Transition metal mediated total synthesis of the potent neuronal cell protecting alkaloid (±)-lavanduquinocin

Wolfgang Fröhner, Kethiri R. Reddy, and Hans-Joachim Knölker*

Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany
E-mail: hans-joachim.knoelker@tu-dresden.de

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

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 (**1**), 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 EC_{50} 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 *o*-benzoquinone moiety, an (*R*)-2-hydroxypropyl substituent at the 1-position of the carbazole nucleus and a monoterpenoidal β-cyclolavandulyl side chain at C-6.
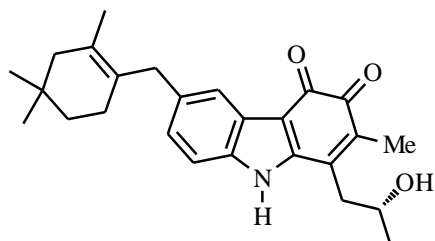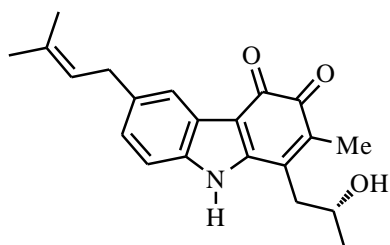

1 Lavanduquinocin
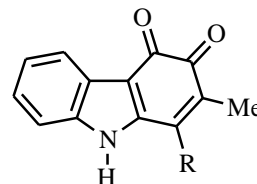
3 Carbazoquinocin A R = $(CH_2)_2CHMeCH_2Me$
4 Carbazoquinocin B R = $(CH_2)_4CHMe_2$
5 Carbazoquinocin C R = $(CH_2)_6Me$
6 Carbazoquinocin D R = $(CH_2)_4CHMeCH_2Me$
7 Carbazoquinocin E R = $(CH_2)_5CHMe_2$
8 Carbazoquinocin F R = $(CH_2)_6CHMe_2$

2 Carquinostatin A

Figure 1. Naturally occurring carbazole-3,4-quinone alkaloids.

Results and Discussion

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 (*rac*-**1**) in full detail.[12]

Results and Discussion

For the total synthesis of (±)-lavanduquinocin (*rac*-**1**) we envisaged a nickel-mediated introduction of the β-cyclolavandulyl residue. Thus, (±)-lavanduquinocin (*rac*-**1**) should derive from β-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).
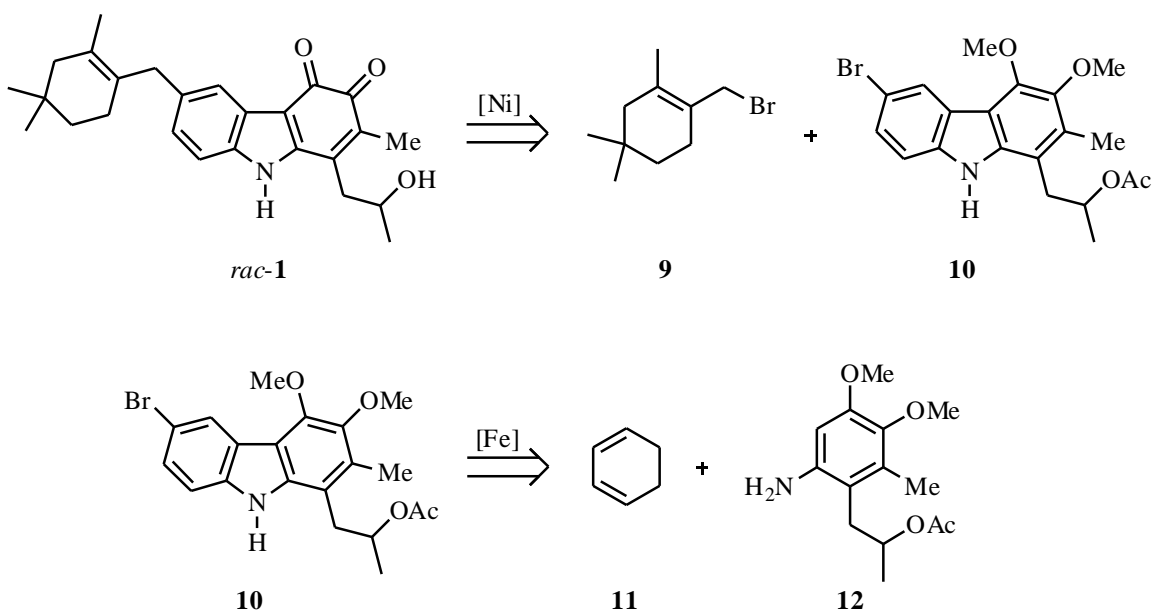
**Scheme 1.** Retrosynthetic analysis of (±)-lavanduquinocin (*rac*-**1**).

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 pentacarbonyliron[17] 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]
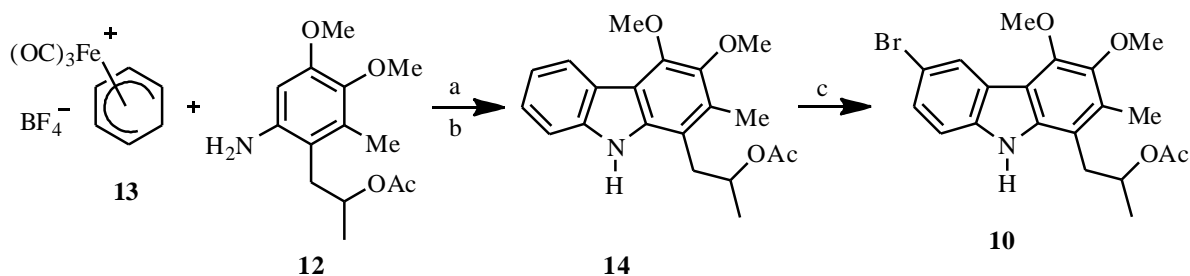
Scheme 2. Iron-mediated synthesis of the 6-bromocarbazole **10**. *Reagents and conditions*: (a) MeCN, air, r.t., 7 d, 88%; (b) 1. Me₃NO, acetone, 56 °C, 4.5 h; 2. 10% Pd/C, *o*-xylene, 145 °C, 4 h, 82% over two steps; (c) NBS, CCl₄, 77 °C, 30 min, 93%.

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 *o*-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 (±)-lavanduquinocin (*rac*-**1**) is β-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 β-cyclolavandulic acid (**17**) in 78% yield. Reduction of **17** with lithium aluminum hydride provided β-cyclolavandulyl alcohol (**18**).[23] Base-catalyzed allylic bromination of compound **18** with phosphorus tribromide afforded the desired β-cyclolavandulyl bromide (**9**).[24] Using this route β-cyclolavandulyl bromide (**9**) is available in five steps and 62% overall yield based on ethyl senecioate (**15**) (Scheme 3).
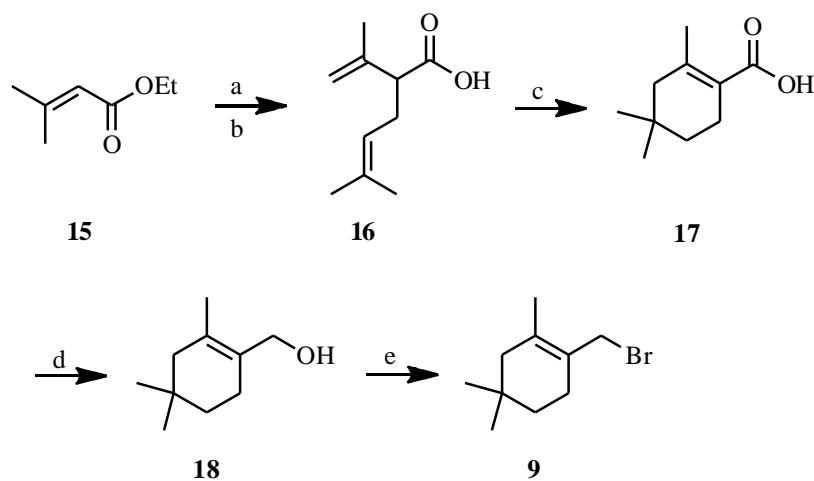

Scheme 3. Improved synthesis of β-cyclolavandulyl bromide (**9**). *Reagents and conditions*: (a) 1. LDA, THF, –78 °C, 30 min; 2. prenyl bromide, –78 °C to r.t., 15 h; (b) NaOH, EtOH/H_2O, reflux, 48 h; then HCl, 87% over two steps; (c) HCOOH/H_2SO_4 (5.3:1), r.t., 6.5 d, 78%; (d) $LiAlH_4$, Et_2O, 0 °C, 3 h, 100%; (e) PBr_3, pyridine, Et_2O, –78 °C to r.t., 1.5 h, 92%.

The dinuclear nickel complex **19** was prepared analogously to the known dimeric π-prenylnickel 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 β-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 π-allylnickel bromide complex **19** (Scheme 4). The

presumed complex **19** was not isolated and characterized, since this type of dimeric π-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.
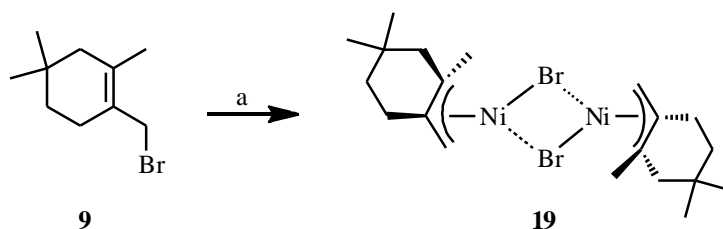
Scheme 4. Synthesis of the dimeric π-(β-cyclolavandulyl)nickel bromide complex **19**. *Reagents and conditions*: (a) excess of Ni(CO)$_4$, benzene, 60–65 °C, 2.5–3.5 h.
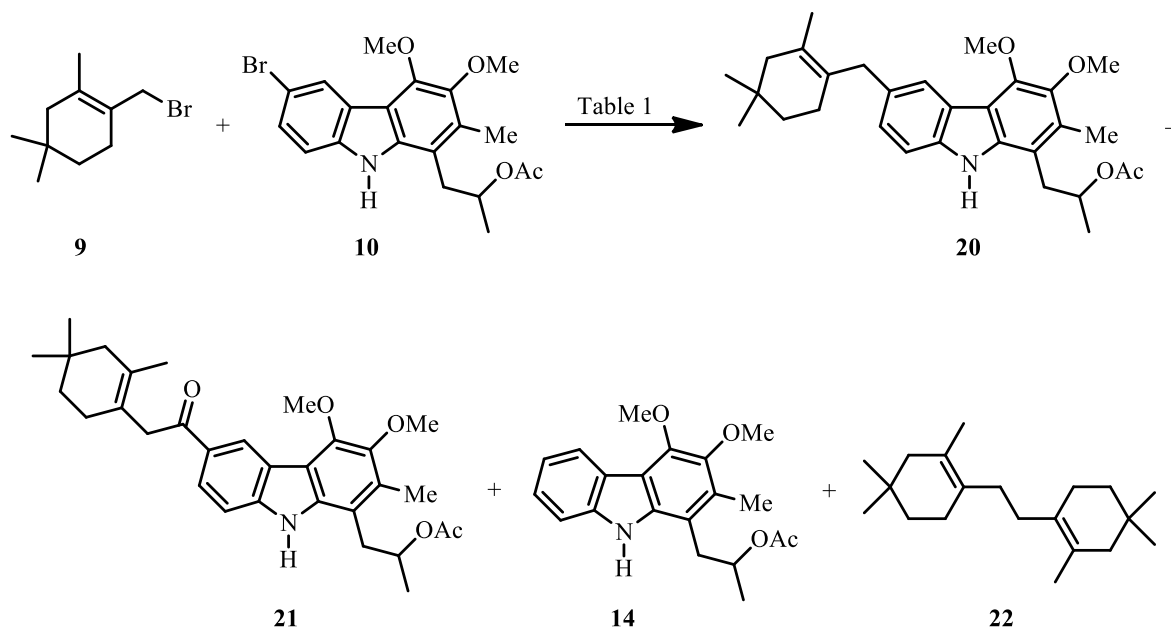
Scheme 5. Synthesis of 6-(β-cyclolavandulyl)carbazole **20**.

Initially, cross coupling of the dimeric π-allylnickel bromide **19** and the 6-bromocarbazole **10** was achieved by reaction of 6-bromocarbazole **10**, β-cyclolavandulyl bromide (**9**) and tetracarbonylnickel in a ratio of 1:2:6 (Scheme 5, Table 1). The mixture of β-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,N*-dimethylformamide (DMF) at 70 °C under the strict exclusion of oxygen. This procedure provided the desired 6-(β-cyclolavandulyl)carbazole **20** in 50% yield. Moreover, 37% of the starting material **10**, the carbazole **14** (formed by hydrodebromination of **10**, 8% yield) 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* (H$_{37}$Rv 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**

Stoichiometry **10** : **9** : Ni(CO)$_4$	Reaction Conditions	Yield [%]				
		20	**21**	**10**	**14**	**22**[a]
1 : 2 : 6	1. Ni(CO)$_4$, **9**, C$_6$H$_6$, 60 °C, 1 h; 2. 65 °C, 1.5 h; 3. addition of **10**, DMF, 70 °C, 17 h	50	–	37	8	34
1 : 2 : 10	1. Ni(CO)$_4$, **9**, C$_6$H$_6$, 65 °C, 3.5 h; 2. addition of **10**, DMF, 70 °C, 16 h	44	13	33	4	34

[a] 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).
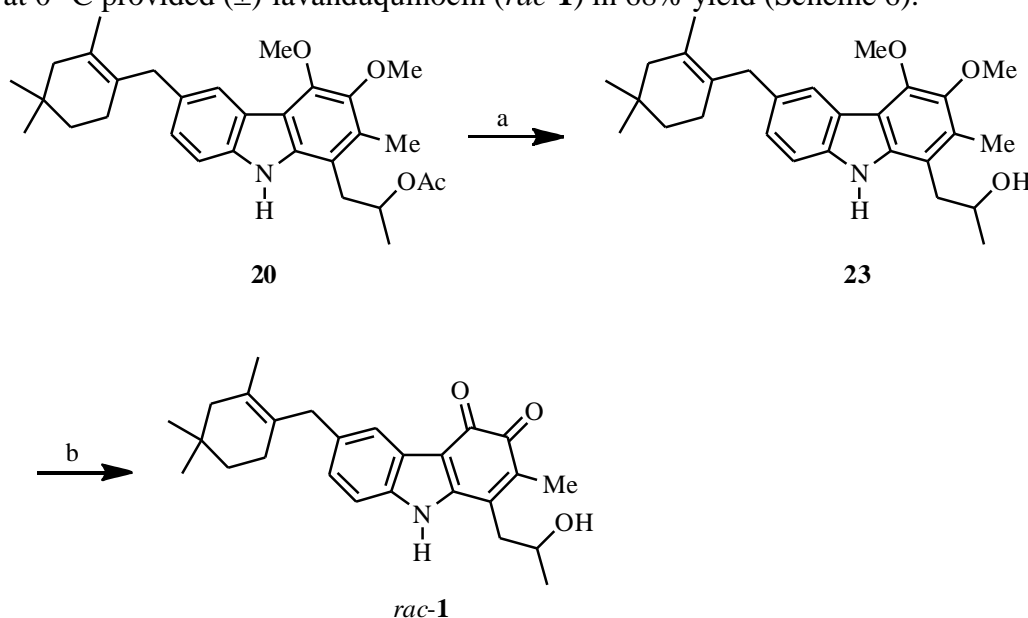
Scheme 6. Synthesis of (±)-lavanduquinocin (*rac*-**1**). *Reagents and conditions*: (a) LiAlH$_4$, Et$_2$O, r.t., 1 h, 98%; (b) Ce(NH$_4$)$_2$(NO$_3$)$_6$, MeCN/H$_2$O (2:1), 0 °C, 30 min, 68%.

Conclusions

The spectroscopic data of our synthetic (±)-lavanduquinocin (*rac*-**1**) are in good agreement with those reported for the natural product (UV, IR, ^{1}H NMR, ^{13}C NMR).[5] 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). ^{1}H NMR and ^{13}C 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-(9*H*-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; ^{1}H NMR (250 MHz, CDCl$_3$): 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 and washed with water until the filtrate was neutral. Then, the precipitate was washed with methanol/water (1:1, 20 mL) and dried in vacuo to afford β-cyclolavandulic acid (**17**), yield: 6.73 g (78%). Colorless crystals; mp: 110–111 °C (lit.[23] 110–111 °C); ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.91 (s, 6 H), 1.38 (t, *J* = 6.5 Hz, 2 H), 1.95 (br s, 2 H), 2.07 (s, 3 H), 2.34 (m, 2 H). For further spectral data, see ref.[23]

(2,4,4-Trimethyl-1-cyclohexen-1-yl)methanol (β-Cyclolavandulyl alcohol) (18). 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-cyclolavandulyl alcohol (**18**), yield: 2.29 g (100%). Light yellow oil; ^{1}H NMR (250 MHz, CDCl$_3$): 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; ^{1}H NMR (250 MHz, CDCl$_3$): 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)-9*H*-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-9*H*-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** (R_f = 0.70), 6-(β-cyclolavandulyl)carbazole **20** (R_f = 0.39), carbazole **14** (R_f = 0.31) and reisolated 6-bromocarbazole **10** (R_f = 0.28). Recrystallization of compound **20** from *n*-hexane afforded colorless crystals.

22. Yield: 250 mg (34%). Light yellow oil; ^{1}H NMR (500 MHz, CDCl$_3$): 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); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 19.15 (2 CH$_3$), 27.53 (2 CH$_2$), 28.32 (4 CH$_3$), 29.21 (2 C), 31.81 (2 CH$_2$), 36.19 (2 CH$_2$), 46.02 (2 CH$_2$), 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 C$_{20}$H$_{34}$ [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}; ^{1}H NMR (500 MHz, CDCl$_3$): 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); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 12.83 (CH$_3$), 19.33 (CH$_3$), 19.87 (CH$_3$), 21.53 (CH$_3$), 27.41 (CH$_2$), 28.38 (CH$_3$), 28.41 (CH$_3$), 29.37 (C), 35.05 (CH$_2$), 36.12 (CH$_2$), 38.90 (CH$_2$), 46.25 (CH$_2$), 60.41 (CH$_3$), 61.03 (CH$_3$), 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 C$_{30}$H$_{39}$NO$_4$ [M$^+$]: 477.2879, found: 477.2869; Anal. calc. for C$_{30}$H$_{39}$NO$_4$: C 75.44, 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)-9*H*-carbazol-1-yl]propan-2-yl acetate (20), 1-[3,4-Dimethoxy-2-methyl-6-(2,4,4-trimethyl-1-cyclohexen-1-ylacetyl)-9*H*-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-9*H*-carbazol-1-yl]propan-2-yl acetate (14).
β-Cyclolavandulyl bromide (**9**) (1.44 g, 6.63 mmol) was added to a stirred solution of

tetracarbonylnickel (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 extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with 5% HCl (40 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** (R_f = 0.70), 6-(β-cyclolavandulyl)carbazole **20** (R_f = 0.39), carbazole **14** (R_f = 0.31), reisolated 6-bromocarbazole **10** (R_f = 0.28) and 6-acylcarbazole **21** (R_f = 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, 1607, 1503, 1447, 1396, 1373, 1310, 1259, 1111, 1057, 1008 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): 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); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 12.84 (CH$_3$), 19.32 (CH$_3$), 19.89 (CH$_3$), 21.51 (CH$_3$), 28.15 (CH$_2$), 28.22 (2 CH$_3$), 29.27 (C), 35.00 (CH$_2$), 35.85 (CH$_2$), 43.27 (CH$_2$), 46.09 (CH$_2$), 60.40 (CH$_3$), 60.89 (CH$_3$), 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 C$_{31}$H$_{39}$NO$_5$ [M$^+$]: 505.2828, found: 505.2817; Anal. calc. for C$_{31}$H$_{39}$NO$_5$: 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)-(9*H*-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}; ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR and DEPT (100 MHz, CDCl$_3$): δ = 12.70 (CH$_3$), 19.88 (CH$_3$), 23.51 (CH$_3$), 27.43 (CH$_2$), 28.41 (2 CH$_3$), 29.38 (C), 36.12 (CH$_2$), 38.02 (CH$_2$), 38.89 (CH$_2$), 46.24 (CH$_2$), 60.44 (CH$_3$), 61.06 (CH$_3$), 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 C$_{28}$H$_{37}$NO$_3$ [M$^+$]: 435.2773, found: 435.2787; Anal. calc. for C$_{28}$H$_{37}$NO$_3$: 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, 2908, 2863, 1653, 1639, 1618, 1600, 1587, 1475, 1383, 1370, 1351, 1323, 1284, 1252, 1205, 1164, 1119, 1101, 1084, 1048, 989 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 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); ^{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 (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 C$_{26}$H$_{31}$NO$_3$ [M$^+$]: 405.2304, found: 405.2289.

Acknowledgements

References

1.　Fort part 97, see: Martin, R.; Jäger, A.; Knölker, H.-J. *Synlett* **2011**, 2795.

2.　(a) Chakraborty, D. P.; Roy, S. In *Progress in the Chemistry of Organic Natural Products*, Eds. Herz, W.; Grisebach, H.; Kirby, G. W.; Tam, C. Springer-Verlag: Wien, 1991, Vol. 57, p 71. (b) Chakraborty, D. P. In *The Alkaloids*, Ed. Cordell, G. A. Academic Press, New York, 1993, Vol. 44, p 257. (c) Knölker, H.-J. In *Advances in Nitrogen Heterocycles*, Ed. Moody, C. J. JAI Press: Greenwich (CT), 1995, Vol. 1, p 173. (d) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (e) Knölker, H.-J.; *Curr. Org. Synth.* **2004**, *1*, 309. (f) Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2004**, *63*, 2393. (g) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115. (h) Agarwal, S.; Cämmerer, S.; Filali, S.; Fröhner, W.; Knöll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (i) Knölker, H.-J. In *Modern Alkaloids*, Eds. Fattorusso, E.; Taglialatela-Scafati, O. Wiley-VCH: Weinheim, 2008, p 475. (j) Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*, Ed. Cordell, G. A. Academic: Amsterdam, 2008, Vol. 65, p 1. (k) Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8. (l) Gruner, K. K.; Knölker, H.-J. In *Heterocycles in Natural Product Synthesis*, Eds. Majumdar, K. C.; Chattopadhyay, S. K. Wiley-VCH: Weinheim, 2011, p 341. (m) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, *309*, 203.

3.　(a) Wu, T.-S.; Ohta, T.; Furukawa, H. Kuoh, C. S. *Heterocycles* **1983**, *20*, 1267. (b) Furukawa, H. *J. Indian Chem. Soc.* **1994**, *71*, 303.

4.　(a) Shin-ya, K.; Tanaka, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1993**, *34*, 4943. (b) Tanaka, M.; Shin-ya, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 326.

5.　Shin-ya, K.; Shimizu, S.; Kunigami, T.; Furihata, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 574.

6.　(a) Hammond, B.; Kantos, H. A.; Hess, M. L. *Can. J. Physiol. Pharmacol.* **1985**, *63*, 173. (b) Cerutti, P. A. *Science* **1985**, *227*, 375. (c) Halliwell, B.; Gutteridge, J. M. C. *Methods Enzymol.* **1990**, *186*, 1.

7.　(a) Knölker, H.-J.; Bauermeister, M.; Bläser, D.; Boese, R.; Pannek, J.-B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 223; *Angew. Chem.* **1989**, *101*, 225. (b) Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc. Chem. Commun.* **1989**, 1468. (c) Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc. Chem. Commun.* **1990**, 664. (d) Knölker, H.-J.; Bauermeister, M. *Heterocycles* **1991**, *32*, 2443. (e) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B.; *Chem. Ber.* **1992**, *125*, 2783. (f) Knölker, H.-J.; Jones, P. G.; Pannek, J.-B.; Weinkauf, A. *Synlett* **1991**, 147. (g) Knölker, H.-J.; *Synlett* **1992**, 371. (h) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B.; Bläser, D.; Boese, R. *Tetrahedron* **1993**, *49*, 841. (i) Knölker, H.-J.; Bauermeister, M. *Helv. Chim. Acta* **1993**, *76*, 2500. (j) Knölker, H.-J.; Bauermeister, M. *Tetrahedron* **1993**, *49*, 11221. (k) Knölker, H.-J.; *Chem. Soc. Rev.* **1999**, *28*, 151. (l) Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron* **1999**, *55*, 10391. (m) Knölker, H.-J.; Braier, A.; Bröcher, D. J.; Cämmerer, S.; Fröhner, W.; Gonser, P.; Hermann, H.; Herzberg, D.; Reddy, K. R.; Rohde, G. *Pure Appl. Chem.* **2001**, *73*, 1075. (n) Knölker, H.-J.; Fröhner, W.; Reddy, K. R.

Synthesis **2002**, 557. (o) Knölker, H.-J.; Hopfmann, T. *Tetrahedron* **2002**, *58*, 8937. (p) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Eur. J. Org. Chem.* **2003**, 740. (q) Knott, K. E.; Auschill, S.; Jäger, A.; Knölker, H.-J. *Chem. Commun.* **2009**, 1467. (r) Gruner, K. K.; Hopfmann, T.; Matsumoto, K.; Jäger, A.; Katsuki, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2011**, *9*, 2057.

8. (a) Knölker, H.-J.; Wolpert, M.; *Tetrahedron Lett*. **1997**, *38*, 533; (b) Knölker, H.-J.; Wolpert, M. *Tetrahedron* **2003**, *59*, 5317.

9. Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett*. **1997**, *38*, 1535.

10. (a) Knölker, H.-J.; Fröhner, W. *Synlett* **1997**, 1108. (b) Fröhner, W.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2007**, *74*, 895.

11. Knölker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett*. **2000**, *41*, 1171.

12. Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett*. **1998**, *39*, 2537.

13. Knölker, H.-J.; Baum, E.; Reddy, K. R. *Chirality* **2000**, *12*, 526.

14. (a) Knölker, H.-J.; Fröhner, W.; Wagner, A. *Tetrahedron Lett*. **1998**, *39*, 2947. (b) Czerwonka, R.; Reddy, K. R.; Baum, E.; Knölker, H.-J. *Chem. Commun*. **2006**, 711.

15. Knölker, H.-J.; Fröhner, W. *Tetrahedron Lett*. **1999**, *40*, 6915.

16. Thomas, C.; Kataeva, O.; Knölker, H.-J. *Synlett* **2011**, 2663.

17. (a) Knölker, H.-J.; Gonser, P.; *Synlett* **1992**, 517. (b) Knölker, H.-J.; Gonser, P.; Jones, P. G. *Synlett* **1994**, 405. (c) Knölker, H.-J.; Baum, G.; Foitzik, N.; Goesmann, H.; Gonser, P.; Jones, P. G.; Röttele, H. *Eur. J. Inorg. Chem.* **1998**, 993. (d) Knölker, H.-J.; Baum, E.; Gonser, P.; Rohde, G.; Röttele, H. *Organometallics* **1998**, *17*, 3916. (e) Knölker, H.-J. *Chem. Rev*. **2000**, *100*, 2941.

18. Fischer, E. O.; Fischer, R. D. *Angew. Chem*. **1960**, *72*, 919.

19. Shvo, Y.; Hazum, E. *J. Chem. Soc. Chem. Commun.* **1974**, 336.

20. Knölker, H.-J. *J. Prakt. Chem*. **1996**, *338*, 190.

21. Knölker, H.-J.; Baum, G.; Pannek, J.-B. *Tetrahedron* **1996**, *52*, 7345.

22. Furuhata, A.; Hirano, M.; Fujimoto, I.; Matsui, M. *Agric. Biol. Chem.* **1987**, *51*, 1633.

23. Kuhn, W.; Schinz, H. *Helv. Chim. Acta* **1952**, *35*, 2008.

24. Ferrero, C.; Schinz, H. *Helv. Chim. Acta* **1956**, *39*, 2109.

25. (a) Wilke, G.; Bogdanovic, B.; Hardt, P.; Heimbach, P.; Keim, W.; Kröner, M.; Oberkirch, W.; Tanaka, K.; Steinrücke, E.; Walter, D.; Zimmermann, H. *Angew. Chem.* **1966**, *78*, 157; *Angew. Chem. Int. Ed. Engl*. **1966**, *5*, 151. (b) Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc*. **1967**, *89*, 2755. (c) Plieninger, H.; Sirowej, H. *Chem. Ber*. **1971**, *104*, 2027. (d) Sato, K.; Inoue, S.; Yamaguchi, R. *J. Org. Chem*. **1972**, *37*, 1889. (e) Inoue, S.; Yamaguchi, R.; Saito, K.; Sato, K. *Bull. Chem. Soc. Jpn*. **1974**, *47*, 3098. (f) Billington, D. C. *Chem. Soc. Rev*. **1985**, *14*, 93.

26. Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812.