First total synthesis of the biscarbazole alkaloid oxydimurrayafoline†‡

Carsten Börger, Micha P. Krahle, Margit Gruner, Olga Kataeva and Hans-Joachim Knölker*

Received 2nd May 2012, Accepted 23rd May 2012

DOI: 10.1039/c2ob25842k

We report the first total synthesis of oxydimurrayafoline via nucleophilic substitution at the benzylic position at C-3 of the carbazole framework.

A broad range of structurally diverse carbazole alkaloids has been isolated from various natural sources.¹ Their useful biological activities induced the development of novel synthetic routes with a special focus on methods using transition metals.² We have described an iron-mediated approach and a palladium-catalysed approach to carbazoles, both of which have proven to be very efficient for numerous applications in natural product synthesis.^{3,4} Biscarbazoles are a class of carbazole alkaloids in which two carbazole moieties are connected by different linkages.^{1,5} In the present project, we aimed at the synthesis of oxydimurrayafoline (**1**), a special biscarbazole connecting two carbazole units via a benzylic ether linkage at the 3-position (Fig. 1).

Oxydimurrayafoline (**1**) was isolated in 1987 by Furukawa and co-workers from *Murraya euchrestifolia* Hayata as a colourless oil.⁶ So far, no synthesis of oxydimurrayafoline (**1**) has been reported. In 2005, Rahman and Gray isolated from the stem bark extract of *Murraya koenigii* 3,3'-[oxybis(methylene)]bis-(9-methoxy-9H-carbazole) (**2**) which can be designated as isooxydimurrayafoline.⁷ Isooxydimurrayafoline (**2**) showed potent inhibitory activity against Gram-negative bacteria and fungi.⁷ Another structurally related biscarbazole alkaloid is murrayafoline-F (**3**), which was isolated in 1988 by Furukawa *et al.* from the root bark of *Murraya euchrestifolia* Hayata.⁸ No synthetic approach towards murrayafoline-F (**3**) has been reported yet. The biscarbazole alkaloid **1** obviously derives from the monomeric 1-methoxycarbazoles **4**, a series of alkaloids which has been found to have the carbon substituent at C-3 in all possible oxidation states.¹ The envisaged synthesis of oxydimurrayafoline (**1**) should be feasible by etherification of the corresponding monomeric carbazole building block koenoline (**4b**) (Scheme 1). We decided to focus on mukonine (**4e**) as initial target carbazole

Fig. 1 Oxydimurrayafoline (**1**), isooxydimurrayafoline (**2**), murrayafoline-F (**3**), and the 1-methoxycarbazole alkaloids **4a–e**.

Scheme 1 Retrosynthetic analysis of oxydimurrayafoline (**1**).

as the ester group can be easily reduced to provide koenoline (**4b**). The synthesis of mukonine (**4e**) starting from commercially available methyl 4-amino-3-methoxybenzoate (**5**) using our iron-mediated approach was already reported more than 20 years ago.^{9,10}

Mukonine (**4e**) was isolated in 1978 by Chakraborty *et al.* from *Murraya koenigii* and later also by Wu *et al.* from *Clausena excavata*.^{11,12} A range of different synthetic routes to mukonine (**4e**) has been reported.^{9–11,13} For the total synthesis of

Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany. E-mail: hans-joachim.knoelker@tu-dresden.de; Fax: +49 351-463-37030

†Part 102 of Transition Metals in Organic Synthesis; for Part 101, see: ref. 4r.

‡Electronic supplementary information (ESI) available: ¹H and ¹³C NMR data of compounds **1**, **4e**, **14** and **16**. CCDC 878261. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25842k

Scheme 2 Synthesis of mukonine (**4e**). *Reagents and conditions:* (a) 2.3 equiv. **5**, MeCN, rt to 82 °C, 90 h, 68%; (b) very active MnO₂, rt, 2 d, 71%; (c) 5 mol% Pd(OAc)₂, 11 mol% SPhos, 0.9 equiv. **5**, 1.3 equiv. Cs₂CO₃, toluene, reflux, 40 h, 100%; (d) 10 mol% Pd(OAc)₂, 10 mol% K₂CO₃, PivOH, 115 °C, 14 h, 91%.

mukonine (**4e**), our iron-mediated and our palladium-catalysed synthesis can be both applied (Scheme 2). The iron complex salt **6** is prepared almost quantitatively by 1-azabutadiene-catalysed complexation of cyclohexa-1,3-diene with pentacarbonyliron and subsequent hydride abstraction with triphenylmethyl tetrafluoroborate.^{14,15} In an optimisation of our earlier approach,^{9,10} reaction of **6** with the arylamine **5** afforded the iron complex **7** in 68% yield. Oxidative cyclisation of complex **7** using very active manganese dioxide¹⁶ occurred with concomitant aromatisation and demetalation to provide directly mukonine (**4e**) in 71% yield. Alternatively, we have synthesised mukonine (**4e**) via our palladium-catalysed route.¹⁷ Using SPhos as ligand,¹⁸ the Buchwald–Hartwig coupling of bromobenzene (**8**) with the arylamine **5** afforded quantitatively the diarylamine **9**. Our conditions for this coupling provided **9** in significantly higher yield than those described by Fagnou *et al.*, who obtained the diarylamine **9** in 76% yield using XPhos as ligand.^{13g} On the other hand, our original conditions for the palladium(II)-catalysed oxidative cyclisation [20 mol% Pd(OAc)₂, Cu(OAc)₂, HOAc, reflux]^{4f} provided mukonine (**4e**) only in 51% yield.¹⁷ Whereas, using Fagnou's conditions [10 mol% Pd(OAc)₂, 10 mol% K₂CO₃, PivOH, 110 °C] for this transformation, mukonine (**4e**) is obtained in 91% yield.^{13g} Thus, using our present conditions for the Buchwald–Hartwig coupling and Fagnou's conditions for the oxidative cyclisation provides the best access to mukonine (**4e**) (2 steps, 91% overall yield). The best previous routes have been reported by Larock *et al.* (3 steps, 76% overall yield)^{13f} and Buchwald *et al.* (4 steps in 74% overall yield).^{13h} The structural assignment for mukonine (**4e**) was based on the spectroscopic data, which are in full agreement with those reported in the literature.^{§11}

The nitrogen atom of mukonine (**4e**) was protected either by a Boc group or a tosyl group to afford **10a** and **10b**, which on reduction with DIBAL-H afforded the protected koenolines **11a** and **11b** (Scheme 3). All attempts to convert the hydroxy group to the corresponding mesylate group by reaction with methanesulfonyl chloride provided exclusively the chloromethylcarbazoles **12a** and **12b**. Obviously, the initially formed mesylate is highly reactive and is prone to nucleophilic substitution by the chloride ion which has been released.

Scheme 3 Conversion of mukonine (**4e**) to the 3-chloromethylcarbazoles **12**. *Reagents and conditions:* (a) **a**: 2 equiv. Boc₂O, 1 equiv. DMAP, MeCN, rt, 17 h, 97% **10a**, **b**: 6.8 equiv. NaH, 3.4 equiv. TsCl, THF, 0 °C to rt, 15 h, 96% **10b**; (b) Et₂O, –78 °C, **a**: 3.2 equiv. DIBAL-H, 3.5 h, 100% **11a**, **b**: 6 equiv. DIBAL-H, 4.5 h, 100% **11b**; (c) 3 equiv. Et₃Pr₂N, CH₂Cl₂, **a**: 1.2 equiv. MsCl, 0 °C, 6.5 h, 90% **12a**, **b**: 2 equiv. MsCl, 0 °C to 5 °C, 7.5 h, 100% **12b**.

Fig. 2 Molecular structure of the chloromethylcarbazole **12b** in the crystal.

The structural assignment for the chloromethylcarbazole **12b** was confirmed by an X-ray crystal structure determination (Fig. 2).¶ In 1978, Witiak and co-workers already described the formation of a benzyl chloride by treatment of a benzylic alcohol with mesyl chloride.¹⁹ An attempted Williamson ether synthesis by deprotonation of the hydroxymethylcarbazole **11a** with sodium hydride and subsequent alkylation with chloromethylcarbazole **12a** failed to provide the protected oxydimurrayafoline **13**.

In view of the results described above, we decided to prepare the mesylate of *N*-Boc-koenoline (**11a**) in the strict absence of any nucleophile. Thus, compound **11a** was treated with substoichiometric amounts of methanesulfonyl anhydride in the presence of *N*-ethyldiisopropylamine to provide directly the di-Boc-oxydimurrayafoline **13** by reaction of **11a** with the intermediate mesylate (Scheme 4).

Scheme 4 Synthesis of oxydimurrayafoline (**1**). Reagents and conditions: (a) 0.75 equiv. Ms_2O , 3 equiv. $\text{Et}_3\text{Pr}_2\text{N}$, CH_2Cl_2 , 0 °C to rt, 15 h, 56% **13** and 24% **14**; (b) KOH, H_2O , MeOH, rt, 15 d, 86%.

Fig. 3 NOESY spectrum of compound **14**.

Under optimised conditions, the di-Boc-oxydimurrayafoline **13** was obtained in 56% yield along with compound **14** resulting from Friedel–Crafts alkylation. Presumably, the intermediate mesylate readily generates a benzylic cation. Thus, on treatment of the hydroxymethylcarbazoles **11** with mesyl chloride, attack of the liberated chloride ion as nucleophile leads to the chloromethylcarbazoles **12**. The present conditions, generation of the mesylate with substoichiometric amounts of methanesulfonic anhydride in the absence of chloride ions, open up the possibility of nucleophilic attack by the remaining benzylic alcohol **11a** to provide ether **13**. Electrophilic substitution by attack of the benzylic cation at C-2 of the carbazole nucleus of **11a** affords **14**. The structural assignment for **14** is supported by the spectroscopic data (^1H NMR, ^{13}C NMR, COSY and HSQC) and the linkage is confirmed by the NOESY spectrum (Fig. 3 and ESI†).

For completion of the synthesis of oxydimurrayafoline (**1**), the two Boc protecting groups had to be removed from

Scheme 5 Synthesis of 1-methoxy-2-(1-methoxy-9H-carbazol-3-ylmethyl)-3-methyl-9H-carbazole (**16**). Reagents and conditions: (a) KOH, H_2O , MeOH, rt, 36 d, 78%; (b) 5 equiv. LiAlH_4 , Et_2O , CH_2Cl_2 , rt, 18 h, 70%.

compound **13**. Thermal removal of the Boc group from *N*-Boc-carbazoles requires temperatures of about 180 °C.²⁰ However, at 140 °C complete decomposition of **13** occurred. Unfortunately, **13** is also not stable against strong acids, like trifluoroacetic acid. Finally, treatment of di-Boc-oxydimurrayafoline **13** with potassium hydroxide in aqueous methanol for 15 days at room temperature provided oxydimurrayafoline (**1**). The spectroscopic data of oxydimurrayafoline (**1**) are in good agreement with those reported in the literature.^{||6} The ^1H NMR spectrum of **1** has been additionally compared with the original spectrum of the isolated natural product, kindly provided by Professor Furukawa and Professor Ito. Our approach leads to oxydimurrayafoline (**1**) in six steps and 43% overall yield based on the arylamine **5**.

Carbazoles are of interest due to their antibiotic activity and the resulting pharmacological potential.^{1,21} However, the biological activity of biscarbazoles has not been studied extensively yet. Thus, we aimed at transforming compound **14** into 1-methoxy-2-(1-methoxy-9H-carbazol-3-ylmethyl)-3-methyl-9H-carbazole (**16**) which represents an isomurrayafoline-F (Scheme 5). The structure of by-product **14** resulting from Friedel–Crafts alkylation resembles that of murrayafoline-F (**3**) but has a different oxygenation pattern. Removal of the Boc groups using the reaction conditions described above led to the deprotected biscarbazole **15**. Reduction of **15** with lithium aluminium hydride afforded the isomurrayafoline-F **16**.||

Conclusions

In conclusion, *via* our palladium-catalysed approach we have achieved a highly efficient access to mukonine (**4e**) in only two steps and 91% overall yield. This represents the best current route to mukonine (**4e**). Using mukonine (**4e**) as key intermediate, we have completed the first total synthesis of oxydimurrayafoline (**1**) in six steps and 43% overall yield starting from commercially available compounds.

We are indebted to Professor Hiroshi Furukawa and Professor Chihiro Ito (Faculty of Pharmacy, Meijo University, Nagoya,

Japan) for providing the original ^1H NMR spectrum of oxydimurrayafoline. H.-J. K. is grateful to the Japan Society for Promotion of Science (JSPS) for a fellowship. We thank the Deutsche Forschungsgemeinschaft for financial support (grant KN 240/16-1).

Notes and references

§ Spectroscopic data for mukonine (**4e**): colourless crystals, mp 199–200 °C (lit.¹¹: 195 °C); UV (MeOH): λ = 219 (sh), 236, 247, 267, 276, 310, 320, 335 (sh) nm; IR (ATR): ν = 3371, 3315, 3007, 2949, 2845, 1692, 1631, 1609, 1582, 1499, 1447, 1435, 1407, 1348, 1315, 1291, 1257, 1230, 1181, 1157, 1106, 1092, 1034, 1010, 989, 912, 880, 841, 756, 732, 683, 638 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 3.98 (s, 3 H), 4.06 (s, 3 H), 7.29 (ddd, J = 7.8 Hz, 6.3 Hz, 1.3 Hz, 1 H), 7.46 (m, 2 H), 7.60 (d, J = 1.4 Hz, 1 H), 8.10 (dd, J = 7.8 Hz, 0.9 Hz, 1 H), 8.48 (d, J = 0.9 Hz, 1 H), 8.49 (br s, 1 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 52.19 (CH_3), 55.88 (CH_3), 106.80 (CH), 111.37 (CH), 116.36 (CH), 120.42 (CH), 120.90 (CH), 122.03 (C), 123.72 (C), 123.87 (C), 126.49 (CH), 133.02 (C), 139.62 (C), 145.19 (C), 168.11 (C=O); MS (EI): m/z (%) = 255 (M^+ , 100), 240 (42), 224 (33), 212 (8), 196 (10), 181 (14), 153 (17), 126 (11), 112 (8); anal. calc. for $\text{C}_{15}\text{H}_{13}\text{NO}_3$: C 70.58, H 5.13, N 5.49; found: C 70.31, H 5.36, N 5.39.

¶ Crystal data for 3-chloromethyl-1-methoxy-9-tosyl-9H-carbazole (**12b**): $\text{C}_{21}\text{H}_{18}\text{ClNO}_3\text{S}$, crystal size $0.42 \times 0.28 \times 0.15 \text{ mm}^3$, M = 399.87 g mol^{-1} , monoclinic, space group $P2_1/c$, λ = 0.71073 Å, a = 11.270(2), b = 12.954(2), c = 13.331(1) Å, β = 108.90(1)°, V = 1841.3(5) Å³, Z = 4, ρ_c = 1.442 g cm^{-3} , μ = 0.343 mm^{-1} , T = 198(2) K, θ range = 3.18 to 27.03°, reflections collected: 64 231; independent: 4022 (R_{int} = 0.1037). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 ; R_1 = 0.0352, wR_2 = 0.0728 [$I > 2\sigma(I)$]; maximal residual electron density: 0.235 e Å^{-3} . CCDC 878261.

|| Spectroscopic data for oxydimurrayafoline (**1**): colourless crystals, mp 114–115 °C (decomp.) (lit.⁶: oil); UV (MeOH): λ = 226, 243, 253, 260 (sh), 281, 291, 326, 338 nm; IR (ATR): ν = 3405, 3051, 2927, 2850, 2051, 1724, 1585, 1543, 1502, 1449, 1393, 1337, 1308, 1265, 1229, 1134, 1104, 1035, 1012, 948, 835, 767, 745, 732, 665 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 4.01 (s, 6 H), 4.76 (s, 4 H), 6.98 (d, J = 0.7 Hz, 2 H), 7.23 (ddd, J = 8.2 Hz, 6.9 Hz, 1.3 Hz, 2 H), 7.41 (ddd, J = 8.2 Hz, 7.3 Hz, 0.9 Hz, 2 H), 7.47 (d, J = 8.1 Hz, 2 H), 7.69 (d, J = 0.7 Hz, 2 H), 8.04 (d, J = 7.8 Hz, 2 H), 8.28 (br s, 2 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 55.70 (2 CH_3), 72.83 (2 CH_2), 106.60 (2 CH), 111.14 (2 CH), 113.04 (2 CH), 119.57 (2 CH), 120.67 (2 CH), 123.75 (2 C), 124.09 (2 C), 125.83 (2 CH), 129.60 (2 C), 130.30 (2 C), 139.53 (2 C), 145.82 (2 C); ESI-MS (10 eV): m/z = 437 [$\text{M} + \text{H}$]⁺, 890 [$2\text{M} + \text{NH}_4$]⁺.

Spectroscopic data for 1-methoxy-2-(1-methoxy-9H-carbazole-3-ylmethyl)-3-methyl-9H-carbazole (**16**): colourless crystals, mp 49.5–50.5 °C; UV (MeOH): λ = 226, 235, 241, 250 (sh), 292, 328, 339, 382, 417 nm; IR (ATR): ν = 3412, 3055, 2920, 2851, 2056, 1918, 1711, 1617, 1587, 1500, 1453, 1392, 1337, 1308, 1255, 1229, 1132, 1104, 1067, 1037, 1010, 943, 903, 870, 829, 766, 741, 629 cm^{-1} ; ^1H NMR (500 MHz, acetone- d_6): δ = 2.40 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.42 (s, 2 H), 6.91 (s, 1 H), 7.07 (ddd, J = 7.9 Hz, 6.9 Hz, 0.9 Hz, 1 H), 7.16 (ddd, J = 7.9 Hz, 6.9 Hz, 0.9 Hz, 1 H), 7.31 (ddd, J = 8.2 Hz, 7.3 Hz, 1.3 Hz, 1 H), 7.37 (ddd, J = 8.5 Hz, 7.3 Hz, 1.3 Hz, 1 H), 7.41 (s, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 7.53 (d, J = 8.8 Hz, 1 H), 7.73 (s, 1 H), 7.90 (d, J = 7.9 Hz, 1 H), 8.06 (d, J = 7.6 Hz, 1 H), 10.21 (br s, 1 H), 10.35 (br s, 1 H); ^{13}C NMR (125 MHz, acetone- d_6): δ = 20.43 (CH_3), 33.17 (CH_2), 55.76 (CH_3), 61.31 (CH_3), 107.88 (CH), 111.97 (CH), 112.10 (CH), 112.35 (CH), 117.73 (CH), 119.43 (CH), 119.61 (CH), 120.76 (CH), 120.90 (CH), 124.15 (C), 124.42 (C), 124.46 (C), 124.89 (C), 126.03 (CH), 126.13 (CH), 129.36 (C), 129.81 (C), 130.10 (C), 132.69 (C), 133.50 (C), 141.04 (C), 141.27 (C), 144.85 (C), 146.68 (C); ESI-MS (10 eV): m/z = 421.2 [$\text{M} + \text{H}$]⁺, 858.5 [$2\text{M} + \text{NH}_4$]⁺; MS (EI): m/z (%) = 420 (M^+ , 100), 405 (12), 389 (8), 373 (7), 359 (5), 223 (8), 210 (7); HRMS: m/z calc. for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_2$ (M^+): 420.1838; found: 420.1822.

1 (a) D. P. Chakraborty and S. Roy, in *Progress in the Chemistry of Organic Natural Products*, ed. W. Herz, H. Grisebach, G. W. Kirby, W. Steglich and C. Tamm, Springer-Verlag, Wien, 1991, vol. 57, p. 71;

- (b) D. P. Chakraborty, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, New York, 1993, vol. 44, p. 257; (c) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (d) H.-J. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, p. 1; (e) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, DOI: 10.1021/cr200447s.
- 2 (a) H.-J. Knölker, *Top. Curr. Chem.*, 2005, **244**, 115; (b) I. Bauer and H.-J. Knölker, *Top. Curr. Chem.*, 2012, **309**, 203.
- 3 Iron-mediated synthesis, reviews: (a) H.-J. Knölker, *Synlett*, 1992, 371; (b) H.-J. Knölker, *Chem. Soc. Rev.*, 1999, **28**, 151; applications: (c) H.-J. Knölker, M. Bauermeister and J.-B. Pannek, *Chem. Ber.*, 1992, **125**, 2783; (d) H.-J. Knölker and M. Bauermeister, *Helv. Chim. Acta*, 1993, **76**, 2500; (e) H.-J. Knölker and W. Fröhner, *Tetrahedron Lett.*, 1997, **38**, 1535; (f) H.-J. Knölker, W. Fröhner and K. R. Reddy, *Eur. J. Org. Chem.*, 2003, 740; (g) R. Czerwonka, K. R. Reddy, E. Baum and H.-J. Knölker, *Chem. Commun.*, 2006, 711; (h) C. Thomas, O. Kataeva and H.-J. Knölker, *Synlett*, 2011, 2663.
- 4 Palladium-catalysed synthesis, reviews: (a) H.-J. Knölker, *Curr. Org. Synth.*, 2004, **1**, 309; (b) H.-J. Knölker, *Chem. Lett.*, 2009, **38**, 8; applications: (c) H.-J. Knölker and N. O'Sullivan, *Tetrahedron*, 1994, **50**, 10893; (d) H.-J. Knölker and W. Fröhner, *J. Chem. Soc., Perkin Trans. 1*, 1998, 173; (e) H.-J. Knölker, K. R. Reddy and A. Wagner, *Tetrahedron Lett.*, 1998, **39**, 8267; (f) H.-J. Knölker, W. Fröhner and K. R. Reddy, *Synthesis*, 2002, 557; (g) H.-J. Knölker and K. R. Reddy, *Heterocycles*, 2003, **60**, 1049; (h) M. P. Krah, A. Jäger, T. Krause and H.-J. Knölker, *Org. Biomol. Chem.*, 2006, **4**, 3215; (i) R. Forke, M. Krah, T. Krause, G. Schlechtingen and H.-J. Knölker, *Synlett*, 2007, 268; (j) C. Börger and H.-J. Knölker, *Synlett*, 2008, 1698; (k) R. Forke, A. Jäger and H.-J. Knölker, *Org. Biomol. Chem.*, 2008, **6**, 2481; (l) R. Forke, M. P. Krah, F. Däbritz, A. Jäger and H.-J. Knölker, *Synlett*, 2008, 1870; (m) K. K. Gruner and H.-J. Knölker, *Org. Biomol. Chem.*, 2008, **6**, 3902; (n) M. Schmidt and H.-J. Knölker, *Synlett*, 2009, 2421; (o) M. Fuchsenberger, R. Forke and H.-J. Knölker, *Synlett*, 2011, 2056; (p) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H.-J. Knölker, *Chem.-Eur. J.*, 2012, **18**, 770; (q) L. Huet, R. Forke and H.-J. Knölker, *Synlett*, 2012, **23**, 1230; (r) C. Börger and H.-J. Knölker, *Tetrahedron*, 2012, **68**, DOI: 10.1016/j.tet.2012.05.105.
- 5 (a) H. Furukawa, *Trends Heterocycl. Chem.*, 1993, **3**, 185; (b) S. Tasler and G. Bringmann, *Chem. Rev.*, 2002, **2**, 115.
- 6 C. Ito, T.-S. Wu and H. Furukawa, *Chem. Pharm. Bull.*, 1987, **35**, 450.
- 7 M. M. Rahman and A. I. Gray, *Phytochemistry*, 2005, **66**, 1601.
- 8 C. Ito, T.-S. Wu and H. Furukawa, *Chem. Pharm. Bull.*, 1988, **36**, 2377.
- 9 (a) H.-J. Knölker and M. Bauermeister, *J. Chem. Soc., Chem. Commun.*, 1990, 664; (b) H.-J. Knölker and M. Bauermeister, *Tetrahedron*, 1993, **49**, 11221.
- 10 (a) H.-J. Knölker and M. Wolpert, *Tetrahedron Lett.*, 1997, **38**, 533; (b) H.-J. Knölker and M. Wolpert, *Tetrahedron*, 2003, **59**, 5317.
- 11 D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya and A. K. Biswas, *Phytochemistry*, 1978, **17**, 834.
- 12 (a) T.-S. Wu, S.-C. Huang, P.-L. Wu and C.-M. Teng, *Phytochemistry*, 1996, **43**, 133; (b) T.-S. Wu, S.-C. Huang, P.-L. Wu and C.-S. Kuoh, *Phytochemistry*, 1999, **52**, 523.
- 13 (a) E. Brenna, C. Fuganti and S. Serra, *Tetrahedron*, 1998, **54**, 1585; (b) G. Bringmann, S. Tasler, H. Endress, K. Peters and E.-M. Peters, *Synthesis*, 1998, 1501; (c) A. Zempoalteca and J. Tamariz, *Heterocycles*, 2002, **57**, 259; (d) A. Kuwahara, K. Nakano and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413; (e) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581; (f) Z. Liu and R. C. Larock, *Tetrahedron*, 2007, **63**, 347; (g) B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart and K. Fagnou, *J. Org. Chem.*, 2008, **73**, 5022; (h) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7603; (i) S. Tohyama, T. Choshi, S. Azuma, H. Fujioka and S. Hibino, *Heterocycles*, 2009, **79**, 955.
- 14 (a) H.-J. Knölker and P. Gonser, *Synlett*, 1992, 517; (b) H.-J. Knölker, P. Gonser and P. G. Jones, *Synlett*, 1994, 405; (c) H.-J. Knölker, G. Baum, N. Foitzik, H. Goesmann, P. Gonser, P. G. Jones and H. Röttele, *Eur. J. Inorg. Chem.*, 1998, 993; (d) H.-J. Knölker, E. Baum, P. Gonser, G. Rohde and H. Röttele, *Organometallics*, 1998, **17**, 3916; (e) H.-J. Knölker, *Chem. Rev.*, 2000, **100**, 2941.
- 15 E. O. Fischer and R. D. Fischer, *Angew. Chem.*, 1960, **72**, 919.
- 16 (a) A. J. Fatiadi, *Synthesis*, 1976, 65; (b) H.-J. Knölker, *J. Prakt. Chem.*, 1995, **337**, 75.
- 17 M. P. Krah, PhD thesis, TU Dresden, December 2006.

- 18 (a) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685; (b) M. D. Charles, P. Schultz and S. L. Buchwald, *Org. Lett.*, 2005, **7**, 3965.
- 19 D. T. Witiak, R. C. Cavestri, H. A. I. Newman, J. R. Baldwin, C. L. Sober and D. R. Feller, *J. Med. Chem.*, 1978, **21**, 1198.
- 20 (a) V. H. Rawal and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 6141; (b) C. J. Moody and P. Shah, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2463; (c) K. E. Knott, S. Auschill, A. Jäger and H.-J. Knölker, *Chem. Commun.*, 2009, 1467.
- 21 (a) T. A. Choi, R. Czerwonka, W. Fröhner, M. P. Krah, K. R. Reddy, S. G. Franzblau and H.-J. Knölker, *ChemMedChem*, 2006, **1**, 812; (b) T. A. Choi, R. Czerwonka, R. Forke, A. Jäger, J. Knöll, M. P. Krah, T. Krause, K. R. Reddy, S. G. Franzblau and H.-J. Knölker, *Med. Chem. Res.*, 2008, **17**, 374.