Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5317–5322

TETRAHEDRON

Transition metal complexes in organic synthesis. Part 68: Iron-mediated total synthesis of mukonine and mukonidine by oxidative cyclization with air as the oxidizing agent☆

Hans-Joachim Knölker* and Marcus Wolpert

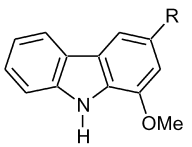
Institut für Organische Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany

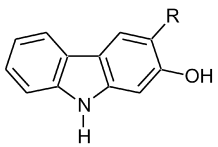
Received 7 April 2003; accepted 12 May 2003

Abstract—The oxidative cyclization of 5-(2-amino-5-methoxycarbonylphenyl)-substituted tricarbonyl[η^4-cyclohexa-1,3-diene]iron complexes by air in protic medium provides the corresponding tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complexes. This procedure is applied to the total synthesis of the 3-methoxycarbonylcarbazole alkaloids mukonine and mukonidine.

1. Introduction

Most of the naturally occurring biologically active carbazole alkaloids were isolated from higher plants of the genus *Murraya* (*Rutaceae* family), trees growing in southern Asia.[2] Extracts of the leaves and bark of this tree have been used as a folk medicine for analgesia and local anesthesia, as well as for the treatment of eczema, rheumatism, and dropsy. The search for the biologically active compounds of *Murraya* led to the discovery of a broad variety of carbazole alkaloids including the 1-methoxycarbazoles **1**–**5** and the 2-hydroxycarbazoles **6**–**8** (Scheme 1).[2] The co-occurrence of all these carbazole alkaloids in plants of the same family strongly suggests the parent 3-methylcarbazole as the common biosynthetic key precursor which is transformed in vivo by hydroxylation and oxidation of the methyl group.[2] Murrayafoline A (**1**) was isolated from the root bark of *Murraya euchrestifolia* collected in Taiwan.[3] The cytotoxic carbazole alkaloid koenoline (**2**),[4] its more highly oxidized derivatives murrayanine (**3**),[5] mukoeic acid (**4**),[6] and the corresponding methyl ester mukonine (**5**)[2a] were obtained from the Indian curry-leaf tree (*Murraya koenigii*). Murrayanine shows antimicrobial activity[5b] and was also isolated from *Clausena heptaphylla*, another plant belonging to the *Rutaceae* family.[7] 2-Hydroxy-3-methylcarbazole (**6**)[8] was obtained from the roots and mukonal (**7**)[9] from the stem bark of *M. koenigii*. The isolation of mukonidine (**8**) was claimed independently by Chakraborty from the stem bark of *M. koenigii*[10] and by Wu from the root bark of *Clausena excavata*.[11] The structural elucidation of mukonidine (**8**) by both groups identified it as methyl 2-hydroxycarbazole-3-carboxylate. However, the reported spectral





1	Murrayafoline A	R = Me
2	Koenoline	R = CH_2OH
3	Murrayanine	R = CHO
4	Mukoeic acid	R = COOH
5	Mukonine	R = COOMe
6	2-Hydroxy-3-methylcarbazole	R = Me
7	Mukonal	R = CHO
8	Mukonidine	R = COOMe

Scheme 1.

☆ For Part 67, see Ref. 1.

Keywords: iron complexes; arylamines; electrophilic substitution; oxidative cyclization; carbazole alkaloids.
* Corresponding author. Fax: +49-351-463-37030; e-mail: hans-joachim.knoelker@chemie.tu-dresden.de

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00786-5

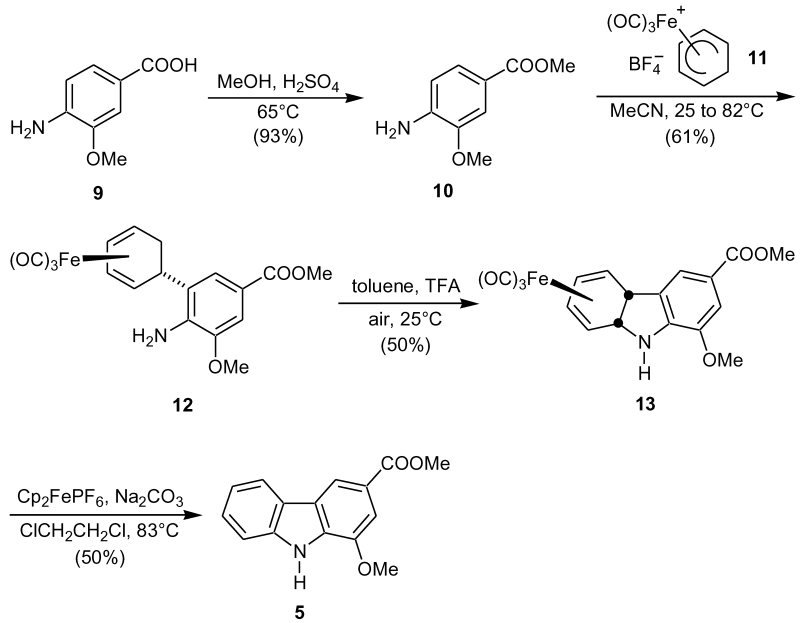
data and the melting points were not in agreement and therefore, one of the structures must be different.[9–12] We projected a total synthesis of mukonidine (**8**) to reconcile this contradiction.

The broad range of useful biological activities which have been reported for the carbazole alkaloids isolated from the plant extracts of *Murraya* species prompted several research groups to develop strategies for their total synthesis.[2] We have described an efficient iron-mediated approach to several 1-oxygenated, 3-oxygenated, and 3,4-dioxygenated carbazole alkaloids.[13] The iron-mediated construction of the carbazole framework led to a two-step synthesis of mukonine (**5**).[14,15] However, for the synthesis of 2-oxygenated carbazoles this method was of limited success.[16] Therefore, a complementary molybdenum-mediated synthesis was developed, which opened up a simple route to 2-oxygenated carbazole alkaloids, e.g. 2-hydroxy-3-methylcarbazole (**6**) and mukonal (**7**).[17] Initial attempts to synthesize mukonidine (**8**) using the iron-mediated approach and the molybdenum-mediated approach failed.[16,17] In this paper we now describe full details of our iron-mediated total synthesis of mukonine (**5**) and mukonidine (**8**) using air as the oxidizing agent in the presence of acid.[18]

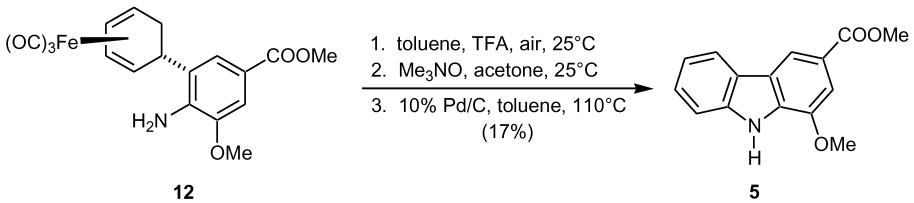
2. Results and discussion

2.1. Synthesis of mukonine

The commercial benzoic acid **9** was converted to the methyl ester **10** (Scheme 2).[19] Tricarbonyl[(1-5-η)-cyclohexadienylium]iron tetrafluoroborate (**11**) was obtained on large scale in almost quantitative overall yield by 1-azabutadiene-catalyzed complexation of cyclohexa-1,3-diene with pentacarbonyliron[20] and subsequent hydride abstraction using triphenylmethyl tetrafluoroborate.[21] Electrophilic substitution of compound **10** with the iron-complex salt **11** in acetonitrile at room temperature for 3 days led to the iron complex **12** in 36% yield.[14] Addition of compound **10** to the iron complex salt **11** in acetonitrile under reflux (82°C) gave only 5% yield of complex **12**. However, starting the reaction at room temperature followed by gradual increase of the temperature up to reflux during the reaction (see Section 4) afforded complex **12** in 61% yield. This result is explained by the initial N-alkylation of the arylamine **10** leading to the kinetic product, which in the present case obviously proceeds best at room temperature.[22] The subsequent rearrangement of this intermediate to the C-alkylated arylamine **12** (thermodynamic product) has a high barrier due to the decreased nucleophilicity resulting from the acceptor substituent in the position *para* to the amino group and therefore, requires more drastic reaction conditions. The oxidative cyclization of complex **12** using very active manganese dioxide[23] in toluene at room temperature provided after 25 h mukonine (**5**) in 54% yield.[14] Thus, using this iron-mediated oxidative cyclization with concomitant aromatization and demetalation, mukonine (**5**) was obtained in two steps and 33% overall yield based on the iron complex salt **11**. For iron-mediated arylamine cyclizations to carbazoles with acceptor (methoxycarbonyl or formyl) substituents at the arylamine moiety, we noticed a higher stability of the intermediate tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complexes as emphasized by the longer reaction times required for the aromatization with very active manganese dioxide.[14,24] In a protic medium air could be used as an oxidizing agent for the oxidative cyclization in these cases. Stirring of a solution of the iron complex **12** in toluene with trifluoroacetic acid in the air resulted in a smooth cyclodehydrogenation and afforded the tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **13**. Oxidation of the iron complex **13** with ferricenium hexafluorophosphate in the presence of sodium carbonate[22b] in dichloroethane under reflux provided mukonine (**5**) by aromatization and demetalation (Scheme 2). Lower reaction temperatures led to reisolation of the starting material.



Scheme 2.



Scheme 3.

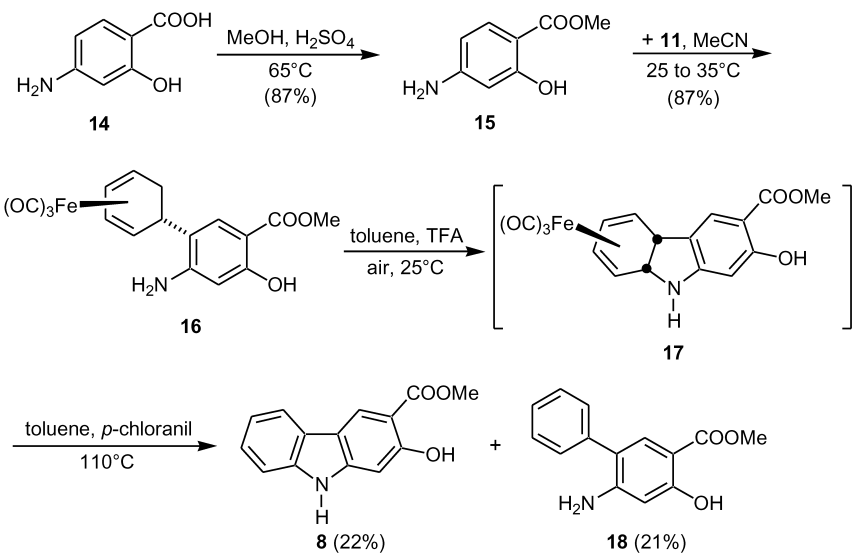
An alternative method for the aromatization of the intermediate tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]-iron complex **13** is provided by demetalation[25] and subsequent catalytic dehydrogenation.[26] Stirring a solution of the iron complex **13** with trimethylamine *N*-oxide in acetone at room temperature followed by aromatization of the intermediate 4a,9a-dihydro-8-methoxy-6-methoxy-carbonyl-9*H*-carbazole with palladium on activated carbon in toluene under reflux afforded mukonine (**5**) (Scheme 3).

2.2. Synthesis of mukonidine

The reaction of commercial 4-aminosalicylic acid (**14**) with diazomethane afforded quantitatively the arylamine **15**.[16] However, on large scale this transformation was better achieved by reacting 4-aminosalicylic acid (**14**) with sulfuric acid and methanol (Scheme 4). Treatment of the iron complex salt **11** with the arylamine **15** in acetonitrile provided the iron complex **16** in 87% yield. The yield of the C–C bond formation is higher than for the synthesis of mukonine (**5**) (see above) because the hydroxy group in the 3-position of the arylamine enhances the nucleophilicity of the *o*-amino position. The iron-mediated arylamine cyclization of complex **16** using very active manganese dioxide, iodine in pyridine, or ferricenium hexafluorophosphate failed,[16] which was ascribed to the known problems caused by free hydroxy groups in these reactions.[13a] The oxidative cyclization of complex **16** in toluene in the presence of trifluoroacetic acid in the air afforded the tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **17**. Various attempts to transform complex **17** to mukonidine (**8**) using very active manganese dioxide[23] or ferricenium hexafluorophosphate in the presence of sodium carbonate[22b] led to complete decomposition. However, the oxidation of complex **17** with *p*-chloranil (tetrachloro-1,4-benzoquinone) in toluene under reflux provided by aromatization and demetalation directly mukonidine (**8**) in 22% yield based on complex **16** along with the biphenyl derivative **18** (21% yield). Alternatively, the final transformation of complex **17** to mukonidine (**8**) was achieved by demetalation with trimethylamine *N*-oxide in acetone[25] followed by catalytic dehydrogenation with palladium on activated carbon in toluene under reflux[26] (11% yield based on complex **16**).

3. Conclusion

The iron-mediated synthesis with very active manganese dioxide as the oxidizing agent provided mukonine (**5**) in two steps and 33% overall yield based on the iron complex salt **11**. Alternatively, the iron-mediated oxidative cyclization using air as the oxidizing agent provided tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complexes which were oxidized to the aromatized carbazoles. This procedure afforded mukonidine (**8**) in three steps and 19% overall yield based on **11**. The spectroscopic data (UV, IR, ^{1}H NMR, and MS) of our synthetic mukonidine (**8**) (colorless crystals, mp 190°C) are in good agreement with the corresponding data described by Wu for natural mukonidine (**8**) (mp 168–170°C).[11] However, the melting point we found is in better agreement with that of compound **8** obtained in a partial synthesis by Venkataraman (mp 188°C).[12] We conclude that the natural product isolated by Chakraborty (mp 245°C)[10] may have a different structure.



Scheme 4.

4. Experimental

4.1. General

All reactions were carried out using dry solvents and under argon atmosphere unless otherwise stated. Flash chromatography: Merck silica gel (0.03–0.06 mm). Mp: 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 AM-400; internal standard: TMS 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.

4.1.1. Methyl 4-amino-3-methoxybenzoate (10). A solution of 4-amino-3-methoxybenzoic acid (**9**) (1.61 g, 9.63 mmol) and sulfuric acid (2.8 mL) in methanol (100 mL) was heated under reflux for 17 h. After addition of $NaHCO_3$, the solvent was removed in vacuo. The residue was taken up in a solution of $NaCl/Na_2CO_3$ and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. Flash chromatography (ether/hexane, 3:1) of the residue on silica gel provided the arylamine **10** as a colorless solid, yield: 1.62 g (93%). For an alternative preparation of **10**, see Ref. 19.

4.1.2. [(1-4-η)-5-(2-Amino-3-methoxy-5-methoxycarbonylphenyl)-cyclohexa-1,3-diene]tricarbonyliron (12). A solution of the iron complex salt **11** (2.00 g, 6.54 mmol) and the arylamine **10** (2.60 g, 14.4 mmol) in acetonitrile (60 mL) was stirred at room temperature for 24 h, then at 35°C for 48 h, and at 55°C for 16 h. Finally, the solution was heated under reflux for a short period of time to complete the reaction. Evaporation of the solvent and flash chromatography (ethyl acetate/hexane, 1:8) of the residue on silica gel afforded the iron complex **12** as pale yellow crystals, yield: 1.60 g (61%). For spectral data, see Ref. 14b.

4.1.3. Tricarbonyl[(1-4-η)-4a,9a-dihydro-8-methoxy-6-methoxycarbonyl-9*H*-carbazole]iron (13). Trifluoroacetic acid (1 mL) was added to a solution of the iron complex **12** (250 mg, 0.626 mmol) in toluene (50 mL). The solution was stirred in the air for 18 h at room temperature, then poured into a saturated aqueous solution of Na_2CO_3, and extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (ether/hexane, 1:1) of the residue on silica gel provided the tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **13** as bright yellow crystals, yield: 123 mg (50%), mp 206°C (decomp.). UV (EtOH): λ_{max}=205, 313 (sh), 329 nm; IR (drift): $\tilde{\nu}$=3404, 2951, 2842, 2047, 1966, 1700, 1691, 1604, 1505, 1457, 1437, 1411, 1346, 1309, 1284, 1261, 1222, 1196, 1146, 1131, 1102, 1075, 1023, 1008, 998, 966, 938, 899, 868, 769, 721, 619 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.21 (ddd, *J*=5.6, 3.7, 1.4 Hz, 1H), 3.52 (ddd, *J*=6.1, 4.5, 1.5 Hz, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 3.88 (dd, *J*=11.0, 4.5 Hz, 1H), 4.47 (dd, *J*=11.0, 3.7 Hz, 1H), 5.37 (m, 2H), 7.31 (d, *J*=1.1 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=45.66 (CH), 51.60 (CH_3), 55.33 (CH_3), 61.92 (CH), 62.15 (CH), 62.45 (CH), 85.57 (CH), 86.45 (CH), 111.05 (CH), 118.92 (CH), 119.80 (C), 131.54 (C), 142.46 (C), 143.05 (C), 167.27 (C=O), 210.88 (3 CO). MS (120°C): *m*/*z*=397 (M^+, 83), 369 (6), 341 (49), 313 (100), 311 (56), 283 (18), 257 (23), 255 (12), 253 (33), 237 (15), 235 (81), 226 (12), 224 (69), 197 (22), 183 (20), 182 (15), 154 (22); HRMS: calcd for $C_{18}H_{15}FeNO_6$ (M^+): 397.0249; found: 397.0229. Anal. calcd for $C_{18}H_{15}FeNO_6$: C, 54.44; H, 3.81; N 3.53; found: C, 54.68; H, 3.95; N, 3.35.

4.1.4. Mukonine (methyl 1-methoxy-9*H*-carbazole-3-carboxylate) (5). *Method A*. Ferricenium hexafluorophosphate (208 mg, 0.629 mmol) and Na_2CO_3 (133 mg, 1.26 mmol) were added to a solution of the tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **13** (50 mg, 0.126 mmol) in 1,2-dichloroethane (10 mL) and the resulting mixture was heated under reflux for 16 h. Filtration through a short path of silica gel followed by removal of the solvent and flash chromatography (ether/hexane, 1:1) of the residue on silica gel afforded mukonine (**5**) as colorless crystals, yield: 17 mg (50%). For spectral data, see Ref. 14b.

Method B. Trifluoroacetic acid (1 mL) was added to a solution of the iron complex **12** (250 mg, 0.626 mmol) in toluene (50 mL). After stirring for 18 h at room temperature in the presence of air, the solution was poured into a saturated aqueous solution of Na_2CO_3, and extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The resulting tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **13** was dissolved in acetone (25 mL), trimethylamine *N*-oxide dihydrate (696 mg, 6.26 mmol) was added, and the reaction mixture was stirred for 16 h at room temperature. The mixture was filtered through a short path of silica gel, which was subsequently washed with ethyl acetate. After removal of the solvent, the intermediate 4a,9a-dihydro-8-methoxy-6-methoxycarbonyl-9*H*-carbazole was dissolved in toluene (20 mL), palladium on activated carbon (10%, 100 mg) was added, and the reaction mixture was heated under reflux for 5 h. Filtration through a short path of silica gel, evaporation of the solvent, and flash chromatography (ether/hexane, 1:1) of the residue on silica gel provided mukonine (**5**) as colorless crystals, yield: 27 mg (17%). For spectral data, see Ref. 14b.

4.1.5. Methyl 4-amino-2-hydroxybenzoate (15). A solution of 4-amino-2-hydroxybenzoic acid (4-aminosalicyclic acid) (**14**) (10.0 g, 65.3 mmol) and sulfuric acid (14 mL) in methanol (200 mL) was heated under reflux for 14 h. After addition of $NaHCO_3$ (until the evolution of CO_2 ceased) the reaction mixture was filtered. The filtrate was poured into water and extracted with ether (1 L). The combined organic layers were dried over magnesium sulfate and the solvent was removed. Flash chromatography (ether/hexane, 1:1) of the residue on silica gel provided the arylamine **15** as a colorless solid, yield: 9.53 g (87%). For spectral data, see Ref. 16.

4.1.6. [(1-4-η)-5-(2-Amino-4-hydroxy-5-methoxycarbonylphenyl)-cyclohexa-1,3-diene]tricarbonyliron (16). A solution of the iron complex salt **11** (1.22 g, 3.99 mmol) and the arylamine **15** (1.47 g, 8.79 mmol) in acetonitrile (50 mL) was stirred at room temperature for 48 h. Subsequently, the reaction mixture was warmed at 35°C

for 16 h to complete the reaction. Removal of the solvent and flash chromatography (ethyl acetate/hexane, 1:9) of the residue on silica gel afforded the iron complex **16** as light yellow crystals, yield: 1.34 g (87%). For spectral data, see Ref. 16.

4.1.7. Mukonidine (methyl 2-hydroxy-9*H*-carbazole-3-carboxylate) (8) and methyl 4-amino-2-hydroxy-5-phenylbenzoate (18). *Method A*. Trifluoroacetic acid (1 mL) was added to a solution of the iron complex **16** (300 mg, 0.779 mmol) in toluene (50 mL) and air was bubbled into the solution for 2 h. Additional trifluoroacetic acid (1 mL) was added and the bubbling of air into the solution was continued for 1 h. The solvent was removed, the intermediate tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **17** was dissolved in toluene (50 mL), tetrachloro-1,4-benzoquinone (*p*-chloranil) (483 mg, 1.96 mmol) was added, and the reaction mixture was heated under reflux for 16 h. Evaporation of the solvent and flash chromatography (ether/hexane, 1:1) of the residue on silica gel provided mukonidine (**8**) (yield: 42 mg, 22%) and the biphenyl derivative **18** (yield: 40 mg, 21%).

Mukonidine (**8**). Colorless crystals, mp 190°C. UV (EtOH): λ_{max}=235, 243, 272 (sh), 278 (sh), 284, 325, 338 nm; IR (drift): $\tilde{\nu}$=3355, 1647, 1632, 1466, 1435, 1376, 1262, 1240, 1168, 1097, 1016, 951, 899, 872, 823, 786, 764, 742, 722, 700 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ=3.98 (s, 3H), 6.93 (s, 1H), 7.19 (t, *J*=7.7 Hz, 1H), 7.36 (t, *J*=8.1 Hz, 1H), 7.46 (d, *J*=8.1 Hz, 1H), 8.06 (d, *J*=7.7 Hz, 1H), 8.59 (s, 1H), 10.50 (br s, 1H), 11.10 (br s, 1H); ^{13}C NMR and DEPT (100 MHz, acetone-d_6): δ=53.17 (CH_3), 98.26 (CH), 106.50 (C), 112.36 (CH), 118.40 (C), 121.15 (CH), 121.45 (CH), 123.97 (CH), 124.87 (C), 127.06 (CH), 142.51 (C), 147.17 (C), 162.18 (C), 172.78 (C=O). MS (95°C): *m*/*z*=241 (M^+, 52), 210 (17), 209 (100), 208 (6), 181 (13), 154 (6), 153 (24), 126 (6); HRMS: calcd for $C_{14}H_{11}NO_3$ (M^+): 241.0739; found: 241.0729.

Methyl 4-amino-2-hydroxy-5-phenylbenzoate (**18**). UV (EtOH): λ_{max}=202 (sh), 226, 243, 286, 314 nm; IR (drift): $\tilde{\nu}$=3350, 2953, 2925, 2854, 1663, 1629, 1441, 1351, 1245, 1200, 1109, 793, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=3.87 (s, 3H), 4.24 (br s, 2H), 6.25 (s, 1H), 7.40 (m, 5H), 7.60 (s, 1H), 10.90 (s, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=51.74 (CH_3), 100.84 (CH), 103.15 (C), 119.91 (C), 127.40 (CH), 128.98 (2 CH), 129.21 (2 CH), 132.20 (CH), 138.01 (C), 150.58 (C), 162.67 (C), 170.54 (C=O). MS (60°C): *m*/*z*=243 (M^+, 100), 212 (21), 211 (83), 183 (38), 154 (39); HRMS: calcd for $C_{14}H_{13}NO_3$ (M^+): 243.0895; found: 243.0915.

4.1.8. Mukonidine (methyl 2-hydroxy-9*H*-carbazole-3-carboxylate) (8). *Method B*. Trifluoroacetic acid (1 mL) was added to a solution of the iron complex **16** (250 mg, 0.649 mmol) in toluene (50 mL) and air was bubbled into the solution for 2 h. Additional trifluoroacetic acid (1 mL) was added, the bubbling of air into the solution was continued for 1 h, and the solvent was evaporated. The resulting tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **17** was dissolved in acetone (25 mL), trimethylamine *N*-oxide dihydrate (721 mg, 6.49 mmol) was added, and the reaction mixture was stirred for 16 h at room temperature. The mixture was filtered through a short path of silica gel, which was subsequently washed with ethyl acetate. After removal of the solvent, the intermediate 4a,9a-dihydro-7-hydroxy-6-methoxycarbonyl-9*H*-carbazole was dissolved in toluene (20 mL), palladium on activated carbon (10%, 100 mg) was added, and the reaction mixture was heated under reflux for 5 h. Filtration through a short path of silica gel, evaporation of the solvent, and flash chromatography (ether/hexane, 1:1) of the residue on silica gel afforded mukonidine (**8**) as colorless crystals, yield: 18 mg (11%). Spectral data, see above.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are grateful to the BASF AG, Ludwigshafen, for a generous gift of pentacarbonyliron.

References

1. Part 67: Knölker, H.-J.; Knöll, J. *Chem. Commun.* **2003**, 1170.
2. For reviews, see: (a) Chakraborty, D. P. *Prog. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1977; Vol. 34, p 299. (b) Bhattacharyya, P.; Chakraborty, D. P. *Prog. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1987; Vol. 52, p 159. (c) Chakraborty, D. P.; Roy, S. *Prog. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer: Wien, 1991; Vol. 57, p 71. (d) Chakraborty, D. P. *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, 1993; Vol. 44, p 257. (e) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.
3. (a) Wu, T.-S.; Ohta, T.; Furukawa, H.; Kuoh, C.-S. *Heterocycles* **1983**, *20*, 1267. (b) Furukawa, H.; Wu, T.-S.; Ohta, T.; Kuoh, C.-S. *Chem. Pharm. Bull.* **1985**, *33*, 4132.
4. Fiebig, M.; Pezzuto, J. M.; Soejarto, D. D.; Kinghorn, A. D. *Phytochemistry* **1985**, *24*, 3041.
5. (a) Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Tetrahedron* **1965**, *21*, 681. (b) Das, K. C.; Chakraborty, D. P.; Bose, P. K. *Experientia* **1965**, *21*, 340.
6. (a) Chowdhury, B. K.; Chakraborty, D. P. *Chem. Ind. (London)* **1969**, 549. (b) Chowdhury, B. K.; Chakraborty, D. P. *Phytochemistry* **1971**, *10*, 1967.
7. Bhattacharyya, P.; Chakraborty, D. P. *Phytochemistry* **1973**, *12*, 1831.
8. Bhattacharyya, P.; Jash, S. S.; Chowdhury, B. K. *Chem. Ind. (London)* **1986**, 246.
9. Bhattacharyya, P.; Chakraborty, A. *Phytochemistry* **1984**, *23*, 471.
10. Chakraborty, D. P.; Roy, S.; Guha, R. *J. Indian Chem. Soc.* **1978**, *55*, 1114.
11. Wu, T.-S.; Huang, S.-C.; Lai, J.-S.; Teng, C.-M.; Ko, F.-N.; Kuoh, C.-S. *Phytochemistry* **1993**, *32*, 449.
12. Partial synthesis of mukonidine: Bhagwanth, M. R. R.; Rama Rao, A. V.; Venkataraman, K. *Indian J. Chem.* **1969**, *7*, 1065.
13. For reviews, see: (a) Knölker, H.-J. *Synlett* **1992**, 371. (b) Knölker, H.-J. *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI: Greenwich (CT), 1995; Vol. 1, p 173. (c) Knölker, H.-J. *Transition Metals for Organic*

Synthesis; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, p 534. (d) Knölker, H.-J. *Chem. Soc. Rev.* **1999**, *28*, 151.
14. (a) Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1990**, 664. (b) Knölker, H.-J.; Bauermeister, M. *Tetrahedron* **1993**, *49*, 11221.
15. For recent alternative syntheses of mukonine, see: (a) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron* **1998**, *54*, 1585. (b) Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E.-M. *Synthesis* **1998**, 1501. (c) Zempoalteca, A.; Tamariz, J. *Heterocycles* **2002**, *57*, 259.
16. Knölker, H.-J.; Bauermeister, M. *J. Indian Chem. Soc.* **1994**, *71*, 345.
17. Knölker, H.-J.; Goesmann, H.; Hofmann, C. *Synlett* **1996**, 737.
18. Knölker, H.-J.; Wolpert, M. *Tetrahedron Lett.* **1997**, *38*, 533.
19. Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1988**, *41*, 1087.
20. (a) Knölker, H.-J.; Baum, E.; Gonser, P.; Rohde, G.; Röttele, H. *Organometallics* **1998**, *17*, 3916. (b) Knölker, H.-J. *Chem. Rev.* **2000**, *100*, 2941.
21. Fischer, E. O.; Fischer, R. D. *Angew. Chem.* **1960**, *72*, 919.
22. (a) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B. *Chem. Ber.* **1992**, *125*, 2783. (b) Knölker, H.-J.; Hopfmann, T. *Tetrahedron* **2002**, *58*, 8937.
23. Fatiadi, A. J. *Synthesis* **1976**, 65.
24. Knölker, H.-J.; Bauermeister, M. *Heterocycles* **1991**, *32*, 2443.
25. (a) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336. (b) Knölker, H.-J. *J. Prakt. Chem.* **1996**, *338*, 190.
26. Knölker, H.-J.; Baum, G.; Pannek, J.-B. *Tetrahedron* **1996**, *52*, 7345.