Total synthesis of the cyclic monoterpenoid pyrano[3,2-a]carbazole alkaloids derived from 2-hydroxy-6-methylcarbazole

Cemenia Gassner, Ronny Hesse, Arndt W. Schmidt and Hans-Joachim Knölker*

The synthesis of seven pyrano[3,2-a]carbazole alkaloids has been achieved using their putative biogenetic precursor 2-hydroxy-6-methylcarbazole as key intermediate.

Introduction

The research groups of Chakraborty, Furukawa, Ito and Wu have isolated a wide range of biologically active carbazole alkaloids from plants of the family Rutaceae (genera Murraya, Clusia and Glycosmis). The pyrano[3,2-a]carbazoles, e.g. 1–9, are an important subgroup of carbazole alkaloids which exhibit diverse structural features (Fig. 1). In 1964, girinimbine (1) was among the first carbazole alkaloids which have been isolated by Chakraborty et al. from terrestrial plants. Only two years later, the same group described the isolation of the corresponding prenyl-substituted homologue mahanimbine (2). Biogenetically, both compounds derive from 2-hydroxy-3-methylcarbazole by fusion with either prenyl or geranyl diphosphate. Originally, girinimbine was erroneously assigned as structure 3, but subsequently it had to be reassigned as 1. Isogirinimbine (3) biogenetically could have been formed from 2-hydroxy-6-methylcarbazole (10) and geranyl diphosphate as C₉ building block (Scheme 1). Interestingly, although isogirinimbine (3) has not been found in nature so far, the corresponding carbazole alkaloids 4–9 resulting from fusion of 2-hydroxy-6-methylcarbazole (10) and geranyl diphosphate were isolated from natural sources. In 1970, Kapil et al. isolated mahanimbine [(+)-4] and bicyclomahanimbine (6) from Murraya koenigii. Subsequently, Crombie and Whiting et al. proposed the correct structure for bicyclomahanimbine (6). It is interesting to note that also in 1970, Joshi et al. obtained (−)-4 from the leaves of the same plant and named it isomahanimbine, however, the absolute configuration was not determined. The structures of 4 and 6 were supported by synthesis.

Wu et al. isolated murrayamine-J (5), murrayamine-M (7) and murrayamine-G (8) from the leaves of Murraya euchrestifolia. The hexacyclic pyrano[3,2-a]carbazole alkaloid isomurrayazoline (9) was obtained in 1982 by Chakraborty et al. from the stem bark of Murraya koenigii.

We have developed diverse synthetic approaches to pyrano[3,2-a]carbazoles including girinimbine (1), mahanimbine (2), pyrayafoline A-E and monoterpenoid pyrano[3,2-a]carbazole alkaloids. Herein, we describe the synthesis of isogirinimbine (3), (±)-mahanimbine [(±)-isomahanimbine] [(±)-4], murrayamine-J (5) and the cyclic monoterpenoid pyrano[3,2-a]carbazole alkaloids 6–9, which biogenetically derive from

---

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

*Part 121 of Transition Metals in Organic Synthesis; for Part 120, see ref. 14.

†Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra for all compounds. CCDC 1000251. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01151a
2-hydroxy-6-methylcarbazole (10). Key steps of our approach are an efficient construction of the carbazole 10 based on our palladium-catalyzed route\textsuperscript{15} and a subsequent annulation of either a C\textsubscript{5} or a C\textsubscript{10} building block (Scheme 1). The substitution pattern present in compound 10 has been generated previously in our synthesis of 7-oxygenated carbazole alkaloids.\textsuperscript{16}

**Results and discussion**

Buchwald–Hartwig coupling of \( p \)-toluidine (11) and \( m \)-bromoanisole (12) in the presence of SPhos (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl)\textsuperscript{17} afforded the diarylamine 13 (Scheme 2). Alternatively, compound 13 has been prepared quantitatively on a 25 g scale by Buchwald–Hartwig coupling of \( m \)-anisidine and \( p \)-bromotoluene (see Experimental section).\textsuperscript{16} Palladium\([\sigma]\)-catalyzed oxidative cyclization of 13 provided the desired 2-methoxy-6-methylcarbazole (14)\textsuperscript{16} as major product (89% yield) and up to 5% of glycoborine (15)\textsuperscript{18} as by-product. Cleavage of the methyl ether led to 2-hydroxy-6-methylcarbazole (10). Formation of the dimethylpropargyl ether via Godfrey’s method,\textsuperscript{19} followed by a thermally induced sequence of Claisen rearrangement, 1,5-hydrogen shift and electrocyclic ring closure\textsuperscript{20} provided isogirinimbine (3) in 63% yield and as a by-product the furo[3,2-\( a \)]carbazole 17 in up to 3% yield. The structure of isogirinimbine (3) has been fully supported by its spectroscopic data which confirm it as an isomer of the natural product girinimbine (1). The 3-methylregioisomer of 17 was obtained previously as by-product in our synthesis of girinimbine (1).\textsuperscript{12}

We envisaged (\( \pm \))-mahanimbicine [(\( \pm \))-isomahanimbine] [(\( \pm \))-4] as crucial intermediate for the synthesis of the formyl derivative murrayamine-J (5) and the cyclic monoterpenoid pyrano[3,2-\( a \)]carbazole alkaloids 6–9. Thus, we have developed two alternative synthetic routes for the synthesis of (\( \pm \))-4. The first approach requires no protecting group (Scheme 3). Reaction of 2-hydroxy-6-methylcarbazole (10) with the carbonate \textsuperscript{18,21} in the presence of catalytic amounts of copper(\( i \)) iodide and subsequent thermally induced rearrangement provided (\( \pm \))-mahanimbicine [(\( \pm \))-4] in 49% yield along with the furo[3,2-\( a \)]carbazole 19 in up to 5% yield as by-product.

Alternatively, 2-methoxy-6-methylcarbazole (14) was initially protected by transformation to the N-tosylcarbazole 20
Scheme 4 Alternative route to (+)-mahanimbicine ([±]-4). Reagents and conditions: (a) 4.1 equiv. NaH, 1.5 equiv. TsCl, THF, 0 °C to rt, 16.25 h, 80%; (b) 1. 3.0 equiv. BBr₃, CH₂Cl₂, −78 °C to rt, 2.5 h; 2. 2.0 equiv. 18, 3.0 equiv. DBU, 0.5 mol% CuI, MeCN, rt, 22 h; 3. xylene, reflux, 27.5 h, 82% (3 steps, ratio 21/22 = 7.7:1); (c) 4.0 equiv. TBAF, THF, 75 °C, 6 h, 79% ([±]-4) and 9% 23.

Using the first approach (Scheme 3), (+)-mahanimbicine ([±]-4) is available in 5 steps and 40% overall yield based on p-bromotoluene. Our second route (Scheme 4) leads to (+)-4 in 7 steps and 46% overall yield based on the same starting material. It is interesting to note, that annulation of the pyran ring with the carbonate 18 at 2-hydroxy-6-methylcarbazole (10) provides the furan-[3,2-a]carbazole 19 as by-product, whereas annulation at the corresponding N-tosylcarbazole gives the pyran-[2,3-b]carbazole 22 as by-product. This outcome is explained by the steric demand of the tosyl group which suppresses the formation of N-tosyl-19 with the quaternary carbon center in close proximity to the protecting group; instead linear pyran annulation and thus formation of compound 22 is observed.

Using (+)-mahanimbicine ([±]-4) as relay compound the carbazole alkaloids 5–9 are accessible, following putative biogenic routes. Oxidation of (+)-mahanimbicine ([±]-4) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded murrayamine-J (5) (Scheme 5). Intramolecular [2 + 2] cycloaddition of ([±]-4) led to bicyclomahanimbicine (6). Oxidation of 6 with DDQ gave murrayamine-M (7).

For the Brønsted acid promoted cycloisomerization of (+)-mahanimbicine ([±]-4), we took advantage of our previous study on the conversion of mahanimbine (2) into cyclomahanimbine and mahanimbidine. On treatment of (+)-4 with one equivalent camphor-10-sulfonic acid (CSA) at room temperature to 70 °C for 16 d, (+)-4 and rapidly formed 9 were both completely converted into 8. Thus, murrayamine-G (8) was obtained in 65% yield (Scheme 6, Table 1). Cycloisomerization of (+)-mahanimbicine ([±]-4) in the presence of catalytic amounts of CSA in hexane at room temperature afforded in 70% yield a 1:1 mixture of 8 and 9 which after separation by preparative HPLC led to pure isomurrayazoline (9).
used: s: singlet, d: doublet, t: triplet, m: multiplet and br: broad. Mass spectra were recorded on a Finnigan MAT-95 spectrometer (electron impact, 70 eV) or by GC/MS-coupling using an Agilent Technologies 6890 N GC System equipped with a 5973 Mass Selective Detector (electron impact, 70 eV). ESI-MS spectra were recorded on an Esquire LC with an ion trap detector from Bruker. Positive and negative ions were detected. Elemental analyses were measured on an EuroVector EuroEA3000 elemental analyzer.

3-Methoxy-N-(4-methylphenyl)aniline (13). Method A: A solution of m-bromoisoulnic (12) (2.0 g, 10.7 mmol) in toluene (5 mL) was added dropwise over a period of 5 h to a suspension of p-toluidine (11) (1.51 g, 14.1 mmol), palladium(u) acetate (123 mg, 0.74 µmol) and caesium carbonate (4.90 g, 15.0 mmol) in toluene (18 mL) at reflux and the mixture was heated at reflux for 12.5 h (total reaction time: 17.5 h). After cooling to room temperature, the mixture was filtered through a short pad of Celite (diethyl ether) and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, 12:5:1) provided 3-methoxy-N-(4-methylphenyl)aniline (13) as colourless solid, yield: 2.24 g (98%), m.p. 68–70 °C. UV (MeOH): λ = 283 nm. IR (ATR): ν = 3365, 3000, 1591, 1492, 1463, 1389, 1324, 1302, 1283, 1256, 1237, 1198, 1158, 1107, 1032, 992, 951, 832, 774, 753, 686, 649, 632 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ = 3.21 (s, 3 H), 3.77 (s, 3 H), 5.62 (br s, 1 H), 6.43–6.45 (m, 1 H), 6.58–6.60 (m, 2 H), 7.01–7.04 (m, 2 H), 7.09–7.11 (m, 2 H), 7.13–7.16 (m, 1 H). 13C NMR and DEPT (125 MHz, CDCl₃): δ = 20.68 (CH₃), 55.16 (CH₃), 102.33 (CH), 105.43 (CH), 109.32 (CH), 119.36 (2 CH), 129.83 (2 CH), 130.03 (CH), 131.18 (C), 139.91 (C), 145.39 (C), 160.67 (C). El-MS: m/z (%) = 213 (100) [M⁺], 197 (4), 182 (4), 168 (4), 154 (5). HRMS: m/z calcd for C₁₄H₁₄NO [M⁺]: 213.1154; found: 213.1158. Elemental analysis calcd for C₁₄H₁₄NO: C 78.84, H 7.09, N 6.57; found: C 78.97, H 7.08, N 6.40%.

Crystal data for 13: C₁₄H₁₄NO, M = 213.27 g mol⁻¹, crystal size: 0.50 × 0.40 × 0.10 mm³, monoclinic, space group P2₁/c, a = 8.856(1) Å, b = 13.861(1) Å, c = 10.868(1) Å, β = 92.41(1)°, V = 1332.9(2) Å³, Z = 4, ρcalcd = 1.063 g cm⁻³, μ = 0.067 mm⁻¹, T = 293(2) K, λ = 0.71073 Å, θ range 3.26–25.37°, 18 034 reflections collected, 2165 independent reflections (Rint = 0.0280), 151 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F²; final R indices [I > 2σ(I)]: R₁ = 0.0436, wR₂ = 0.1205; maximal residual electron density: 0.179 e Å⁻³ (Fig. S1) CCD1000251.

Method B: m-Anisidine (18.9 g, 153 mmol) was added portionwise over a period of 3 h to a solution of p-bromotoluene (20.0 g, 117 mol), caesium carbonate (45.7 g, 140 mmol), rac-BINAP (3.61 g, 5.80 mmol) and palladium(u) acetate (1.53 g, 6.82 mmol) in toluene (80 mL) at reflux. The mixture was heated at reflux for 13 h (total reaction time 16 h), then cooled to room temperature, filtered over a short pad of silica gel and Celite (diethyl ether), and the solvent was removed. Purification of the residue by column chromatography on silica gel (petroleum ether–acetonitrile, 15:1) provided the diarylamine 13
as light yellow solid, yield: 25.4 g (100%). Spectroscopic data, see above.

2-Methoxy-6-methylcarbazole (14) and glycoborine (5-methoxy-3-methylcarbazole) (15). Palladium(II) acetate (126 mg, 561 µmol) was added at 100 °C to a mixture of the diarylamine 13 (4.02 g, 18.8 mmol), potassium carbonate (261 mg, 1.89 mmol) and pivalic acid (10.2 g) in a 50 mL test tube. The mixture was heated and vigorously stirred at 100 °C for 20.5 h, then cooled to room temperature, diluted with ethyl acetate and washed with a saturated solution of potassium carbonate, brine and water. The aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 119:1:0.2 to 29:1:0.2) provided 2-methoxy-6-methylcarbazole (14) as colourless yellow solid, yield: 3.52 g (89%), m.p. 147 °C (ref. 16). For spectroscopic data, see ref. 16. Glycoborine (5-methoxy-3-methylcarbazole) (15) was obtained from the less polar fraction as by-product in up to 75% yield, m.p. 138 °C. UV (MeOH): λ = 226, 238, 244, 254 (sh), 277 (sh), 287, 323, 337 nm. Fluorescence (MeOH): ex = 287 nm, δem = 3398, 3048, 3012, 2913, 2846, 1624, 1604, 1585, 1554, 1506, 1474, 1453, 1438, 1388, 1345, 1314, 1294, 1258, 1225, 1178, 1101, 1058, 973, 915, 879, 802, 781, 745, 716, 698, 620, 590, 553 cm−1. 1H NMR (500 MHz, CDCl3): δ = 2.54 (s, 3 H), 4.09 (s, 3 H), 6.67 (d, J = 8.0 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 7.21 (dd, J = 8.2, 1.3 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 1 H), 7.94 (br s, 1 H), 8.12 (d, J = 8.0 Hz, 1 H). 13C NMR and DEPT (125 MHz, CDCl3): δ = 21.43 (CH3), 55.37 (CH3), 100.10 (CH), 103.48 (CH), 109.52 (CH), 112.40 (C), 122.77 (C), 122.89 (CH), 126.16 (CH), 126.42 (CH), 128.86 (C), 136.82 (C), 141.16 (C), 156.19 (C). ESI-MS (70 eV): m/z (%) = 211 (100) [M]+, 197 (68), 183 (27), 151 (10), 139 (7), 127 (7), 115 (7), 103 (7), 91 (7), 79 (7), 67 (7), 55 (7), 43 (7), 31 (7). HRMS: m/z calcd for C13H12NO [M]+: 233.0981; found: 233.0975.

Isogirinimbine (3,3,8-trimethyl-3,11-dihydropyran-3,2-α-carbazole) (3) and 1,1,7-trimethyl-2-methylene-1,10-dihydro-2H-furo[3,2-α]carbazole (17). A solution of 2-methylbut-3-yn-2-ol (16) [54 µL, 47 mg, 0.56 mmol], DBU (114 µL, 116 mg, 762 µmol) and trifluoroacetic anhydride (78 µL, 0.12 g, 0.56 mmol) in acetonitrile (2 mL) was stirred at −15 °C for 90 min. The mixture was then added to a solution of 2-hydroxy-6-methylcarbazole (10) (100 mg, 507 µmol) and copper(i) iodide (0.2 mg, 1 µmol) in acetonitrile (4 mL) and the mixture was stirred at −15 °C for 40 min. DBU (98 µL, 0.10 g, 0.66 mmol) was added and the mixture was stirred at −15 °C for 3 h and at room temperature for 90 min. The mixture was washed twice with water and brine and the solvent was evaporated. Toluene (10 mL) was added to the residue, the solution was heated to reflux for 23 h and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (petroleum ether–dichloromethane, gradient elution, 99:1 to 3:1) provided isogirinimbine (3) as colourless solid, yield: 84.4 mg (63%), m.p. 186–187 °C. UV (MeOH): λ = 221 (sh), 237, 278 (sh), 289, 332, 337, 353 nm. Fluorescence (MeOH): δem = 289 nm, δm = 362, 378 nm. IR (ATR): ν = 3415, 2969, 2919, 2853, 1604, 1519, 1474, 1460, 1418, 1400, 1373, 1359, 1339, 1295, 1207, 1157, 1071, 1036, 898, 882, 859, 800, 746, 721, 704, 562, 578, 562, 540 cm−1. 1H NMR (500 MHz, acetone-d6): δ = 1.43 (s, 6 H), 2.45 (s, 3 H), 4.09 (d, J = 9.8 Hz, 1 H), 6.63 (d, J = 8.4 Hz, 1 H), 6.90 (d, J = 9.8 Hz, 1 H), 7.11 (dd, J = 8.2, 1.1 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.76 (d, J = 0.6 Hz, 1 H), 7.79 (d, J = 8.4 Hz, 1 H), 10.25 (br s, 1 H). 13C NMR and DEPT (125 MHz, acetone-d6): δ = 21.48 (CH3), 27.84 (CH2), 76.48 (C), 105.66 (C), 109.71 (CH), 111.18 (CH), 111.18 (C), 113.34 (CH), 119.98 (CH), 121.01 (CH), 124.70 (CH), 126.42 (CH), 128.88 (C), 129.99 (CH), 137.99 (C), 139.34 (C), 152.32 (C). ESI-MS: m/z (%) = 263 (28) [M]+, 252 (19), 233 (5), 217 (4), 204 (9), 124 (14). HRMS: m/z calcd for C21H14NO [M]+: 263.1301; found: 263.1302.

1,1,7-Trimethyl-2-methylene-1,10-dihydro-2H-furo[3,2-α]carbazole (17) was obtained as a by-product in up to 3% yield as colourless oil. 1H NMR (300 MHz, acetone-d6): δ = 1.68 (s, 6 H), 2.46 (s, 3 H), 4.35 (d, J = 2.6 Hz, 1 H), 4.61 (d, J = 2.6 Hz, 1 H), 6.80 (d, J = 8.3 Hz, 1 H), 7.14 (dd, J = 8.1, 1.0 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 1.0 Hz, 1 H), 7.92, (d, J = 8.3 Hz, 1 H), 10.21 (br s, 1 H). 13C NMR and DEPT (75 MHz, acetone-d6): δ = 21.46 (CH3), 28.69 (2 CH3), 44.78 (C), 82.67 (CH3), 105.52 (CH), 111.39 (CH), 116.22 (C), 120.02 (CH), 120.25 (C), 120.48 (C), 124.56 (C), 126.83 (CH), 129.07 (C), 136.56 (C), 139.62 (C), 155.55 (C), 173.56 (C). ESI-MS (−25 V): m/z = 262 [(M−H)−].

Methyl 3,7-dimethyloct-6-en-1-yn-3-yl carbonate (18). A 0.5 M solution of ethynylmagnesium bromide in THF (51.0 mL,
25.5 mmol) was added dropwise over a period of 15 min to a solution of 6-methylhept-3-en-2-one (2.94 mL, 2.52 g, 20.0 mmol) in THF (20 mL) at −78 °C. The cooling was removed and the mixture was stirred for 2.5 h. The mixture was cooled to −78 °C, methyl chloroforame (3.06 mL, 3.74 g, 39.6 mmol) was added dropwise over a period of 5 min, the cooling was removed and the mixture was stirred for 2 h. A saturated aqueous solution of sodium hydrogen carbonate and diethyl ether were added, and the layers were separated. The organic layer was washed with water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–diethyl ether, gradient elution, 100:1 to 20:1) provided carbazole 18 as colourless liquid, yield: 3.68 g (88%). IR (ATR): ν = 3287, 2959, 2923, 2853, 1754, 1699, 1684, 1651, 1635, 1441, 1376, 1338, 1257, 1165, 1143, 1074, 1022, 940, 884, 834, 790, 666, 631 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.60 (s, 3 H), 1.66 (d, J = 0.8 Hz, 3 H), 1.70 (s, 3 H), 1.82 (dd, J = 13.6, 11.0, 1 H, 1 H), 1.96 (dd, J = 13.6, 10.6, 6.0 Hz, 1 H, 1 H), 2.11–2.23 (m, 2 H), 2.58 (s, 1 H), 3.75 (s, 3 H), 5.09 (m, 1 H). ¹³C NMR and DEPT (125 MHz, CDCl₃): δ = 23.59 (CH₃), 26.17 (CH₁), 41.17 (CH₂), 54.29 (CH₂), 73.85 (CH), 76.78 (C), 83.03 (C), 122.85 (CH₃), 134.37 (C), 153.49 (C = O). EI-MS (70 eV): m/z (%) = 210 (100) [M⁺], 151 (7), 119 (100), 105 (13), 91 (50), 69 (44). Elemental analysis: calcd for C₁₂H₁₄NO: C 68.54, H 6.83, found: C 68.38, H 8.93%. 

(±)-Mahanimbinic [(±)-isomahanimbinic] [(±)-4] and 1,7-dimethyl-2-methylene-1-(4-methylpent-3-en-1-yl)-1,10-dihydro-2H-furo[3,2-a]carbazole (19). Method A: A solution of 3,7-dimethylcyclohex-1-en-1-yl methyl carbamate (18) (724 mg, 3.44 mmol) in acetonitrile (11.5 mL) was added at room temperature over a period of 8 h to a solution of 2-hydroxy-6-methyl-9-tosylcarbazole (19) (453 mg, 2.30 mmol), DBU (0.69 mL, 0.70 g, 7.01 mmol) and 78 °C. The cooling was removed and the mixture was stirred for 16.25 h. The mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by flash chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 294 : 5 : 1 to 69 : 5 : 1) provided 2-methoxy-6-methyl-carbazole (20). Sodium hydride (539 mg of a 60% dispersion in mineral oil, 13.5 mmol) was added at 0 °C to a solution of 2-methoxy-6-methylcarbazole (14) (701 mg, 3.32 mmol) in THF (35 mL) and the mixture was stirred at 0 °C for 1.25 h. p-Toluenesulfonyl chloride (949 mg, 4.98 mmol) was added at 0 °C, the cooling was removed and the mixture was stirred for 16.25 h. The mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated.

Fluorescence (MeOH): λₑₓ = 268 nm, λₑₘᵢₐₓ = 396 nm. IR (ATR): ν = 3091, 2992, 2947, 2831, 1622, 1580, 1477, 1453, 1361, 1299, 1283, 1200, 1192, 1167, 1147, 1130, 1090, 1044, 985, 938, 869, 842, 801, 777, 736, 705, 675 cm⁻¹. ¹H NMR (500 MHz, acetone-d₆): δ = 2.27 (s, 3 H), 2.43 (s, 3 H), 3.95 (s, 3 H), 7.01 (dd, J = 8.6, 2.3 Hz, 1 H), 7.25–7.27 (m, 3 H), 7.73–7.77 (m, 3 H), 7.86 (d, J = 2.3 Hz, 1 H), 7.90 (d, J = 8.6 Hz, 1 H), 8.14 (d, J = 8.5 Hz, 1 H). ¹³C NMR and DEPT (125 MHz, acetone-d₆): δ = 21.21 (CH₃), 21.35 (CH₃), 56.07 (CH₂), 100.72 (CH), 112.87 (CH), 115.55 (CH), 120.43 (CH), 120.60 (C), 121.76 (CH), 127.38 (2 CH), 127.63 (C), 128.10 (CH), 130.73 (2 CH), 134.78 (C), 135.54 (C), 137.25 (C), 140.76 (C), 146.38 (C), 160.86 (C). EI-MS (70 eV): m/z (%) = 365 [M⁺], 210 (100), 167 (26). HRMS: m/z calced for C₂₃H₂₅NO:S [M⁺]: 365.1086; found: 365.1099. Elemental analysis: calcd for C₂₃H₂₅NO:S: C 69.02, H 5.24, N 3.83, S 8.77; found: C 69.14, H 5.20, N 3.82, S 9.31%.
N-Tosylmahanimbinic (21). A 1 M solution of boron tribromide in dichloromethane (4.1 mL, 4.1 mmol) was added dropwise at −78 °C to a solution of 2-methoxy-6-methyl-9-tosylcarbazole (20) (502 mg, 1.37 mmol). The cooling was removed and the mixture was stirred for 2.5 h. Methanol (4 mL) was added, the mixture was diluted with diethyl ether, and washed with water and brine. The aqueous layer was extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Drying in vacuum provided crude 2-hydroxy-6-methyl-9-tosylcarbazole (539 mg) as light yellow solid, m.p. 166–168 °C.

2-Hydroxy-6-methyl-9-tosylcarbazole: UV (MeOH): \( \lambda_{	ext{ex}} = 222, 244 \) (sh), 260, 267, 275, 297, 308 nm. Fluorescence (MeOH): \( \lambda_{	ext{ex}} = 260 \) nm, \( \lambda_{	ext{em}} = 381 \) nm. IR (ATR): 3432, 2967, 2921, 2853, 1725, 1631, 1596, 1476, 1451, 1398, 1368, 1272, 1172, 1086, 1035, 960, 918, 890, 810, 782, 749, 726, 703, 672, 662, 629, 575, 542 cm\(^{-1}\). \(^1\)H NMR (500 MHz, acetone-\( \text{d}_6 \)): \( \delta = 2.28 (s, 3 H), 2.42 (s, 3 H), 2.92 (dd, \( J = 8.5, 2.1 \) Hz, 1 H), 7.23–7.27 (m, 3 H), 7.69–7.74 (m, 3 H), 7.81 (dd, \( J = 2.4 \) Hz, 1 H), 7.82 (dd, \( J = 8.2 \) Hz, 1 H), 8.11 (dd, \( J = 8.5 \) Hz, 1 H), 8.80 (s, 1 H). \(^{13}\)C NMR and DEPT (125 MHz, acetone-\( \text{d}_6 \)): \( \delta = 21.17 (\text{CH}_3), 21.32 (\text{CH}_3), 102.55 (\text{CH}), 113.72 (\text{CH}), 115.44 (\text{CH}), 119.70 (\text{C}), 120.16 (\text{CH}), 121.77 (\text{CH}), 122.78 (\text{CH}), 127.72 (\text{CH}), 128.87 (\text{C}), 130.66 (\text{CH}), 134.62 (\text{C}), 135.64 (\text{C}), 140.09 (\text{C}), 146.26 (\text{C}), 158.55 (\text{C}). \) EI-MS (70 eV): m/z (%): 351 (79) [M⁺], 196 (100), 167 (12), 91 (5). HRMS: m/z calculated for C\(_{20}\)H\(_{17}\)NO\(_3\)S \([M⁺]\): 351.0929; found: 351.0926. Elemental analysis calculated for C\(_{20}\)H\(_{17}\)NO\(_3\)S: C 68.36, H 4.88, N 2.97, S 6.49%; found: C 68.55, H 4.86, N 3.94, S 7.98%.

A solution of 3,7-dimethyloct-6-en-1-yn-3-yl methyl carbonate (18) (577 mg, 2.74 mmol) in acetonitrile (12 mL) was added over a period of 12 h at room temperature to a solution of the crude 2-hydroxy-6-methyl-9-tosylcarbazole (539 mg), DBU (0.62 mL, 0.63 g, 4.1 mmol) and copper(i) iodide (1.3 mg, 0.007 µmol) in methanol (20 mL), THF (2 mL) and sodium iodide (1.63 mg, 10.0 µmol) in methanol (2 mL). The mixture was stirred at room temperature for 2.75 h (total reaction time: 6.25 h). The mixture was diluted with diethyl ether and washed with water, methanol, saturated aqueous sodium carbonate, and then with brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–diethyl ether, gradient elution, 119 : 1 : 0 : 0 to 13 : 5 : 1 : 0) provided murrayamine-J (68.7 mg, 141 µmol, ratio 22 : 22 : 7.7 : 1, see above). The mixture was irradiated in the microwave reactor at 300 W and 75 °C for 3 h and then at 75 °C for 2 h. A 1 M solution of TBAF in THF (0.28 mL, 0.28 mmol) was added and the mixture was irradiated in the microwave reactor at 300 W and 75 °C for 1 h. The mixture was diluted with diethyl ether, and washed first with an aqueous solution of ammonium chloride and then with brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–diethyl ether, gradient elution, 119 : 1.02 : 0 : 0 to 14 : 1 : 0 : 0.2) provided (±)-mahanimbinic (±)-4 as colourless solid (yield: 37.1 mg, 79%; spectroscopic data, see above) and 23 as light yellow solid, yield: 4.0 mg (9%). \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta = 1.43 (s, 3 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.67–1.80 (m, 2 H), 2.14–2.17 (m, 2 H), 2.49 (s, 3 H), 5.10 (br t, \( J = 7.1 \) Hz, 1 H), 5.55 (d, \( J = 9.8 \) Hz, 1 H), 6.53 (d, \( J = 9.8 \) Hz, 1 H), 6.78 (s, 1 H), 7.12 (dd, \( J = 8.1, 1.1 \) Hz, 1 H), 7.23 (d, \( J = 8.1 \) Hz, 1 H), 7.57 (s, 1 H), 7.71 (br s, 1 H), 7.82 (br s, 1 H).

Murrayamine-J (5). DDQ (109 mg, 480 µmol) was added at room temperature to a solution of (±)-mahanimbinic (±)-4 (39.7 mg, 120 µmol) in methanol (20 mL), THF (2 mL) and water (2 mL). The mixture was stirred at room temperature for 2 h. DDQ (54.4 mg, 240 µmol) was added, the mixture was stirred for 1.5 h, an additional portion of DDQ (54.4 mg, 240 µmol) was added and the mixture was stirred at room temperature for 2.75 h (total reaction time: 6.25 h). The mixture was diluted with diethyl ether and washed with 2 N aqueous NaOH, water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl ether, gradient elution, 1 : 0 : 0 to 13 : 5 : 1) provided murrayamine-J (5) (34.1 mg, 97.9 µmol) as white solid (yield: 74.6 mg, 79%; spectroscopic data, see above) and murrayamine-J (6) (31.0 mg, 79.8 µmol) as white solid (yield: 37.1 mg, 79%; spectroscopic data, see above).
Bicyclomahanibincine (6). A solution of (+)-mahanimbicine [(+)-4] (40.1 mg, 121 µmol) in toluene (40 mL) was placed in a water bath and irradiated using a daylight lamp (600 nm, 6500 K) for 14 d under continuous stirring at room temperature. Evaporation of the solvent and purification of the residue by column chromatography on silica gel (pentane-dichloromethane-ethyl acetate, 1:0:2 to 23:1:0:2) provided bicyclomahanibincine (6) as colourless solid, yield: 15.7 mg (39%), m.p. 169 °C (ref. 9: 173–176 °C). UV (MeOH): λem = 242 nm, λex = 234 nm. IR (ATR): ν = 3463, 3074, 2963, 2920, 2856, 1711, 1609, 1508, 1483, 1454, 1415, 1381, 1365, 1339, 1293, 1217, 1194, 1177, 1142, 1085, 972, 916, 873, 802, 766, 740, 672, 645, 589 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ = 0.77 (s, 3 H), 1.45 (s, 3 H), 1.57 (s, 3 H), 1.63–1.76 (m, 3 H), 2.07–2.14 (m, 1 H), 2.49–2.54 (m, 1 H), 2.50 (s, 3 H), 2.72 (dd, J = 9.4, 7.7 Hz, 1 H), 3.28 (dd, J = 9.4 Hz, 1 H), 6.77 (dd, J = 8.4 Hz, 1 H), 7.14 (dd, J = 8.2, 1.2 Hz, 1 H), 7.28 (dd, J = 8.2 Hz, 1 H), 7.40 (br s, 1 H), 7.75 (br s, 1 H), 7.76 (dd, J = 8.4 Hz, 1 H). 13C NMR and DEPT (125 MHz, CDCl₃): δ = 18.53 (CH₃), 21.42 (CH₃), 25.61 (CH₃), 27.57 (CH₃), 35.08 (CH₂), 37.12 (CH), 37.65 (CH), 38.00 (CH₂), 39.22 (CH), 46.39 (CH), 83.54 (CH), 106.48 (CH), 109.99 (CH), 111.14 (CH), 116.62 (CH), 118.94 (CH), 114.44 (C), 124.35 (C), 125.41 (C), 128.88 (C₁), 137.46 (C), 139.64 (C), 151.85 (C). EI-MS (70 eV): m/z (%) = 331 (30 [M⁺], 248 (100), 234 (3), 218 (2). HRMS: m/z calcd for C₁₉H₁₉NO: M⁺ = 285.1105, found: 285.1106. Murrayamine-M (7). DDQ (59 mg, 260 µmol) was added at 0 °C to a solution of bicyclomahanibincine (6) (28.3 mg, 85.4 µmol) in methanol (10 mL), THF (1 mL) and water (2 mL). The cooling was removed and the mixture was stirred for 2 h at room temperature. DDQ (38.6 mg, 0.17 mmol) was added, the mixture was stirred for 1.5 h, an additional portion of DDQ (29 mg, 130 µmol) was added and the mixture was stirred for 1.5 h (total reaction time: 5 h). The mixture was diluted with diethyl ether and washed with 2 N aqueous NaOH, water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane-dichloromethane-ethyl acetate, gradient elution, 1:0:0.2:14:5:1) provided murrayamine-M (7) as light yellow solid, yield: 15 mg (51%), m.p. 216–218 °C (ref. 8: oil). UV (MeOH): λ = 243, 255, 293, 329 (sh) nm. Fluorescence (MeOH): λex = 293 nm, λem = 368 nm. IR (ATR): ν = 3416, 3385, 2947, 2863, 1735, 1698, 1673, 1654, 1605, 1572, 1508, 1474, 1458, 1414, 1318, 1220, 1128, 1151, 1088, 1021, 926, 981, 818, 787, 729, 686, 632, 610 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ = 0.80 (s, 1 H), 1.45 (s, 3 H), 1.59 (s, 3 H), 1.62–1.78 (m, 3 H), 2.04–2.12 (m, 1 H), 2.54 (m, 1 H), 2.74 (dd, J = 9.5, 7.7 Hz, 1 H), 3.30 (d, J = 9.5 Hz, 1 H), 6.88 (dd, J = 8.5 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.82 (br s, 1 H), 7.85 (d, J = 8.5 Hz, 1 H), 7.88 (dd, J = 8.4, 1.6 Hz, 1 H), 8.48 (m, 1 H), 10.07 (s, 1 H). 13C NMR and DEPT (125 MHz, CDCl₃): δ = 18.72 (CH₃), 25.59 (CH₃), 27.42 (CH₃), 35.10 (CH₃), 36.96 (CH), 37.66 (CH), 38.19 (CH₃), 39.30 (C), 46.40 (CH), 83.88 (C), 107.17 (C), 110.68 (CH), 112.77 (CH), 116.48 (C), 119.44 (CH₂), 122.88 (CH), 124.46 (C), 126.01 (CH), 129.32 (C), 139.84 (C), 143.10 (C), 152.92 (C), 192.03 (CHO). EI-MS (70 eV): m/z (%) = 345 (24 [M⁺], 262 (100), 233 (3), 204 (4). HRMS: m/z calcd for C₁₉H₁₉NO: M⁺ = 285.1105, found: 285.1106.
Isomurrayazoline (9). A solution of (±)-mahanimbine ([±]-4) (40.5 mg, 122 μmol) and CSA (2.3 mg, 10 μmol) in hexane (12 mL) was stirred at room temperature for 11.5 d. The mixture was diluted with diethyl ether and washed with an aqueous solution of sodium hydrogencarbonate and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 59 : 16 : 1 : 0.2) provided a mixture of murrayamine (4) and isomurrayazoline (9) as colourless solid, yield: 28.4 mg (70%), ratio of 8 : 9 = 1 : 1 (determined by the 1H NMR spectrum).

The two isomers were separated by preparative HPLC on a Grace Vydac C8 column (208TP1050, 50 × 250 mm), gradient elution, 59 : 1 : 0.2 to 27% THF in 25 min) to afford murrayamine-G (4) as colourless crystals (spectroscopic data: see above) and isomurrayazoline (9) as colourless solid, m.p. 224 °C (ref. 10: 269 °C) as colourless solid, m.p. 224 °C (ref. 10: 269 °C) as colourless solid.

Acknowledgements

We thank Micha P. Kralh for experimental support.

Notes and references


