PAPER

Palladium(II)-catalysed total synthesis of naturally occurring pyrano[3,2-a]carbazole and pyrano[2,3-b]carbazole alkaloids†‡

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Seven naturally occurring pyranocarbazole alkaloids (pyrayafoline A–E, *O*-methylmurrayamine A and *O*-methylmahanine) have been obtained by total synthesis using a palladium(II)-catalysed oxidative cyclisation of a diarylamine to an orthogonally diprotected 2,7-dihydroxycarbazole as key step.

Introduction

Plants of the genera *Murraya*, *Clausena* and *Glycosmis* are the main terrestrial source for the isolation of carbazole alkaloids.[1] Various species of these plants have been applied in Asian folk medicine for the treatment of numerous diseases. It is assumed that carbazole alkaloids play a central role in the pharmacological effect of the plant extracts because of their wide range of biological activities.[2] Therefore, a variety of classical methods and new procedures using transition metals have been developed for the synthesis of carbazoles.[1,3] We reported the application of iron-mediated[4] and palladium(II)-catalysed approaches for the synthesis of carbazole derivatives.[5] Herein, we describe the application of our palladium(II)-catalysed cyclisation of diarylamines to the synthesis of seven pyranocarbazole natural products: the pyrayafolines A–E (**1–5**), *O*-methylmurrayamine A (**6**) and *O*-methylmahanine (**7**) (Fig. 1).

Pyrayafoline A (**1**) was first isolated by Furukawa and co-workers in 1986 from the stem bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[6] The structure was assigned based on the spectroscopic data and confirmed by synthesis. In 1991, the same group reported the isolation of the pyrayafolines B (**2**), C (**3**) and D (**4**) from the same natural source.[7] In their studies, Furukawa *et al.* reported the *O*-methylation of natural pyrayafoline B–D (**2–4**) using diazomethane, and the total synthesis of *O*-methylpyrayafoline B and *O*-methylpyrayafoline C, which is equivalent to pyrayafoline A (**1**). The structural assignments for **2** and **3** were then confirmed by comparison of the spectroscopic data of the different *O*-methyl derivatives.
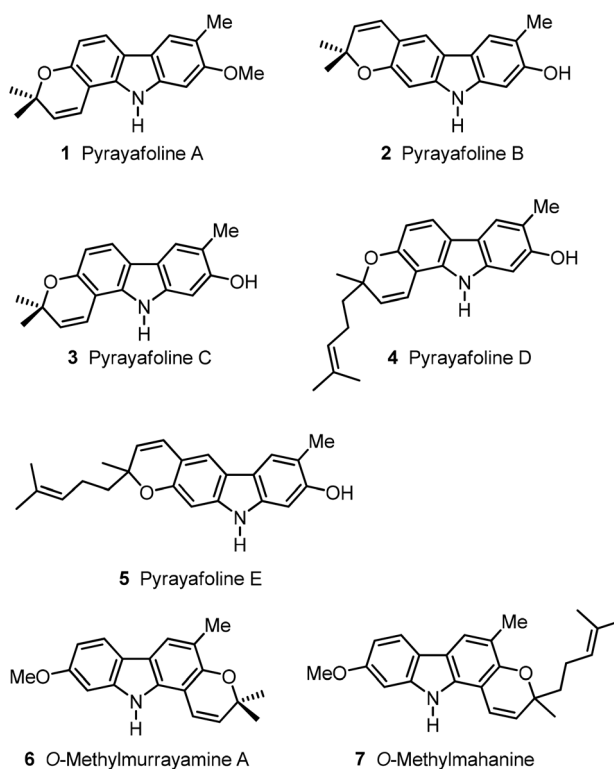

Fig. 1 Naturally occurring pyrano[3,2-*a*]carbazole and pyrano[2,3-*b*]-carbazole alkaloids.

Although pyrayafoline D (**4**) is chiral, the natural product did not show any optical rotation ($[\alpha]_D = \pm 0$, *c* 0.0013, MeOH). Pyrayafoline D (**4**) was also obtained by Itoigawa *et al.* from the leaves of *Murraya koenigii* collected in Bangladesh.[8] In 1991, Furukawa and co-workers reported the isolation of pyrayafoline E (**5**) from the stem bark of *Murraya euchrestifolia* Hayata.[9] The structural assignment for **5** was based solely on its spectroscopic data. As reported for pyrayafoline D (**4**), pyrayafoline E

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(**5**) did not exhibit any optical rotation ($[\alpha]_D$ = ±0, c 0.0007, CHCl$_3$). In the plant material which afforded pyrayafoline E (**5**), Furukawa and co-workers also identified pyrayafolines B–D (**2–4**) and other carbazole alkaloids. *O*-Methylmurrayamine A (**6**) was mentioned first in 1991 by Wu as a synthetic derivative of murrayamine A, which had been isolated from the leaves of *Murraya euchrestifolia* collected in Taiwan.[10] In 2003, Nakatani and co-workers described the isolation of *O*-methylmurraya-mine A (**6**) from the leaves of *Murraya koenigii* collected in Malaysia.[11] In 2009, compound **6** was also isolated by Mukha-padhyay *et al.* from *Murraya koenigii* collected in India.[12] In 2011, we reported the first total synthesis of *O*-methylmurraya-mine A (**6**) using an iron-mediated approach.[4c] *O*-Methylmaha-nine (**7**) was mentioned first in 1972 by Kapil and co-workers as a synthetic derivative of Mahanine.[13] However, no spectro-scopic data were disclosed. In 2003, Nakatani *et al.* described the first isolation of *O*-methylmahanine (**7**) from the leaves of *Murraya koenigii* collected in Malaysia.[11] *O*-Methylmahanine (**7**) was obtained as an optically active compound ($[\alpha]_D$ = +3, c 0.10, CHCl$_3$). However, the absolute configuration has not been assigned. Not much is known about the biological activi-ties of the compounds **1–7**, except for pyrayafoline D (**4**) which has shown a promising cytotoxicity against a variety of cancer cell lines.[8,14]
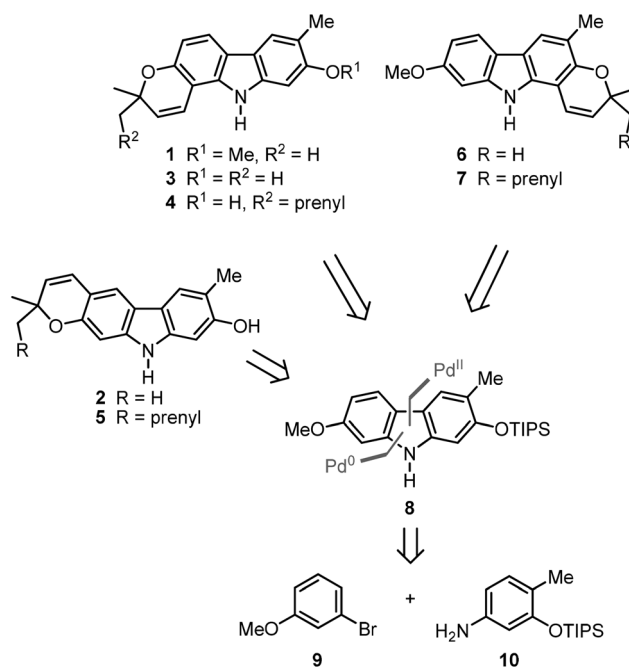
Results and discussion

We have developed a synthesis for the natural products **1–7** from a common precursor using our palladium(II)-catalysed approach for the construction of the carbazole framework. Retrosynthetic analysis led to the orthogonally diprotected 2,7-dihydroxycarbazole **8** as a relay compound (Scheme 1). The pyran ring was thought to be annulated at a later stage of the synthesis. Carbazole **8** should be available by a palladium(II)-catalysed oxidative cyclisation of a corresponding diarylamine which can be obtained by the Buchwald–Hartwig amination[15] of *meta*-bromoanisole (**9**) and the arylamine **10**.
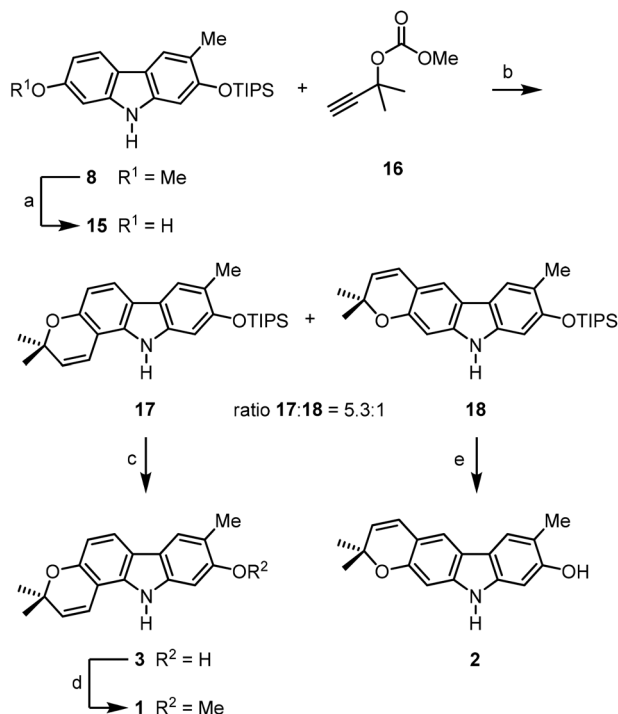
The arylamine **10**[16] was obtained from the nitrophenol **11** by formation of the triisopropylsilyl ether followed by reduction of the nitro group (Scheme 2). The Buchwald–Hartwig amination of *m*-bromoanisole (**9**) with the arylamine **10** using catalytic amounts of palladium(II) acetate and SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl)[15b] as ligand led quantitatively to the diarylamine **12**. Alternatively, compound **12** is available by Buchwald–Hartwig coupling of the silyl-protected bromocresol **14** and *m*-anisidine (96% yield). The best results for the oxidative cyclisation of the diaryl-amine **12** were achieved by heating in a microwave reactor in the presence of catalytic amounts of freshly recrystallised palla-dium(II) acetate and 2.5 equivalents of copper(II) acetate as reoxidant in pivalic acid. These reaction conditions afforded the orthogonally diprotected 2,7-dihydroxycarbazole **8** in 82% yield.

For the synthesis of the pyrayafolines A–C (**1–3**), the methyl ether at C-7 of carbazole **8** was cleaved using boron tribromide

Scheme 1 Retrosynthetic analysis of the pyranocarbazoles **1–7**.
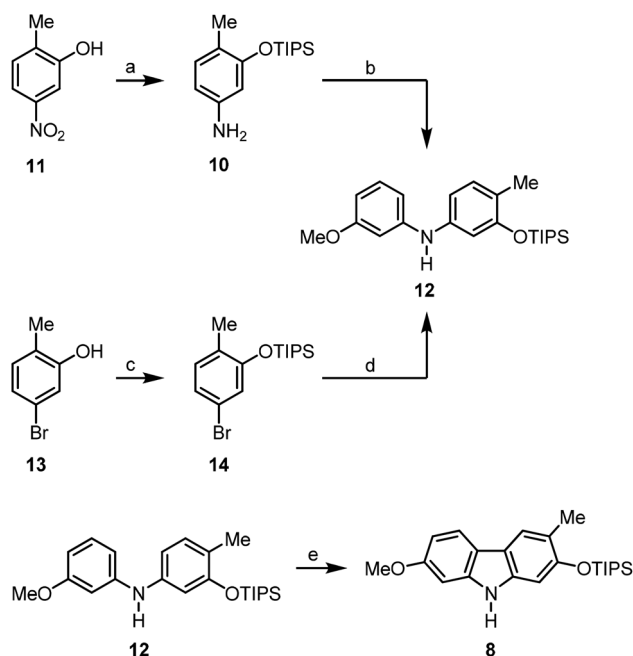
Scheme 2 Synthesis of the orthogonally diprotected 2,7-dihydroxycar-bazole **8**. *Reagents and conditions*: (a) 1. 1.2 equiv. TIPSCl, 1.8 equiv. ImH, DMF, rt; 2. 4.7 equiv. iron powder, AcOH, 60 °C, 100% (two steps); (b) 1.3 equiv. **10**, 1.0 equiv. *m*-bromoanisole (**9**), 5 mol% Pd(OAc)$_2$, 10 mol% SPhos, 1.4 equiv. Cs$_2$CO$_3$, PhMe, 100 °C, 100%; (c) 1.6 equiv. TIPSCl, 2.0 equiv. ImH, DMF, rt, 97%; (d) 1.3 equiv. *m*-anisidine, 1.0 equiv. **14**, 5 mol% Pd(OAc)$_2$, 10 mol% SPhos, 1.4 equiv. Cs$_2$CO$_3$, PhMe, 100 °C, 96%; (e) 0.2 equiv. Pd(OAc)$_2$, 2.5 equiv. Cu(OAc)$_2$, PivOH, microwave (300 W), 110 °C, 82%.

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Scheme 3 Synthesis of pyrayafoline A–C (**1**–**3**). *Reagents and conditions*: (a) 2.0 equiv. BBr$_3$, CH$_2$Cl$_2$, −78 °C to rt; (b) 1. 2.0 equiv. **16**, 2.0 equiv. DBU, 0.9 mol% CuCl$_2$·2H$_2$O, MeCN, rt; 2. PhMe, reflux, 48% **17** and 9% **18** (three steps); (c) 1.5 equiv. TBAF, DMF, −10 °C, 100%; (d) 1.3 equiv. NaH, 1.5 equiv. Me$_2$SO$_4$, THF, 0 °C to rt, 93%; (e) 1.5 equiv. TBAF, DMF, −10 °C, 78%.

(Scheme 3). Annulation of the pyran ring was achieved by formation of the dimethylpropargyl ether using Godfrey's method[17] and subsequent thermally induced rearrangement of the resulting aryl propargyl ether.[18] Treatment of the 7-hydroxycarbazole **15** with methyl dimethylpropargyl carbonate (**16**) in the presence of 1,8-diazabicyclo[5.4.0]undec-1(8)-ene (DBU) and catalytic amounts of copper(II) chloride followed by heating of the intermediate propargyl ether in toluene at reflux afforded a mixture of the protected pyranocarbazoles **17** and **18** in a ratio of 5.3 : 1 in favour of the pyrano-[3,2-*a*]carbazole **17**. Both isomers were separated from each other by column chromatography and fully characterised by their spectroscopic data (see the Experimental section). The pyran ring formation results from a thermally induced sequence of an aryl-Claisen rearrangement followed by a 1,5-hydrogen shift and electrocyclic ring closure (Scheme 4).[19] Pyran annulation following Casiraghi's method (reaction of **15** with prenal in the presence of titanium tetraisopropoxide in toluene at room temperature),[20] which proved to be superior in our previous study,[5k] provided compound **17** only in up to 34% yield. Cleavage of the silyl ether of **17** afforded pyrayafoline C (**3**) in eight steps and 39% overall yield based on compound **11**. Chemoselective *O*-methylation of pyrayafoline C (**3**) provided pyrayafoline A (**1**) in nine steps and 37% overall yield based on **11**. The spectroscopic data of synthetic **1** and **3** are in agreement with those reported for the natural products.[6,7] The
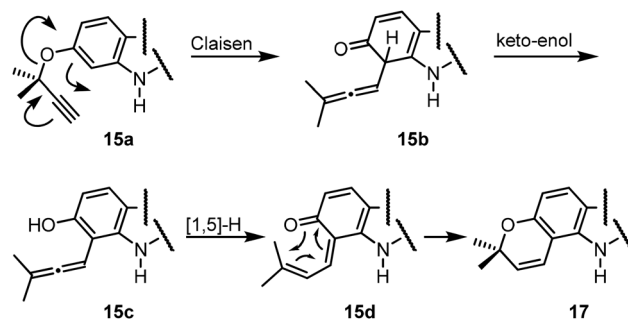
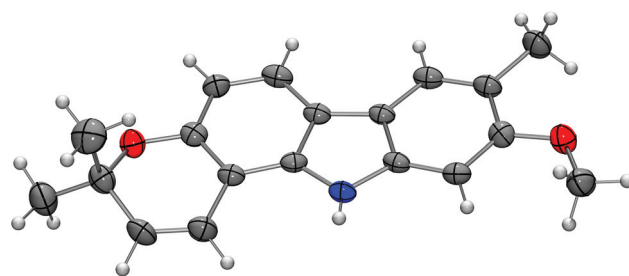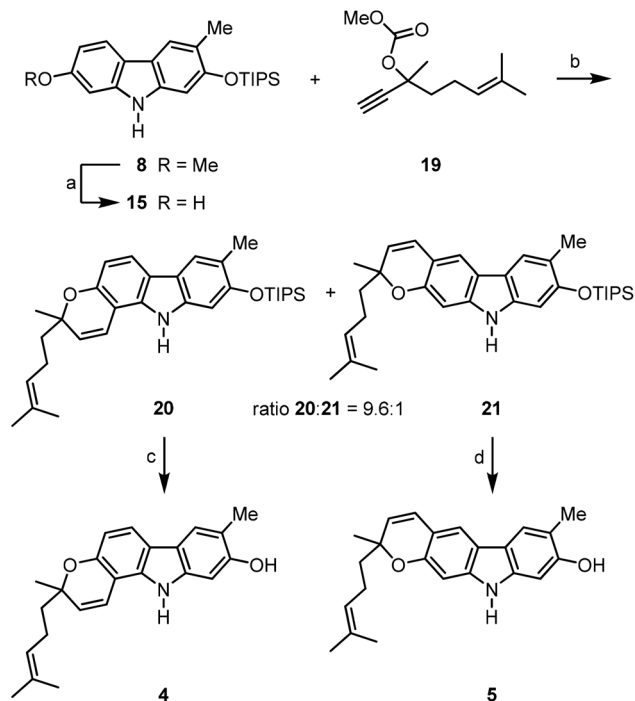**Scheme 4** Mechanism for annulation of the pyran ring.[19]

Fig. 2 Molecular structure of pyrayafoline A (**1**) in the crystal. ORTEP plot showing thermal ellipsoids at the 50% probability level.

structure of pyrayafoline A (**1**) has been additionally confirmed by single-crystal X-ray analysis (Fig. 2). Pyrayafoline B (**2**) was obtained from the minor isomer **18** by cleavage of the silyl ether in eight steps and 6% overall yield based on **11**. The spectroscopic data of our synthetic **2** are matching those reported by Furukawa *et al.* for the natural product.[7]

The prenylated pyrayafolines D (**4**) and E (**5**) were synthesised from the diprotected carbazole **8** by reaction with a C$_{10}$-building block (Scheme 5). Cleavage of the methyl ether of **8** and reaction of crude 7-hydroxycarbazole **15** with the carbonate **19**[21] in the presence of DBU and catalytic amounts of copper(II) chloride followed by thermal rearrangement afforded the pyrano[3,2-*a*]carbazole **20** and the pyrano[2,3-*b*]-carbazole **21** in a ratio of 9.6 : 1. Both isomers were separated from each other by flash chromatography and fully characterised. Also in this case, application of Casiraghi's method for annulation of the pyran ring (reaction of **15** with citral in the presence of titanium tetraisopropoxide in toluene at room temperature)[20] was inferior (25% yield of carbazole **20**). Cleavage of the silyl ether of the pyrano[3,2-*a*]carbazole **20** provided pyrayafoline D (**4**) in eight steps and 40% overall yield based on compound **11**. Analogously, silyl ether cleavage of the pyrano[2,3-*b*]carbazole **21** afforded pyrayafoline E (**5**) in eight steps and 3% overall yield based on **11**. The spectroscopic data of synthetic **4** and **5** are in full agreement with those reported for the natural products.[7,9]

For the synthesis of the carbazole alkaloids **6** and **7** with a pyran annulated at ring A, the silyl ether of the orthogonally diprotected 2,7-dihydroxycarbazole **8** was cleaved first to afford

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Scheme 5 Synthesis of pyrayafoline D (**4**) and E (**5**). *Reagents and conditions*: (a) 2.0 equiv. BBr₃, CH₂Cl₂, −78 °C to rt; (b) 1. 2.0 equiv. **19**, 2.0 equiv. DBU, 0.5 mol% CuCl₂·2H₂O, MeCN, rt; 2. PhMe, reflux, 49% **20** and 4% **21** (three steps); (c) 1.5 equiv. TBAF, DMF, −5 °C, 100%; (d) 1.5 equiv. TBAF, DMF, −12 °C, 83%.
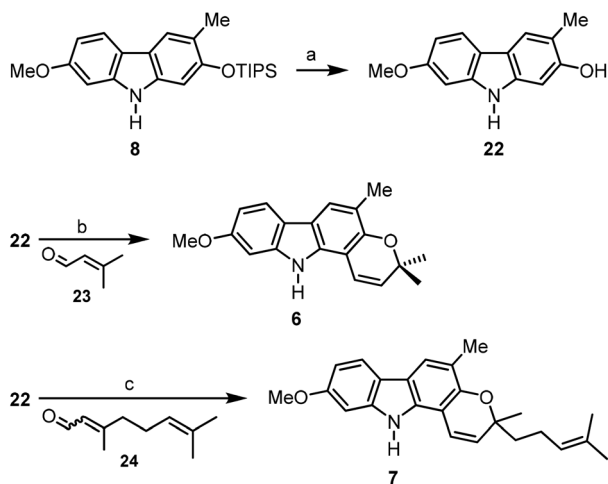
Scheme 6 Synthesis of *O*-methylmurrayamine A (**6**) and *O*-methylmahanine (**7**). *Reagents and conditions*: (a) 1.5 equiv. TBAF, DMF, −10 °C to rt, 100%; (b) 2.0 equiv. prenal (**23**), 4.0 equiv. Ti(OiPr)₄, PhMe, −78 °C to rt, 88%; (c) 2.0 equiv. citral (**24**), 4.0 equiv. Ti(OiPr)₄, PhMe, −78 °C to rt, 75%.

the 2-hydroxycarbazole **22** (Scheme 6). Pyran ring annulation by reaction of **22** with prenal (**23**) in the presence of titanium tetraisopropoxide in toluene (Casiraghi's method)[20] provided *O*-methylmurrayamine A (**6**). The present route leads to *O*-methylmurrayamine A (**6**) in a total number of six steps and 72% overall yield which is superior to our previous synthesis
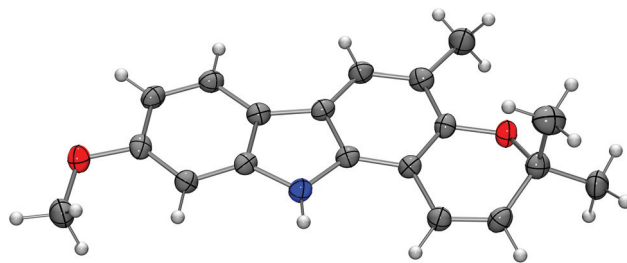

Fig. 3 Molecular structure of *O*-methylmurrayamine A (**6**) in the crystal. ORTEP plot showing thermal ellipsoids at the 50% probability level.

reported for this natural product.[4c] The structure of **6** has been unambiguously confirmed by an X-ray crystal structure determination (Fig. 3). Reaction of the 2-hydroxycarbazole **22** with citral (**24**) and titanium tetraisopropoxide afforded *O*-methylmahanine (**7**) in six steps and 62% overall yield based on **11**. The spectroscopic data of our synthetic carbazole alkaloids **6** and **7** are in full agreement with those reported in the literature.[10]

Conclusions

Using our palladium(ɪɪ)-catalysed oxidative cyclisation of diarylamines as key step, we have achieved the total syntheses of the seven pyranocarbazole alkaloids **1–7**. The orthogonally diprotected 2,7-dihydroxycarbazole **8** served as the crucial intermediate for these natural products. Following our synthetic route, compound **8** is accessible in four steps and 82% overall yield. Chemoselective deprotection of one of the oxygen substituents followed by pyran ring annulation provided pyrayafoline A (**1**) (9 steps, 37% overall yield), B (**2**) (8 steps, 6% overall yield), C (**3**) (8 steps, 39% overall yield), D (**4**) (8 steps, 40% overall yield) and E (**5**) (8 steps, 3% overall yield), as well as *O*-methylmurrayamine A (**6**) (6 steps, 72% overall yield) and *O*-methylmahanine (**7**) (6 steps, 62% overall yield). For the pyrayafolines B–E (**2–5**), we have described the first total synthesis.

Experimental

General methods

All reactions were carried out in oven-dried glassware using dry solvents under an argon atmosphere unless stated otherwise. Acetonitrile, dichloromethane, tetrahydrofuran and toluene were dried using a solvent purification system (MBraun-SPS). Palladium(ɪɪ) acetate was recrystallised from glacial acetic acid. All other chemicals were used as received from commercial sources. Flash chromatography was performed on a Büchi Sepacore system equipped with an UV monitor using silica gel from Acros Organics (0.035–0.070 mm). Thin layer chromatography was performed with TLC plates from Merck (60 F₂₅₄) using UV-light for visualisation. Melting points were measured on a Gallenkamp MPD

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350 melting point apparatus. Ultraviolet spectra were recorded on a Perkin Elmer 25 UV/VIS spectrometer. Infrared spectra were recorded on a Thermo Nicolet Avatar 360 FT-IR spectrometer using the ATR method (Attenuated Total Reflectance). NMR spectra were recorded on Bruker DRX 500 and Avance III 600 spectrometers. Chemical shifts δ are reported in parts per million with the non-deuterated solvent as an internal standard.[22] The following abbreviations have been 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 analyser. X-ray analyses: Bruker–Nonius Kappa CCD equipped with a 700 series Cryostream low temperature device from Oxford Cryosystems. Software: SHELXS-97 (G. M. Sheldrick, 1997), SADABS version 2.10 (G. M. Sheldrick, Bruker AXS Inc., 2002), SHELXL-97 (G. M. Sheldrick, 1997), ORTEP-3 for Windows.[23]

4-Methyl-3-(triisopropylsilyloxy)aniline (10). Chlorotriisopropylsilane (4.92 g, 25.5 mmol) was added at room temperature to a solution of 2-methyl-5-nitrophenol (11) (3.27 g, 21.4 mmol) and imidazole (2.67 g, 39.2 mmol) in DMF (20 mL) and the reaction mixture was stirred for 17.5 h at room temperature. The mixture was diluted with diethyl ether, washed with water, 2 M hydrochloric acid, and brine. The aqueous layers were extracted with ethyl acetate, the organic layers were combined and the solvent was evaporated. The residue was dried under high vacuum to provide 4-nitro-2-(triisopropylsilyloxy)toluene in sufficient purity. This material was dissolved in glacial acetic acid (100 mL) and iron powder (5.57 g, 99.7 mmol) was added. The mixture was vigorously stirred at 60 °C in air for 3 h. This was most conveniently done in a large flask on the rotary evaporator. The solvent was removed under reduced pressure. Diethyl ether and a saturated solution of sodium hydrogencarbonate were added and the suspension was transferred to a separation funnel. The organic layer was separated and washed with water, a saturated solution of sodium hydrogencarbonate and brine. The combined aqueous layers were extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether–diethyl ether, gradient elution, 5 : 1 to 1 : 1) to provide 4-methyl-3-(triisopropylsilyloxy)aniline (10) as a light red oil, yield: 5.98 g (21.4 mmol, 100%). UV (MeOH): λ (nm) = 290 nm; IR (ATR): ν = 3350, 2942, 2892, 2865, 1611, 1585, 1557, 1541, 1509, 1460, 1435, 1392, 1311, 1277, 1258, 1204, 1179, 1126, 1070, 1001, 969, 919, 881, 843, 798, 750, 677, 618 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.12 (d, J = 7.4 Hz, 18 H), 1.29 (m, 3 H), 2.13 (s, 3 H), 3.46 (br s, 2 H), 6.18 (d, J = 2.3 Hz, 1 H), 6.22 (dd, J = 7.9, 2.3 Hz, 1 H), 6.88 (d, J = 7.9 Hz, 1 H); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 13.02 (3 CH), 16.18 (CH$_3$), 18.04

(6 CH$_3$), 105.90 (CH), 107.84 (CH), 118.72 (C), 131.11 (CH), 145.06 (C), 154.85 (C); MS (EI): m/z (%) = 279 (63) [M$^+$], 236 (100), 208 (39), 180 (26), 106 (25).

N-(3-Methoxyphenyl)-4-methyl-3-(triisopropylsilyloxy)aniline (12). *Method A*: A solution of *m*-bromoanisole (9) (802 mg, 4.29 mmol) in toluene (5 mL) was added at 100 °C dropwise over a period of 10 h (using a syringe pump) to a solution of 4-methyl-3-(triisopropylsilyloxy)aniline (10) (1.56 g, 5.57 mmol), palladium acetate (48.6 mg, 216 μmol), SPhos (178 mg, 432 μmol) and caesium carbonate (1.96 g, 6.03 mmol) in toluene (15 mL). The mixture was stirred at 100 °C for 21 h. After cooling to room temperature the solvent was evaporated and the residue was purified by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 140 : 5 : 1 to 80 : 5 : 1) to provide N-(3-methoxyphenyl)-4-methyl-3-(triisopropylsilyloxy)aniline (12) as a light yellow oil, yield: 1.65 g (4.29 mmol, 100%). UV (MeOH): λ = 215 (sh), 281, 306 nm; IR (ATR): ν = 3390, 2943, 2892, 2865, 1595, 1558, 1500, 1459, 1436, 1389, 1279, 1206, 1178, 1153, 1125, 1047, 1005, 947, 923, 881, 838, 804, 763, 717, 681 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.12 (d, J = 7.5 Hz, 18 H), 1.32 (m, 3 H), 2.17 (s, 3 H), 3.74 (s, 3 H), 6.40 (ddd, J = 8.1, 2.1, 0.5 Hz, 1 H), 6.62 (t, J = 2.2 Hz, 1 H), 6.64–6.66 (m, 2 H), 6.71 (d, J = 2.1 Hz, 1 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.10 (t, J = 8.1 Hz, 1 H), 7.31 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 13.73 (3 CH), 16.54 (CH$_3$), 18.42 (6 CH$_3$), 55.29 (CH$_3$), 103.32 (CH), 105.80 (CH), 108.98 (CH), 110.07 (CH), 111.80 (CH), 120.94 (C), 130.62 (CH), 131.94 (CH), 143.27 (C), 146.42 (C), 155.48 (C), 161.75 (C); MS (EI): m/z (%) = 385 (96) [M$^+$], 342 (100), 314 (24), 300 (14), 143 (22); Elemental analysis calcd for C$_{23}$H$_{35}$NO$_2$Si: C 71.64, H 9.15, N 3.63; found: C 71.85, H 9.39, N 3.73%.

4-Bromo-2-(triisopropylsilyloxy)toluene (14). Chlorotriisopropylsilane (4.36 g, 25.6 mmol) was added to a solution of 5-bromo-2-methylphenol (13) (3.02 g, 16.1 mmol) and imidazole (2.20 g, 32.3 mmol) in DMF (20 mL) and the reaction mixture was stirred at room temperature for 21.5 h. The mixture was diluted with diethyl ether, washed with water, 2 M hydrochloric acid, and brine. The aqueous layers were extracted with diethyl ether and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane) provided 4-bromo-2-(triisopropylsilyloxy)toluene (14) as a colourless oil, yield: 5.35 g (15.6 mmol, 97%). UV (MeOH): λ = 224 (sh), 277, 285 nm; IR (ATR): ν = 2944, 2891, 2867, 1589, 1575, 1484, 1465, 1420, 1396, 1266, 1249, 1191, 1125, 1072, 1013, 989, 932, 881, 850, 797, 723, 704, 680, 645, 630 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.11 (d, J = 7.4 Hz, 18 H), 1.30 (m, 3 H), 2.18 (s, 3 H), 6.90 (m, 1 H), 6.95–6.99 (m, 2 H); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 12.92 (3 CH), 16.63 (CH$_3$), 17.97 (6 CH$_3$), 118.84 (C), 121.04 (CH), 123.59 (CH), 127.68 (C), 131.81 (CH), 155.06 (C); MS (EI): m/z (%) = 344 (27), 342 (27) [M$^+$], 301 (100), 299 (98), 273 (46), 271 (46), 245 (68), 243 (69), 231 (31), 229 (35), 149 (46); Elemental analysis calcd for C$_{16}$H$_{27}$BrOSi: C 55.97, H 7.93; found: C 56.04, H 8.19%.

N-(3-Methoxyphenyl)-4-methyl-3-(triisopropylsilyloxy)aniline (12). *Method B*: A solution of 4-bromo-2-(triisopropylsilyloxy)-

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toluene (**14**) (1.00 g, 2.92 mmol) in toluene (10 mL) was added at 100 °C dropwise over a period of 7.5 h (using a syringe pump) to a solution of *m*-anisidine (466 mg, 3.79 mmol), palladium acetate (33.4 mg, 149 μmol), SPhos (121 mg, 294 μmol) and caesium carbonate (1.33 g, 4.08 mmol) in toluene (20 mL). The mixture was stirred at 100 °C for 20.5 h. After cooling to room temperature, the mixture was filtered over Celite® 557 (ethyl acetate), the solvent was evaporated and the residue was purified by flash chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 140 : 5 : 1 to 80 : 5 : 1) to provide diarylamine **12** as a light yellow oil, yield: 1.08 g (2.79 mmol, 96%). Spectral data: see above.

7-Methoxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (8). Three batches of cyclisation mixture were prepared as follows: A 10 mL microwave tube was charged with diarylamine **12**, palladium acetate, copper(II) acetate and pivalic acid in air and the tube was irradiated in the microwave reactor at 110 °C and 300 W for 3 h. Batch 1: 511 mg (1.33 mmol) **12**, 64.8 mg (289 μmol) Pd(OAc)$_2$, 602 mg (3.31 mmol) Cu(OAc)$_2$, 1.13 g (11.1 mmol) PivOH; Batch 2: 519 mg (1.35 mmol) **12**, 63.9 mg (285 μmol) Pd(OAc)$_2$, 614 mg (3.38 mmol) Cu(OAc)$_2$, 1.09 g (10.6 mmol) PivOH; Batch 3: 457 mg (1.19 mmol) **12**, 56.3 mg (251 μmol) Pd(OAc)$_2$, 538 mg (2.96 mmol) Cu(OAc)$_2$, 1.10 g (10.8 mmol) PivOH. After completion of the reaction the three batches were combined, diluted with diethyl ether and the suspension was washed with water, a saturated aqueous solution of potassium carbonate 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, 100 : 5 : 1 to 30 : 5 : 1) provided the carbazole **8** as light yellow crystals, yield: 1.21 g (3.16 mmol, 82%). m.p. 175–176 °C. UV (MeOH): λ = 211, 236, 259 (sh), 264, 311, 323 nm; Fluorescence (MeOH): $λ_{ex}$ = 264 nm, $λ_{em}$ = 354 nm; IR (ATR): ν = 3387, 3058, 3008, 2943, 2889, 2864, 1612, 1500, 1470, 1397, 1344, 1325, 1301, 1269, 1226, 1198, 1160, 1144, 1105, 1072, 1033, 1008, 944, 860, 826, 806, 767, 709, 675, 645, 608 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.16 (d, *J* = 7.5 Hz, 18 H), 1.38 (m, 3 H), 2.37 (s, 3 H), 3.83 (s, 3 H), 6.74 (dd, *J* = 8.5, 2.3 Hz, 1 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 6.97 (s, 1 H), 7.72 (s, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 9.88 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 13.81 (3 CH), 17.80 (CH$_3$), 18.48 (6 CH$_3$), 55.69 (CH$_3$), 95.52 (CH), 100.78 (CH), 108.16 (CH), 117.99 (C), 118.19 (C), 120.56 (CH), 120.74 (C), 121.39 (CH), 140.57 (C), 142.28 (C), 153.05 (C), 159.07 (C); MS (EI): *m/z* (%) = 383 (100) [M$^+$], 340 (49), 325 (12), 312 (12), 298 (13), 238 (21), 226 (21), 167 (11); Elemental analysis calcd for C$_{23}$H$_{33}$NO$_2$Si: C 72.01, H 8.67, N 3.65; found: C 71.94, H 8.70, N 3.78%.

7-Hydroxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (15). A 1 M solution of boron tribromide in dichloromethane (1.05 mL, 1.05 mmol) was added at −78 °C over a period of 3 min to a solution of 7-methoxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (**8**) (202 mg, 527 μmol) in dichloromethane (20 mL) and the solution was allowed to gradually warm to room temperature. The reaction mixture was stirred for 14 h

45 min and methanol (1 mL) was added. The solution was diluted with dichloromethane 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 column chromatography on silica gel (petroleum ether–ethyl acetate, gradient elution, 1 : 0 to 7 : 3) afforded 7-hydroxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (**15**) as a yellow oil, yield: 185 mg (501 μmol, 95%). ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.16 (d, *J* = 7.5 Hz, 18 H), 1.38 (m, 3 H), 2.36 (s, 3 H), 6.68 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.86 (d, *J* = 2.1 Hz, 1 H), 6.93 (s, 1 H), 7.68 (s, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 8.17 (s, 1 H), 9.77 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 13.80 (3 CH), 17.78 (CH$_3$), 18.48 (6 CH$_3$), 97.40 (CH), 100.71 (CH), 108.81 (CH), 117.34 (C), 118.45 (C), 120.46 (C), 120.55 (CH), 121.18 (CH), 140.46 (C), 142.56 (C), 152.80 (C), 156.41 (C); MS (EI): *m/z* (%) = 369 (100) [M$^+$], 326 (58), 298 (16), 284 (15), 224 (25), 196 (16), 135 (25).

***O*-(Triisopropylsilyl)pyrayafoline C (17) and *O*-(triisopropylsilyl)pyrayafoline B (18).** A 1 M solution of boron tribromide in dichloromethane (2.13 mL, 2.13 mmol) was added dropwise at −78 °C over a period of 5 min to a solution of carbazole **8** (409 mg, 1.07 mmol) in dichloromethane (15 mL). The reaction mixture was stirred for 18 h while gradually warming to room temperature. Methanol (3 mL) was added, and the mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were extracted with diethyl ether and the combined organic layers were dried over sodium sulfate. The solvent was evaporated and the resulting oil was dried under high vacuum to provide crude 7-hydroxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (**15**), yield: 421 mg. A solution of methyl 2-methylbut-3-yn-2-yl carbonate (**16**) (303 mg, 2.13 mmol) in acetonitrile (10 mL) was added dropwise over a period of 10 h to a solution of crude **15** (421 mg), copper(II) chloride dihydrate (1.6 mg, 9.4 μmol) and DBU (319 μL, 325 mg, 2.13 mmol) in degassed acetonitrile (60 mL) and the mixture was stirred at room temperature for 19 h. Diethyl ether was added and the mixture was washed with water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate, the solvent was evaporated and the residue was dried under high vacuum. The crude mixture was dissolved in toluene (30 mL) and heated at reflux for 23 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 140 : 5 : 1 to 70 : 5 : 1) provided the less polar *O*-TIPS-pyrayafoline C (**17**) as light yellow crystals, yield: 222 mg (509 μmol, 48%), m.p. 191–193 °C. UV (MeOH): λ = 221, 239, 284 (sh), 295, 336, 352 (sh) nm; Fluorescence (MeOH): $λ_{ex}$ = 239 nm, $λ_{em}$ = 353 nm; IR (ATR): ν = 3357, 3041, 3015, 2941, 2883, 2862, 1629, 1592, 1576, 1471, 1419, 1401, 1362, 1316, 1297, 1273, 1221, 1162, 1116, 1069, 1034, 988, 915, 882, 851, 836, 795, 740, 720, 674, 602 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.16 (d, *J* = 7.5 Hz, 18 H), 1.38 (m, 3 H), 1.43 (s, 6 H), 2.36 (s, 3 H), 5.75 (d, *J* = 9.8 Hz, 1 H), 6.59 (d, *J* = 8.3 Hz, 1 H), 6.86 (d, *J* =

9.8 Hz, 1 H), 6.94 (s, 1 H), 7.68 (d, J = 8.3 Hz, 1 H), 7.70 (s, 1 H), 10.08 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 13.80 (3 CH), 17.79 (CH$_3$), 18.47 (6 CH$_3$), 27.78 (2 CH$_3$), 76.30 (C), 100.85 (CH), 105.67 (C), 109.52 (CH), 118.33 (CH), 118.46 (C), 118.50 (C), 120.12 (CH), 121.01 (C), 121.42 (CH), 130.12 (CH), 137.59 (C), 140.60 (C), 151.39 (C), 153.11 (C); MS (EI): m/z (%) = 435 (16) [M$^+$], 420 (100), 292 (7), 161 (16); Elemental analysis calcd for C$_{27}$H$_{37}$NO$_2$Si: C 74.43, H 8.56, N 3.21; found: C 74.09, H 8.32, N 3.14%.

O-TIPS-pyrayafoline B (**18**) was obtained from the more polar fraction as a light yellow oil, yield: 40.6 mg (93.2 µmol, 9%). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.16 (d, J = 7.5 Hz, 18 H), 1.35 (m, 3 H), 1.48 (s, 6 H), 2.40 (s, 3 H), 5.59 (d, J = 9.8 Hz, 1 H), 6.52 (d, J = 9.8 Hz, 1 H), 6.786 (s, 1 H), 6.789 (s, 1 H), 7.52 (s, 1 H), 7.66 (s, 1 H), 7.88 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 13.05 (3 CH), 17.54 (CH$_3$), 18.06 (6 CH$_3$), 27.76 (2 CH$_3$), 76.20 (C), 97.94 (CH), 99.79 (CH), 114.83 (C), 116.80 (CH), 117.24 (C), 117.57 (C), 120.66 (CH), 121.04 (C), 123.41 (CH), 128.23 (CH), 138.96 (C), 140.45 (C), 151.23 (C), 152.54 (C); MS (EI): m/z (%) = 435 (46) [M$^+$], 420 (100), 161 (22), 153 (13).

Pyrayafoline C (3). A 1 M solution of TBAF in THF (180 µL, 180 µmol) was added at −10 °C to a solution of O-(triisopropyl-silyl)pyrayafoline C (**17**) (52.4 mg, 120 µmol) in DMF (10 mL), the cooling bath was removed and the reaction mixture was stirred for 10 min at room temperature. Water (10 mL) and diethyl ether were added and the mixture 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–ethyl acetate, gradient elution, 5 : 1 to 3 : 1) provided pyraya-foline C (**3**) as pale grey crystals, yield: 33.5 mg (120 µmol, 100%), m.p. 216 °C (ref. 7: pale yellow oil). UV (MeOH): λ = 221, 237, 285 (sh), 295, 337 nm; Fluorescence (MeOH): λ_{ex} = 237 nm, λ_{em} = 354 nm; IR (ATR): ν = 3412, 3329, 3052, 2986, 2912, 2853, 1630, 1607, 1590, 1577, 1554, 1471, 1418, 1399, 1367, 1350, 1297, 1257, 1213, 1155, 1133, 1115, 1064, 1028, 995, 940, 887, 841, 823, 805, 778, 740, 718, 690, 647, 616 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.48 (s, 6 H), 2.38 (s, 3 H), 4.72 (br s, 1 H), 5.70 (d, J = 9.8 Hz, 1 H), 6.59 (d, J = 9.8 Hz, 1 H), 6.70 (d, J = 8.3 Hz, 1 H), 6.82 (s, 1 H), 7.643 (s, 1 H), 7.645 (d, J = 8.3 Hz, 1 H), 7.75 (br s, 1 H); ^{13}C NMR and DEPT (150 MHz, CDCl$_3$): δ = 16.11 (CH$_3$), 27.52 (2 CH$_3$), 75.85 (C), 96.74 (CH), 104.77 (C), 109.41 (CH), 116.24 (C), 116.92 (CH), 117.71 (C), 117.91 (C), 119.47 (CH), 120.96 (CH), 129.76 (CH), 136.12 (C), 139.20 (C), 150.60 (C), 152.07 (C); MS (EI): m/z (%) = 279 (16) [M$^+$], 264 (100), 234 (6), 132 (10); Elemental analysis calcd for C$_{18}$H$_{17}$NO$_2$: C 77.40, H 6.13, N 5.01; found: C 77.09, H 6.53, N 4.92%.

Pyrayafoline A (1). A 1 M solution of TBAF in THF (282 µL, 282 µmol) was added at −10 °C to a solution of O-(triisopropyl-silyl)pyrayafoline C (**17**) (81.8 mg, 188 µmol) in DMF (10 mL), the cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, 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, the solvent was evaporated and the residue was dried under high vacuum to provide crude pyrayafoline C (**3**). Without further purification, compound **3** was dissolved in THF (10 mL), the solution was cooled to 0 °C and sodium hydride (60% suspension in mineral oil, 9.8 mg, 0.25 mmol) was added. The mixture was stirred for a few minutes, dimethyl sulfate (27 µL, 36 mg, 0.28 mmol) was added, the cooling bath was removed and the mixture was stirred for 24 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 column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 20 : 1 to 9 : 1) provided pyrayafoline A (**1**) as pale grey crystals, yield: 51.5 mg (176 µmol, 93%), m.p. 229–233 °C (ref. 6: 228–231 °C). UV (MeOH): λ = 221, 238, 284 (sh), 294, 337, 349 (sh) nm; Fluorescence (MeOH): λ_{ex} = 238 nm, λ_{em} = 353 nm; IR (ATR): ν = 3421, 2968, 2913, 1627, 1590, 1488, 1462, 1416, 1398, 1373, 1346, 1319, 1297, 1267, 1231, 1213, 1186, 1141, 1116, 1068, 1038, 1010, 939, 919, 881, 846, 824, 809, 779, 740, 718, 652 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.48 (s, 6 H), 2.34 (s, 3 H), 3.89 (s, 3 H), 5.70 (d, J = 9.8 Hz, 1 H), 6.61 (d, J = 9.8 Hz, 1 H), 6.70 (d, J = 8.3 Hz, 1 H), 6.85 (s, 1 H), 7.65 (s, 2 H), 7.81 (br s, 1 H); ^{13}C NMR and DEPT (150 MHz, CDCl$_3$): δ = 16.65 (CH$_3$), 27.52 (2 CH$_3$), 55.57 (CH$_3$), 75.80 (C), 92.74 (CH), 104.74 (C), 109.38 (CH), 116.82 (C), 116.97 (CH), 117.85 (C), 119.31 (C), 119.45 (CH), 120.78 (CH), 129.70 (CH), 135.89 (C), 139.00 (C), 150.37 (C), 156.43 (C); MS (EI): m/z (%) = 293 (32) [M$^+$], 278 (100), 263 (18), 234 (11); HRMS: m/z calcd for C$_{19}$H$_{19}$NO$_2$ [M$^+$]: 293.1416; found: 293.1418.

Crystal data for **1**: C$_{19}$H$_{19}$NO$_2$, crystal size: 0.52 × 0.18 × 0.11 mm^3, M = 293.35 g mol^{-1}, monoclinic, space group: $P2_1$, a = 6.508(1), b = 25.907(3), c = 9.1340(1) Å, β = 99.33(1)°, V = 1519.6(3) Å^3, Z = 4, ρ_c = 1.282 g cm^{-3}, μ = 0.083 mm^{-1}, T = 198(2) K, λ = 0.71073 Å, θ range = 3.15–25.40°, reflections collected: 17 349, independent: 5336 (R_{int} = 0.0353), 413 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0428, wR_2 = 0.0783 [$I > 2\sigma(I)$]; maximal residual electron density: 0.161 e Å^{-3}. CCDC 959119.

Pyrayafoline B (2). A 1 M solution of TBAF in THF (351 µL, 351 µmol) was added at −10 °C to a solution of O-(triisopropyl-silyl)pyrayafoline B (**18**) (102 mg, 234 µmol) in DMF (10 mL), the cooling bath was removed and the reaction mixture was stirred for 10 min. Water (10 mL) was added, 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 column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 5 : 1 to 3 : 1) provided pyrayafoline B (**2**) as pale grey crystals, yield: 51.0 mg (183 µmol, 78%), m.p. 187–190 °C (ref. 7: no m.p. reported). UV (MeOH): λ = 229, 253, 284, 298 (sh), 329, 353 nm; Fluorescence (MeOH): λ_{ex} = 284 nm, λ_{em} =

397 nm; IR (ATR): ν = 3529, 3397, 3038, 2969, 2921, 2855, 1697, 1619, 1485, 1463, 1420, 1372, 1324, 1289, 1246, 1215, 1140, 1096, 1007, 975, 943, 884, 829, 752, 699, 681 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.46 (s, 6 H), 2.38 (s, 3 H), 4.75 (br s, 1 H), 5.58 (d, J = 9.8 Hz, 1 H), 6.49 (d, J = 9.8 Hz, 1 H), 6.747 (s, 1 H), 6.751 (s, 1 H), 7.49 (s, 1 H), 7.63 (s, 1 H), 7.70 (br s, 1 H); ^{13}C NMR and DEPT (150 MHz, CDCl$_3$): δ = 16.12 (CH$_3$), 27.87 (2 CH$_3$), 76.27 (C), 96.63 (CH), 98.01 (CH), 115.02 (C), 116.11 (C), 116.85 (CH), 117.44 (C), 117.59 (C), 120.91 (CH), 123.30 (CH), 128.45 (CH), 139.20 (C), 140.45 (C), 151.51 (C), 152.10 (C); ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.40 (s, 6 H), 2.31 (s, 3 H), 5.61 (d, J = 9.8 Hz, 1 H), 6.52 (d, J = 9.8 Hz, 1 H), 6.74 (s, 1 H), 6.89 (s, 1 H), 7.55 (s, 1 H), 7.63 (s, 1 H), 8.11 (br s, 1 H), 9.84 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 16.71 (CH$_3$), 28.08 (2 CH$_3$), 76.51 (C), 97.18 (CH), 98.64 (CH), 115.22 (C), 117.28 (C), 117.33 (CH), 117.45 (C), 118.54 (C), 121.41 (CH), 124.28 (CH), 128.78 (CH), 140.88 (C), 141.83 (C), 152.07 (C), 154.65 (C); MS (EI): m/z (%) = 279 (29) [M$^+$], 264 (100), 132 (10); Elemental analysis calcd for C$_{18}$H$_{17}$NO$_2$: C 77.40, H 6.13, N 5.01; found: C 77.52, H 6.18, N 4.80%.

_O_-(Triisopropylsilyl)pyrayafoline D (20) and _O_-(triisopropylsilyl)pyrayafoline E (21). A 1 M solution of boron tribromide in dichloromethane (1.58 mL, 1.58 mmol) was added dropwise at −78 °C over a period of 5 min to a solution of carbazole 8 (303 mg, 790 μmol) in dichloromethane (12.5 mL). The reaction mixture was stirred for 16 h while gradually warming to room temperature. Methanol (3 mL) was added, and the mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were extracted with diethyl ether and the combined organic layers were dried over sodium sulfate. The solvent was evaporated and the resulting oil was dried under high vacuum to provide crude 7-hydroxy-3-methyl-2-(triisopropylsilyloxy)-9H-carbazole (15), yield: 315 mg. A solution of methyl 3,7-dimethyloct-6-en-1-yn-3-yl carbonate (19) (332 mg, 1.58 mmol) in acetonitrile (10 mL) was added dropwise over a period of 10 h to a solution of crude 15 (315 mg), copper(II) chloride dihydrate (0.7 mg, 4 μmol) and DBU (236 μL, 240 mg, 1.58 mmol) in degassed acetonitrile (40 mL) and the mixture was stirred at room temperature for 20 h 30 min. Diethyl ether was added and the mixture was washed with water and brine. The aqueous layers were extracted with diethyl ether, the combined organic layers were dried over sodium sulfate, the solvent was evaporated and the residue was dried under high vacuum. The crude mixture was dissolved in toluene (30 mL) and heated at reflux for 23 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–dichloromethane–ethyl acetate, gradient elution, 200 : 5 : 1 to 80 : 5 : 1) provided the less polar _O_-TIPS-pyrayafoline D (20) as light yellow crystals, yield: 193 mg (384 μmol, 49%), m.p. 99–102 °C. UV (MeOH): λ = 222, 239, 285 (sh), 296, 324, 331, 352 (sh) nm; Fluorescence (MeOH): λ_{ex} = 296 nm, λ_{em} = 354 nm; IR (ATR): ν = 3369, 3329, 2962, 2942, 2864, 1629, 1593, 1575, 1472, 1420, 1401, 1317, 1298, 1274, 1223, 1170, 1148, 1076, 1034, 1013, 918, 880, 851,

799, 741, 722, 682, 644 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.16 (d, J = 7.5 Hz, 18 H), 1.38 (m, 3 H), 1.41 (s, 3 H), 1.56 (s, 3 H), 1.63 (s, 3 H), 1.72–1.75 (m, 2 H), 2.16 (m, 2 H), 2.36 (s, 3 H), 5.12 (m, 1 H), 5.75 (d, J = 9.8 Hz, 1 H), 6.60 (d, J = 8.3 Hz, 1 H), 6.90 (d, J = 9.8 Hz, 1 H), 6.94 (s, 1 H), 7.68 (d, J = 8.3 Hz, 1 H), 7.70 (s, 1 H), 10.07 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 13.81 (3 CH), 17.64 (CH$_3$), 17.78 (CH$_3$), 18.47 (6 CH$_3$), 23.42 (CH$_2$), 25.79 (CH$_3$), 26.18 (CH$_3$), 41.50 (CH$_2$), 78.67 (C), 100.86 (CH), 105.57 (C), 109.41 (CH), 118.44 (C), 118.51 (C), 118.76 (CH), 120.14 (CH), 121.01 (C), 121.42 (CH), 125.13 (CH), 129.25 (CH), 131.89 (C), 137.63 (C), 140.61 (C), 151.60 (C), 153.11 (C); ESI-MS (+25 V): m/z = 504.5 [(M + H)$^+$]; ESI-MS (−25 V): m/z = 502.2 [(M − H)$^-$]; Elemental analysis calcd for C$_{32}$H$_{45}$NO$_2$Si: C 76.29, H 9.00, N 2.78; found: C 75.95, H 9.29, N 2.65%.

_O_-TIPS-pyrayafoline E (21) was obtained from the more polar fraction as a light yellow oil, yield: 14.1 mg (28.0 mmol, 4%). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.15 (d, J = 7.5 Hz, 18 H), 1.35 (m, 3 H), 1.43 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.64–1.79 (m, 2 H), 2.16 (m, 2 H), 2.38 (s, 3 H), 5.11 (m, 1 H), 5.54 (d, J = 9.8 Hz, 1 H), 6.53 (d, J = 9.8 Hz, 1 H), 6.76 (s, 1 H), 6.78 (s, 1 H), 7.49 (s, 1 H), 7.64 (s, 1 H), 7.75 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, CDCl$_3$): δ = 13.07 (3 CH), 17.55 (CH$_3$), 17.61 (CH$_3$), 18.09 (6 CH$_3$), 22.74 (CH$_2$), 25.65 (CH$_3$), 26.26 (CH$_3$), 41.11 (CH$_2$), 78.48 (C), 97.71 (CH), 99.79 (CH), 114.81 (C), 116.85 (CH), 117.31 (C), 117.39 (C), 120.66 (CH), 121.10 (C), 123.87 (CH), 124.23 (CH), 127.23 (CH), 131.54 (C), 138.90 (C), 140.47 (C), 151.64 (C), 152.51 (C); ESI-MS (+10 V): m/z = 504.5 [(M + H)$^+$]; ESI-MS (−50 V): m/z = 502.3 [(M − H)$^-$].

Pyrayafoline D (4). A 1 M solution of TBAF in THF (159 μL, 159 μmol) was added at −5 °C to a solution of _O_-(triisopropylsilyl)pyrayafoline D (20) (53.0 mg, 105 μmol) in DMF (10 mL), the cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, 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–ethyl acetate, gradient elution, 6 : 1 to 4 : 1) provided pyrayafoline D (4) as pale grey crystals, yield: 36.6 mg (105 μmol, 100%), m.p. 176–177 °C (ref. 7: no m.p. reported). UV (MeOH): λ = 221, 238, 286 (sh), 296, 321, 330, 352 (sh) nm; Fluorescence (MeOH): λ_{ex} = 238 nm, λ_{em} = 353 nm; IR (ATR): ν = 3541, 3415, 3048, 2964, 2920, 2853, 1698, 1629, 1578, 1554, 1472, 1446, 1419, 1403, 1375, 1349, 1319, 1284, 1268, 1224, 1206, 1174, 1125, 1080, 1031, 954, 907, 886, 843, 816, 780, 743, 722, 695, 655, 614 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.44 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.69–1.81 (m, 2 H), 2.09–2.20 (m, 2 H), 2.38 (s, 3 H), 4.82 (br s, 1 H), 5.10 (m, 1 H), 5.66 (d, J = 9.8 Hz, 1 H), 6.61 (d, J = 9.8 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 6.80 (s, 1 H), 7.633 (d, J = 8.3 Hz, 1 H), 7.635 (s, 1 H), 7.75 (br s, 1 H); ^{13}C NMR and DEPT (150 MHz, CDCl$_3$): δ = 16.12 (CH$_3$), 17.62 (CH$_3$), 22.72 (CH$_2$), 25.65 (CH$_3$), 25.87 (CH$_3$), 40.72 (CH$_2$), 78.15 (C), 96.74 (CH), 104.61 (C), 109.30 (CH), 116.24 (C), 117.30 (CH), 117.57 (C),

117.89 (C), 119.43 (CH), 120.92 (CH), 124.12 (CH), 128.82 (CH), 131.69 (C), 136.13 (C), 139.19 (C), 150.79 (C), 152.04 (C); MS (EI): m/z (%) = 347 [56] [M$^+$], 332 (6), 278 (6), 264 (100); HRMS: m/z calcd for $C_{23}H_{25}NO_2$ [M$^+$]: 347.1885; found: 347.1899; Elemental analysis calcd for $C_{23}H_{25}NO_2$: C 79.51, H 7.25, N 4.03; found: C 79.55, H 7.24, N 3.87%.

Pyrayafoline E (5). A 1 M solution of TBAF in THF (126 µL, 126 µmol) was added at −10 °C to a solution of O-(triisopropyl-silyl)pyrayafoline E (**21**) (42.2 mg, 83.8 µmol) in DMF (10 mL), the cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, 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 column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 6 : 1 to 7 : 2) provided pyrayafoline E (**5**) as pale grey crystals, yield: 24.1 mg (69.4 µmol, 83%), m.p. 148–149 °C (ref. 9: pale brown oil). UV (MeOH): λ = 229 (sh), 239, 253, 285, 296 (sh), 322, 354 nm; Fluorescence (MeOH): λ_{ex} = 285 nm, λ_{em} = 394 nm; IR (ATR): ν = 3533, 3389, 2967, 2919, 2850, 1698, 1613, 1485, 1466, 1372, 1322, 1290, 1221, 1144, 1075, 1009, 975, 912, 884, 826, 757, 683, 600 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 1.42 (s, 3 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.65–1.79 (m, 2 H), 2.12–2.17 (m, 2 H), 2.38 (s, 3 H), 4.69 (br s, 1 H), 5.10 (m, 1 H), 5.53 (d, J = 9.8 Hz, 1 H), 6.51 (d, J = 9.8 Hz, 1 H), 6.75 (s, 1 H), 6.78 (s, 1 H), 7.48 (s, 1 H), 7.62 (s, 1 H), 7.72 (br s, 1 H); ^{13}C NMR and DEPT (150 MHz, CDCl$_3$): δ = 16.12 (CH$_3$), 17.62 (CH$_3$), 22.76 (CH$_2$), 25.66 (CH$_3$), 26.35 (CH$_3$), 41.19 (CH$_2$), 78.55 (C), 96.61 (CH), 97.78 (CH), 114.94 (C), 116.03 (C), 116.88 (CH), 117.27 (C), 117.67 (C), 120.88 (CH), 123.77 (CH), 124.23 (CH), 127.38 (CH), 131.59 (C), 139.19 (C), 140.50 (C), 151.88 (C), 152.05 (C); ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.38 (s, 3 H), 1.56 (s, 3 H), 1.63 (d, J = 0.8 Hz, 3 H), 1.68–1.73 (m, 2 H), 2.13–2.18 (m, 2 H), 2.31 (s, 3 H), 5.11 (m, 1 H), 5.59 (d, J = 9.8 Hz, 1 H), 6.56 (d, J = 9.8 Hz, 1 H), 6.74 (s, 1 H), 6.89 (s, 1 H), 7.54 (s, 1 H), 7.63 (s, 1 H), 8.11 (s, 1 H), 9.84 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 16.71 (CH$_3$), 17.63 (CH$_3$), 23.46 (CH$_2$), 25.79 (CH$_3$), 26.55 (CH$_3$), 41.85 (CH$_2$), 78.85 (C), 97.0719 (CH), 98.39 (CH), 115.14 (C), 117.29 (C), 117.38 (CH), 117.44 (C), 118.40 (C), 121.38 (CH), 124.80 (CH), 125.21 (CH), 127.73 (CH), 131.80 (C), 140.74 (C), 141.73 (C), 152.33 (C), 154.52 (C); ESI-MS (+25 V): m/z = 348.2 [[M + H]$^+$]; ESI-MS (−50 V): m/z = 345.9 [[M − H]$^−$]; MS (EI): m/z (%) = 347 (14) [M$^+$], 332 (4), 279 (5), 269 (16), 264 (100); HRMS: m/z calcd for $C_{23}H_{25}NO_2$ [M$^+$]: 347.1885; found: 347.1865.

2-Hydroxy-7-methoxy-3-methyl-9H-carbazole (22). A 1 M solution of TBAF in THF (803 µL, 803 µmol) was added at −10 °C to a solution of 7-methoxy-3-methyl-2-(triisopropylsilyloxy)-9H-carbazole (**8**) (205 mg, 535 µmol) in DMF (10 mL). The cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, the mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were dried over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–ethyl acetate, gradient

elution, 4 : 1 to 2 : 1) provided 2-hydroxy-7-methoxy-3-methyl-9H-carbazole (**22**) as colourless crystals, yield: 122 mg (535 µmol, 100%), m.p. 243–244 °C. UV (MeOH): λ = 209, 235, 264, 310, 322 nm; Fluorescence (MeOH): λ_{ex} = 264 nm, λ_{em} = 353 nm; IR (ATR): ν = 3387, 2926, 1612, 1499, 1469, 1450, 1397, 1374, 1329, 1307, 1268, 1223, 1197, 1153, 1129, 1025, 1008, 943, 880, 851, 811, 727, 618 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 2.32 (s, 3 H), 3.82 (s, 3 H), 6.72 (dd, J = 8.5, 2.2 Hz, 1 H), 6.91 (s, 1 H), 6.92 (d, J = 2.2 Hz, 1 H), 7.66 (s, 1 H), 7.78 (d, J = 8.5 Hz, 1 H), 8.09 (s, 1 H), 9.81 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 16.70 (CH$_3$), 55.66 (CH$_3$), 95.51 (CH), 97.16 (CH), 107.89 (CH), 117.16 (C), 117.33 (C), 118.28 (C), 120.23 (CH), 121.39 (CH), 140.82 (C), 142.06 (C), 154.53 (C), 158.79 (C); MS (EI): m/z (%) = 227 (100) [M$^+$], 212 (82), 184 (33), 154 (9), 113 (10); Elemental analysis calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16; found: C 73.60, H 5.75, N 6.20%.

O-Methylmurrayamine A (6). A 1 M solution of TBAF in THF (393 µL, 393 µmol) was added at −10 °C to a solution of 7-methoxy-3-methyl-2-(triisopropylsilyloxy)-9H-carbazole (**8**) (101 mg, 262 µmol) in DMF (10 mL). The cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, 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, the solvent was evaporated and the residue was dried under high vacuum to provide crude 2-hydroxy-7-methoxy-3-methyl-9H-carbazole (**22**) (92.3 mg). Prenal (**23**) (51 mL, 44 mg, 0.53 mmol) was added at −78 °C to a solution of crude **22** (92.3 mg) in toluene (17 mL). At the same temperature, titanium(IV) isopropoxide (314 µL, 1.05 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature over a period of 22 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 column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 11 : 1 to 7 : 1) provided O-methylmurrayamine A (**6**) as light yellow crystals, yield: 67.4 mg (0.230 mmol, 88%), m.p. 257–258 °C (ref. 10: 232–233 °C). UV (MeOH): λ = 220, 241, 283 (sh), 293, 342, 357 (sh) nm; Fluorescence (MeOH): λ_{ex} = 241 nm, λ_{em} = 357 nm; IR (ATR): ν = 3381, 3051, 2967, 2919, 2833, 1697, 1642, 1613, 1495, 1445, 1403, 1358, 1309, 1264, 1246, 1211, 1192, 1154, 1127, 1056, 1013, 978, 939, 892, 874, 830, 809, 781, 749, 728, 682, 664, 641 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 1.45 (s, 6 H), 2.27 (s, 3 H), 3.83 (s, 3 H), 5.76 (d, J = 9.8 Hz, 1 H), 6.74 (dd, J = 8.5, 2.3 Hz, 1 H), 6.87 (d, J = 9.8 Hz, 1 H), 6.93 (d, J = 2.3 Hz, 1 H), 7.60 (s, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 10.14 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 16.20 (CH$_3$), 27.84 (2 CH$_3$), 55.68 (CH$_3$), 76.33 (C), 95.68 (CH), 105.49 (C), 108.26 (CH), 117.78 (C), 118.09 (C), 118.30 (C), 118.65 (CH), 120.53 (CH), 121.00 (CH), 129.94 (CH), 136.21 (C), 142.28 (C), 149.46 (C), 159.06 (C); MS (EI): m/z (%) = 293 (35) [M$^+$], 278 (100), 263 (12), 235 (7); Elemental analysis calcd for

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$C_{19}H_{19}NO_2$: C 77.79, H 6.53, N 4.77; found: C 77.29, H 6.60, N 4.75%.

Crystal data for **6**: $C_{19}H_{19}NO_2$, crystal size: 0.35 × 0.21 × 0.17 mm³, M = 293.35 g mol⁻¹, monoclinic, space group: $P2_1$, a = 6.763(1), b = 8.187(1), c = 13.881(1) Å, β = 91.33(1)°, V = 768.37(16) Å³, Z = 2, ρ_c = 1.268 g cm⁻³, μ = 0.082 mm⁻¹, T = 198(2) K, λ = 0.71073 Å, θ range = 3.01–26.00°, reflections collected: 12481, independent: 2940 (R_{int} = 0.0421), 207 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0386, wR_2 = 0.0854 [$I > 2\sigma(I)$]; maximal residual electron density: 0.201 e Å⁻³. CCDC 959120.

***O*-Methylmahanine (7).** A 1 M solution of TBAF in THF (399 µL, 399 µmol) was added at −10 °C to a solution of 7-methoxy-3-methyl-2-(triisopropylsilyloxy)-9*H*-carbazole (**8**) (102 mg, 266 µmol) in DMF (10 mL). The cooling bath was removed and the mixture was stirred for 10 min. Water (10 mL) was added, 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, the solvent was evaporated and the residue was dried under high vacuum to provide crude 2-hydroxy-7-methoxy-3-methyl-9*H*-carbazol (**22**), yield: 71.2 mg. Citral (**24**) (0.091 mL, 0.53 mmol) was added at −78 °C to a solution of crude 2-hydroxy-7-methoxy-3-methyl-9*H*-carbazol (**22**) (71.2 mg) in toluene (15 mL). Titanium(IV) isopropoxide (318 µL, 1.06 mmol) was added slowly at the same temperature and the reaction mixture was allowed to warm to room temperature over a period of 23 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 column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 15 : 1 to 9 : 1) provided *O*-methylmahanine A (**7**) as light yellow crystals, yield: 72.2 mg (200 µmol, 75%), m.p. 181–182 °C (ref. 13: 126 °C). UV (MeOH): λ = 219, 241, 284 (sh), 294, 341 nm; Fluorescence (MeOH): λ_{ex} = 241 nm, λ_{em} = 357 nm; IR (ATR): ν = 3395, 3038, 3002, 2970, 2923, 2846, 1643, 1625, 1494, 1472, 1454, 1402, 1379, 1310, 1271, 1244, 1211, 1193, 1155, 1105, 1081, 1058, 1030, 1015, 980, 948, 915, 875, 829, 808, 777, 747, 721, 678, 641, 615, 580 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.44 (s, 3 H), 1.58 (s, 3 H), 1.66 (d, J = 0.8 Hz, 3 H), 1.76 (t, J = 8.4 Hz, 2 H), 2.10–2.23 (m, 2 H), 2.32 (d, J = 0.4 Hz, 3 H), 3.88 (s, 3 H), 5.11 (m, 1 H), 5.66 (d, J = 9.8 Hz, 1 H), 6.62 (d, J = 9.8 Hz, 1 H), 6.80 (dd, J = 8.5, 2.2 Hz, 1 H), 6.89 (d, J = 2.2 Hz, 1 H), 7.56 (s, 1 H), 7.77 (d, J = 8.5 Hz, 1 H), 7.78 (br s, 1 H); ¹³C NMR and DEPT (125 MHz, CDCl₃): δ = 16.03 (CH₃), 17.56 (CH₃), 22.73 (CH₂), 25.66 (CH₃), 25.74 (CH₃), 40.68 (CH₂), 55.63 (CH₃), 77.96 (C), 95.12 (CH), 104.26 (C), 107.61 (CH), 116.71 (C), 117.49 (CH), 117.88 (C), 118.24 (C), 119.89 (CH), 120.43 (CH), 124.19 (CH), 128.68 (CH), 131.65 (C), 134.70 (C), 140.63 (C), 148.90 (C), 157.89 (C); MS (EI): m/z (%) = 361 (91) [M⁺], 346 (11), 278 (100), 240 (12), 239 (14); Elemental analysis calcd for $C_{24}H_{27}NO_2$: C 79.74, H 7.53, N 3.87; found: C 79.45, H 7.69, N 3.88%.

Notes and references

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) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (c) 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, 2003, vol. 85, p. 125; (d) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193.

2 (a) T. A. Choi, R. Czerwonka, R. Forke, A. Jäger, J. Knöll, M. P. Krahl, T. Krause, K. R. Reddy, S. G. Franzblau and H.-J. Knölker, *Med. Chem. Res.*, 2008, **17**, 374; (b) H.-J. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, p. 1; (c) N. Kongkathip and B. Kongkathip, *Heterocycles*, 2009, **79**, 121; (d) K. Thevissen, A. Marchand, P. Chaltin, E. M. K. Meert and B. P. A. Cammue, *Curr. Med. Chem.*, 2009, **16**, 2205; (e) T. Nagappan, P. Ramasamy, M. E. A. Wahid, T. C. Segaran and C. S. Vairappan, *Molecules*, 2011, **16**, 9651.

3 (a) J. Bergmann and B. Pelcman, *Pure Appl. Chem.*, 1990, **62**, 1967; (b) U. Pindur, *Chimia*, 1990, **44**, 406; (c) T. Kawasaki and M. Sakamoto, *J. Indian Chem. Soc.*, 1994, **71**, 443; (d) H.-J. Knölker, in *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, Jai Press Inc., Greenwich, CT, 1995, vol. 1, p. 173; (e) H.-J. Knölker, *Curr. Org. Synth.*, 2004, **1**, 309; (f) H.-J. Knölker, *Top. Curr. Chem.*, 2005, **244**, 115; (g) S. Agarwal, S. Cämmerer, S. Filali, W. Fröhner, J. Knöll, M. P. Krahl, K. R. Reddy and H.-J. Knölker, *Curr. Org. Chem.*, 2005, **9**, 1601; (h) H.-J. Knölker, *Chem. Lett.*, 2009, **38**, 8; (i) M. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2243; (j) R. Forke, K. K. Gruner, K. E. Knott, S. Auschill, S. Agarwal, R. Martin, M. Böhl, S. Richter, G. Tsiavaliaris, R. Fedorov, D. J. Manstein, H. O. Gutzeit and H.-J. Knölker, *Pure Appl. Chem.*, 2010, **82**, 1975; (k) K. K. Gruner and H.-J. Knölker, in *Heterocycles in Natural Product Synthesis*, ed. K. C. Majumdar and S. K. Chattopadhyay, Wiley-VCH, Weinheim, 2011, p. 341; (l) J. Roy, A. K. Jana and D. Mal, *Tetrahedron*, 2012, **68**, 6099; (m) I. Bauer and H.-J. Knölker, *Top. Curr. Chem.*, 2012, **309**, 203.

4 (a) H.-J. Knölker, *Chem. Soc. Rev.*, 1999, **28**, 151; (b) K. E. Knott, S. Auschill, A. Jäger and H.-J. Knölker, *Chem. Commun.*, 2009, 1467; (c) K. K. Gruner, T. Hopfmann, K. Matsumoto, A. Jäger, T. Katsuki and H.-J. Knölker, *Org. Biomol. Chem.*, 2011, **9**, 2057; (d) C. Thomas, O. Kataeva and H.-J. Knölker, *Synlett*, 2011, 2663; (e) C. Börger, M. P. Krahl, M. Gruner, O. Kataeva and H.-J. Knölker, *Org. Biomol. Chem.*, 2012, **10**, 5189; (f) M. P. Krahl, A. W. Schmidt and H.-J. Knölker, *Heterocycles*, 2012, **86**, 357; (g) M. P. Krahl, O. Kataeva, A. W. Schmidt and H.-J. Knölker, *Eur. J. Org. Chem.*, 2013, 59; (h) I. Bauer and H.-J. Knölker, in *The Chemistry of Organoiron Compounds – PATAI's Chemistry of Functional Groups*,

ed. I. Marek and Z. Rappoport, Wiley, Chichester, 2014, ch. 5, pp. 155.

5 (*a*) H.-J. Knölker and N. O'Sullivan, *Tetrahedron*, 1994, **50**, 10893; (*b*) R. Forke, A. Jäger and H.-J. Knölker, *Org. Biomol. Chem.*, 2008, **6**, 2481; (*c*) R. Forke, M. P. Krahl, F. Däbritz, A. Jäger and H.-J. Knölker, *Synlett*, 2008, 1870; (*d*) K. K. Gruner and H.-J. Knölker, *Org. Biomol. Chem.*, 2008, **6**, 3902; (*e*) C. Börger, O. Kataeva and H.-J. Knölker, *Org. Biomol. Chem.*, 2012, **10**, 7269; (*f*) C. Börger and H.-J. Knölker, *Tetrahedron*, 2012, **68**, 6727; (*g*) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H.-J. Knölker, *Chem. – Eur. J.*, 2012, **18**, 770; (*h*) L. Huet, R. Forke, A. Jäger and H.-J. Knölker, *Synlett*, 2012, 1230; (*i*) C. Thomas and H.-J. Knölker, *Tetrahedron Lett.*, 2013, **54**, 591; (*j*) A. Berndt, M. Gruner, A. W. Schmidt and H.-J. Knölker, *Synlett*, 2013, **24**, 2102; (*k*) R. Hesse, K. K. Gruner, O. Kataeva, A. W. Schmidt and H.-J. Knölker, *Chem. – Eur. J.*, 2013, **19**, 14098; (*l*) V. P. Kumar, K. K. Gruner, O. Kataeva and H.-J. Knölker, *Angew. Chem., Int. Ed.*, 2013, **52**, 11073; (*m*) C. Thomas, O. Kataeva, A. W. Schmidt and H.-J. Knölker, *Org. Biomol. Chem.*, 2014, **12**, 872.

6 H. Furukawa, C. Ito, M. Yogo and T.-S. Wu, *Chem. Pharm. Bull.*, 1986, **34**, 2672.

7 C. Ito, M. Nakagawa, T.-S. Wu and H. Furukawa, *Chem. Pharm. Bull.*, 1991, **39**, 1668.

8 C. Ito, M. Itoigawa, K. Nakao, T. Murata, M. Tsuboi, N. Kaneda and H. Furukawa, *Phytomedicine*, 2006, **13**, 359.

9 C. Ito, M. Nakagawa, T.-S. Wu and H. Furukawa, *Chem. Pharm. Bull.*, 1991, **39**, 2525.

10 T.-S. Wu, *Phytochemistry*, 1991, **30**, 1048.

11 Y. Tachibana, H. Kikuzaki, N. H. Lajis and N. Nakatani, *J. Agric. Food Chem.*, 2003, **51**, 6461.

12 M. Chakraborty, S. Saha and S. Mukhapadhyay, *Nat. Prod. Commun.*, 2009, **4**, 355.

13 F. Anwer, R. S. Kapil and S. P. Popli, *Experientia*, 1972, **28**, 769.

14 M. Itoigawa, Y. Kashiwada, C. Ito, H. Furukawa, Y. Tachibana, K. F. Bastow and K. H. Lee, *J. Nat. Prod.*, 2000, **63**, 893.

15 (*a*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*b*) M. D. Charles, P. Schultz and S. L. Buchwald, *Org. Lett.*, 2005, **7**, 3965–3968; (*c*) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338.

16 G. Eisenbrand and F. Hippe, *WO* 2003070703, 2003.

17 J. D. Godfrey Jr., R. H. Mueller, T. C. Sedergran, N. Soundararajan and V. J. Colandrea, *Tetrahedron Lett.*, 1994, **35**, 6405.

18 (*a*) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, 1962, **10**, 926; (*b*) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, 1963, **11**, 1042; (*c*) J. Hlubucek, E. Ritchie and W. C. Taylor, *Tetrahedron Lett.*, 1969, **10**, 1369; (*d*) P. E. Brown and R. A. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 1992, 573.

19 J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1510.

20 G. Sartori, G. Casiraghi, L. Bolzoni and G. Casnati, *J. Org. Chem.*, 1979, **44**, 803.

21 (*a*) J. Tsuji, T. Sugiura and I. Minami, *Synthesis*, 1987, 603; (*b*) S. Yamaguchi, M. Maekawa, Y. Murayama, M. Miyazawa and Y. Hirai, *Tetrahedron Lett.*, 2004, **45**, 6971; (*c*) S. Yamaguchi, M. Nedachi, M. Maekawa, Y. Murayama, M. Miyazawa and Y. Hirai, *J. Heterocycl. Chem.*, 2006, **43**, 29.

22 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.

23 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

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