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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-mediated4 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.

Although pyrayafoline D (4) is chiral, the natural product did not show any optical rotation ($[\alpha]_D = \pm 0, c 0.0013, \text{MeOH}$), 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

Fig. 1 Naturally occurring pyrano[3,2-a]carbazole and pyrano[2,3-b]-carbazole alkaloids.
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 annihilated 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 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)16 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 diarylamine 12 were achieved by heating in a microwave reactor in the presence of catalytic amounts of freshly recrystallised palladium(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 (5) did not exhibit any optical rotation ([α]D = ±0, c 0.0007, CHCl₃). 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-methylmurrayamine A (6) from the leaves of Murraya koenigii collected in Malaysia.11 In 2009, compound 6 was also isolated by Mukhadhyay et al. from Murraya koenigii collected in India.12 In 2011, we reported the first total synthesis of O-methylmurrayamine A (6) using an iron-mediated approach.13 O-Methylmahaine (7) was mentioned first in 1972 by Kapil and co-workers as a synthetic derivative of Mahanine.13 However, no spectroscopic data were disclosed. In 2003, Nakatani et al. described the first isolation of O-methylmahaine (7) from the leaves of Murraya koenigii collected in Malaysia.11 O-Methylmahaine (7) was obtained as an optically active compound ([α]D = +3, c 0.10, CHCl₃). However, the absolute configuration has not been assigned. Not much is known about the biological activities 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

Scheme 1 Retrosynthetic analysis of the pyranocarbazoles 1–7.
Synthesis of pyrayafoline A–C (1–3). Reagents and conditions: (a) 2.0 equiv. BBr3, CH2Cl2, −78 °C to rt; (b) 1. 2.0 equiv. 16, 2.0 equiv. DBU, 0.9 mol% CuCl2·2H2O, 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. Me2SO4, THF, 0 °C to rt, 93%; (e) 1.5 equiv. TBAF, DMF, −10 °C, 78%.

Scheme 3

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 C10-building block (Scheme 5). Cleavage of the methyl ether of 8 and reaction of crude 7-hydroxy carbazole 15 with the carbonate 1921 in the presence of DBU and catalytic amounts of copper(II) chloride followed by thermal rearrangement afforded the pyrano[3,2-α] 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-α] 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

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
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 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(II)-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 (9) (three steps); (c) 1.5 equiv. TBAF, DMF, \(-5^\circ C\), 100%; (d) 1.5 equiv. TBAF, DMF, \(-12^\circ C\), 85%. 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(II) 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 F\(_{254}\)) using UV-light for visualisation. Melting points were measured on a Gallenkamp MPD.
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, 1585, 1500, 1459, 1346, 1389, 1279, 1206, 1178, 1153, 1125, 1047, 1005, 947, 923, 881, 838, 804, 763, 717, 681 cm⁻¹. 1H NMR (500 MHz, acetone-d6): 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 (dd, J = 2.1, 1 Hz), 7.01 (d, J = 8.1 Hz, 1 H), 7.10 (t, J = 8.1 Hz, 1 H), 7.31 (br s, 1 H). 13C NMR and DEPT (125 MHz, acetone-d6): δ = 13.73 (3 CH), 16.54 (CH3), 18.42 (6 CH3), 55.29 (CH3), 103.32 (CH), 105.80 (CH), 108.98 (CH), 110.07 (CH), 111.80 (CH), 120.94 (C), 130.62 (CH), 131.94 (CH), 143.07 (C), 144.62 (C), 154.58 (C), 161.75 (C); MS (EI): m/z (%) = 385 (96) [M]+, 342 (100), 314 (24), 300 (14), 143 (22); Elemental analysis calcd for C23H35NO2Si: 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). Chlorotriisopropylsilanes (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 ethyl acetate, the organic layers were combined 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 = 3394, 2942, 2892, 2865, 1651, 1585, 1557, 1541, 1509, 1460, 1435, 1392, 1311, 1277, 1258, 1204, 1179, 1126, 1070, 1001, 989, 932, 881, 843, 798, 750, 677, 618 cm⁻¹; 1H NMR (500 MHz, CDCl3): 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); 13C NMR and DEPT (125 MHz, CDCl3): δ = 12.92 (3 CH), 16.63 (CH3), 17.97 (6 CH3), 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 calced for C14H9Br3O5Si: 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)-
toulene (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 14-aminoisidine (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, 1:10 to 80:5:1) to provide diarylamine (11.1 mmol) PivOH; Batch 2: 519 mg (1.35 mmol)

λ(MeOH): UV (MeOH):

C23H33NO2Si: 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)-9H-carbazole (15).

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 (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 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)-9H-carbazole (15) as a yellow oil; yield: 185 mg (501 µmol, 95%).

1H NMR (500 MHz, acetone-d6): 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); 13C NMR and DEPT (125 MHz, acetone-d6): δ = 13.80 (3 CH), 17.78 (CH3), 18.48 (6 CH3), 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), 154.11 (C); MS (EI): m/z (%) = 204 (100 [M]+), 326 (58), 298 (16), 284 (15), 224 (25), 196 (16), 135 (25).

O-(Triisopropylsilyl)pyrazafoline C (17) and O-(Triisopropylsilyl)pyrazafoline 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 (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 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 carbazole 8 as light yellow crystals, yield: 222 mg (509 µmol, 82%).

UV (MeOH): λ = 211, 236, 259 (sh), 264, 311, 323 nm; Fluorescence (MeOH): λex = 264 nm, λem = 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, 946, 860, 826, 806, 767, 709, 675, 645, 608 cm−1; 1H NMR (500 MHz, acetone-d6): 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), 7.82 (d, J = 8.5 Hz, 1 H), 9.88 (br s, 1 H); 13C NMR and DEPT (125 MHz, acetone-d6): δ = 13.81 (3 CH), 17.80 (CH3), 18.48 (6 CH3), 55.69 (CH3), 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]+), 304 (49), 325 (12), 312 (12), 298 (13), 218 (21), 226 (21), 167 (11); Elemental analysis calcd for C23H23NO2Si: C 72.01, H 8.67, N 3.65; found: C 71.94, H 8.70, N 3.78%.
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); 31C NMR and DEPT (125 MHz, acetone-d6): δ = 13.80 (3 CH), 17.19 (CH3), 18.47 (6 CH3), 27.78 (2 CH3), 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 calcld for C27H25NO3Si: 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, 93%), 1H NMR (500 MHz, CDCl3): 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), 6.78 (s, 1 H), 6.89 (s, 1 H), 7.52 (s, 1 H), 7.66 (s, 1 H), 7.88 (br s, 1 H); 13C NMR and DEPT (150 MHz, CDCl3): δ = 13.05 (3 CH), 17.54 (CH3), 18.06 (6 CH3), 27.76 (2 CH3), 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 (CH3), 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-(trisopropylsilyl)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 washed over sodium sulfate and the solvent was evaporated. Purification of the residue by column chromatography on silica gel (pentane–ethyl acetate, gradient elution, 1:1 to 3:1) provided pyrayafoline A (1) as pale green crystals, yield: 51.5 mg (176 µmol, 93%), m.p. 229–233 °C (ref: 6: 228–231 °C). UV (MeOH): λex = 221, 238, 284 (sh), 294, 337, 349 (sh) nm; Fluorescence (MeOH): λex = 238 nm, λem = 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, 811, 846, 824, 809, 779, 740, 718, 652 cm−1; 1H NMR (600 MHz, CDCl3, CD3CN): δ = 1.48 (s, 6 H), 3.24 (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); 13C NMR and DEPT (150 MHz, CDCl3): δ = 16.65 (CH3), 27.52 (2 CH3), 55.57 (CH3), 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 C18H17NO2 [M+]: 293.1416; found: 293.1414.

Crystal data for 1: C18H17NO2, crystal size: 0.52 × 0.18 × 0.07 mm3, M = 293.35 g mol−1, monoclinic, space group: P21, a = 6.508 (1), b = 25.907(3), c = 9.1340(1) Å, β = 99.33(1)°, V = 1519.63(3) Å3, Z = 4, p = 1.282 g cm−3, µ = 0.083 mm−1, T = 198(2) K, λ = 0.1073 Å, θ range = 3.15–25.40°, reflections collected: 17.349, independent: 5336 (Rint = 0.0353), 413 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F2; R1 = 0.0428, wR2 = 0.0783 [I > 2σ(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-(trisopropylsilyl)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, 1:0 to 1:0:1) provided pyrayafoline B (2) as pale green crystals, yield: 51.0 mg (183 µmol, 78%), m.p. 187–190 °C (ref. 7: no m.p. reported). UV (MeOH): λex = 229, 253, 284, 298 (sh), 329, 353 nm; Fluorescence (MeOH): λex = 284 nm, λem =...
1H, 6.751 (s, 1 H), 7.49 (s, 1 H), 7.63 (s, 1 H), 7.70 (br s, 1 H); 13C NMR and DEPT (150 MHz, CDCl3): 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); 13C NMR and DEPT (125 MHz, acetone-d6): δ = 13.81 (3 CH), 17.64 (CH3), 17.78 (CH3), 18.47 (6 CH3), 23.42 (CH3), 23.79 (CH3), 26.18 (CH3), 41.50 (CH2), 78.67 (CH), 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), 122.13 (CH), 129.25 (CH), 131.89 (C), 137.63 (C), 140.61 (C), 151.60 (C), 153.11 (C); ESI-MS (+2 V): m/z = 504.5 ([M + H]+); ESI-MS (+5 V): m/z = 502.2 ([M – H]+); Elemental analysis calcd for C32H45NO2Si: C 76.29, H 9.00, N 2.78; found: C 75.95, H 9.29, N 2.65%.

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, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. The less polar fraction as a light yellow oil, yield: 14.1 mg (28.0 mmol, 4%). 1H NMR (500 MHz, CDCl3): 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); 13C NMR and DEPT (125 MHz, CDCl3): δ = 13.07 (3 CH), 17.55 (CH3), 17.61 (CH3), 18.09 (6 CH3), 22.74 (CH3), 25.65 (CH3), 26.26 (CH3), 41.11 (CH3), 78.48 (CH), 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 (+5 V): m/z = 502.2 ([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): λex = 221, 238, 286 (sh) nm; Fluorescence (MeOH): λex = 238 nm, λem = 353 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; 1H NMR (500 MHz, acetone-d6): 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); 13C NMR and DEPT (125 MHz, acetone-d6): δ = 13.81 (3 CH), 17.64 (CH3), 17.78 (CH3), 18.47 (6 CH3), 23.42 (CH3), 23.79 (CH3), 26.18 (CH3), 41.50 (CH2), 78.67 (CH), 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), 122.13 (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]+).
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]+, 322 (3), 278 (6), 264 (100); HRMS: m/z calec for C31H29NO2 [M]+: 437.1885; found: 437.1899; Elemental analysis calec for C31H29NO2: C 79.51, H 7.25, N 3.87%.

Pyrafoline E (5). A 1 M solution of TBAF in THF (126 µL, 126 µmol) was added at −10 °C to a solution of O-(trisopropylsilyl)pyrafoline 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, 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 pyrafoline 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 (CH), 322, 354 nm; Fluorescence (MeOH): λex = 285 nm, λem = 394 nm; IR (ATR): ν = 3338, 2967, 2919, 2850, 1698, 1613, 1485, 1466, 1372, 1322, 1290, 1221, 1144, 1075, 1009, 979, 912, 884, 826, 757, 683, 600 cm−1; 1H NMR (500 MHz, CDCl3): 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 (br s, 1 H), 7.72 (br s, 1 H); 13C NMR and DEPT (125 MHz, acetone−d6): δ = 22.76 (CH3), 25.66 (CH3), 26.35 (CH3), 41.19 (CH2), 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); 1H NMR (500 MHz, acetone−d6): 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), 7.14 (m, 1 H), 7.54 (s, 1 H), 7.63 (s, 1 H), 8.11 (s, 1 H), 9.84 (br s, 1 H); 13C NMR and DEPT (125 MHz, acetone−d6): δ = 16.71 (CH3), 17.63 (CH3), 23.46 (CH2), 25.79 (CH2), 26.55 (CH3), 41.85 (CH2), 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]+, 322 (4), 279 (5), 269 (16), 264 (100); HRMS: m/z calcld for C31H29NO2 [M]+: 437.1885; found: 437.1865.

O-Methylmurayamine 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-(trisopropylsilyloxy)-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 mg, 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-methylmurayamine 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): λex = 241 nm, λem = 357 nm; IR (ATR): ν = 3381, 2951, 2920, 2854, 1697, 1642, 1613, 1495, 1445, 1403, 1358, 1309, 1264, 1246, 1211, 1192, 1154, 1127, 1013, 978, 939, 892, 874, 830, 809, 781, 749, 728, 682, 664, 641 cm−1; 1H NMR (500 MHz, acetone−d6): δ = 1.45 (s, 6 H), 2.27 (s, 3 H), 3.83 (s, 3 H), 5.76 (dd, 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); 13C NMR and DEPT (125 MHz, acetone−d6): δ = 16.20 (CH3), 27.84 (2 CH2), 55.68 (CH2), 76.33 (C), 95.68 (CH), 105.49 (C), 108.26 (CH), 117.78 (C), 118.09 (C), 118.30 (C), 118.65 (C), 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 calcld for...
C_{12}H_{13}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_{12}H_{13}NO_{2}, crystal size: 0.35 × 0.21 × 0.17 mm, \( M = 203.25 \text{ g mol}^{-1} \), monoclinic, space group: \( P2_1 \), \( a = 6.763(1), b = 8.187(1), c = 13.831(1), \beta = 91.33(1)^\circ, V = 768.7(16) \text{ Å}^3 \), \( Z = 2, \rho_c = 1.268 \text{ g cm}^{-3}, \mu = 0.082 \text{ mm}^{-1}, T = 198(2) \text{ K}, \kappa = 0.70763, \theta \text{ range} = 30.01–26.00^\circ, \) 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-5-methyl-2-(trisopropylsilyloxy)-9H-carbazol (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 and the solvent was evaporated.

Purification of the residue by column chromatography on silica gel (pentane−ethyl acetate, gradient elution, 15 : 1 to 1 : 0.1) provided O-methylmahanine A (7) as light yellow crystals, yield: 72.2 mg (200 µmol, 75%), m.p. 181–182 °C.

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