Tetrahedron 68 (2012) 6727–6736

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Transition metals in organic synthesis. Part 101: Convergent total synthesis of 1,6-dioxygenated carbazole alkaloids☆

Carsten Börger, Hans-Joachim Knölker*

Department Chemie, Technische Universität Dresden, Bergstraße 66, 01069 Dresden, Germany

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form 22 May 2012
Accepted 24 May 2012
Available online 31 May 2012

Keywords:
Alkaloids
Antibiotics
Catalysis
Cyclisations
Palladium

ABSTRACT

Using a palladium(II)-catalysed oxidative cyclisation as key step, we describe a highly efficient total synthesis of a series of naturally occurring 1,6-dioxygenated carbazole alkaloids: clausenine, 6-methoxymurrayanine, clausenol, clausine G, clausine I, clausine Z and methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate.

1. Introduction

The structural diversity and promising biological activities of carbazole alkaloids has led to an intense research activity in this area.[1–9] All 1,6-dioxygenated carbazoles isolated from nature so far have a one-carbon substituent at C-3 of the carbazole framework. The central relay compound for the biogenesis of carbazole alkaloids in higher plants is 3-methylcarbazole. Further oxygenation reactions at the carbazole nucleus and oxidations at the 3-methyl group take place afterwards.[1b,3] Herein, we describe full details of our palladium-catalysed route to the 1,6-dioxygenated carbazole alkaloids clausenine (**1**), 6-methoxymurrayanine (**2**), clausenol (**3**), clausine I (**4**), clausine G (**5**), clausine Z (**6**) and methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) (Fig. 1).[10]

In 1991, El-Feraly et al. reported the first isolation of a 1,6-dioxygenated carbazole, 6-methoxymurrayanine (**2**), from the roots of *Clausena lansium*.[11] Four years later, Chakraborty et al. isolated clausenine (**1**) and clausenol (**3**) from the dried stem bark of *Clausena anisata* and described their antibiotic activity against Gram-positive and Gram-negative bacteria as well as fungi.[12] Clausenol (**3**) is much more active than clausenine (**1**) and the inhibition against some bacteria is similar to that reported for streptomycin.[12] In 1996, Wu et al. described the isolation of clausine I (**4**) and clausine G (**5**) from the stem bark of *Clausena excavata*.[13,14] Clausine I (**4**) showed an inhibition of rabbit platelet aggregation induced by arachidonic acid. In 2005, Potterat et al. from Boehringer Ingelheim Pharma GmbH reported the isolation of clausine Z (**6**) from the stems and leaves of *C. excavata*.[15] Clausine Z (**6**) showed an inhibitory activity against cyclin-dependent kinase 5 (CDK5) and a protective effect on cerebral granule neurons against free radical induced cell death. In 2010, Laphookhieo et al. described the isolation of methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) from the stems of *C. excavata*.[16]

Due to their biological activity, several syntheses of 1,6-dioxygenated carbazoles have been described. In 1995, Chakraborty et al. reported the first synthesis of clausenine (**1**) and clausenol (**3**)

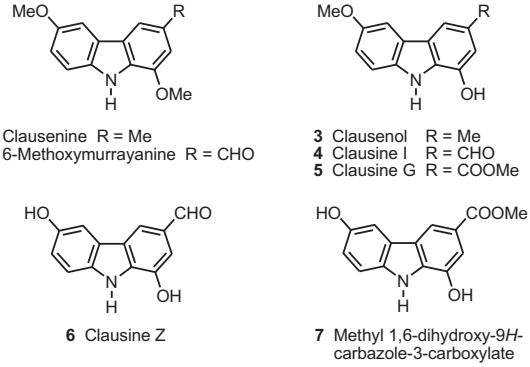


Fig. 1. The naturally occurring 1,6-dioxygenated carbazole alkaloids **1**–**7**.

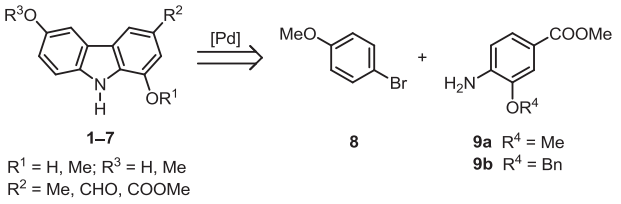
☆ For part 100, see: Ref. 6.

* Corresponding author. Fax: +49 351 463 37030; e-mail address: hans-joachim.knoelker@tu-dresden.de (H.-J. Knölker).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.05.105

(three to four steps and 6% overall yield).[12] In 1999, Lin and Zhang's optimisation of Chakraborty's earlier synthetic route provided clausenol (**3**) in 17% overall yield.[17,18] In 2007, Tamariz et al. reported a synthesis of 6-methoxymurrayanine (**2**) (six steps, 16% overall yield) and clausenine (**1**) (six steps, 20% overall yield).[19] In 2008, Fagnou et al. described the synthesis of clausenine (**1**) in three steps and 69% overall yield.[9]

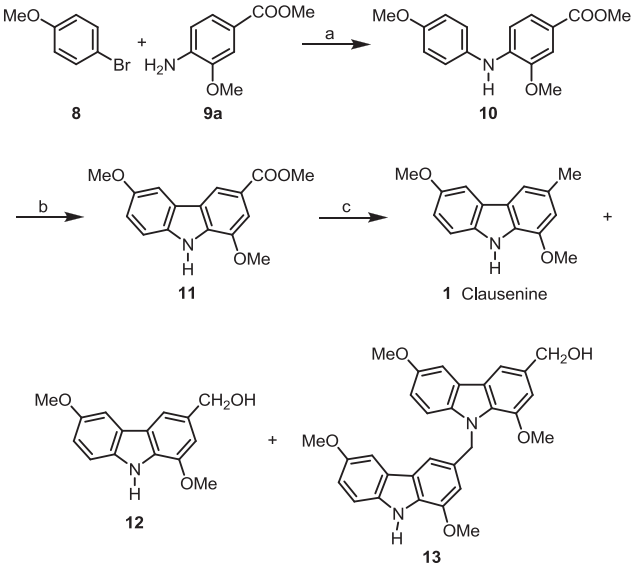
We have developed a highly efficient palladium-catalysed synthesis of the whole series of 1,6-dioxygenated carbazole alkaloids described above (Fig. 1).[10] Key steps of our route are a Buchwald–Hartwig coupling providing diarylamines and a subsequent palladium(II)-catalysed oxidative cyclisation.[1–5] This approach has also been successfully applied to the synthesis of 2-oxygenated,[20,21] 6-oxygenated,[22] 7-oxygenated,[23] 1,7-dioxygenated,[24] 2,6-dioxygenated,[25] 2,7-dioxygenated[26] and 1,7,8-trioxygenated carbazoles.[6] Retrosynthetic analysis of the seven 1,6-dioxygenated carbazole alkaloids **1**–**7** led to identification of 4-bromoanisole (**8**) and the methyl 4-aminobenzoates **9a** and **9b** as starting materials (Scheme 1).



Scheme 1. Retrosynthetic analysis of the 1,6-dioxygenated carbazole alkaloids **1**–**7**.

2. Results and discussion

Buchwald–Hartwig amination of 4-bromoanisole (**8**) and methyl 4-amino-3-methoxybenzoate (**9a**) led quantitatively to the diarylamine **10** (Scheme 2). As described by Åkermark for acceptor-substituted diarylamines,[27] oxidative cyclisation of **10** using over-stoichiometric amounts of palladium(II) acetate afforded directly the carbazole **11** in 96% yield (Scheme 2, Table 1). Our first experiments with catalytic amounts of palladium(II) acetate in the presence of copper(II) acetate for reoxidation of palladium using either thermal induction[28] or microwave heating[25,29] provided carbazole **11** only in poor yield (Table 1, entry 2). However, in the presence of copper(II) acetate, 1.3 equiv of palladium(II) acetate were sufficient to achieve satisfactory yields of carbazole **11** (Table 1, entry 3). Finally, using 10 mol % of palladium(II) acetate and potassium carbonate in pivalic acid,[9] carbazole **11** was obtained in 75% yield (Table 1, entry 4).



Scheme 2. Synthesis of clausenine (**1**). Reagents and conditions: (a) 1.1 equiv **8**, 6 mol % $Pd(OAc)_2$, 12 mol % SPhos, 1.4 equiv Cs_2CO_3, toluene, 110 °C, 5 d, 100%; (b) see Table 1; (c) see Table 2.

Table 1
Oxidative cyclisation of the diarylamine **10** to methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**)

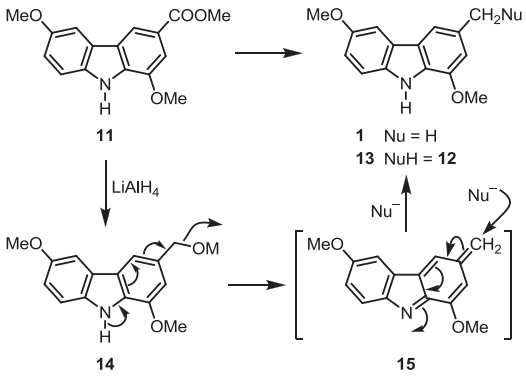
Reagents and conditions	**11**, Yield [%]	**10**, Yield [%]
2 equiv $Pd(OAc)_2$, HOAc, 117 °C, 4 h, Ar	96	—
0.1 equiv $Pd(OAc)_2$, 2.5 equiv $Cu(OAc)_2$, DMF, 130 °C, MW 300 W, 4 h, air	11	75
1.3 equiv $Pd(OAc)_2$, 2.5 equiv $Cu(OAc)_2$, HOAc, 117 °C, 40 h, Ar	76	—
0.1 equiv $Pd(OAc)_2$, 0.1 equiv K_2CO_3, HOPiv, 115 °C, 14 h, Ar	75	—

Reduction of carbazole **11** using lithium aluminium hydride in diethyl ether/dichloromethane at room temperature afforded clausenine (**1**) in only 48% yield along with 1,6-dimethoxy-3-hydroxymethyl-9*H*-carbazole (**12**) in 36% yield and the previously unknown biscarbazole **13** in up to 9% yield (Table 2). Reduction with lithium aluminium hydride in tetrahydrofuran at elevated temperature provided clausenine (**1**) in 74% yield (Scheme 2, Table 2). Thus, clausenine (**1**) was obtained in three steps and 71% overall yield.

Table 2
Reduction of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) with lithium aluminium hydride

Reagents and conditions	**1**, Yield [%]	**12**, Yield [%]	**13**, Yield [%]
4 equiv $LiAlH_4$, Et_2O/CH_2Cl_2 (1:1), rt, 6 h	48	36	9
4 equiv $LiAlH_4$, THF, 67 °C, 4 h	74	—	1

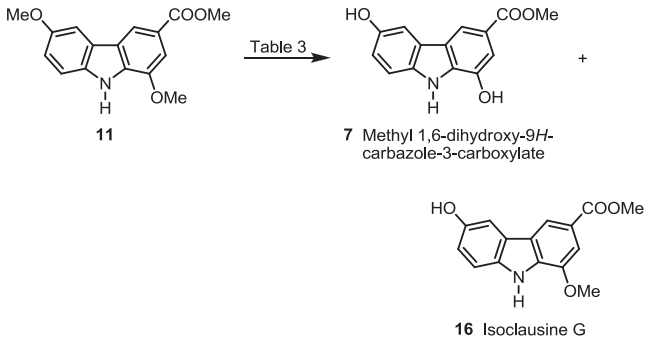
Lithium aluminium hydride reductions of alkyl carbazole-3-carboxylates to 3-methylcarbazoles have been known for a long time.[31] In 2001, Bringmann et al. obtained biscarbazoles as side products of the reduction of carbazole-3-carboxylic acid esters and proposed a mechanistic pathway for this transformation.[30] Reduction of the ester group of carbazole **11** followed by elimination of metal oxide from intermediate **14** would lead to the quinone imine methide **15** (Scheme 3). Subsequent attack of different nucleophiles at the quinone imine methide **15** would afford the



Scheme 3. Proposed mechanism for the formation of clausenine (**1**) and the biscarbazole **13**.

observed products. Addition of hydride provides clausenine (**1**), whereas addition of a second carbazole moiety leads to the biscarbazole **13**. The formation of the biscarbazole **13** is explained by attack of carbazole **11** at intermediate **15** followed by reduction of the ester group to a hydroxymethyl group.

A selective cleavage of the methyl ether at the 1-position of the carbazole **11** would afford clausine G (**5**). However, treatment of **11** with 4 equiv of boron tribromide at low temperature led to methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) in 67% yield along with the non-natural isoclausine G (**16**) in 33% yield (Scheme 4, Table 3). Thus, using mild reaction conditions the methyl ether at C-6 is cleaved first. Subsequent to our original communication on this work,[10] the carbazole **7** was isolated from the stems of *C. excavata* collected in southern Thailand by Laphookhieo et al.[16] Therefore, we aimed at an optimisation of the double ether cleavage of carbazole **11**. Using 6 equiv of boron tribromide and warming to room temperature provided exclusively methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) in 75% yield. Using this route, methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) is accessible in three steps and 72% overall yield.

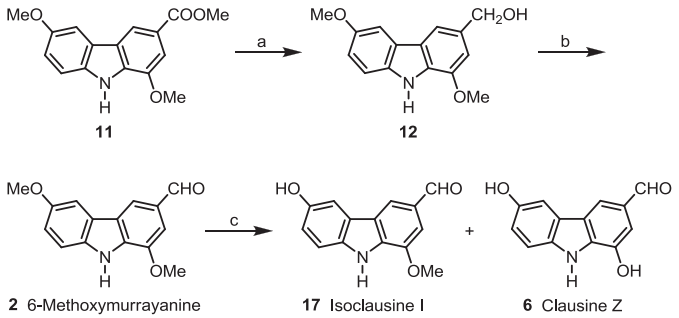


Scheme 4. Synthesis of methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) and isoclausine G (**16**). Reagents and conditions: see Table 3.

Table 3
Ether cleavage of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**)

Reagents and conditions	**7**, Yield [%]	**16**, Yield [%]
4 equiv BBr_3, CH_2Cl_2, −78 °C to −10 °C, 17.5 h	67	33
6 equiv BBr_3, CH_2Cl_2, −78 °C to rt, 16.5 h	75	—

Reduction of carbazole **11** using diisobutylaluminium hydride (DIBAL-H)[32] followed by oxidation with commercially available manganese(IV) oxide[33,34] led to 6-methoxymurrayanine (**2**) in 87% yield over both steps (four steps and 84% overall yield) (Scheme 5).

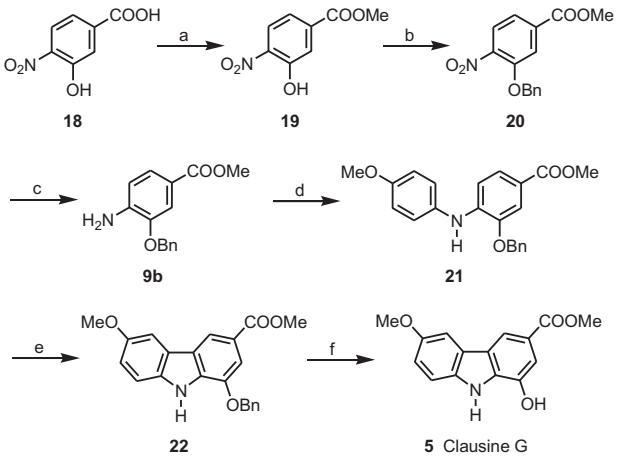


Scheme 5. Synthesis of 6-methoxymurrayanine (**2**), isoclausine I (**17**) and clausine Z (**6**). Reagents and conditions: (a) 2.6 equiv DIBAL-H, Et_2O, −78 °C, 3.5 h, 87%; (b) 5 equiv MnO_2, CH_2Cl_2, rt, 24 h, 100%; (c) 3 equiv BBr_3, CH_2Cl_2, −78 °C to rt, 24 h, 73% of **17** and 24% of **6**.

Ether cleavage of 6-methoxymurrayanine (**2**) using boron tribromide afforded clausine Z (**6**) and the non-natural isoclausine I (**17**). This approach leads to clausine Z (**6**) in five steps and 20% overall yield.

Obviously, the methoxy group at C-1 of the carbazole ring is more stable towards ether cleavage than the methyl ether in the 6-position. This finding led us to devise a different protecting group strategy for the synthesis of the 1-hydroxy-6-methoxycarbazoles clausenol (**3**), clausine I (**4**) and clausine G (**5**).

Following a literature procedure, 3-hydroxy-4-nitrobenzoic acid (**18**) was converted into the benzyloxy-substituted arylamine **9b** via three steps (Scheme 6).[35] Benzyl ethers are cleaved selectively in the presence of methyl ethers using hydrogen and palladium on



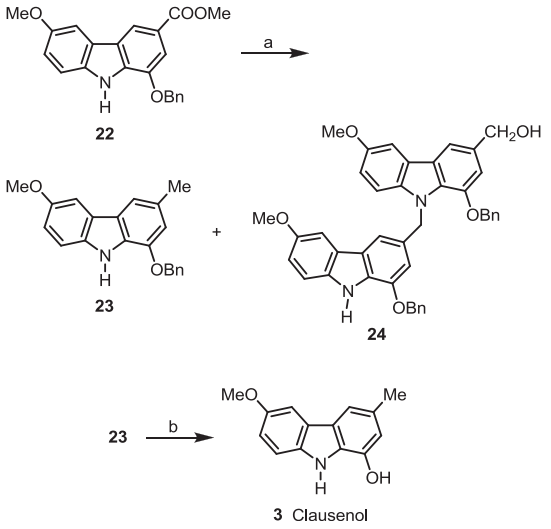
Scheme 6. Synthesis of clausine G (**5**). Reagents and conditions: (a) MeOH, cat. H_2SO_4, 65 °C, 17 h, 99%; (b) BnBr, K_2CO_3, acetone, 56 °C, 17 h, 100%; (c) Fe, HOAc, rt to 40 °C, 4 h, 100%; (d) 6 mol % $Pd(OAc)_2$, 12 mol % SPhos, 1.4 equiv Cs_2CO_3, 1.1 equiv 4-bromoanisole (**8**), toluene, 80 °C, 64 h, 90%; (e) see Table 4; (f) 10% Pd/C, H_2, CH_2Cl_2/MeOH (1:1), rt, 18 h, 89%.

activated carbon. Moreover, both protecting groups can be removed in a one pot reaction using boron tribromide. Buchwald–Hartwig amination using similar conditions as described for the diarylamine **10** provided the diarylamine **21**. The best results for the cyclisation of **21** were achieved using 2 equiv of palladium(II) acetate, which led to the carbazole **22** in 62% yield (Table 4). Using 1 equiv of palladium(II) acetate in the presence of 2.5 equiv of copper(II) acetate provided the carbazole **22** in 53% yield. Using catalytic amounts of palladium(II) acetate and potassium carbonate in pivalic acid afforded the carbazole **22** in up to 54% yield. Cleavage of the benzyl ether with palladium on activated carbon under hydrogen atmosphere provided clausine G (**5**) in six steps and 49% overall yield based on commercially available 3-hydroxy-4-nitrobenzoic acid (**18**).

Table 4
Oxidative cyclisation to methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**)

Reagents and conditions	**22**, Yield [%]	**21**, Yield [%]
2 equiv $Pd(OAc)_2$, HOAc, 100 °C, 14 h, Ar	62	3
1 equiv $Pd(OAc)_2$, 2.5 equiv $Cu(OAc)_2$, HOAc, 100 °C, 40 h, Ar	53	29
0.1 equiv $Pd(OAc)_2$, 0.1 equiv K_2CO_3, HOPiv, 100 °C, 14 h, air	48	41
0.2 equiv $Pd(OAc)_2$, 0.1 equiv K_2CO_3, HOPiv, 115 °C, 40 h, air	54	17

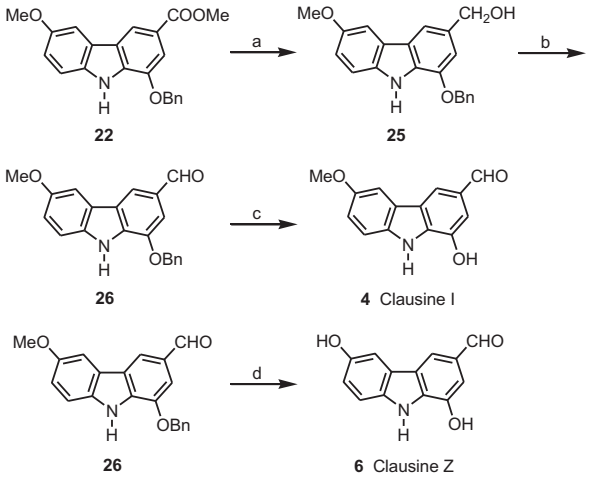
Reduction of compound **22** using lithium aluminium hydride afforded the benzyl-protected clausenol **23** in 94% yield along with the biscarbazole **24** in 3% yield (Scheme 7). Catalytic hydrogenolysis of **23** provided clausenol (**3**) in seven steps and 52% overall yield.



Scheme 7. Synthesis of clausenol (**3**). Reagents and conditions: (a) 4 equiv $LiAlH_4$, THF, 67 °C, 7 h, 94% of **23** and 3% of **24**; (b) 10% Pd/C, H_2, CH_2Cl_2/MeOH (1:1), rt, 40 h, 100%.

Reduction of carbazole **22** with diisobutylaluminium hydride (DIBAL-H) led to the carbinol **25** (Scheme 8).[32] Subsequent oxidation using activated manganese(IV) oxide afforded the benzyl-protected clausine I **26**.[33,34] Using aluminium trichloride as Lewis acid in refluxing 1,4-dioxane resulted in selective removal of the benzyl ether and provided quantitatively clausine I (**4**).[36] Treatment of compound **26** with boron tribromide led to cleavage of both ethers and provided clausine Z (**6**). Thus, the present route affords clausine I (**4**) in eight steps and 52% overall yield and clausine Z (**6**) in eight steps and 29% overall yield both starting from commercially available starting materials.

Many naturally occurring carbazoles exhibit useful antibiotic activities.[1,3] Previously, we have reported on the anti-TB activity of carbazole derivatives.[40] Therefore, a selection of the carbazoles described in the present paper (compounds **4**, **5**, **6**, **22**, **23**, **25** and **26**) has been tested for their inhibitory effect on *Mycobacterium tuberculosis* (MTB) $H_{37}Rv$ strain using the microplate alamar blue assay (MABA).[41] Compound **23** was found to exhibit an inhibitory activity; minimum inhibitory concentration (MTB $H_{37}Rv$): MIC_{90}=31.7 μM; toxicity (vero cells): IC_{50} >128 μM; selectivity index (IC_{50}/MIC_{90}): SI >4.



Scheme 8. Synthesis of clausine I (**4**) and clausine Z (**6**). Reagents and conditions: (a) 2.6 equiv DIBAL-H, Et_2O, −78 °C, 3.5 h, 95%; (b) 5 equiv MnO_2, CH_2Cl_2, rt, 24 h, 100%; (c) 10 equiv $AlCl_3$, dioxane, 101 °C, 3 h, 100%; (d) 4 equiv BBr_3, CH_2Cl_2, −78 °C to rt, 24 h, 55%.

3. Conclusion

We have described efficient synthetic routes to all seven 1,6-dioxygenated carbazoles, which have been isolated so far from natural sources. Clausenine (**1**), 6-methoxymurrayanine (**2**), clausenol (**3**), clausine I (**4**), clausine G (**5**), clausine Z (**6**) and methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (**7**) are available in three to eight steps and up to 83% overall yield via a sequence of Buchwald–Hartwig amination and oxidative cyclisation as key steps for construction of the carbazole framework. One derivative (compound **23**) showed a moderate activity against *M. tuberculosis*.

4. Experimental section

4.1. General

All reactions were carried out in oven-dried glassware using dry solvents under an argon atmosphere unless stated otherwise. Dichloromethane, diethyl ether, dioxane, tetrahydrofuran and toluene were dried using a solvent purification system (MBraun-SPS). Acetone was distilled from phosphorus(V) oxide and stored over 3 Å molecular sieves. Palladium(II) acetate was recrystallised from glacial acetic acid. All other chemicals were used as received from commercial sources. Flash chromatography was performed 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 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 Avance II 300 and DRX 500 spectrometers. Chemical shifts δ are reported in parts per million with the non-deuterated solvent as internal standard.[37] The following abbreviations have been used: s: singlet, d: doublet, dd: doublet of doublets, t: triplet, tt: triplet of triplets, 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.

4.2. Methyl 3-methoxy-4-(4-methoxyphenylamino)benzoate (10)

4-Bromoanisole (**8**) (233 μL, 1.86 mmol) was added to a solution of methyl 4-amino-3-methoxybenzoate (**9a**) (306 mg, 1.69 mmol), palladium(II) acetate (22.8 mg, 0.101 mmol), SPhos (83.2 mg, 0.203 mmol) and caesium carbonate (771 mg, 2.37 mmol) in toluene (31 mL). After stirring for 120 h at reflux, the solvent was removed under reduced pressure. The residue was directly submitted to flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to provide methyl 3-methoxy-4-(4-methoxyphenylamino)-benzoate (**10**) as colourless solid, yield: 485 mg (100%), mp 58.5–59 °C.

UV (MeOH): λ_{max}=233 (sh), 325 nm. IR (ATR): ν=3400, 3000, 2948, 2835, 2636, 1699, 1598, 1523, 1507, 1452, 1431, 1406, 1356, 1273, 1255, 1218, 1171, 1124, 1101, 1030, 987, 898, 874, 825, 760, 724,

660, 610 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.82 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 6.30 (br s, 1H), 6.90 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.4 Hz, 1H), 7.16 (d, J=8.8 Hz, 2H), 7.49 (d, J=1.7 Hz, 1H), 7.55 (dd, J=8.4, 1.7 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=51.84 (CH_3), 55.64 (CH_3), 55.75 (CH_3), 109.85 (CH), 110.78 (CH), 114.81 (2 CH), 119.07 (C), 124.19 (CH), 124.56 (2 CH), 133.40 (C), 140.07 (C), 146.03 (C), 156.48 (C), 167.40 (C=O). MS (EI): m/z (%)=287 (100, M^+), 272 (66), 256 (9), 241 (35), 228 (11), 213 (4), 198 (4), 184 (5), 170 (5), 128 (10), 121 (4). Anal. Calcd (%) for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88. Found: C 67.01, H 6.10, N 4.96.

4.3. Methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (11)

Method A (2 equiv of palladium(II) acetate). A solution of methyl 3-methoxy-4-(4-methoxyphenylamino)benzoate (**10**) (159 mg, 0.554 mmol) and palladium(II) acetate (259 mg, 1.11 mmol) in glacial acetic acid (7 mL) was heated at reflux for 4 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) to afford methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) as colourless crystals, yield: 152 mg (96%), mp 144.5–145.0 °C.

Method B (catalytic amounts of palladium(II) acetate). A solution of methyl 3-methoxy-4-(4-methoxyphenylamino)benzoate (**10**) (53.1 mg, 0.185 mmol), palladium(II) acetate (4.2 mg, 0.018 mmol) and potassium carbonate (2.6 mg, 0.018 mmol) in pivalic acid (175 mg) was heated at 115 °C for 14 h under air. Dichloromethane was added and the solution was washed twice with a saturated aqueous solution of potassium carbonate. The combined aqueous layers were extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (isohexane/ethyl acetate 4:1) afforded methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) as colourless crystals, yield: 39.5 mg (75%), mp 144.5–145.0 °C.

UV (MeOH): λ_{max}=224, 238, 248, 258, 268, 285, 321, 348 (sh) nm. IR (ATR): ν=3355, 3013, 2998, 2921, 2851, 1761, 1686, 1629, 1609, 1585, 1506, 1482, 1462, 1435, 1404, 1357, 1310, 1261, 1202, 1174, 1132, 1102, 1036, 995, 947, 915, 880, 840, 812, 792, 767, 755, 729, 675 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.93 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 7.09 (dd, J=8.8, 2.5 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 7.56 (m, 2H), 8.35 (br s, 1H), 8.44 (d, J=0.9 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=52.18 (CH_3), 55.87 (CH_3), 56.11 (CH_3), 103.23 (CH), 106.55 (CH), 112.14 (CH) 116.02 (CH), 116.39 (CH), 121.58 (C), 123.66 (C), 124.37 (C), 133.82 (C), 134.41 (C), 145.27 (C), 154.56 (C), 168.12 (C=O). MS (EI): m/z (%)=285 (100, M^+), 270 (74), 254 (10), 242 (8), 224 (8), 211 (8), 183 (5), 168 (5), 142 (6), 127 (13), 120 (5), 105 (5). Anal. Calcd (%) for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91. Found: C 67.33, H 5.49, N 4.96.

4.4. Clausenine (1,6-dimethoxy-3-methyl-9*H*-carbazole) (1) and 1,6-dimethoxy-3-(3-hydroxymethyl-1,6-dimethoxy-9*H*-carbazol-9-yl)methyl-9*H*-carbazole (13)

A 1 M solution of lithium aluminium hydride in tetrahydrofuran (1.3 mL, 1.3 mmol) was added within 5 min at room temperature to a solution of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) (R_f=0.53, petroleum ether/ethyl acetate 1:1) (92.3 mg, 0.325 mmol) in tetrahydrofuran (9 mL). The mixture was heated at reflux for 4 h. Water was carefully added and the mixture was neutralised with 1 M hydrochloric acid. The aqueous layer was separated and extracted four times with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) afforded clausenine (1,6-dimethoxy-3-methyl-9*H*-carbazole) (**1**), R_f=0.65 (petroleum ether/ethyl acetate 1:1) as colourless crystals, yield: 57.8 mg (74%), mp 149–150 °C (lit.:[12] 151 °C) along with 1,6-dimethoxy-3-(3-hydroxymethyl-1,6-dimethoxy-9*H*-carbazol-9-yl)methyl-9*H*-carbazole (**13**), R_f=0.14 (petroleum ether/ethyl acetate 1:1) as a colourless solid, yield: 1.0 mg (1%).

Compound **1**: UV (MeOH): λ_{max}=226, 241, 258 (sh), 287 (sh), 299, 340, 354 nm. IR (ATR): ν=3385, 2955, 2918, 2852, 1619, 1581, 1505, 1486, 1459, 1451, 1437, 1394, 1304, 1268, 1207, 1145, 1129, 1035, 1025, 940, 838, 821, 800, 769 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=2.45 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H), 6.78 (s, 1H), 6.97 (dd, J=8.7, 2.4 Hz, 1H), 7.33 (d, J=8.7 Hz, 1H), 7.46 (s, 1H), 7.55 (d, J=2.4 Hz, 1H), 10.92 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ=21.57 (CH_3), 55.23 (CH_3), 55.51 (CH_3), 102.64 (CH), 107.53 (CH), 111.97 (CH), 112.31 (CH), 114.56 (CH), 122.75 (C), 123.48 (C), 127.45 (C), 128.56 (C), 134.68 (C), 145.33 (C), 152.80 (C). MS (EI): m/z (%)=241 (91, M^+), 226 (100), 211 (11), 198 (20), 183 (7), 167 (9), 155 (17), 154 (14). Anal. Calcd (%) for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81. Found: C 74.88, H 6.36, N 5.50.

Compound **13**: ^1H NMR (300 MHz, $CDCl_3$): δ=3.84 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.86 (s, 2H), 5.98 (s, 2H), 6.75 (d, J=1.1 Hz, 1H), 6.98 (d, J=1.3 Hz, 1H), 6.99–7.05 (m, 2H), 7.28–7.35 (m, 2H), 7.38 (d, J=2.5 Hz, 1H), 7.41 (s, 1H), 7.54 (d, J=2.5 Hz, 1H), 7.70 (d, J=1.3 Hz, 1H), 8.02 (br s, 1H). MS (ESI, −10 V): m/z=495 $(M-H)^-$.

4.5. Methyl 1,6-dihydroxy-9*H*-carbazole-3-carboxylate (7) and isoclausine G (methyl 6-hydroxy-1-methoxy-9*H*-carbazole-3-carboxylate) (16)

Method A. A 1 M solution of boron tribromide in dichloromethane (1.5 mL, 1.5 mmol) was added at −78 °C to a solution of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) (108 mg, 0.378 mmol) in dichloromethane (15 mL). After stirring for 30 min at this temperature the solution was allowed to warm to −10 °C and stirring was continued for 17 h. Methanol (4 mL) was added and the solvents were evaporated. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) afforded methyl 1,6-dihydroxy-9*H*-carbazol-3-carboxylate (**7**) as light brown crystals, yield: 66.2 mg (67%) mp 198–200 °C, along with methyl 6-hydroxy-1-methoxy-9*H*-carbazole-3-carboxylate (**16**) as light brown crystals, yield: 34.0 mg (33%), mp 205–206 °C.

Method B. A 1 M solution of boron tribromide in dichloromethane (2.1 mL, 2.1 mmol) was added at −78 °C to a solution of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) (102 mg, 0.358 mmol) in dichloromethane (15 mL). After stirring for 30 min at this temperature the solution was allowed to warm to room temperature and stirring was continued for 16 h. Methanol (5.6 mL) was added and the solvents were evaporated. Purification of the residue by flash chromatography on silica gel (isohexane/ethyl acetate 4:1) afforded methyl 1,6-dihydroxy-9*H*-carbazol-3-carboxylate (**7**) as light brown crystals, yield: 68.8 mg (75%), mp 198–200 °C.

Compound **7**: UV (MeOH): λ_{max}=223, 242, 251, 268, 285, 326, 339 (sh), 356 (sh) nm. IR (ATR): ν=3339, 3237, 2955, 2921, 2850, 1672, 1614, 1589, 1504, 1460, 1435, 1342, 1315, 1283, 1244, 1205, 1182, 1088, 1002, 918, 879, 847, 806, 731, 656 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=3.84 (s, 3H), 6.91 (dd, J=8.6, 2.3 Hz, 1H), 7.31 (d, J=8.6 Hz, 1H), 7.40 (d, J=1.2 Hz, 1H), 7.41 (d, J=2.3 Hz, 1H), 8.15 (d, J=1.2 Hz, 1H), 8.31 (br s, 1H), 10.0 (br s, 1H), 11.21 (s, 1H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ=51.70 (CH_3), 104.92 (CH), 109.62 (CH), 112.18 (CH), 114.12 (CH), 115.60 (CH), 119.72 (C), 123.13 (C), 123.67 (C), 133.34 (C), 134.15 (C), 142.72 (C), 150.99 (C), 167.12 (C=O). MS (ESI, −10 V): m/z=256 $(M-H)^-$, 513 $(2M-H)^-$. MS (EI): m/z (%)=257 (100, M^+), 256 (9), 226 (40), 198 (16), 170 (4), 169 (4), 113 (8). HRMS: m/z calcd for $C_{14}H_{11}NO_4$: 257.0688, found: 257.0697.

Compound **16**: UV (MeOH): λ_{max}=223, 239, 248, 258, 268, 286, 324, 353 (sh) nm. IR (ATR): ν=3327, 3015, 2955, 2924, 2846, 2476,

1698, 1681, 1608, 1583, 1500, 1460, 1432, 1329, 1294, 1273, 1234, 1212, 1108, 1033, 985, 950, 911, 890, 856, 802, 768, 754, 729, 672 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ=3.90 (s, 3H), 4.04 (s, 3H), 7.04 (dd, J=8.7, 2.4 Hz, 1H), 7.46 (d, J=8.7 Hz, 1H), 7.53 (d, J=1.1 Hz, 1H), 7.59 (d, J=2.4 Hz, 1H), 8.14 (s, 1H), 8.37 (s, 1H), 10.51 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ=52.01 (CH_3), 55.98 (CH_3), 105.97 (CH), 106.74 (CH), 113.12 (CH), 116.60 (CH), 116.76 (CH), 121.68 (C), 124.12 (C), 125.09 (C), 134.70 (C), 135.49 (C), 146.29 (C), 152.47 (C), 168.02 (C=O). MS (EI): m/z (%)=272 (100), 271 (91, M^+), 270 (7), 257 (31), 256 (28), 241 (17), 240 (14), 213 (5), 212 (6), 199 (6), 198 (9), 197 (7), 170 (7), 169 (7), 121 (7), 120 (7). HRMS: m/z calcd for $C_{15}H_{13}NO_4$: 271.0845, found: 271.0856.

4.6. 3-Hydroxymethyl-1,6-dimethoxy-9*H*-carbazole (12)

A 1.5 M solution of diisobutylaluminium hydride in toluene (380 μL, 0.570 mmol) was added in 5 min at −78 °C to a solution of methyl 1,6-dimethoxy-9*H*-carbazole-3-carboxylate (**11**) (109 mg, 0.385 mmol) in diethyl ether (10 mL). After stirring for 1.5 h at this temperature, a further portion of a 1.5 M solution of diisobutylaluminium hydride in toluene (280 μL, 0.420 mmol) was added in 5 min and stirring was continued for 2 h. The solution was allowed to warm to room temperature and ice water was added. The aqueous layer was separated and extracted with diethyl ether four times. The combined organic layers were washed with water, dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 3:1 to 1:3) afforded 3-hydroxymethyl-1,6-dimethoxy-9*H*-carbazole (**12**) as colourless crystals, yield: 85.9 mg (87%), mp 114.5–115.5 °C.

UV (MeOH): λ_{max}=226, 246, 257, 265 (sh), 286 (sh), 298, 337, 351 nm. IR (ATR): ν=3445, 3188, 2998, 2934, 2889, 2834, 1617, 1582, 1505, 1486, 1459, 1438, 1395, 1309, 1266, 1238, 1214, 1189, 1146, 1039, 1018, 985, 941, 863, 832, 803, 774, 756, 693, 668, 617 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.92 (s, 3H), 4.01 (s, 3H), 4.83 (s, 2H), 6.93 (d, J=0.8 Hz, 1H), 7.06 (dd, J=8.7, 2.5 Hz, 1H), 7.35 (d, J=8.7 Hz, 1H), 7.50 (d, J=2.5 Hz, 1H), 7.61 (s, 1H), 8.14 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=55.67 (CH_3), 56.15 (CH_3), 66.65 (CH_2), 103.17 (CH), 105.64 (CH), 111.75 (CH), 111.91 (CH) 115.37 (CH), 124.09 (C), 124.13 (C), 130.39 (C), 132.60 (C), 134.50 (C), 145.99 (C), 154.01 (C). MS (EI): m/z (%)=257 (100, M^+), 255 (21), 242 (55), 240 (36), 226 (10), 214 (6), 212 (6), 198 (8), 183 (8), 170 (5), 154 (8), 140 (6), 127 (5), 115 (6). Anal. Calcd (%) for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44. Found: C 70.19, H 5.82, N 5.58.

4.7. 6-Methoxymurrayanine (3-formyl-1,6-dimethoxy-9*H*-carbazole) (2)

Manganese(IV) oxide (77.5 mg, 0.892 mmol) was added to a solution of 3-hydroxymethyl-1,6-dimethoxy-9*H*-carbazole (**12**) (45.9 mg, 0.178 mmol) in dichloromethane (10 mL) and the suspension was stirred for 24 h at room temperature. The suspension was filtered using dichloromethane over silica gel and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded 6-methoxymurrayanine (3-formyl-1,6-dimethoxy-9*H*-carbazole) (**2**) as colourless crystals, yield: 45.5 mg (100%), mp 230.5–231.5 °C (lit.:[11] 231–233 °C).

UV (MeOH): λ_{max}=221 (sh), 240, 253, 277, 296, 337, 350 nm. IR (ATR): ν=3138, 3010, 2921, 2852, 1655, 1628, 1608, 1578, 1496, 1466, 1437, 1360, 1327, 1305, 1262, 1239, 1217, 1185, 1139, 1105, 1031, 1023, 944, 844, 805, 782, 749, 705, 668 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ=3.92 (s, 3H), 4.08 (s, 3H), 7.12 (dd, J=8.8, 2.4 Hz, 1H), 7.43 (d, J=1.0 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.79 (d, J=2.4 Hz, 1H), 8.34 (d, J=1.0 Hz, 1H), 10.03 (s, 1H), 10.83 (br s, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ=56.06 (CH_3), 56.08 (CH_3), 103.64 (CH), 103.78 (CH), 113.50 (CH), 116.86 (CH), 120.81 (CH), 124.44 (C), 124.87 (C), 130.71 (C), 135.45 (C), 135.80 (C), 147.27 (C), 155.60 (C), 191.72 (CHO). MS (EI): m/z (%)=255 (100, M^+), 240 (67), 225 (5), 224 (5), 212 (6), 184 (4). HRMS: m/z calcd for $C_{15}H_{13}NO_3$: 255.0895, found: 255.0885.

4.8. Clausine Z (3-formyl-1,6-dihydroxy-9*H*-carbazole) (6) and isoclausine I (3-formyl-6-hydroxy-1-methoxy-9*H*-carbazole) (17)

A 1 M solution of boron tribromide in dichloromethane (250 μL, 0.250 mmol) was added at −78 °C to a solution of 6-methoxymurrayanine (3-formyl-1,6-dimethoxy-9*H*-carbazole) (**2**) (23.5 mg, 0.083 mmol) in dichloromethane (5 mL). The solution was allowed to warm slowly to room temperature in 24 h. Methanol (1.5 mL) was added and the solvents were removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded clausine Z (3-formyl-1,6-dihydroxy-9*H*-carbazole) (**6**) as colourless crystals, yield: 4.7 mg (24%), mp 151 °C (decomp.), along with isoclausine I (3-formyl-6-hydroxy-1-methoxy-9*H*-carbazole) (**17**) as colourless crystals, yield: 14.7 mg (73%) mp 229–230.5 °C.

Compound **6**: UV (MeOH): λ_{max}=226, 246, 279, 298, 342, 355 nm. IR (ATR): ν=3219, 2922, 2853, 1657, 1579, 1457, 1327, 1196, 1136, 958, 851, 800, 711 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=6.93 (dd, J=8.6, 2.4 Hz, 1H), 7.24 (d, J=1.0 Hz, 1H), 7.34 (d, J=8.6 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 8.13 (d, J=1.0 Hz, 1H), 9.12 (br s, 1H), 9.90 (s, 1H), 10.29 (br s, 1H), 11.41 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=104.93 (CH), 106.44 (CH), 112.42 (CH), 115.73 (CH), 118.88 (CH), 123.15 (C), 123.84 (C), 128.71 (C), 134.04 (C), 134.48 (C), 143.65 (C), 151.30 (C), 191.72 (CHO). MS (EI): m/z (%)=227 (100, M^+), 226 (60), 198 (27), 197 (24), 170 (13), 169 (10). HRMS: m/z calcd for $C_{13}H_9NO_3$: 227.0582, found: 227.0573.

Compound **17**: UV (MeOH): λ_{max}=221, 240, 253, 277, 297, 340, 352 nm. IR (ATR): ν=3359, 3304, 3003, 2922, 2848, 2507, 2456, 1655, 1627, 1574, 1493, 1463, 1388, 1371, 1330, 1297, 1257, 1207, 1132, 1035, 996, 954, 852, 807, 793, 760, 734, 712, 672 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ=4.07 (s, 3H), 7.06 (dd, J=8.6, 2.4 Hz, 1H), 7.41 (d, J=1.0 Hz, 1H), 7.49 (d, J=8.6 Hz, 1H), 7.62 (d, J=2.4 Hz, 1H), 8.25 (d, J=1.0 Hz, 1H), 10.02 (s, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ=56.05 (CH_3), 103.68 (CH), 105.93 (CH), 113.31 (CH), 116.69 (CH), 120.89 (CH), 124.21 (C), 125.18 (C), 130.54 (C), 135.29 (C), 135.56 (C), 147.21 (C), 152.65 (C), 191.75 (CHO). MS (EI): m/z (%)=241 (100, M^+), 240 (13), 227 (24), 226 (40), 171 (8), 170 (15), 121 (5). HRMS: m/z calcd for $C_{14}H_{11}NO_3$: 241.0739, found: 241.0736.

4.9. Methyl 3-hydroxy-4-nitrobenzoate (19)

Concentrated sulfuric acid (0.5 mL) was added slowly to a solution of 3-hydroxy-4-nitrobenzoic acid (**18**) (1.88 g, 10.3 mmol) in methanol (not dried, HPLC grade, 60 mL) and the solution was heated under reflux for 18 h. Sodium bicarbonate was added and the solvent was removed under reduced pressure. Water and ethyl acetate were added to the residue and the aqueous layer was separated. The aqueous layer was extracted five times with ethyl acetate. The combined organic layers were washed twice with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to afford methyl 3-hydroxy-4-nitrobenzoate (**19**) as yellow crystals, yield: 2.00 g (99%), mp 89.5–90.5 °C (lit.: 86–88 °C,[38] 91–92 °C[39]).

UV (MeOH): λ_{max}=238, 270, 351 nm. IR (ATR): ν=3310, 3124, 3050, 2962, 2842, 1720, 1622, 1587, 1521, 1476, 1434, 1323, 1283, 1222, 1147, 1098, 1067, 967, 891, 843, 798, 780, 743, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.96 (s, 3H), 7.61 (dd, J=8.8, 1.7 Hz, 1H), 7.83 (d, J=1.7 Hz, 1H), 8.17 (d, J=8.8 Hz, 1H), 10.50 (s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=53.08 (CH_3), 120.73 (CH), 121.80 (CH), 125.41 (CH), 135.90 (C), 138.10 (C), 154.79 (C), 164.97 (C=O).

MS (ESI, −10 V): m/z=196 $(M-H)^-$. Anal. Calcd (%) for $C_8H_7NO_5$: C 48.74, H 3.58, N 7.10. Found: C 48.58, H 3.44, N 7.25.

4.10. Methyl 3-benzyloxy-4-nitrobenzoate (20)

Potassium carbonate (771 mg, 5.75 mmol) and then benzyl bromide (692 μL, 5.83 mmol) were added to a solution of methyl 3-hydroxy-4-nitrobenzoate (**19**) (878 mg, 4.45 mmol) in acetone (27 mL). The suspension was heated under reflux for 17 h and then water was added. The aqueous layer was separated and extracted four times with ethyl acetate. The combined organic layers were washed twice with 2 M aqueous sodium hydroxide solution, twice with a saturated aqueous solution of ammonium chloride, and twice with brine. The combined organic layers were dried over magnesium sulfate and the solvents were removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) afforded methyl 3-benzyloxy-4-nitrobenzoate (**20**) as light yellow crystals, yield: 1.28 g (100%), mp 93–94.5 °C (lit.:[35] 91–93 °C).

UV (MeOH): λ_{max}=241 (sh), 266 (sh), 327 nm. IR (ATR): ν=3118, 3085, 3061, 3037, 2964, 2878, 1730, 1606, 1525, 1497, 1440, 1422, 1384, 1372, 1297, 1269, 1235, 1213, 1190, 1115, 1083, 1003, 979, 918, 883, 852, 831, 802, 743, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.96 (s, 3H), 5.29 (s, 2H), 7.35 (t, J=7.4 Hz, 1H), 7.40 (t, J=7.4 Hz, 2H), 7.47 (d, J=7.4 Hz, 2H), 7.70 (dd, J=8.4, 1.6 Hz, 1H), 7.83 (d, J=1.6 Hz, 1H), 7.85 Hz (d, J=8.4 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=53.01 (CH_3), 71.49 (CH_2), 116.17 (CH), 121.84 (CH), 125.53 (CH), 127.40 (2 CH), 128.56 (CH), 128.90 (2 CH), 134.92 (C), 135.14 (C), 142.94 (C), 151.56 (C), 165.30 (C=O). MS (ESI, 10 V): m/z=305 $(M+NH_4)^+$, 597 $(2M+Na)^+$. Anal. Calcd (%) for $C_{15}H_{13}NO_5$: C 62.72, H 4.56, N 4.88. Found: C 62.93, H 4.35, N 4.90.

4.11. Methyl 4-amino-3-benzyloxybenzoate (9b)

Iron powder (2.62 g, 46.9 mmol) was added carefully to a solution of methyl 3-benzyloxy-4-nitrobenzoate (**20**) (1.35 g, 4.69 mmol) in glacial acetic acid (20 mL). The resulting mixture was stirred for 2 h at room temperature and then for 2 h at 40 °C. The suspension was filtered with ethyl acetate over Hyflo Super Cel® medium and the solvents were removed under reduced pressure. Water was added to the residue and the mixture was extracted four times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) afforded methyl 4-amino-3-benzyloxybenzoate (**9b**) as colourless solid, yield: 1.21 g (100%), mp 99–100 °C (lit.:[35] 99–101 °C).

UV (MeOH): λ_{max}=230, 278 (sh), 306 nm. IR (ATR): ν=3475, 3447, 3353, 3199, 3080, 3024, 2985, 2945, 1681, 1618, 1578, 1522, 1499, 1438, 1399, 1363, 1315, 1298, 1264, 1219, 1186, 1148, 1106, 1016, 994, 927, 905, 889, 841, 824, 789, 765, 736, 692, 626 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.86 (s, 3H), 4.20 (br s, 2H), 5.12 (s, 2H), 6.69 (dd, J=6.7, 2.0 Hz, 1H), 7.36 (tt, J=7.2, 2.5 Hz, 1H), 7.41 (tt, J=8.0, 2.2 Hz, 2H), 7.46 (d, J=7.4 Hz, 2H), 7.56 (m, 1H), 7.57 (dd, J=6.7, 1.8 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=51.86 (CH_3), 70.65 (CH_2), 112.72 (CH), 113.41 (CH), 119.54 (C), 124.50 (CH), 127.97 (2 CH), 128.34 (CH), 128.75 (2 CH), 136.74 (C), 141.51 (C), 145.38 (C), 167.39 (C=O). MS (EI): m/z (%)=257 (34, M^+), 226 (6), 166 (44), 138 (9), 91 (100), 79 (6), 65 (9), 52 (5). Anal. Calcd (%) for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44. Found: C 69.86, H 5.92, N 5.35.

4.12. Methyl 3-benzyloxy-4-(4-methoxyphenylamino) benzoate (21)

4-Bromoanisole (**8**) (108 μL, 0.860 mmol) was added to a solution of methyl 4-amino-3-benzyloxybenzoate (**9b**) (202 mg, 0.787 mmol), palladium(II) acetate (10.6 mg, 0.047 mmol), SPhos (38.8 mg, 0.094 mmol) and caesium carbonate (359 mg, 1.10 mmol) in toluene (16 mL). After stirring for 64 h at 80 °C, the solvent was removed under reduced pressure. The residue was directly submitted to flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to provide methyl 3-benzyloxy-4-(4-methoxyphenylamino)benzoate (**21**) as colourless solid, yield: 257 mg (90%), mp 92.5–94 °C along with 16.2 mg (8%) of unreacted methyl 4-amino-3-benzyloxybenzoate (**9b**).

UV (MeOH): λ_{max}=235 (sh), 325 nm. IR (ATR): ν=3402, 3035, 2991, 2947, 2835, 1701, 1598, 1508, 1437, 1355, 1272, 1220, 1179, 1123, 1101, 1012, 907, 872, 825, 760, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.81 (s, 3H), 3.87 (s, 3H), 5.18 (s, 2H), 6.35 (br s, 1H), 6.90 (dd, J=8.6, 2.2 Hz, 2H), 6.93 (d, J=8.4 Hz, 1H), 7.15 (d, J=8.6 Hz, 2H), 7.38 (tt, J=7.3, 1.4 Hz, 1H), 7.43 (tt, J=6.9, 1.3 Hz, 2H), 7.49 (dd, J=7.9, 1.6 Hz, 2H), 7.58 (dd, J=8.4, 1.4 Hz, 1H), 7.62 (d, J=1.4 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=51.85 (CH_3), 55.63 (CH_3), 70.95 (CH_2), 110.07 (CH), 112.27 (CH), 114.79 (2 CH), 118.99 (C), 124.49 (CH), 124.89 (2 CH), 128.15 (2 CH), 128.48 (CH), 128.82 (2 CH), 133.26 (C), 136.54 (C), 140.44 (C), 145.22 (C), 156.59 (C), 167.34 (C=O). MS (ESI, 10 V): m/z=364 $(M+H)^+$, 727 $(2M+H)^+$. Anal. Calcd (%) for $C_{22}H_{21}NO_4$: C 72.71, H 5.82, N 3.85. Found: C 71.92, H 5.60, N 4.02.

4.13. Methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (22)

Method A (2 equiv of palladium(II) acetate). A solution of methyl 3-benzyloxy-4-(4-methoxyphenylamino)benzoate (**21**) (241 mg, 0.663 mmol) and palladium(II) acetate (298 mg, 1.33 mmol) in glacial acetic acid (15 mL) was heated at 100 °C for 14 h. The solvent was removed in vacuum and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to afford methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**) as colourless crystals, yield: 148 mg (62%), mp 174–175 °C along with 7.7 mg (3%) of unreacted methyl 3-benzyloxy-4-(4-methoxyphenylamino)benzoate (**21**).

Method B (catalytic amounts of palladium(II) acetate). A solution of methyl 3-benzyloxy-4-(4-methoxyphenylamino)benzoate (**21**) (138 mg, 0.381 mmol), palladium(II) acetate (8.5 mg, 0.038 mmol) and potassium carbonate (5.2 mg, 0.038 mmol) in pivalic acid (400 mg) was heated at 115 °C for 16 h under air. A further portion of palladium(II) acetate (8.5 mg, 0.038 mmol) was added and stirring was continued for another 24 h. Dichloromethane was added and the solution was washed twice with a saturated aqueous solution of potassium carbonate. The combined aqueous layers were extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed in vacuum. Purification of the residue by flash chromatography on silica gel (isohexane/ethyl acetate 4:1) afforded methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**) as colourless crystals, yield: 74.1 mg (54%), mp 174–175 °C along with 23.8 mg (17%) of unreacted methyl 3-benzyloxy-4-(4-methoxyphenylamino)benzoate (**21**).

UV (MeOH): λ_{max}=225 (sh), 238, 248, 258, 268, 285, 321, 334 (sh), 350 (sh) nm. IR (ATR): ν=3380, 3090, 3031, 2921, 2849, 1707, 1688, 1678, 1612, 1581, 1499, 1484, 1437, 1406, 1337, 1306, 1267, 1232, 1203, 1176, 1129, 1093, 1024, 993, 956, 912, 883, 857, 839, 811, 796, 756, 729, 686, 622 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.93 (s, 3H), 3.98 (s, 3H), 5.29 (s, 2H), 7.09 (dd, J=8.8, 2.5 Hz, 1H), 7.36 (d, J=8.8 Hz, 1H), 7.40 (tt, J=7.4, 1.4 Hz, 1H), 7.44 (tt, J=7.2, 1.4 Hz, 2H), 7.53 (dd, J=7.8, 1.4 Hz, 2H), 7.57 (d, J=2.5 Hz, 1H), 7.68 (d, J=1.0 Hz, 1H), 8.38 (br s, 1H), 8.46 (d, J=1.0 Hz, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=52.20 (CH_3), 56.10 (CH_3), 70.78 (CH_2), 103.22 (CH), 107.68 (CH), 112.13 (CH), 116.08 (CH), 116.62 (CH), 121.53 (C), 123.82 (C), 124.36 (C), 128.29 (2 CH), 128.56 (CH), 128.85 (2 CH),

133.87 (C), 134.42 (C), 136.57 (C), 144.48 (C), 154.57 (C), 168.06 (C=O). MS (ESI, 25 V): m/z=362 $(M+H)^+$, 379 $(M+NH_4)^+$, 384 $(M+Na)^+$, 723 $(2M+H)^+$, 740 $(2M+NH_4)^+$, 745 $(2M+Na)^+$. Anal. Calcd (%) for $C_{22}H_{19}NO_4$: C 73.12, H 5.30, N 3.88. Found: C 72.91, H 5.41, N 3.92.

4.14. Clausine G (methyl 1-hydroxy-6-methoxy-9*H*-carbazole-3-carboxylate) (5)

A suspension of methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**) (76.5 mg, 0.212 mmol) and palladium on activated carbon (10% Pd) (15.3 mg) in dichloromethane (5 mL) and methanol (5 mL) was stirred under hydrogen (1 atm) for 18 h at room temperature. The reaction mixture was filtered with dichloromethane over a short pad of Celite® 557 and the solvents were removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1) afforded clausine G (methyl 1-hydroxy-6-methoxy-9*H*-carbazole-3-carboxylate) (**5**) as beige crystals, yield: 51.0 mg (89%), mp 145–147 °C (lit.:[14] >280 °C).

UV (MeOH): λ_{max}=224, 241, 250, 268, 284, 325 (sh), 334, 349 nm. IR (ATR): ν=3355, 2952, 2922, 2833, 1667, 1630, 1612, 1582, 1500, 1471, 1455, 1431, 1355, 1322, 1297, 1251, 1202, 1172, 1125, 1087, 1026, 1001, 916, 871, 828, 793, 765, 751, 723, 658 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ=3.88 (s, 3H), 3.92 (s, 3H), 7.08 (dd, J=8.8, 2.5 Hz, 1H), 7.52 (d, J=8.8 Hz, 1H), 7.55 (d, J=1.1 Hz, 1H), 7.77 (d, J=2.5 Hz, 1H), 8.37 (d, J=1.1 Hz, 1H), 9.04 (br s, 1H), 10.45 (br s, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ=51.91 (CH_3), 56.07 (CH_3), 103.59 (CH), 111.10 (CH), 113.23 (CH), 115.71 (CH), 116.67 (CH), 121.96 (C), 124.94 (C), 124.98 (C), 134.35 (C), 136.09 (C), 143.46 (C), 155.26 (C), 168.01 (C=O). MS (ESI, 10 V): m/z=272 $(M+H)^+$, 543 $(2M+H)^+$, 560 $(2M+NH_4)^+$, 565 $(2M+Na)^+$. Anal. Calcd (%) for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16. Found: C 66.43, H 4.95, N 4.76.

4.15. 1-Benzyloxy-6-methoxy-3-methyl-9*H*-carbazole (23) and 1-benzyloxy-3-(1-benzyloxy-3-hydroxymethyl-6-methoxy-9*H*-carbazol-9-yl)methyl-6-methoxy-9*H*-carbazole (24)

A 1 M solution of lithium aluminium hydride in tetrahydrofuran (1.2 mL, 1.2 mmol) was added within 5 min at room temperature to a solution of methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**) (108 mg, 0.298 mmol) in tetrahydrofuran (14 mL). The mixture was heated under reflux for 7 h and then, water was added slowly. The aqueous layer was separated and extracted four times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 6:1 to 1:1) afforded 1-benzyloxy-6-methoxy-3-methyl-9*H*-carbazole (**23**) as colourless crystals, yield: 89.4 mg (94%), mp 119.5–120 °C along with 1-benzyloxy-3-(1-benzyloxy-3-hydroxymethyl-6-methoxy-9*H*-carbazol-9-yl)methyl-6-methoxy-9*H*-carbazole (**24**) as a colourless solid, yield 5.7 mg (3%).

Compound **23**: UV (MeOH): λ_{max}=223, 226, 242, 259 (sh), 287 (sh), 299, 341, 355 nm. IR (ATR): ν=3437, 3033, 2998, 2917, 2828, 1618, 1578, 1504, 1480, 1459, 1432, 1393, 1379, 1315, 1305, 1264, 1210, 1180, 1145, 1125, 1038, 1027, 969, 948, 905, 841, 826, 802, 769, 737, 697, 621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=2.53 (s, 3H), 3.92 (s, 3H), 5.23 (s, 2H), 6.81 (s, 1H), 7.04 (dd, J=8.7, 2.5 Hz, 1H), 7.31 (d, J=8.7 Hz, 1H), 7.39 (t, J=7.3 Hz, 1H), 7.44 (t, J=7.3 Hz, 2H) 7.47 (s, 1H), 7.50 (d, J=2.5 Hz, 1H), 7.52 (d, J=6.9 Hz, 2H), 8.04 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=22.06 (CH_3), 56.15 (CH_3), 70.49 (CH_2), 103.19 (CH), 108.89 (CH), 111.73 (CH), 112.83 (CH), 115.06 (CH), 124.00 (C), 124.54 (C), 128.03 (2 CH), 128.31 (CH), 128.77 (2 CH), 129.10 (C), 129.14 (C), 134.55 (C), 137.13 (C), 144.80 (C), 153.79 (C). MS (ESI, −10 V): m/z=316 $(M-H)^-$ Anal. Calcd (%) for $C_{21}H_{19}NO_2$: C 79.47, H 6.03, N 4.41. Found: C 79.55, H 5.77, N 4.38.

Compound **24**: UV (MeOH): λ_{max}=222, 238 (sh), 250 (sh), 272 (sh), 291, 299 (sh), 339 nm. IR (ATR): ν=3326, 3064, 3028, 2922, 2852, 1721, 1676, 1580, 1466, 1434, 1310, 1262, 1203, 1137, 1024, 942, 910, 836, 799, 735, 696, 621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.86 (s, 3H), 3.93 (s, 3H), 4.85 (s, 2H), 4.90 (s, 2H), 5.12 (s, 2H), 5.96 (s, 2H), 6.63 (d, J=0.9 Hz, 1H), 7.00 (dd, J=8.8, 2.5 Hz, 1H), 7.05 (dd, J=8.8, 2.5 Hz, 1H), 7.03–7.06 (m, 1H), 7.18–7.21 (m, 3H), 7.25–7.27 (m, 1H), 7.29 (d, J=8.8 Hz, 1H), 7.30–7.32 (m, 3H), 7.32–7.35 (m, 6H), 7.58 (d, J=2.2 Hz, 1H), 7.74 (d, J=1.3 Hz, 1H), 8.07 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=49.42 (CH_2), 56.14 (CH_3), 56.24 (CH_3), 66.43 (CH_2), 70.25 (CH_2), 70.85 (CH_2), 102.93 (CH), 103.32 (CH), 105.73 (CH), 108.17 (CH), 110.51 (CH), 110.70 (CH), 111.73 (CH), 112.16 (CH), 115.35 (CH), 115.49 (CH), 123.51 (C), 123.97 (C), 124.32 (C), 124.89 (C), 127.77 (2 CH), 128.01 (2 CH), 128.26 (CH), 128.58 (2 CH), 128.67 (CH), 128.72 (2 CH), 129.81 (C), 129.83 (C), 130.64 (C), 131.94 (C), 134.29 (C), 136.03 (C), 136.56 (C), 136.63 (C), 136.68 (C), 144.81 (C), 146.31 (C), 153.69 (C). MS (ESI, 10 V): m/z=647 $(M+H-H_2)^+$ (ESI, 75 V): m/z=631 $(M-OH)^+$.

4.16. Clausenol (1-hydroxy-6-methoxy-3-methyl-9*H*-carbazole) (3)

A suspension of 1-benzyloxy-6-methoxy-3-methyl-9*H*-carbazole (**23**) (59.5 mg, 0.187 mmol) and palladium on activated carbon (10% Pd) (11.9 mg) in dichloromethane (7 mL) and methanol (7 mL) was stirred under a hydrogen atmosphere for 40 h at room temperature. The reaction mixture was filtered using dichloromethane over a small plug of Celite® 557 fine and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1) afforded clausenol (1-hydroxy-6-methoxy-3-methyl-9*H*-carbazole) (**3**) as beige crystals, yield: 42.5 mg (100%), mp 190.5–191 °C (lit.:[12] 192 °C).

UV (MeOH): λ_{max}=227, 242, 292 (sh), 299, 343, 357 nm. IR (ATR): ν=3367, 3228, 2921, 2851, 1652, 1621, 1590, 1578, 1520, 1481, 1457, 1434, 1388, 1318, 1298, 1269, 1210, 1178, 1142, 1095, 1024, 1005, 988, 943, 871, 833, 796, 748, 662, 623 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=2.37 (s, 3H), 3.81 (s, 3H), 6.61 (s, 1H), 6.95 (dd, J=8.7, 2.5 Hz, 1H), 7.31 (s, 1H), 7.32 (d, J=8.7 Hz, 1H), 7.51 (d, J=2.5 Hz, 1H), 9.59 (s, 1H), 10.64 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ=21.36 (CH_3), 55.53 (CH_3), 102.65 (CH), 110.90 (CH), 111.36 (CH), 111.89 (CH), 114.37 (CH), 122.98 (C), 123.98 (C), 127.43 (C), 128.45 (C), 134.72 (C), 142.86 (C), 152.66 (C). MS (ESI, −10 V): m/z=226 $(M-H)^-$, 453 $(2M-H)^-$.

4.17. 1-Benzyloxy-3-hydroxymethyl-6-methoxy-9*H*-carbazole (25)

A 1.5 M solution of diisobutylaluminium hydride in toluene (220 μL, 0.330 mmol) was added within 5 min at −78 °C to a solution of methyl 1-benzyloxy-6-methoxy-9*H*-carbazole-3-carboxylate (**22**) (77.9 mg, 0.216 mmol) in diethyl ether (15 mL). After stirring for 1.5 h at this temperature, an additional portion of a 1.5 M solution of diisobutylaluminium hydride in toluene (160 μL, 0.240 mmol) was added within 5 min and stirring was continued for 2 h. Water (2 mL) was added and the solution was allowed to warm to room temperature. Additional water was added, the aqueous layer was separated and extracted with diethyl ether four times. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded 1-benzyloxy-3-hydroxymethyl-6-methoxy-9*H*-carbazole (**25**) as colourless crystals, yield: 67.9 mg (95%), mp 120–120.5 °C.

UV (MeOH): λ_{max}=226, 247, 258, 287 (sh), 298, 324 (sh), 338, 352 nm. IR (ATR): ν=3488, 3278, 3030, 2990, 2929, 2828, 1618, 1581, 1505, 1485, 1463, 1434, 1383, 1318, 1299, 1265, 1214, 1144, 1029, 1009, 961, 947, 827, 799, 776, 738, 698, 673 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.92 (s, 3H), 4.83 (s, 2H), 5.26 (s, 2H), 7.03 (d, J=0.9 Hz, 1H), 7.06 (dd, J=8.8, 2.4 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.35–7.39 (m, 1H), 7.44 (tt, J=7.3, 1.6 Hz, 2H), 7.49–7.52 (m, 3H), 7.64 (d, J=0.9 Hz, 1H), 8.17 (br s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=56.15 (CH_3), 66.63 (CH_2), 70.59 (CH_2), 103.17 (CH), 106.84 (CH), 111.90 (CH), 112.05 (CH), 115.45 (CH), 124.08 (C), 124.31 (C), 128.11 (2 CH), 128.44 (CH), 128.83 (2 CH), 130.57 (C), 132.55 (C), 134.51 (C), 136.88 (C), 145.22 (C), 154.03 (C). MS (ESI, 100 V): m/z=316 $(M-OH)^+$, 356 $(M+Na)^+$ 631 $(2M-H_2O-OH)^+$, 689 $(2M+Na)^+$. Anal. Calcd (%) for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20. Found: C 75.81, H 5.88, N 4.24.

4.18. 1-Benzyloxy-3-formyl-6-methoxy-9*H*-carbazole (26)

Manganese(IV) oxide (63.9 mg, 0.736 mmol) was added to a solution of 1-benzyloxy-3-hydroxymethyl-6-methoxy-9*H*-carbazole (**25**) (49.1 mg, 0.147 mmol) in dichloromethane (10 mL) and the suspension was stirred for 24 h at room temperature. The suspension was filtered using dichloromethane over silica gel and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded 1-benzyloxy-3-formyl-6-methoxy-9*H*-carbazole (**26**) as colourless crystals, yield: 48.8 mg (100%), mp 209.5–210 °C.

UV (MeOH): λ_{max}=240, 255 (sh), 278, 296, 338, 350 nm. IR (ATR): ν=3147, 3009, 2924, 2853, 1655, 1632, 1607, 1575, 1497, 1477, 1434, 1396, 1359, 1325, 1308, 1263, 1236, 1217, 1180, 1140, 1031, 1021, 952, 924, 874, 839, 812, 786, 752, 709, 699, 682, 632 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=3.94 (s, 3H), 5.31 (s, 2H), 7.12 (dd, J=8.8, 2.5 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 7.40 (m, 1H), 7.45 (m, 2H), 7.53 (d, J=7.7 Hz, 2H), 7.54 (d, J=1.0 Hz, 1H), 7.58 (d, J=2.5 Hz, 1H), 8.19 (d, J=1.0 Hz, 1H), 8.50 (br s, 1H), 10.05 (s, 1H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ=56.12 (CH_3), 70.83 (CH_2), 103.23 (CH), 104.50 (CH), 112.39 (CH), 116.29 (CH), 120.79 (CH), 123.86 (C), 124.32 (C), 128.32 (2 CH), 128.68 (CH), 128.90 (2 CH), 129.89 (C), 134.29 (C), 134.96 (C), 136.29 (C), 145.46 (C), 154.88 (C), 191.88 (CHO). MS (ESI, 75 V): m/z=332 $(M+H)^+$, 354 $(M+Na)^+$. Anal. Calcd (%) for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23. Found: C 76.12, H 5.16, N 4.10.

4.19. Clausine I (3-formyl-1-hydroxy-6-methoxy-9*H*-carbazole) (4)

Aluminium trichloride (176 mg, 1.32 mmol) was added to a solution of 1-benzyloxy-3-formyl-6-methoxy-9*H*-carbazole (**26**) (43.8 mg, 0.132 mmol) in 1,4-dioxane (8 mL) at room temperature. The reaction mixture was heated under reflux for 3 h, then water was added. The aqueous layer was separated and extracted with diethyl ether four times. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvents were removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded clausine I (3-formyl-1-hydroxy-6-methoxy-9*H*-carbazole) (**4**) as colourless crystals, yield: 31.8 mg (100%), mp 221.5–223 °C (lit.:[13] 222–224 °C).

UV (MeOH): λ_{max}=225 (sh), 242, 255, 278, 296, 340 (sh), 354 nm. IR (ATR): ν=3385, 2955, 2919, 2852, 1619, 1581, 1486, 1460, 1437, 1393, 1304, 1268, 1207, 1184, 1145, 1130, 1111, 1035, 1025, 940, 838, 821, 800, 769, 733, 712, 674 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ=3.92 (s, 3H), 7.11 (dd, J=8.8, 2.4 Hz, 1H), 7.40 (d, J=0.6 Hz, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.77 (d, J=2.4 Hz, 1H), 8.25 (d, J=0.6 Hz, 1H), 9.27 (s, 1H), 9.99 (s, 1H), 10.64 (br s, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ=56.05 (CH_3), 103.66 (CH), 107.95 (CH), 113.46 (CH), 116.76 (CH), 119.60 (CH), 125.04 (C), 125.08 (C), 130.79 (C), 135.43 (C), 136.03 (C), 144.40 (C), 155.47 (C), 191.76 (CHO). MS (EI): m/z (%)=241 (100, M^+), 240 (10), 226 (78), 198 (15). HRMS: m/z calcd for $C_{14}H_{11}NO_3$: 241.0739, found: 241.0735.

4.20. Clausine Z (3-formyl-1,6-dihydroxy-9*H*-carbazole) (6)

A 1 M solution of boron tribromide in dichloromethane (510 μL 0.510 mmol) was added at −78 °C to a solution of 1-benzyloxy-3-formyl-6-methoxy-9*H*-carbazole (**26**) (41.9 mg, 0.126 mmol) in dichloromethane (10 mL). The solution was allowed to warm slowly to room temperature over 18 h. Methanol (4 mL) was added and the solvents were removed in vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 1:1) afforded clausine Z (3-formyl-1,6-dihydroxy-9*H*-carbazole) (**6**) as colourless crystals, yield: 15.8 mg (55%), mp 151 °C (decomp.).

Spectroscopic data, see above.

Acknowledgements

We are grateful to Professor Scott G. Franzblau (Institute for Tuberculosis Research, University of Illinois at Chicago, USA) for investigating the anti-TB activity of the carbazoles. We thank Dr. Margit Gruner (TU Dresden) for the 2D-NMR experiments.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.105. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For comprehensive reviews, see: (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427; (b) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193–3328.
2. (a) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309–331; (b) Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2004**, *63*, 2393–2407.
3. Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: Amsterdam, 2008; Vol. 65, pp 1–430.
4. Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8–13.
5. (a) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115–148; (b) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, *309*, 203–253.
6. Huet, L.; Forke, R.; Knölker, H.-J. *Synlett* **2012**, 1230–1234.
7. Gensch, T.; Rönnefahrt, M.; Czerwonka, R.; Jäger, A.; Kataeva, O.; Bauer, I.; Knölker, H.-J. *Chem.—Eur. J.* **2012**, *18*, 770–776.
8. Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590.
9. Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028.
10. For a preliminary communication, see: Börger, C.; Knölker, H.-J. *Synlett* **2008**, 1698–1702.
11. Li, W.-S.; McChesney, J. D.; El-Feraly, F. S. *Phytochemistry* **1991**, *30*, 343–346.
12. Chakraborty, A.; Chowdhury, B. K.; Bhattacharyya, P. *Phytochemistry* **1995**, *40*, 295–298.
13. Wu, T.-S.; Huang, S.-C.; Wu, P.-L.; Teng, C.-M. *Phytochemistry* **1996**, *43*, 133–140.
14. Wu, T.-S.; Huang, S.-C.; Wu, P.-L. *Phytochemistry* **1996**, *43*, 1427–1429.
15. Potterat, O.; Puder, C.; Bolek, W.; Wagner, K.; Ke, C.; Ye, Y.; Gillardon, F. *Pharmazie* **2005**, *60*, 637–639.
16. Sripisut, T.; Laphookhieo, S. *J. Asian Nat. Prod. Res.* **2010**, *12*, 614–617.
17. Lin, G.; Zhang, A. *Tetrahedron Lett.* **1999**, *40*, 341–344.
18. Lin, G.; Zhang, A. *Tetrahedron* **2000**, *56*, 7163–7171.
19. Bernal, P.; Benavides, A.; Bautista, R.; Tamariz, J. *Synthesis* **2007**, 1943–1948.
20. Gruner, K. K.; Knölker, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 3902–3904.
21. Forke, R.; Jäger, A.; Knölker, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 2481–2483.
22. Forke, R.; Krahl, M.; Krause, T.; Schlechtingen, G.; Knölker, H.-J. *Synlett* **2007**, 268–272.
23. Krahl, M. P.; Jäger, A.; Krause, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2006**, *4*, 3215–3219.
24. Fuchsenberger, M.; Forke, R.; Knölker, H.-J. *Synlett* **2011**, 2056–2058.
25. Schmidt, M.; Knölker, H.-J. *Synlett* **2009**, 2421–2424.
26. Forke, R.; Krahl, M. P.; Däbritz, F.; Jäger, A.; Knölker, H.-J. *Synlett* **2008**, 1870–1876.

27. Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365–1367.
28. Knölker, H.-J.; O'Sullivan, N. *Tetrahedron* **1994**, *50*, 10893–10908.
29. Sridharan, V.; Martín, M. A.; Menéndez, J. C. *Synlett* **2006**, 2375–2378.
30. Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 2337–2343.
31. Chakraborty, D. P.; Roy, S.; Dutta, A. K. *J. Indian Chem. Soc.* **1987**, *64*, 215–217.
32. Winterfeldt, E. *Synthesis* **1975**, 617–630.
33. Manganese dioxide (precipitated, active) from Merck (art. 805958).
34. (a) Fatiadi, A. J. *Synthesis* **1976**, 65–104; (b) Knölker, H.-J. *J. Prakt. Chem.* **1995**, *337*, 75–77.
35. Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synthesis* **2006**, 3467–3477.
36. Rajakumar, P.; Murali, V. *Synth. Commun.* **2003**, *33*, 3891–3896.
37. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.
38. Walker, D. P.; Wishka, D. G.; Piotrowski, D. W.; Jia, S.; Reitz, S. C.; Yates, K. M.; Myers, J. K.; Vetman, T. N.; Margolis, B. J.; Jacobsen, E. J.; Acker, B. A.; Groppi, V. E.; Wolfe, M. L.; Thornburgh, B. A.; Tinholt, P. M.; Cortes-Burgos, L. A.; Walters, R. R.; Hester, M. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Olson, B. A.; Fitzgerald, L.; Staton, B. A.; Raub, T. J.; Hajos, M.; Hoffmann, W. E.; Li, K. S.; Higdon, N. R.; Wall, T. M.; Hurst, R. S.; Wong, E. H. F.; Rogers, B. N. *Bioorg. Med. Chem.* **2006**, *14*, 8219–8248.
39. Sathunuru, R.; Rao, U. N.; Biehl, E. *Arkivoc* **2003**, *xv*, 124–133.
40. (a) Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812–815; (b) Choi, T. A.; Czerwonka, R.; Forke, R.; Jäger, A.; Knöll, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *Med. Chem. Res.* **2008**, *17*, 374–385; (c) Knölker, H.-J. *Sitzungsber. d. Sächs. Akad. d. Wiss.* **2008**, *131*, 1–24.
41. (a) Collins, L. A.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004–1009; (b) Pauli, G. F.; Case, R. J.; Inui, T.; Wang, Y.; Cho, S.; Fischer, N. H.; Franzblau, S. G. *Life Sci.* **2005**, *78*, 485–494.