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ORIGINAL PAPER

Facile synthesis of cycloalkanoindole derivatives by aza-Claisen rearrangement

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Abstract Carba analogs of physostigmine were prepared from aniline derivatives with BF_3Et_2O catalyzed cyclization. Suzuki coupling reactions of the new compounds are also discussed.

Keywords Alzheimer's disease · Physostigmine analogs · Ene reaction · Cyclization · Bromination

Introduction

Alzheimer's disease is the most common brain disorder that affects older people. This brain disease slowly destroys memory and ability to learn or recognize new things and friends. As the disease progresses, bodily functions and the ability to carry out daily activities are lost and the person needs total care [1–3].

Alzheimer's disease cannot be cured, but there are treatments which can prevent or slow down the progress of getting worse. The disease is associated with the cholinergic system. The enzyme acetylcholinesterase rapidly hydrolyzes the naturally released acetylcholine causing a shortage in this neurotransmitter [4, 5]. Most of the researches are directed to inhibit this enzyme activity, which would increase the concentration of acetylcholine in the brain. Nowadays, cholinesterase inhibitors—donepezil (aricept) [6, 7], rivastigmine (exelon) [8–10], and galanthamine (nivalin) [11–13]—are used for the treatment in the mild to moderate stages of Alzheimer's disease.

The alkaloid of the African Calabar bean (*Physostigma venesonum*), (−)-physostigmine (eserine) inhibits the acetylcholinesterase. This inhibitory effect comes from the carbamate moiety of the molecule, which transcarbamylates the enzyme. The physostigmine's analog phenserine, a phenylcarbamoyl derivative, is a highly potent inhibitor of this enzyme. Furthermore, the above mentioned rivastigmine is also an aryl carbamate derivative (Fig. 1) [14–17].

In recent years, we have published two papers about the easy preparation of carba analogs of physostigmine [18, 19]. In that work the synthesis of potent inhibitors of the esterase enzyme was based on the aza-Claisen rearrangement of cycloalkenyl-*N*-methylbenzenamine, followed by aza-Alder-ene reaction of the intermediate. To test the scope and limitation of the rearrangement reactions, we have prepared a series of new carba analogs of physostigmine and studied their reactions.

Results and discussion

Synthesis of new analogs **5** is depicted in Scheme 1. The reactions of compounds **1** with allyl halides **2** gave the expected amines **3** in good to excellent yields (Table 1, entries 1–4). Treatment of compounds **3a**, **3b** with BF_3Et_2O in sulfolane yielded a mixture of *cis*- and *trans*-isomers of **5a**, **5b**, which were separated by column chromatography (entries 5, 6). In the reaction of the chloro compound **3c** only the *cis*-isomer was isolated (entry 7).

In the attempted cyclization of **3d**, **3e** we failed to get the wanted **5d**, **5e**. Here, under the forcing condition (170 °C) some degradation and the reduction of the bromine-carbon bond took place. Therefore, compounds **5d**,

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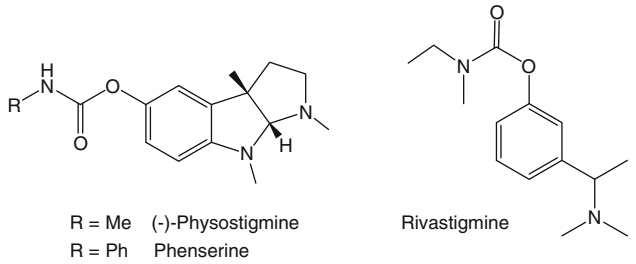
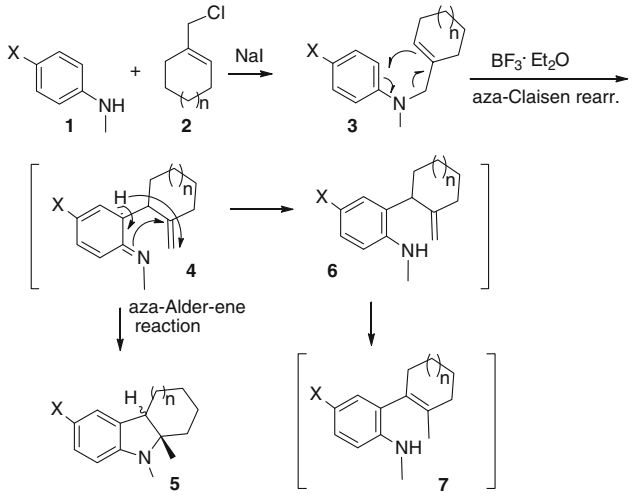


Fig. 1 Alkaloid of the Calabar bean and its analogs



1	X	2	n	3-7	X	n
a	H	**a**	1	**a**	H	1
b	MeO	**b**	2	**b**	H	2
c	Cl			**c**	Cl	1
d	Br			**d**	Br	1
				e	Br	2

Scheme 1

5e were prepared by the bromination of **5a**, **5b** using NBS (entries 8–11). In the bromination of **5a** we get some percent of the 1,3-dibromo derivative, too.

The annulations of rings (*cis* or *trans*) were determined by the Nuclear Overhauser Effect Spectroscopy (NOESY) interaction between the hydrogens of the methyl group (8a-CH_3) and the neighboring CH group. Furthermore, in the ^{13}C NMR spectra the *trans*-**5** diastereomers showed a γ-effect between the methyl group (8a-CH_3) and the methylene group (C-5). In the spectra of the corresponding *cis*-**5** the γ-effect was missing (8a-CH_3 and C-5). This observation, in accordance with other NMR data, was found in *trans*-fused five- and six-membered rings in the *trans*-compounds (Table 2).

In the cyclization reactions we observed the formation of side-products **7**, but no attempts were made to isolate them in a pure state. Compounds **7** were obviously formed through the aromatization of intermediate **4** followed by the double bond migration in the products **6**.

Table 1 Compounds prepared

Entry	Substrate	Reagent	X, Y, *n*	Product	Yield/%
1	**1a**	**2a**	H, -, 1	**3a**	53
2	**1a**	**2b**	H, -, 2	**3b**	69
3	**1c**	**2a**	Cl, -, 1	**3c**	90
4	**1d**	**2a**	Br, -, 1	**3d**	90
5	**3a**	BF_3Et_2O	H	*cis*-**5a**	14
				trans-**5a**	27
6	**3b**	BF_3Et_2O	H, -, 2	**5b**	30 [12]
7	**3c**	BF_3Et_2O	Cl, -, 1	*cis*-**5c**	41
8	*cis*-**5a**	NBS	Br, -, 1	*cis*-**5d**	69
9	*trans*-**5a**	NBS	Br, -, 1	*trans*-**5d**	77
10	*cis*-**5b**	NBS	Br, -, 2	*cis*-**5e**	79
11	*trans*-**5b**	NBS	Br, -, 2	*trans*-**5e**	75
12	*trans*-**5d**	**11a**	H, OPh, 1	*trans*-**12a**	71
13	*trans*-**5e**	**11a**	H, OPh, 2	*trans*-**12b**	73
14	*trans*-**5d**	**11b**	H, NO_2, 1	*trans*-**12c**	24
15	*trans*-**5e**	**11b**	H, NO_2, 2	*trans*-**12d**	21
16	*trans*-**5d**	**11c**	H, CF_3, 1	*trans*-**12e**	58
17	*trans*-**5e**	**11c**	H, CF_3, 2	trans-**12f**	59

In our recent paper [19] we suggested a mechanism for the ring closure reaction (**3** → **5**). On the basis of ab initio calculation of the transition state, a two steps mechanism, namely aza-Claisen rearrangement followed by aza-Alder-ene reaction, was recommended (**3** → **4** → **5**). Now we have found further evidence for this mechanism. In the ring closure reaction of **8** (Scheme 2) we isolated the side-product **10**, beside compound **9**, and treated it with BF_3Et_2O at 170 °C for longer time. However, no ring closure product **9** could be isolated. We observed only some degradation.

Finally, we investigated the reactivity of the bromo compounds in a Suzuki coupling reaction (Scheme 3). The reaction of compounds **5d**, **5e** with 4-phenoxyphenylboronic acid (**11a**), in the presence of tetrakis(triphenylphosphine)palladium (0) catalyst and in DMF, afforded compounds **12a**, **12b** in good yield (entries 12, 13). Using a similar condition, the reaction between compounds **5d**, **5e** and 3-nitrophenylboronic acid (**11b**) afforded the wanted products **12c**, **12d**, but the yields were poor (entries 14, 15). The reaction of these bromo compounds **5d**, **5e** with 4-(trifluoromethyl)phenylboronic acid (**11c**) also furnished the coupling products **12e**, **12f** in acceptable yields (entries 16, 17).

Experimental

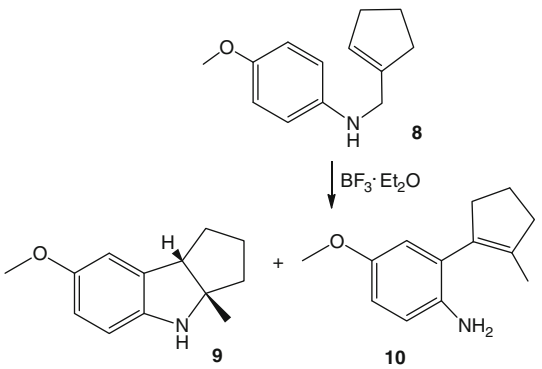
Solvents were used as received from commercial suppliers, and no further attempts were made to purify or dry them. Melting points were determined on a Büchi apparatus and

Table 2 Selected data for stereochemical assignments

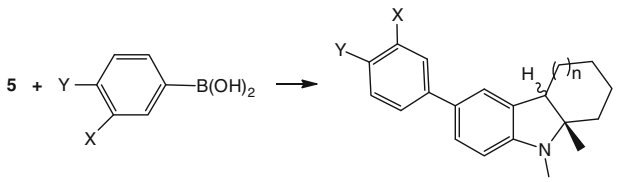
Compound	^{1}H NMR			^{13}C NMR			Ring fusion
	δ_{CH_3}/ppm	δ_{CH}/ppm	NOESY[a]	δ_{CH_3}/ppm	δ_{CH_2}/ppm	γ-effect	CH_3/CH
cis-**5a**	1.24	2.73	+	21.83	24.56		*cis*
trans-**5a**	0.68	2.52	−	10.73	21.48	+	*trans*
cis-**5b**[b]	1.03	2.88	+	24.20	32.02		*cis*
trans-**5b**[b]	0.83	3.06	−	12.76	22.79	+	*trans*
cis-**5d**	1.23	2.75	+	21.74	24.45		*cis*
trans-**5d**	0.69	2.56	−	10.86	21.24	+	*trans*
cis-**5e**	1.03	2.92	+	24.62	31.72		*cis*
trans-**5e**	0.83	3.08	−	12.86	22.47	+	*trans*

[a] Cross peak in NOESY spectrum

[b] See Ref. [19]



Scheme 2



11	Y	X
a	OPh	H
b	H	NO_2
c	CF_3	H

12	Y	X	n
a	OPh	H	1
b	OPh	H	2
c	H	NO_2	1
d	H	NO_2	2
e	CF_3	H	1
f	CF_3	H	2

Scheme 3

are corrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 500 and 125 MHz, respectively. All NMR spectra are reported in ppm relative to TMS. MS spectra were conducted on a Agilent 6140 quadrupole LC/MS instrument. Merck precoated silica gel 60 F_{254} plates were used for TLC and Kieselgel 60 for column chromatography. *N*-Methylbenzenamine, 4-methoxy-*N*-methylbenzenamine, 4-chloro-*N*-methylbenzenamine, and 4-bromo-*N*-methylbenzenamine were obtained from commercial sources and were of the higher grade available. The preparation of compounds **3b** and **5b** has already been described [19].

General procedure for preparation of cycloalkylmethyl-N-methylbenzeneamine ***3***

Compound **2** (16 mmol) was added dropwise to a stirred mixture of **1** (16 mmol) and 2.5 g NaI in 20 cm^3 acetone. The resultant solution was stirred at rt for 2 h. The NaCl precipitated was filtered off and the filtrate was diluted with 50 cm^3 CH_2Cl_2. After washing with 20 cm^3 water, the solution was dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography (hexane:acetone = 9:1).

N-(1-Cyclohexenylmethyl)-N-methylbenzenamine (**3a**, $C_{14}H_{19}N$)

Light yellow oil; TLC (hexane:acetone = 9:1): $R_f = 0.56$; ^{1}H NMR ($CDCl_3$): $\delta = 1.59$ (m, 4H, 2 CH_2), 2.00 (m, 4H, 2 CH_2), 2.90 (s, 3H, CH_3), 3.70 (s, 2H, N–CH_2), 5.52 (m, 1H, CH=), 6.70 (m, $J = 7.95$ Hz, 2H, ArH), 6.72 (t, $J = 7.2$ Hz, 1H, ArH), 7.22 (t, $J = 7.5$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.06$, 22.76, 22.85, 25.19, 26.67, 38.21, 59.29, 112.34, 116.08, 122.46, 129.24, 134.08 ppm.

4-Chloro-N-(1-cyclohexenylmethyl)-N-methylbenzenamine (**3c**, $C_{14}H_{18}ClN$)

Yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.53$; GC: $t_R = 10.22$ min; ^{1}H NMR ($CDCl_3$): $\delta = 1.61$ (m, 4H, 2 CH_2), 1.86 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.89 (s, 3H, CH_3), 3.71 (s, 2H, N–CH_2), 5.48 (m, 1H, CH=), 6.61 (m, 2H, ArH), 7.12 (d, $J = 9.0$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.71$, 22.79, 25.14, 26.63, 38.62, 59.40, 113.53, 122.89, 128.97, 133.54 ppm.

4-Bromo-N-(1-cyclohexenylmethyl)-N-methylbenzenamine (**3d**, $C_{14}H_{18}BrN$)

Light yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.55$; GC: $t_R = 14.2$ min; ^{1}H NMR ($CDCl_3$): $\delta = 1.65$ (m, 4H, 2 CH_2), 1.88 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.89 (s, 3H, CH_3), 3.73 (s, 2H, N-CH_2), 5.49 (m, 1H, CH =), 6.56 (d, $J = 9.0$ Hz, 2H, ArH), 7.25 (d, $J = 9.0$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 22.07$, 24.31, 25.74, 30.64, 38.68, 57.58, 113.61, 121.25, 131.23, 133.49 ppm.

5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-4bH-carbazole (**5a**, $C_{14}H_{19}N$)

To a hot solution (160 °C) of 1 g **3a** (4.8 mmol) in 30 cm^3 sulfolane was added 0.69 g BF_3Et_2O (0.6 cm^3, 4.8 mmol) and the resulting mixture was stirred at 170 °C for 1.5 h. After cooling, 30 cm^3 water was added and the reaction mixture was extracted three times with CH_2Cl_2 (60 cm^3 each). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography to yield a mixture of compounds **5a** and **7a**. This mixture was dissolved in 30 cm^3 ether and 0.5 cm^3 phenyl isocyanate (4.3 mmol) was added, and the reaction mixture was stirred for overnight. The excess of phenyl isocyanide was decomposed by addition of 10 cm^3 water. The layers were separated and the organic layer was dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by column chromatography to give *cis*- and *trans*-isomers of compound **5a**.

cis-Isomer: yield 0.14 g (14 %); light yellow oil; ^{1}H NMR (DMSO-d_6): $\delta = 1.14$ (m, 1H, C_3–H), 1.20 (m, 1H, C_2–H), 1.24 (s, 3H, CH_3), 1.27 (m, 1H, C_1–H), 1.40 (m, 2H, C_1–H, C_3–H), 1.42 (m, 1H, C_2–H), 1.68 (m, 1H, C_4–H), 1.91 (m, 1H, C_4–H), 2.55 (s, 3H, N–CH_3), 2.73 (t, $J = 4.5$ Hz, 1H, C_{4a}–H), 6.37 (d, $J = 7.5$ Hz, 1H, C_8–H), 6.58 (t, $J = 7.5$ Hz, 1H, C_6-H), 6.96 (d, $J = 7.0$ Hz, 1H, C_5-H), 6.98 (t, $J = 7.5$ Hz, 1H, C_7-H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 21.55$ (C-2), 21.83 (CH_3), 22.04 (C-3), 24.56 (C-4), 28.05 (CH_3), 29.60 (C-1), 46.79 (C-4a), 67.18 (C-9a), 106.99 (C-8), 117.08 (C-6), 121.89 (C-5), 127.24 (C-7), 132.10 (C-4b), 151.62 (C-8a) ppm; MS: *m/z* (%) = 201 (M^+, 23), 186 (M^+-CH_3, 36), 158 (M^+-C_3H_7, 100), 144 (M^+-C_4H_9, 30).

trans-Isomer: yield 0.27 g (27 %); yellow oil; ^{1}H NMR (DMSO-d_6): $\delta = 0.68$ (s, 3H, CH_3), 1.38 (m, 1H, C_3–H), 1.42 (m, 1H, C_2–H), 1.46 (m, 1H, C_4–H), 1.58 (m, 1H, C_1–H), 1.70 (m, 1H, C_2–H), 1.82 (m, 1H, C_3–H), 1.94 (m, 1H, C_1–H), 2.06 (m, 1H, C_4–H), 2.52 (br. s, 1H), 2.55 (s, 3H, N–CH_3), 6.41 (d, $J = 7.5$ Hz, 1H, C_8–H), 6.59 (t, $J = 7.5$ Hz, 1H, C_6–H), 6.93 (d, $J = 7.0$ Hz, 1H, C_5–H), 6.98 (t, $J = 7.5$ Hz, 1H, C_7–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 10.73$ (CH_3), 21.48 (C-2), 22.01 (C-2), 25.63 (C-3), 28.93 (CH_3), 35.21 (C-1), 51.33 (C-4a), 69.90 (C-9a), 106.91 (C-8), 117.21 (C-6), 120.29 (C-5), 126.85 (C-7), 132.12 (C-4b), 151.91 (C-8a) ppm.

cis-3-Chloro-5,6,7,8,8a,9-hexahydro-8a,9-dimethyl-4bH-carbazole (**5c**, $C_{14}H_{18}ClN$)

A mixture of 2 g **3c** (8.5 mmol) and 1.31 g BF_3Et_2O (1.1 cm^3, 8.5 mmol) in 40 cm^3 sulfolane was heated at 160 °C for 2 h under Ar. After cooling 40 cm^3 water was added and the reaction mixture was extracted three times with CH_2Cl_2 (40 cm^3 each). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography to give a mixture of **5c** and **7c**. This mixture was dissolved in 50 cm^3 ether and after adding 9.8 g phenyl isocyanate (9 cm^3, 7.5 mmol) the resulting solution was stirred at rt overnight. The excess of phenyl isocyanate was decomposed by 20 cm^3 adding water, the layers were separated, and the organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by column chromatography to give **5c** (0.84 g, 41 %). ^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (s, 3H, CH_3), 1.40–2.15 (m, 8H, 4 CH_2), 2.61 (s, 3H, CH_3), 6.30 (d, $J = 3.3$ Hz, 1H, ArH), 6.94 (m, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.79$, 22.20, 23.47, 25.04, 28.44, 30.14, 47.38, 68.18, 107.86, 122.73, 127.03, 134.76, 150.55 ppm; MS: *m/z* (%) = 235 (M^+, 100), 101 (M^+-$C_6H_{13}ClN$, 15).

3-Bromo-5,6,7,8,8a,9-hexahydro-8a,9-dimethyl-4bH-carbazole (**5d**, $C_{14}H_{18}BrN$)

To a cooled (−20 °C) solution of 1 g compound **5a** (5 mmol) in 20 cm^3 ether was added 0.89 g *N*-bromosuccinimide (5 mmol) and the resulting mixture was stirred at rt for 0.5 h. The reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and evaporated in vacuo, and the residue was purified by column chromatography to yield **5d**.

cis-Isomer: yield 0.96 g (69 %); light yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.44$; ^{1}H NMR (DMSO-d_6): $\delta = 1.13$ (m, 1H, C_6–H), 1.17 (m, 1H, C_7–H), 1.23 (s, 3H, CH_3), 1.27 (m, 1H, C_8–H), 1.41 (m, 3H, C_6–H, C_7–H, C_8–H), 1.67 (m, 1H, C_5–H), 1.88 (m, 1H, C_5–H), 2.55 (s, 3H, N–CH_3), 2.75 (t, $J = 4.5$ Hz, 1H, C_{4b}–H), 6.33 (d, $J = 8.0$ Hz, 1H, C_1–H), 7.10 (s, 1H, C_4–H), 7.12 (d, $J = 8.0$ Hz, 1H, C_2–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 21.34$ (C-7), 21.74 (CH_3), 22.00 (C-6), 24.45 (C-5), 27.94 (N–CH_3), 29.72 (C-8), 46.69 (C-4b), 67.59 (C-8a), 107.87 (C-3), 108.62 (C-1), 124.90 (C-4), 129.67 (C-2), 135.09 (C-4a), 150.83 (C-9a) ppm; MS: *m/z* (%) = 279 (M^+, 26), 264 (M^+-CH_3, 15), 236 (M^+-C_3H_7, 100), 157 (M^+-C_3H_7Br, 60).

trans-Isomer: yield 1.08 g (77 %); yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.42$; ^{1}H NMR (DMSO-d_6): $\delta = 0.69$ (s, 3H, CH_3), 1.36 (m, 1H, C_6–H), 1.43 (m, 2H, C_5–H, C_7–H), 1.57 (m, 1H, C_8–H), 1.68 (m, 1H, C_7–H), 1.81 (m, 1H, C_6–H), 1.93 (m, 1H, C_8–H), 2.06 (m, 1H, C_5–H), 2.55 (s, 3H, N–CH_3), 2.56 (m, 1H, C_{4b}–H), 6.37 (d, $J = 8.0$ Hz, 1H, C_1–H), 7.06 (s, 1H, C_4–H), 7.13 (d,

$J = 8.0$ Hz, 1H, C_2–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 10.86$ (CH_3), 21.24 (C-5), 21.92 (C-7), 25.51 (C-6), 28.83 (CH_3), 35.08 (C-8), 51.33 (C-4b), 70.34 (C-8a), 108.32 (C-3), 108.62 (C-1), 124.03 (C-4), 129.26 (C-2), 135.02 (C-4a), 151.17 (C-9a) ppm.

As a side product 1,3-dibromo-5,6,7,8,8a,9-hexahydro-8a,9-dimethyl-4b*H*-carbazole ($C_{14}H_{17}Br_2N$) has been obtained as light green gum. *cis*-Isomer: ^{1}H NMR (DMSO-d_6): $\delta = 1.18$ (m, 2H, C_6–H, C_7–H), 1.24 (s, 3H, CH_3), 1.32 (m, 1H, C_8–H), 1.42 (m, 2H, C_6–H, C_7–H), 1.50 (m, 1H, C_8–H), 1.67 (m, 1H, C_5–H), 1.88 (m, 1H, C_5–H), 2.75 (m-t, $J = 5$ Hz, 1H, C_{4b}–H), 2.96 (s, 3H, CH_3), 7.14 (br. s, 1H, C_4–H), 7.29 (br. s, 1H, C_2–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 21.26$ (C-7), 21.75 (CH_3), 21.79 (C-6), 24.25 (C-5), 30.11 (C-8), 30.57 (CH_3), 46.54 (C-4b), 68.47 (C-8a), 100.85 (C-1), 108.24 (C-4), 124.52 (C-4), 133.97 (C-2), 138.37 (C-4a), 146.99 (C-9a). *trans*-Isomer: ^{1}H NMR (DMSO-d_6): $\delta = 0.77$ (s, 3H, CH_3), 1.33 (m, 1H, C_6–H), 1.43 (m, 2H, C_7–H), 1.52 (m, 1H, C_8–H), 1.70 (m, 1H, C_7–H), 1.81 (m, 1H, C_6–H), 1.94 (m, 1H, C_8–H), 2.06 (m, 1H, C_5–H), 2.54 (br. s, 1H, C_{4b}–H), 2.96 (s, 3H, CH_3), 7.08 (br. s, 1H, C_4–H), 7.29 (br. s, 1H, C_2–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 11.50$ (CH_3), 21.15 (C-5), 21.99 (C-7), 25.32 (C-6), 31.20 (CH_3), 34.70 (C-8), 51.10 (C-4b), 70.95 (C-8a), 101.05 (C-1), 108.57 (C-3), 123.53 (C-4), 133.54 (C-2), 138.26 (C-4a), 147.08 (C-9a) ppm.

2-Bromo-5,5a,6,7,8,9,10,10a-octahydrocyclohepta-[b]indole (**5e**, $C_{15}H_{20}BrN$)

To a stirred solution of 1 g **5b** (4.7 mmol) in 40 cm^3 ether was added 0.83 g *N*-bromosuccinimide (4.7 mmol) at −20 °C and the resultant mixture was stirred at rt for 0.5 h. The precipitate was filtered off, the solvent was evaporated in vacuo, and the residue was purified by column chromatography to give **5e**.

cis-Isomer: yield 1.1 g (79 %); yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.43$; ^{1}H NMR (DMSO-d_6): $\delta = 1.03$ (s, 3H, C_{5a}-CH_3), 1.41 (m, 6H, C_7–H, C_8–H, C_9–H), 1.60 (m, 1H, C_{10}–H), 1.72 (m, 3H, C_6–H, C_{10}–H), 2.57 (s, 3H, N–CH_3), 2.92 (m, 1H, C_{10a}–H), 6.20 (d, $J = 8.2$ Hz, 1H, C_4–H), 7.05 (s, 1H, C_1–H), 7.07 (dd, $J = 8.2$, 1.0 Hz, 1H, C_3–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 23.72$ (C-7), 24.62 (C_{5a}–CH_3), 27.12 (C-9), 27.60 (N–CH_3), 30.89 (C-8), 31.72 (C-10), 35.62 (C-6), 52.38 (C-10a), 69.37 (C-5a), 106.39 (C-2), 106.42 (C-4), 126.51 (C-1), 129.95 (C-3), 135.02 (C-10b), 150.16 (C-4a) ppm.

trans-Isomer: yield 1.04 g (75 %); yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.40$; ^{1}H NMR (DMSO-d_6): $\delta = 0.83$ (s, 3H, C_{5a}-CH_3), 1.30 (m, 1H, C_7–H), 1.48 (m, 3H, C_8–H, C_9–H, C_{10}–H), 1.51 (m, 1H, C_6–H), 1.67 (m, 1H, C_8–H), 1.85 (m, 1H, C_7–H), 1.89 (m, 1H, C_9–H), 2.06 (m, 1H, C_6–H), 2.18 (m, 1H, C_{10}–H), 2.52 (s, 3H, N–CH_3), 3.08 (m, 1H, C_{10a}–H), 6.24 (d, $J = 8.2$ Hz, 1H, C_4–H), 6.97 (s, 1H, C_1–H), 7.09 (dd, $J = 8.2$, 1.0 Hz, 1H, C_3–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 12.86$ (C_{5a}–CH_3), 22.47 (C-10), 25.28 (C-8), 25.46 (C-9), 26.58 (C-7), 28.38 (N–CH_3), 38.72 (C-6), 47.77 (C-10a), 73.11 (C-5a), 107.38 (C-4), 107.59 (C-2), 124.61 (C-1), 129.53 (C-3), 135.60 (C-10b), 150.64 (C-4a) ppm.

General procedure for the preparation of compounds ***12***

To a mixture of boronic acid **11** (1.07 mmol, 1.2 equiv.) and 58 mg tetrakis(triphenylphosphine) palladium (0) catalyst (0.05 mmol, 0.05 equiv.) in 2 cm^3 2 M K_2CO_3 solution was added the corresponding bromo compound **5** (0.89 mmol) in 2 cm^3 DMF and the resultant mixture was heated under reflux for 2 h. After cooling, 5 cm^3 saturated $NaHCO_3$ was added and the reaction mixture was extracted three times with ether (15 cm^3 each). The combined ethereal solution was dried ($MgSO_4$), the solvent evaporated in vacuo, and the residue was purified by column chromatography.

trans-5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-3-(4-phenoxyphenyl)-4bH-carbazole (**12a**, $C_{26}H_{27}NO$)

Light yellow crystals; m.p.: 91–92 °C; TLC (hexane:EtOAc = 15:1): $R_f = 0.64$; ^{1}H NMR ($CDCl_3$): $\delta = 0.80$ (s, 3H, CH_3), 1.46 (m, 2H, C_6–H, C_7–H), 1.56 (m, 1H, C_5–H), 1.72 (m, 1H, C_8–H), 1.77 (m, 1H, C_7–H), 1.91 (m, 1H, C_6–H), 1.96 (m, 1H, C_8–H), 2.15 (m, 1H, C_5–H), 2.68 (s, 3H, CH_3), 2.72 (m, 1H, C_{4b}–H), 6.49 (d, $J = 8.0$ Hz, 1H, C_1–H), 7.03 (d, $J = 8.5$ Hz, 4H, $C_{3'}$–H, $C_{5'}$–H, $C_{2''}$–H, $C_{6''}$–H), 7.08 (t, $J = 8.0$ Hz, 1H, $C_{4''}$–H), 7.20 (br. s, 1H, C_4–H), 7.29 (d, $J = 8.0$ Hz, 1H, C_2–H), 7.33 (t, $J = 8.0$ Hz, 2H, $C_{3''}$–H, $C_{5''}$–H), 7.50 (d, $J = 8.5$ Hz, 2H, $C_{2'}$–H, $C_{6'}$–H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.04$ (CH_3), 21.84 (C-5), 22.40 (C-7), 25.96 (C-6), 29.15 (CH_3), 35.61 (C-8), 51.69 (C-4b), 70.63 (C-8a), 107.24 (C-1), 118.58 (C-2″, C-6″), 119.27 (C-3′, C-5′), 119.91 (C-4), 122.95 (C-4″), 125.49 (C-2), 127.67 (C-2′, C-6′), 129.68 (C-3″, C-5″), 129.79 (C-3), 133.44 (C-4a), 137.46 (C-1′), 151.30 (C-9a), 155.46 (C-4′), 157.66 (C-1″) ppm; MS: *m/z* (%) = 369 (M^+, 44), 354 (M^+-CH_3, 100), 312 (M^+-C_4H_9, 13).

trans-5,5a,6,7,8,9,10,10a-Octahydro-5,5a-dimethyl-2-(4-phenoxyphenyl)-cyclohepta[b]indole (**12b**, $C_{27}H_{29}NO$)

White solid; m.p.: 95–96 °C; TLC (hexane:EtOAc = 15:1): $R_f = 0.64$; ^{1}H NMR ($CDCl_3$): $\delta = 0.95$ (s, 3H, CH_3), 1.37 (m, 1H, C_7–H), 1.56 (m, 2H, C_8–H, C_9–H), 1.68 (m, 2H, C_6–H, C_{10}–H), 1.76 (m, 1H, C_8–H), 1.96 (m, 1H, C_7–H), 2.01 (m, 1H, C_9–H), 2.12 (m, d-t, $J = 13.0$, 4.0 Hz, 1H, C_6–H), 2.31 (m, 1H, C_{10}–H), 2.65 (s, 3H, CH_3), 3.23 (dd, $J = 12.0$, 4.5 Hz, 1H, C_{10a}–H), 6.37 (d, $J = 8.0$ Hz, 1H, C_4–H), 7.02 (d, $J = 8.5$ Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.08 (t,

$J = 8.0$ Hz, 1H, $C_{4''}$–H), 7.16 (br. s, 1H, C_1–H), 7.27 (br. s, 1H, C_3–H), 7.32 (t, $J = 8.0$ Hz, 2H, $C_{3''}$–H, $C_{5''}$–H), 7.48 (d, $J = 8.5$ Hz, 2H, $C_{2'}$–H, $C_{6'}$–H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.15$ (CH_3), 23.12 (C-10), 25.78 (C-8), 26.06 (C-9), 27.07 (C-7), 28.69 (CH_3), 39.40 (C-6), 48.22 (C-10a), 73.41 (C-5a), 106.03 (C-4), 118.58 (C-2″, C-6″), 119.25 (C-3″, C-5″), 120.67 (C-1), 122.93 (C-4″), 125.89 (C-3), 127.40 (C-2′, C-6′), 129.67 (C-3″, C-5″), 129.76 (C-2), 133.86 (C-10b), 137.54 (C-1′), 150.83 (C-4a), 155.35 (C-4′), 157.67 (C-1″) ppm; MS: *m/z* (%) = 383 (M^+, 50), 368 (M^+-CH_3, 100), 312 (M^+-C_5H_{11}, 13).

trans-5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-3-(3-nitrophenyl)-4bH-carbazole (**12c**, $C_{20}H_{22}N_2O_2$)
Yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.28$; ^{1}H NMR ($CDCl_3$): $\delta = 0.82$ (s, 3H, CH_3), 1.49 (m, 1H, C_7–H), 1.59 (m, 1H, C_5–H), 1.73 (m, 1H, C_8–H), 1.80 (m, 1H, C_7–H), 1.94 (m, 1H, C_6–H), 1.98 (m, 1H, C_8–H), 2.19 (m, 1H, C_5–H), 2.70 (s, 3H, CH_3), 2.73 (m, 1H, C_{4b}–H), 6.51 (d, $J = 8.0$ Hz, 1H, C_1–H), 7.25 (d, $J = 2.8$ Hz, 1H, C_4–H), 7.36 (d, $J = 8.0$ Hz, 1H, C_2–H), 7.51 (t, $J = 8.0$ Hz, 1H, $C_{5'}$–H), 7.86 (d, $J = 8.0$ Hz, 1H, $C_{6'}$–H), 8.06 (d, $J = 8.0$ Hz, 1H, $C_{4'}$–H), 8.40 (s, 1H, $C_{2'}$–H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.19$ (CH_3), 21.81 (C-5), 22.36 (C-7), 25.93 (C-6), 28.96 (CH_3), 35.55 (C-8), 51.69 (C-4b), 70.72 (C-8a), 107.17 (C-1), 119.92 (C-4), 120.41 (C-4′), 120.94 (C-2′), 126.16 (C-2), 127.87 (C-3), 129.38 (C-5′), 132.13 (C-6′), 133.79 (C-4a), 143.73 (C-1′), 148.77 (C-3′), 152.49 (C-9a) ppm.

trans-5,5a,6,7,8,9,10,10a-Octahydro-5,5a-dimethyl-2-(3-nitrophenyl)cyclohepta[b]indole (**12d**, $C_{21}H_{24}N_2O_2$)
Light yellow oil; TLC (hexane:EtOAc = 15:1): $R_f = 0.28$; ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (s, 3H, CH_3), 1.38 (m, 1H, C_7–H), 1.58 (m, 2H, C_8–H, C_9–H), 1.70 (m, 2H, C_6–H, C_{10}–H), 1.78 (m, 1H, C_8–H), 1.96 (m, 1H, C_7–H), 2.03 (m, 1H, C_9–H), 2.12 (m, 1H, C_6–H), 2.32 (m, 1H, C_{10}–H), 2.68 (s, 3H, N–CH_3), 3.25 (dd, $J = 12.5$, 4.8 Hz, 1H, C_{10a}–H), 6.39 (d, $J = 8.0$ Hz, 1H, C_4–H), 7.21 (s, 1H, C_1–H), 7.35 (d, $J = 8.0$ Hz, 1H, C_3–H), 7.50 (t, $J = 8.0$ Hz, 1H, $C_{5'}$–H), 7.83 (d, $J = 8.0$ Hz, 1H, $C_{6'}$–H), 8.04 (dd, $J = 8.0$, 1.2 Hz, 1H, $C_{4'}$–H), 8.37 (s, 1H, $C_{2'}$–H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.35$ (CH_3), 23.08 (C-10), 25.71 (C-8), 25.97 (C-9), 27.00 (C-7), 28.51 (N–CH_3), 39.26 (C-6), 48.14 (C-10a), 73.56 (C-5a), 106.03 (C-4), 120.26 (C-4′), 120.63 (C-1), 120.77 (C-2′), 126.54 (C-3), 127.38 (C-2), 129.36 (C-5′), 131.98 (C-6′), 134.29 (C-10b), 143.72 (C-1′), 148.75 (C-3′), 151.92 (C-4a) ppm; MS: *m/z* (%) = 336 (M^+, 15), 247 (M^+-$C_3H_7NO_2$, 100), 245 (10), 145 (15), 126 (22), 105 (15).

trans-5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-3-[4-(trifluoromethyl)phenyl]-4bH-carbazole (**12e**, $C_{21}H_{22}F_3N$)
Light yellow crystals; m.p.: 45–47 °C; TLC (hexane:EtOAc = 15:1): $R_f = 0.42$; ^{1}H NMR (acetone-d_6): $\delta = 0.82$ (s, 3H, CH_3), 1.47 (m, 1H, C_6–H), 1.51 (m, 1H, C_7–H), 1.61 (m, 1H, C_5–H), 1.69 (m, 1H, C_8–H), 1.78 (m, 1H, C_7–H), 1.92 (m, 1H, C_6–H), 2.03 (m, 1H, C_8–H), 2.21 (m, 1H, C_5–H), 2.68 (m, 1H, C_{4b}–H), 2.70 (s, 3H, N–CH_3), 6.54 (d, $J = 8.0$ Hz, 1H, C_1–H), 7.31 (s, 1H, C_4–H), 7.44 (d, $J = 8.0$ Hz, 1H, C_2–H), 7.69 (d, $J = 8.2$ Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.79 (d, $J = 8.2$ Hz, 2H, $C_{2'}$–H, $C_{6'}$–H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 11.37$ (CH_3), 22.48 (C-5), 23.13 (C-7), 26.78 (C-6), 29.13 (N–CH_3), 36.36 (C-8), 52.66 (C-4b), 71.34 (C-8a), 107.92 (C-1), 120.68 (C-4), 125.83 (CF_3, q, $^1J_{C\text{-}F} = 270$ Hz), 126.44 (q, $^3J_{C\text{-}F} = 3.6$ Hz, C-3′, C-5′), 127.12 (C-2), 127.27 (C-2′), 127.94 (q, $^2J_{C\text{-}F} = 31.7$, C-4′), 129.19 (C-3), 134.43 (C-4a), 146.76 (C-1′), 153.66 (C-9a) ppm; MS: *m/z* (%) = 345 (M^+, 25), 330 (M^+-CH_3, 100), 312 (M^+-C_3H_7, 10), 288 (M^+-C_4H_9, 22).

trans-5,5a,6,7,8,9,10,10a-Octahydro-5,5a-dimethyl-2-[4-(trifluoromethyl)phenyl]cyclohepta[b]indole (**12f**, $C_{22}H_{24}F_3N$)
Yellow solid; m.p.: 42–43 °C; TLC (hexane:EtOAc = 15:1): $R_f = 0.43$; ^{1}H NMR (DMSO-d_6): $\delta = 0.89$ (s, 3H, CH_3), 1.33 (m, 1H, C_8–H), 1.54 (m, 2H, C_7–H, C_9–H), 1.57 (m, 2H, C_6–H, C_{10}–H), 1.70 (m, 1H, C_7–H), 1.90 (m, 1H, C_8–H), 1.95 (m, 1H, C_9–H), 2.12 (m, 1H, C_6–H), 2.35 (m, 1H, C_{10}–H), 2.62 (s, 3H, N–CH_3), 3.16 (m, 1H, C_{10a}–H), 6.42 (d, $J = 8.0$ Hz, 1H, C_4–H), 7.30 (br. s, 1H, C_1–H), 7.40 (d, $J = 8.0$ Hz, 1H, C_3–H), 7.68 (d, $J = 8.2$ Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.77 (d, $J = 8.2$ Hz, 2H, $C_{2'}$–H, $C_{6'}$–H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 13.23$ (CH_3), 22.68 (C-10), 25.36 (C-7), 25.56 (C-9), 26.66 (C-8), 28.38 (N–CH_3), 38.80 (C-6), 47.79 (C-10a), 73.08 (C-5a), 106.04 (C-4), 120.47 (C-1), 124.78 (q, $^1J_{CF} = 271$ Hz, CF_3), 125.67 (q, $^3J_{CF} = 3.6$ Hz, C-3′, C-5′), 125.75 (q, $^2J_{CF} = 30.3$ Hz, C-4′), 126.12 (C-2′, C-6′), 126.54 (C-3), 127.04 (C-2), 133.79 (C-10b), 145.20 (C-1′), 151.95 (C-4a) ppm.

*Attempted cyclization of compound **10***

Compound **10** was treated with an equivalent amount of BF_3Et_2O in sulfolane at 170 °C for 5 h. After cooling water was added and the mixture was extracted with CH_2Cl_2. The solvent was evaporated in vacuo and the residue was purified by column chromatography to get back the unchanged starting compound **10** (82 %).

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