2-Nitro Derivatives of the Alkaloid Epibatidine [1])

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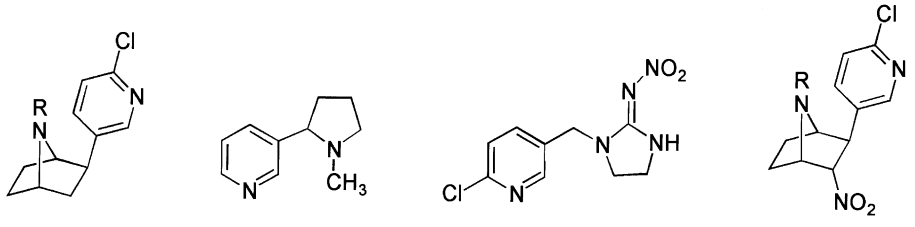
Abstract. 2-Nitro-3-aryl-7-azabicyclo[2.2.1]heptanes **4**, **18** have been synthesized by [1,3]-dipolar cycloadditions of cyclic unstabilized azomethine ylides **14** to β-nitro(hetero) styrenes **15**, **17**; in case of the pyridyl group the cycloadditions proceed stereoselectively to the *exo*-hetaryl products **4b**,**c**. Introduction of an *N*-protecting formimidoyl group allows the regioselective synthesis of the *N*-substituted 2,5-bis(trimethylsilyl)pyrrolidines **12**, **13** in high yields. The ylides **14** were generated by Ag^+ mediated oxidation of these precursors.

Epibatidine (**1a**) has been isolated as a trace component from the skin of the Ecuadoran poison frog *Epipedobates tricolor*. It was shown to be a novel, highly active neurotoxin displaying its mode of action through nicotinic acetylcholine receptors (nAchR) [2]. Since it is very rare in nature, several syntheses have been published [3–11]. Epibatidine is not only a very effective analgesic, but can also act as an insecticide [12]. This is reminiscent of a classical application of nicotine (**2**) [13], being structurally related to **1**, but especially of the very active, novel insecticide imidaclopride (**3**) [14], also being an excellent agonist of nAchR´s. The high activity of imidaclopride is structurally depending on both, the basic nitrogen centers and the electron withdrawing nitro group. It is known, that *N*-methylepibatidine (**1b)** and **1a** are comparably active as analgesics[15].

Therefore, we wanted to combine important structural units of both **1** and **3**, thus possibly leading to biologically even more active compounds, *e.g*. **4a**,**b**. A reliable synthetic pathway had to be developed.

A first synthesis of **4c** (R = Bn) has been published by Pandey *et al*. [16, 17], by [1,3]-dipolar cycloaddition of the β-nitroheterostyrene **15** with the azomethine ylide **14** generated by oxidation of 2,5-bis(trimethylsilyl)-*N*-benzylpyrrolidine (**12**) being the key step. We report here a reliable alternative approach to the precursors of the azomethine ylides *via* formamidines.

The published procedure employs the BOC-group as an α-activating group for the starting pyrrolidine. The lithiation site of 2-trimethylsilyl-*N*-BOC-pyrrolidine (**5**) is strictly dependent on the reaction temperature; at –78 °C it was proven by us to be the 2-position by reacting the anion of **5** with dimethyl disulfide, which resulted in solely the 2,2-disubstituted product **6** after chromatographic work-up. 2-Methyl-*N*-BOC-pyrrolidine has been published to be lithiated in the 5-position by Beak *et al*. [18], who indicated that steric effects are responsible for this effect. A TMS group apparently stabilizes an α-carbanion to such an extent that the steric effect of



1a-b **2** **3** **4a-c**

	R
a	H
b	CH_3

	R
a	H
b	CH_3
c	CH_2Ph

Scheme 1 Epibatidine (**1a**) and structurally related compounds

[1]) Chemistry in the Ambient Field of the Alkaloid Epibatidine. IV [1].

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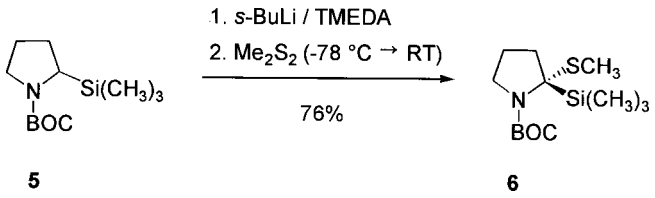
the TMS group plays a less significant role in the deprotonation step at this low temperature. The electrophile, on the other hand, should be sterically compatible with the bulky trimethylsilyl group, such as dimethyl disulfide. At –40 °C the selective 2,5-bis silylation succeeds, although we never reached the reported yield [17] after chromatographic work-up.

Selective debenzylation of **4c** towards the, as expected, biologically active parent system **4a** proved to be impossible, mainly due to the nitro and the chloropyridyl group.

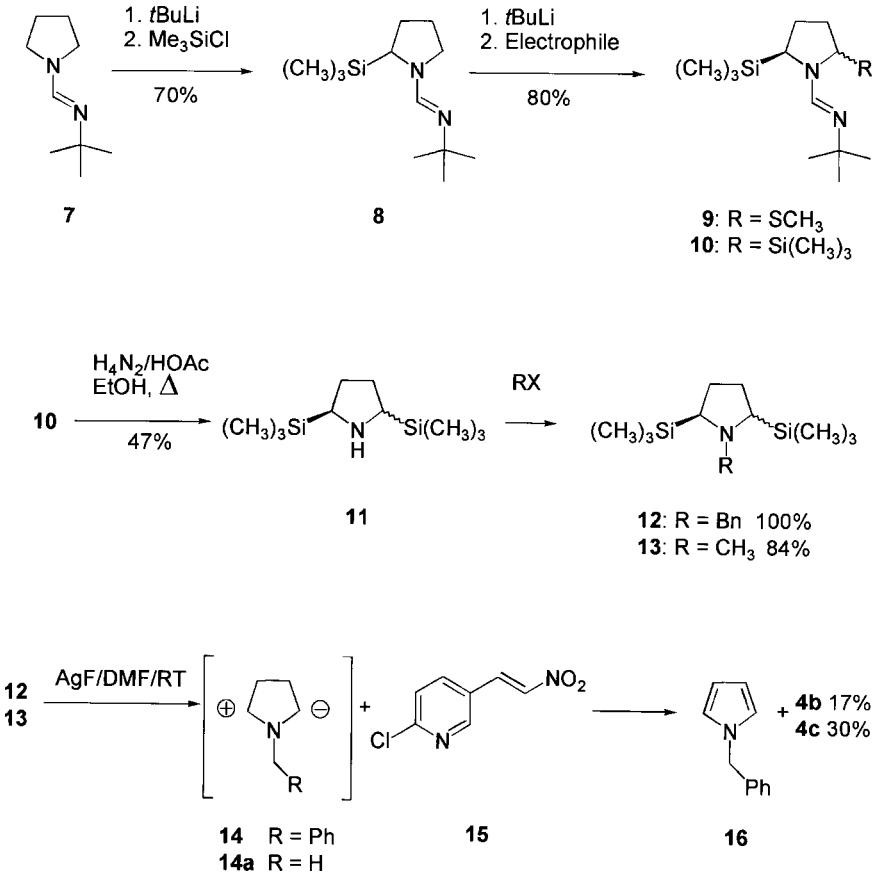


5 **6**

Scheme 2 Regioselective lithiation–substitution of 2-trimethylsilyl-*N*-BOC-pyrrolidine (**5**) at –78 °C

2,5-Disubstituted pyrrolidines have been prepared by repeated lithiation–substitution sequences from *N*-nitrosopyrrolidine [19], a suspect carcinogen. In order to avoid the hazard connected with this compound, we have looked for an alternative activating group [20, 21]. We decided to employ the formamidines, first introduced by A. I. Meyers, for this purpose [22, 23]. We realized the validity of our concept when we treated lithiated 1-[(*tert*-butyl)formimidoyl]-2-trimethylsilylpyrrolidine (**8**) [22] with dimethyl disulfide: the *N*-protected 2-methylthio-5-trimethylsilylpyrrolidine (**9**) was the sole product (1:9 mixture of *cis*- and *trans*-isomers). Consequently, **8** gave the desired 2,5-bis(trimethylsilyl)pyrrolidine (**10**) on reaction with TMSCl in almost complete conversion. In the case of indolines a difference in the site of metalation depending on the *N*-activating group has been noted before [24]. This is also another example of the complex induced proximity effect [25]. Deprotection of **10** with hydrazine in acetic acid/ethanol to **11** and subsequent *N*-benzylation with benzyl bromide to **12** succeeded straightforward.

N-Methylation, on the contrary, could not be effected by methyl iodide or dimethyl sulphate, but was finally achieved with the versatile reagent combination $H_2CO/NaBH_3CN$[26], giving the desired **13** (Scheme 3). With both **12** and **13** in hand we started experiments for the oxidative generation of unstabilized azomethine ylides.



Scheme 3 Synthesis of the 2-nitroepibatidine derivatives **4b**,**c**

A literature survey revealed that there are only a few synthetic methods to generate unstabilized azomethine ylides, and that apparently there is none in which such [1,3]-dipoles are formed bearing β-hydrogens [27–29]. A major problem with the latter is that they are very prone to β-deprotonation, therefore leading to enamines. In our case, the resulting enamine could never be isolated; apparently, it was oxidized further under the reaction conditions to give the corresponding pyrrole. Therefore, *N*-benzylpyrrole (**16**) was a major side product of almost all oxidation methods (AgOAc: traces of **4c**; chloranil, $Cu(OAc)_2$, $(NH_4)_2Ce(NO_3)_6$: **16** sole product) of **12**. Nevertheless, when AgF was used as the oxidant (which could be conveniently prepared *in situ* by addition of first $AgNO_3$ and then TBAF to the reaction medium) in DMF as solvent, substantial amounts of the desired 7-aza-bicyclo[2.2.1]heptanes **4b**,**c** could be isolated after chromatography. These products always proved to be single isomers with the chloropyridyl substituent in *exo*-position, in analogy to the structure of natural epibatidine (**1**). This must be the result of a templating effect of the two nitrogen atoms involved in the reaction, *i.e*. there must be an intermediate complex between a Ag^+-ion, the pyridine and the pyrrolidine nitrogen. Two experimental results account for this hypothesis: Reaction of the dipole **14** with *trans*-β-nitrostyrene (**17**) as the dipolarophile is not diastereoselective; two isomeric *trans*-products **18a**,**b** are formed in a 2:1 ratio, the isomer with the phenyl-group in *exo*-position being the favoured one. Generation of the oxidant AgF by adding solutions of LiF and $AgNO_3$ in DMF to each other was a way to produce both *trans*-diastereomers of **4c**, as shown by GC-MS. In this case, the excess Li-cation apparently is complexed by the pyridine and pyrrolidine nitrogens, thus inhibiting the Ag-cation templating effect. When the reaction is performed in dichloromethane in which AgF is only sparingly soluble, one also finds both diastereomers [17]. Li- and Ag(I)-cations have been shown to exert opposite stereodirecting effects in [1,3]-dipolar cycloadditions with stabilized azomethine ylides [31].

In conclusion, the *N*-(*tert*-butyl)formimidoyl group allows the selective 2,5-bis silylation of pyrrolidine, thus generating a versatile azomethine ylide precursor for the synthesis of 2-nitro-3-(het)aryl-7-azabicyclo[2.2.1] heptanes, being analogs of the trace alkaloid epibatidine. Using 2-chloro-5-*trans*-(β-nitrovinyl)pyridine (**15**) as a cyclophile, the cycloadditions proceed stereoselectively to the *exo*-hetaryl products **4b**,**c**.

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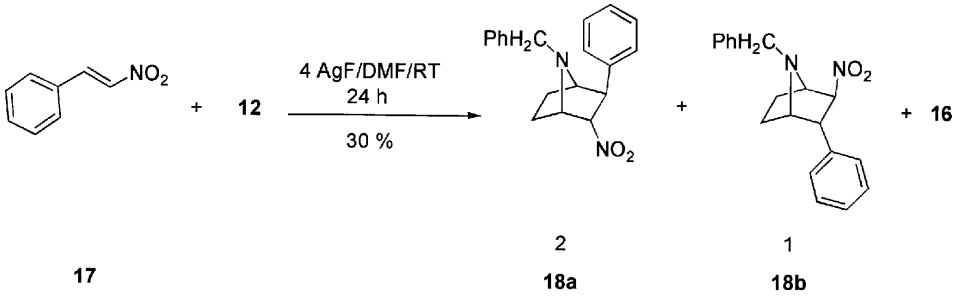
Experimental

NMR-spectra were recorded on a Bruker DPX 200 at 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR) with $CDCl_3$ as solvent and TMS as internal standard. GC-MS was performed with a HP 5890 II (30 m capillary column "HP 5", Helium) coupled to a mass spectrometer HP MS 5989 B. Gaschromatograms were measured with the same apparatus using FID and an HP Integrator. Melting points are uncorrected and were measured on a Büchi apparatus according to Dr. Tottoli. For column chromatography silica gel Merck 60 (70–230 mesh) was employed. TLC was performed with aluminum foils Merck KG 60 F_{254}. Elemental analysis was done by the Institute of Pharmaceutical Chemistry, Braunschweig. Solvents were purified by standard procedures. Starting materials were purchased by Aldrich or Merck-Schuchardt and used as received. All reactions were performed in oven-dried glassware under nitrogen.

2-Methylthio-2-trimethylsilyl-N-BOC-pyrrolidine (**6**)

To a solution of 2-trimethylsilyl-*N*-BOC-pyrrolidine (2.4 g, 10 mmol) (**5**) [32] and TMEDA (3.1 mL, 20 mmol) in anhydrous ether (14 mL) at –78 °C under nitrogen *sec*-BuLi (8.6 mL of a 1.4M solution in cyclohexane, 12 mmol) was added dropwise, and the solution was stirred for 6 h at –78 °C. Dimethyl disulfide (1.13 g, 12 mmol) was added dropwise, and the mixture was allowed to warm to *r.t.* overnight. H_2O (10 mL) was added cautiously, and the phases were separated. The organic layer was washed with H_2O twice, dried ($MgSO_4$), the solvent was evaporated and the residue chro-



Scheme 4 Dipolar cycloaddition of β-nitrostyrene (**17**) with the azomethine ylide **14** in DMF

matographed (SiO_2, Et_2O/petrol ether 1:20). The first fraction afforded **6**, which slowly solidified on standing; *m.p.* 41 °C; yield 2.2 g (76%). – ^{1}H NMR: δ/ppm = 0.17 (s, 9H), 1.43 (s, 9H), 1.75–1.99 (m, 3H), 2.03 (s, 3H), 2.20–2.32 (m, 1H), 3.35–3.55 (m, 2H). – ^{13}C NMR: δ/ppm = –0.7 ($SiMe_3$), 14.0 (SMe), 23.6 (CH_2), 28.9 ($C\underline{Me}_3$), 38.1 (CH_2), 50.0 (C-5), 63.5 (C-2), 79.9 ($\underline{C}Me_3$), 155.5 (NC=O). – MS (70 eV): *m/z* (%) = 242 (15) [M^+ – SCH_3], 218 (18), 186 (20), 170 (10), 142 (3), 73 (21), 57 (100). – HRMS: Calcd. 242.1576; Found 242.1576 [M^+ – SCH_3].

2-Chloro-5-trans-(β-nitrovinyl)pyridine (**15**)

To a stirred mixture of nitromethane (0.68 g, 11.2 mmol) and KOH (10 mg) in methanol (1 mL), 1.41 g (10 mmol) 6-chloropyridine-3-carboxaldehyde [33] (1.41 g, 10 mmol), dissolved in hot methanol (5 mL), was added dropwise. The mixture was stirred 20 h, poured on to saturated aq. NaCl (50 mL) and extracted three times with Et_2O. The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and dissolved in anhydrous CH_2Cl_2 (20 mL). Acetic anhydride (1.25 g, 12.5 mmol) and DMAP (50 mg) were added, and the mixture was stirred for 24 h, during which time yellow crystals of **15** appeared. The solvent was removed *in vacuo* and raw **15** was recrystallized from acetonitrile; yield 1.31 g (71%); *m.p.* 178 °C. – ^{1}H NMR: δ/ppm = 7.45 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 13.8 Hz, 1H), 7.83 (dd, *J* = 8.4 and 2.5 Hz, 1H), 8.00 (d, *J* = 13.8 Hz, 1H), 8.58 (d, *J* = 2.5 Hz, 1H). – MS (70 eV): *m/z* (%) = 184 (21) [M^+], 152 (100), 137 (43), 117 (71), 102 (51).

$C_7H_5ClN_2O_2$	Calcd.:	C 45.55	H 2.73	Cl 19.21	N 15.18
(184.6)	Found:	C 45.66	H 2.69	Cl 19.23	N 15.26.

1-[(tert-Butyl)formimidoyl]-2-trimethylsilylpyrrolidine (**8**)

To 1-[(*tert*-butyl)formimidoyl]pyrrolidine (3.08 g, 20 mmol) (**7**) [17] in anhydrous THF (40 mL) was added *tert*-BuLi (17 mL of a 1.3M solution in pentane, 22 mmol) at –78 °C. The yellow solution was stirred at –10 °C for 1 h and recooled to –78 °C. TMSCl (2.61 g, 24 mmol) was added dropwise, and the mixture was allowed to warm to *r.t.* (3 h). The solvents were removed *in vacuo*, and the resulting slurry of LiCl was extracted 3 times with pentane. The combined pentane fractions were freed from the solvent and distilled; *b.p.* 75 °C/1 Torr; yield 3.2 g (70%); colourless liquid. – ^{1}H NMR: δ/ppm = 0.05 (s, 9H), 1.15 (s, 9H), 1.69–2.02 (m, 4H), 2.96–3.46 (m, 3H), 7.55 (s, 1H). – ^{13}C NMR: δ/ppm = –2.1 ($SiMe_3$), 26.0 (CH_2), 28.4 (CH_2), 32.4 ($C\underline{Me}_3$), 47.4 (C-5), 49.9 (C-2), 53.9 ($\underline{C}Me_3$), 148.5 (N–C=N). – MS (70 eV, CH_4): *m/z* (%) = 226 (10) [M^+], 211 (9), 169 (18), 155 (7), 142 (16), 73 (52), 70 (100), 57 (28).

1-[(tert-Butyl)formimidoyl]-2,5-bis(trimethylsilyl)pyrrolidine (**10**) *from 1-[(tert-butyl)formimidoyl]pyrrolidine* (**7**)

To a solution of 1-[(*tert*-butyl)formimidoyl]pyrrolidine (15.4 g, 0.1 mol) (**7**)[17] in anhydrous THF (200 mL) was added dropwise at –78 °C *tert*-BuLi (69 mL of a 1.6M solution in pentane, 110 mmol). The solution immediately turned bright yellow. It was stirred for 1 h at –20 °C and then cooled to –78 °C. TMSCl (11.4 g, 105 mmol) was added within 5 min, and the solution was allowed to warm to r.t. Colourless LiCl precipitated. After 1 h, it was recooled to –78 °C and more *tert*-BuLi (110 mmol) was added. The identical procedure was then repeated. The THF was evaporated, the oily residue partitioned between 2M KOH (100 mL) and Et_2O (100 mL) and dried (KOH). The solvent was evaporated; yield 30 g of a colourless oil, consisting of 65% **10** and 30% **8** (GC), being suitable for deprotection without further purification. For spectroscopic investigations **10** can be purified by distillation, *b.p.* 115 °C/0.2 Torr. – ^{1}H NMR (*trans*-isomer): δ/ppm = –0.05 (s, 18H), 1.14 (s, 9H), 1.93–1.55 (m, 4H), 2.99–3.08 (m, 2H), 7.54 (s, 1H). – ^{13}C NMR: δ/ppm = –0.2 ($SiMe_3$), 31.1 (C-3,4), 33.4 ($C\underline{Me}_3$), 51.4 (C-2,5), 54.2 ($\underline{C}Me_3$), 148.5 (N–C=N). – CI-MS (70 eV, CH_4): *m/z* (%) = 315 (22) [$M^+ + H + CH_4$], 299 (65) [$M^+ + H$], 241 (100). – HRMS: Calcd. 298.2261, Found 298.2260 [M^+].

1-[(tert-Butyl)formimidoyl]-2,5-bis(trimethylsilyl)pyrrolidine (**10**) from *1-[(tert-butyl)formimidoyl]-2-trimethylsilylpyrrolidine* (**8**)

8 was lithiated and treated with TMSCl in the same fashion as described above. After the usual workup the resulting oil contained a significantly higher proportion of **10** (80%) than in the one-step procedure.

2,5-Bis(trimethylsilyl)pyrrolidine (**11**)

10 (0.1 mol, 30 g), hydrazine hydrate (41 mL), HOAc (19 mL), and ethanol (400 mL) were heated to reflux for 14 h. Ethanol was removed *in vacuo*. The residue was partitioned between 0.1M NaOH (400 mL) and pentane (400 mL). The organic phase was washed with H_2O 5 times and dried (KOH). After evaporation of the solvent the resulting oil was distilled; yield 10.0 g (47%); *b.p.* 86 °C/13 Torr. The lower boiling fractions consisted mostly of 2-trimethylsilylpyrrolidine. – ^{1}H NMR: δ/ppm = –0.04 (s, 18H), 1.30–1.88 (m, 4H), 2.20–2.28 (m, 2H). – ^{13}C NMR: δ/ppm = –3.2 ($SiMe_3$), 30.4 (C-3,4), 49.4 (C-2,5). – MS (70 eV): *m/z* = 215 (5) [M^+), 200 (10), 142 (100). – HRMS: Calcd. 215.1526, Found 215.1525 [M^+].

2,5-Bis(trimethylsilyl)-N-benzylpyrrolidine (**12**) [11, 12]

To **11** (4.3 g, 20 mmol) and K_2CO_3 (3.2 g, 23 mmol) in anhydrous acetonitrile (50 mL) benzyl bromide (3.6 g, 21 mmol) was added dropwise at 0 °C. The solution was allowed to warm to *r.t.* and stirred for an additional 24 h. The reaction mixture was then partitioned between H_2O (100 mL) and hexane (100 mL). The organic phase was extracted 3 times with H_2O, dried (KOH) and concentrated *in vacuo*; yield 6.1 g (100%); colourless oil**,** that should be used up within a few days. – ^{1}H NMR: δ/ppm = 0.02 (s, 18H), 1.67–1.82 (m, 2H), 2.32–2.42 (m, 2H), 3.40 (d, *J* = 13 Hz, 1H), 3.85 (d, *J* = 13 Hz, 1H), 7.25–7.40 (m, 5H). – ^{13}C NMR: δ/ppm = 1.7 ($SiMe_3$), 26.8 (C-3,4), 56.1 (C-2,5), 60.1 (CH_{2benz}), 126.8(C_{ar}), 128.2(C_{ar}), 129.5 (C_{ar}), 141.7(C_{ar}). – GC-MS (70 eV): *m/z* (%) = 305 (5) [M^+], 290 (8), 232 (100). – HRMS: Calcd. 305.1995; Found 305.1995 [M^+].

2,5-Bis(trimethylsilyl)-N-methylpyrrolidine (**13**)

To a rapidly stirred mixture of **11** (5.4 g, 25 mmol) and 37% aq. formaldehyde solution (5 mL) in DMF (30 mL) was add-

ed $NaBH_3CN$ (2.5 g, 40 mmol) in several portions. The solution was cooled with a water bath. After stirring for 24 h, the reaction mixture was partitioned between H_2O (150 mL) and pentane (150 mL). The organic phase was washed with H_2O 5 times and dried (KOH). After evaporation of the solvent the resulting oil was distilled *in vacuo*; yield 4.8 g (84%); colourless liquid; *b.p.* 70 – 72 °C/1 Torr. The compound should be kept in the cold and used up within a few days. – ^{1}H NMR: δ/ppm = 0.04 (s, 18H), 1.51–2.01 (m, 4H), 2.11–2.24 (m, 2H), 2.43 (s, 3H). – ^{13}C NMR: δ/ppm = –1.5 ($SiMe_3$), 29.0 (C-3,4), 44.9 (C-2,5), 58.4 (NCH_3). – GC-MS (70 eV): *m/z* (%) = 229 (5) [M^+], 214 (8), 156 (100). – HRMS: Calcd. 229.1682, Found 229.1682 [M^+].

2-endo-Nitro-3-exo-(2'-chloro-5'-pyridyl)-7-methyl-7-azabicyclo[2.2.1]heptane (**4b**)

To **15** (552 mg, 3 mmol) and $AgNO_3$ (1.36 g, 8 mmol) in DMF (10 mL) under nitrogen a solution of TBAF·$3H_2O$ (2.84 g, 9 mmol) in DMF (7 mL) was added dropwise. To the resulting slurry of freshly precipitated AgF was added dropwise a solution of **13** (756 mg, 3.3 mmol) in DMF (7 mL). The reaction mixture was stirred for 24 h, diluted with Et_2O (100 mL), filtered (Celite) and extracted 5 times with H_2O. It was dried ($MgSO_4$), the solvent evaporated and the residue chromatographed (SiO_2, Et_2O/pentane 1:1); yield 132 mg (17%); yellow oil. – ^{1}H NMR: δ/ppm = 1.45–1.70 (m, 2H), 1.89–2.10 (m, 2H), 2.27 (s, 3H), 3.28 (d, *J* = 4.0 Hz, 1H), 3.39 (d, *J* = 4.5 Hz, 1H), 3.88 (t, *J* = 3.8 Hz, 1H), 4.67 (t, *J* = 4.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 8.0 and 2.5 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H). – ^{13}C NMR: δ/ppm = 21.9 (CH_2), 27.9 (CH_2), 36.5 (NCH_3), 50.6 (C-3), 66.9 (CH_3N–$\underline{C}H$), 70.9 (CH_3N–$\underline{C}H$), 95.2 (C-2), 126.2 (CH_{pyr}), 139.4 (C_{pyr}, q), 139.9 (CH_{pyr}), 149.4 (C_{pyr}, q), 150.9 (CH_{pyr}). – GC-MS (70 eV): *m/z* (%) = 266 (20) [M^+ – H], 221 (100), 193 (7), 82 (8). – ESI-HRMS: Calcd. 268.0853, Found 268.0853 [M^+ + H].

2-endo-Nitro-3-exo-(2'-chloro-5'-pyridyl)-7-benzyl-7-azabicyclo[2.2.1]heptane (**4c**) [11, 12]

To a suspension of **15** (300 mg, 1.6 mmol) and AgF (826 mg, 6.5 mmol) in DMF (10 mL) under nitrogen a solution of **12** (610 mg, 2 mmol) in DMF (2 mL) was added dropwise, and the mixture was stirred vigorously for 24 h. The reaction mixture was partitioned between H_2O (150 mL) and Et_2O (150 mL), washed 5 times with H_2O and dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed (SiO_2), eluting *N*-benzylpyrrole (**16**) first (CH_2Cl_2/petrol ether 1:1), and then **4c** (165 mg, 30%) (ether); amber oil. – ^{1}H NMR: δ/ppm = 1.45–1.63 (m, 2H), 1.87–2.02 (m, 2H), 3.23 (d, *J* = 3.5 Hz, 1H), 3.29 (d, *J* = 4.5 Hz, 1H), 3.44 (dd, *J* = 12.8 Hz, 2H), 3.83 (t, *J* = 4.3 Hz, 1H), 4.57 (t, *J* = 4.5 Hz, 1H), 7.09–7.22 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.85 (dd, *J* = 8.0 and 2.5 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H). – ^{13}C NMR: δ/ppm = 20.9 (CH_2), 27.0 (CH_2), 48.9 (C-3), 52.3 ($N\underline{C}H_2Ph$), 63.3 (N–CH), 67.4 (N–CH), 93.5 (C-2), 126.2 (CH_{pyr}), 128.0 (CH_{ar}), 129.0 (CH_{ar}), 129.1 (CH_{ar}), 138.6 (C_{ar}, q), 139.4 (C_{pyr}, q), 139.9 (CH_{pyr}), 149.3 (C_{pyr}, q), 150.9 (CH_{pyr}). – GC-MS (70 eV): *m/z* (%) = 343 (1) [M^+ – NO], 297 (95), 160 (12), 91 (100). – ESI - HRMS: Calcd. 344.1166, Found 344.1163 [M^+ + H – NO].

2-endo-Nitro-3-exo-phenyl-7-benzyl-7-azabicyclo[2.2.1]heptane (**18a**) and *2-exo-nitro-3-endo-phenyl-7-benzyl-7-azabicyclo[2.2.1]heptane* (**18b**)

The method is identical to the synthesis of **4c**. Yield 30%, 2:1 mixture of **18a**/**b**. – ^{1}H NMR: δ/ppm = 1.50–1.62 (m, 2H), 1.87–2.01 (m, 2H), 3.35 (m, 1.4H), 3.51 (s, 1.4H), 3.54–3.58 (m, 0.9H), 3.85 (t, *J* = 3.8 Hz, 0.7H), 4.02 (d, *J* = 5.3 Hz, 0.3H), 4.18 (t, *J* = 3.3 Hz, 0.3H), 4.48 (d, *J* = 5.3 Hz, 0.3H), 4.71 (t, *J* = 4.5 Hz, 0.7H), 7.08–7.39 (m, 10H). – ^{13}C NMR: δ/ppm = 20.9 (CH_2), 23.8 (CH_2), 27.3 (CH_2), 36.5 (CH_2), 51.5 ($Ph\underline{C}H_2N$), 51.8 (C-3), 52.3 ($Ph\underline{C}H_2N$), 52.9 (C-3), 63.3 ($PhCH_2N$–$\underline{C}H$), 64.5 ($PhCH_2N$–$\underline{C}H$), 65.6 ($PhCH_2N$–$\underline{C}H$), 67.7 ($PhCH_2N$–$\underline{C}H$), 92.6 (C-2), 95.2 (C-2), 126.1 (CH_{ar}), 126.3 (CH_{ar}), 126.4 (CH_{ar}), 127.8 (CH_{ar}), 128.0 (CH_{ar}), 128.1 (CH_{ar}), 128.2 (CH_{ar}), 128.6 (CH_{ar}), 129.0 (CH_{ar}), 129.1 (CH_{ar}), 129.2 (CH_{ar}), 129.9 (CH_{ar}), 135.1 (C_{ar}, q), 137.6 (C_{ar}, q), 138.6 (C_{ar}, q), 143.3 (C_{ar}, q). – GC-MS (70 eV): *m/z* (%) = 308 (1) [M^+], 292 (1), 276 (1), 262 (30), 91 (100). – ESI-HRMS: Calcd. 309.1603, Found 309.1600 [M^+ + H].

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