Inter- and Intramolecular [4+2]-Cycloaddition Reactions with 4,4-Disubstituted *N*-Silyl-1,4-dihydropyridines as Precursors for N-Protonated 2-Azabutadiene Intermediates

Cornelia E. Schmaunz,[a] Peter Mayer,[b] Klaus T. Wanner*[a]

[a] Department of Pharmacy – Center for Drug Research, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus C, 81377 München, Germany
Fax +49(89)218077247; E-mail: klaus.wanner@cup.uni-muenchen.de

[b] Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus D, 81377 München, Germany

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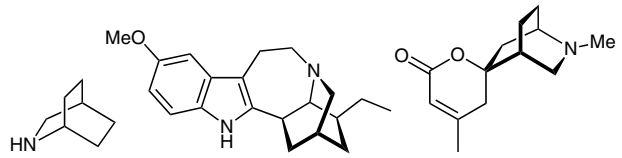
Abstract: An efficient and straightforward method for the synthesis of polycyclic ring systems with a central 2-azabicyclo[2.2.2]octane unit is developed. The process is based on [4+2]-cycloaddition reactions that are performed with N-protonated 2-azabutadiene intermediates as heterodienes, generated from 4,4-disubstituted *N*-silyl 1,4-dihydropyridines. As dienophiles, cyclopentadiene for the intermolecular cycloaddition and an allyl moiety already attached to the 4,4-disubstituted 1,4-dihydropyridines for the intramolecular variant, are used.

Key words: hetero-Diels–Alder reaction, 1,4-dihydropyridines, heterocycles, polycycles, imines

The 2-azabicyclo[2.2.2]octane ring system (**1**) is found in various biologically active compounds. Well-known examples include ibogaine (**2**), a psychoactive indole alkaloid, and dioscorine (**3**), which is a modulator of the nicotinic acetylcholine receptor and leads to disorders in the central nervous system (Figure 1).[1]



2-azabicyclo-[2.2.2]octane (**1**) ibogaine (**2**) dioscorine (**3**)

Figure 1 Structures of 2-azabicyclo[2.2.2]octane (**1**), ibogaine (**2**) and dioscorine (**3**)

The synthesis of 2-azabicyclo[2.2.2]octane derivatives is often carried out via Diels–Alder reactions using pyridines,[2] pyridones,[3] 1,2-dihydropyridines,[4] 3,4-dihydropyridines,[5] or activated 1,4-dihydropyridines,[6,7] as dienes for the cyclizations. In the case of 1,4-dihydropyridines, Craig et al. published, for example, the [4+2] cyclization of *N*-phenyl-3,5-diethyl-2-propyl-1,4-dihydropyridine with maleic anhydride.[6] Further examples of inter- and intramolecular Diels–Alder reactions of 1,4-dihydropyridines, more precisely 4-aryl-substituted dimethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates, with dienophiles have been reported by Hartman et al.[7] The reactions were performed in the presence of an acid as the catalyst to generate N-protonated 2-azabutadienes as intermediates, which underwent intermolecular [4+2] cyclizations with different alkenes (styrene, allyltrimethylsilane, cyclopentadiene, furan, thiophene). Similarly, intramolecular [4+2]-cyclization reactions were also carried out with 4-phenyl-substituted 1,4-dihydropyridines in which the dienophile, an alkene moiety, required for the cyclization with the generated intermediate N-protonated 2-azabutadiene, was already present in the molecule as an *ortho*-substituent attached to a phenyl residue at the 4-position.[7]

We previously demonstrated the high synthetic utility of 4,4-disubstituted *N*-silyl-1,4-dihydropyridines,[8] that are easily accessible by trapping reactions of *N*-silylpyridinium ions, for the synthesis of 5-substituted 7,8-benzomorphans, as well as for 4,4-disubstituted 2-cyanopiperidines and 2,6-dicyanopiperidines.[9]

Herein, we report on the highly efficient synthesis of 10,10-disubstituted 8-azatricyclo[5.2.2.$0^{2,6}$]undeca-3,8-dienes by acid-catalyzed cycloaddition reactions employing 4,4-disubstituted 1,4-dihydropyridines and cyclopentadiene as starting materials. The Diels–Alder addition products derived from 4,4-disubstituted 1,4-dihydropyridines could be successfully used in subsequent intramolecular Friedel–Crafts-type cyclization reactions resulting in polycyclic nitrogen heterocycles possessing both a 2-azabicyclo[2.2.2]octane and a 7,8-benzomorphane substructure. In addition, Diels–Alder reactions were performed with 4-allyl-substituted 1,4-dihydropyridines, which proceeded intramolecularly leading to 1-substituted 4-azatricyclo[3.3.1.$0^{2,7}$]non-3-enes with a unique polycyclic skeleton.

The 4,4-disubstituted *N*-silyl-1,4-dihydropyridines **5a**–**e** that were required as starting materials for the intramolecular cycloaddition reactions were prepared following a published procedure; treatment of the respective pyridine derivatives **4a**–**e** with triisopropylsilyl triflate gave the corresponding pyridinium salts, which were subsequently trapped with diorganomagnesium compounds.[8] The yields for the obtained addition products, 1,4-dihydropyridines **5a**–**e**, are given in Table 1, where, for the sake of

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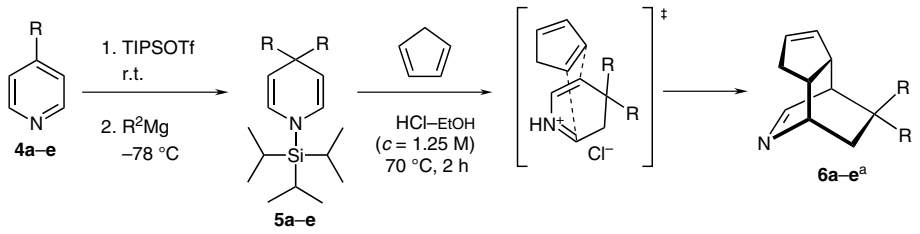
Table 1 Synthesis of 10,10-Disubstituted 8-Azatricyclo[5.2.2.0^{2,6}]undeca-3,8-dienes **6a–e**



Entry	Starting material		Products			
	4	R	**5**	Yield (%)	**6**	Yield (%)
1	**a**	Et	**a**	81[b]	**a**	80
2	**b**	Bn	**b**	85[b]	**b**	84
3	**c**[b]	PMB	**c**	56[b]	**c**	87
4	**d**[c]	4-$FC_6H_4CH_2$	**d**	61	**d**	77
5	**e**[b]	CH_2CH_2Ph	**e**	62[b]	**e**	85

[a] Structures of only one of the two enantiomers of the racemic compounds are shown.
[b] Data obtained from the literature.[8,9]
[c] The preparation of **4d** is described in the experimental section.

completeness, the data for the preparation of compounds published earlier are also listed.[8,9]

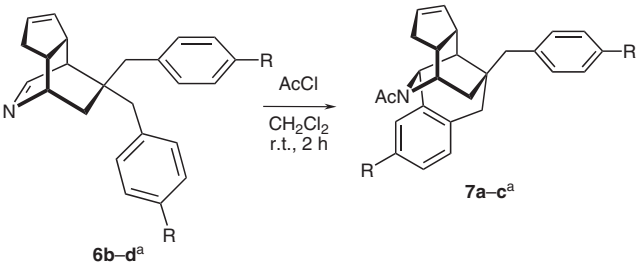
The intermolecular [4+2] cyclizations of the 1,4-dihydropyridines **5a–e** with cyclopentadiene could be realized efficiently by heating the components in ethanolic hydrogen chloride solution (1.25 M) at 70 °C, leading to the desired products **6a–e** in good to high yields (77–87%, Table 1).

In the next step, the obtained 5,5-diarylsubstituted 2-azabicyclo[2.2.2]octane derivatives **6b–d** were used as starting materials for the intramolecular Friedel–Crafts-type cyclization reactions. Treatment of imines **6b–d** with acetyl chloride in dichloromethane to generate the corresponding *N*-acetyliminium ions resulted in smooth intramolecular electrophilic aromatic substitution reactions of the aryl substituents opposite to the cylcopentene bridge in **6b–d**, providing the polycyclic nitrogen heterocycles **7a–c** in high yields (86–94%, Table 2). In addition to the 2-azabicyclo[2.2.2]octane substructure present in the starting materials **6b–d**, the generated polycyclic piperidine derivatives **7a–c** contain a 7,8-benzomorphane subunit.

The structures of the polycyclic piperidine derivatives **7a–c** were deduced from comprehensive 2D NMR studies, and exemplified for **7a** by an X-ray crystal structure analysis, the result of which is given in Figure 2.

Having successfully performed acid-catalyzed intermolecular Diels–Alder reactions between the 1,4-dihydropyridines **5a–e** and cyclopentadiene, we next turned our attention to the intramolecular variant of these cycloaddition reactions. The required 4,4-disubstituted *N*-silyl-1,4-dihydropyridines **5f–i**, possessing an allyl group at the 4-position, were again synthesized via *N*-silylpyridinium ion intermediates following the above described method. Accordingly, the pyridine derivatives **4a** and **4e** were treated with triisopropylsilyl triflate to give the respective *N*-silylpyridinium ions, which were subsequently trapped with diallylmagnesium (allyl$_2$Mg) to afford the 1,4-dihydropyridines **5f** and **5i**. The yields for these compounds, **5f** and **5i**, were quite low, but still in the range common for trapping reactions performed with diallylmagnesium as can be seen from the yields obtained for the preparation of **5g**,**h** reported earlier,[8] that are also listed in Table 3, as these compounds have been used here as well. Upon heating at reflux temperature in ethanolic hydrogen chloride solution (1.25 M) the 1,4-dihydropyridines **5f–i** underwent the desired cyclization into the 1-substituted 4-aza-

Table 2 Synthesis of Polycyclic Nitrogen Heterocycles **7a–c**



Entry	Starting material		Product	
	6	R	**7**	Yield (%)
1	**b**	H	**a**	92
2	**c**	OMe	**b**	94
3	**d**	F	**c**	86

[a] Structures of only one of the two enantiomers of the racemic compounds are shown.

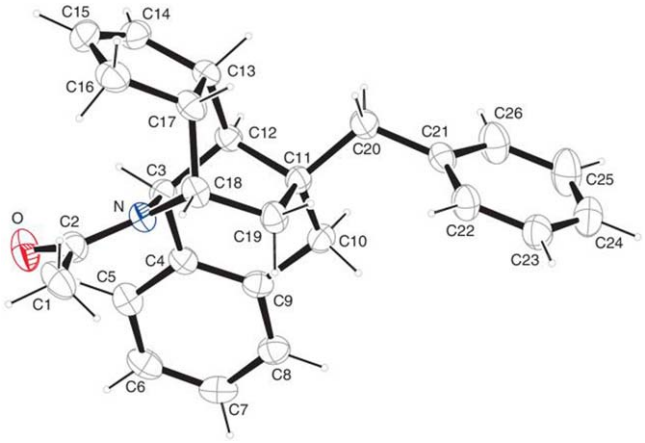


Figure 2 X-ray crystal structure of **7a**[10]

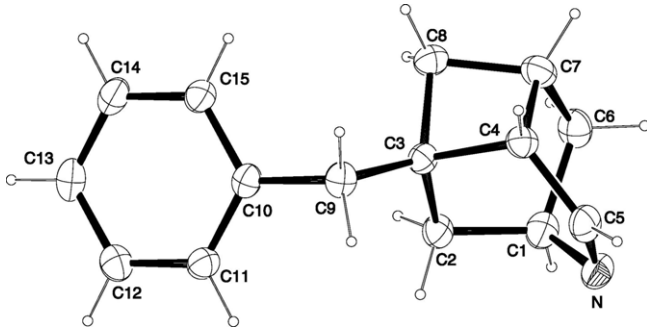


Figure 3 X-ray crystal structure of **8c**[10]

tricyclo[3.3.1.0^{2,7}]non-3-ene derivatives **8a–d** (63–95%, Table 3).

The structures of compounds **8a–d** were established by NMR studies. The respective assignments were corroborated unambiguously by X-ray crystallography of **8c** (Figure 3), which neatly highlights the unique skeleton of this class of compounds.

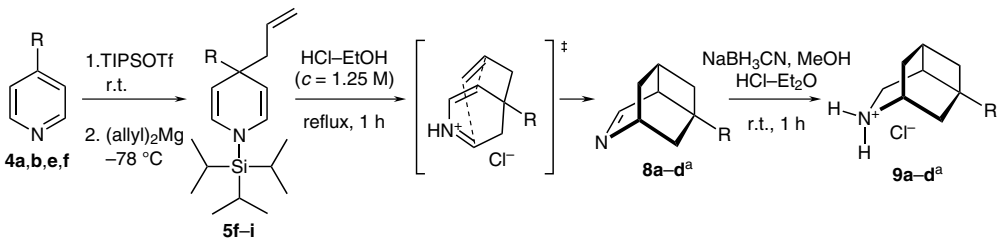
According to the structures of the products, the vinyl group of the allyl moiety has added via the terminal carbon at position 2 and with the inner carbon at position 5 of the piperidine ring. This regioselectivity (leading to **8a–d**) is likely to be a result of the improved charge-stabilizing effects that can operate when the cycloaddition takes place with this orientation. In fact, the regioselectivity observed for the intermolecular cycloaddition reactions leading to the products **6a–e** can be explained in the same way (Table 1).

The fully saturated analogues of imines **8a–d** were finally obtained upon reduction with sodium cyanoborohydride in the presence of ethereal hydrogen chloride in methanol. This afforded the desired 4-azatricyclo[3.3.1.0^{2,7}]nonanes, which were isolated as hydrochlorides **9a–d** in good to high yields (80–92%, Table 3).

In summary, we have described an easy and straightforward method for the synthesis of polycyclic ring systems that starts from *N*-silyl-1,4-dihydropyridine derivatives as key compounds. Upon reaction under acidic conditions, these compounds served as precursors for the generation of N-protonated 2-azabutadienes as heterodienes in [4+2]-cycloaddition reactions. These underwent smooth intermolecular cycloaddition reactions with cyclopentadiene as a dienophile, and with allyl moieties attached to the 1,4-dihydropyridine precursors in intramolecular hetero-Diels–Alder reactions, leading to polycyclic tetrahydropyridine and piperidine derivatives with a 2-azabicyclo[2.2.2]octane ring system as the core unit.

All solvents and chemicals were obtained from commercial sources and were utilized without further purification unless otherwise stated. All reactions were performed using flame-dried glassware under an argon atmosphere. Absolute solvents were freshly dried using standard procedures.[11] Flash chromatography was performed with Merck 40–63 mesh silica gel or Fluka 50–150 mesh alumina (neu-

Table 3 Synthesis of 1-Substituted 4-Azatricyclo[3.3.1.0^{2,7}]nonane Hydrochlorides **9a–d**



Entry	Starting material		Products					
	4	R	**5**	Yield (%)	**8**	Yield (%)	**9**	Yield (%)
1	**a**	Et	**f**	25	**a**	95	**a**	80
2	**f**	Ph	**g**	20[b]	**b**	63	**b**	84
3	**b**	Bn	**h**	12[b]	**c**	92	**c**	89
4	**e**	CH_2CH_2Ph	**i**	19	**d**	83	**d**	92

[a] Structures of only one of the two enantiomers of the racemic compounds are shown.
[b] Data obtained from the literature.[8]

tral Brockmann activity III). Melting points were determined on a Büchi melting point apparatus (no. 510 Dr. Tottoli). IR spectra were obtained using a Perkin-Elmer model 1600 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JNMR-GX 400 (Jeol, 400 MHz) or a JNMR-GX 500 (Jeol, 500 MHz) spectrometer. Multiplicities given for ^{13}C NMR spectra were deduced from DEPT experiments. Low-resolution MS (CI) were recorded on a Hewlett Packard 5989 mass spectrometer. HRMS were obtained on a JEOL MStation 700. Microanalytical data for C, H, and N were determined using a Heraeus Rapid Analyser and an Elementar Vario EL Analyser.

10,10-Disubstituted 8-Azatricyclo[5.2.2.0^{2,6}]undeca-3,8-dienes 6; General Procedure (GP1)

A solution of 4,4-disubstituted *N*-silyl-1,4-dihydropyridine **5** and cyclopentadiene (cyclopentadiene was prepared by heating dicyclopentadiene at 190 °C and collecting the distilled cyclopentadiene which was used immediately) in 1.25 M ethanolic HCl was heated to 70 °C. After 2 h, the solution was quenched by the addition of 1.0 M phosphate buffer (pH 7) until a pH of 7 was reached. The aq layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography to yield the desired product.

8-Substituted *N*-Acetyl-12-aza-10(1,2)-benzenatetracyclo[6.4.1.0^{2,6}.0^{7,11}]tridecaphan-4-enes 7; General Procedure (GP2)

The corresponding 8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene **6** and AcCl were dissolved in CH_2Cl_2 and the mixture was stirred at r.t. After 2 h, the solution was quenched by the addition of 1.0 M phosphate buffer (pH 7). The aq layer was extracted with CH_2Cl_2, and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (alumina) to yield the desired product.

1-Substituted 4-Azatricyclo[3.3.1.0^{2,7}]non-3-enes 8; General Procedure (GP3)

A solution of 4,4-disubstituted *N*-silyl-1,4-dihydropyridine **5** in 1.25 M ethanolic HCl was heated at 100 °C for 1 h. The solvent was evaporated under reduced pressure. The residue was washed carefully with cold *n*-pentane and CH_2Cl_2, and then 1.0 M phosphate buffer (pH 7) was added. The aq layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (alumina) to yield the desired product.

1-Substituted 4-Azatricyclo[3.3.1.0^{2,7}]nonane Hydrochlorides 9; General Procedure (GP4)

The corresponding 4-azatricyclo[3.3.1.0^{2,7}]non-3-ene **8** and $NaBH_3CN$ were dissolved in MeOH. After addition of ethereal HCl, the mixture was stirred at r.t. for 1 h and subsequently quenched with H_2O and then K_2CO_3 was added to the solution until a pH of 11 was reached. The aq layer was extracted with CH_2Cl_2 (× 10). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The product was dissolved in Et_2O, acidified with 2.0 M ethereal HCl, and concentrated in vacuo.

4-(4-Fluorobenzyl)pyridine (4d)[12]

The title product was prepared in analogy to the literature[9a] starting from py (196 mg, 200 µL, 2.47 mmol) and TIPSOTf (833 mg, 731 µL, 2.72 mmol) in CH_2Cl_2 (3 mL), and 0.11 M (4-$FC_6H_4CH_2)_2Mg$ in THF (46.6 mL); (4-$FC_6H_4CH_2)_2Mg$ was prepared according to the literature[12] from Mg (875 mg, 36.0 mmol) in THF (20 mL), 1-chloromethyl-4-fluorobenzene (3.47 mg, 2.87 mL, 24.0 mmol) in THF (60 mL), and 1,4-dioxane (2.33 g, 2.25 mL, 26.4 mmol). Purification was accomplished by flash chromatography (silica gel, EtOAc–MeOH, 97:3). Analytical data were in accordance with literature data.[13]

Yield: 390 mg (84%); light yellow oil.

4,4-Bis(4-fluorobenzyl)-1-triisopropylsilyl-1,4-dihydropyridine (5d)

The title product was prepared in analogy to the literature[8] starting from **4d** (101 mg, 0.540 mmol) and TIPSOTf (182 mg, 160 µL, 0.594 mmol) in CH_2Cl_2 (5 mL) and 0.05 M (4-$FC_6H_4CH_2)_2Mg$ in Et_2O (21.6 mL), at –50 °C for 12 h; (4-$FC_6H_4CH_2)_2Mg$ was prepared according to the literature[13] from Mg (875 mg, 36.0 mmol) in Et_2O (20 mL), 1-chloromethyl-4-fluorobenzene (3.47 mg, 2.87 mL, 24.0 mmol) in Et_2O (60 mL), and 1,4-dioxane (2.33 g, 2.25 mL, 26.4 mmol). Work-up of the crude product was performed with 1.0 M phosphate buffer (10 mL, pH 7) and extraction with CH_2Cl_2 (4 × 20 mL). Purification by flash chromatography (alumina, *n*-pentane) and fractional crystallization (*n*-pentane) gave the desired product.

Yield: 149 mg (61%); colorless crystals; mp 64–67 °C; R_f = 0.67 (alumina, *n*-pentane).

IR (KBr): 3043, 2953, 2892, 2866, 1669, 1600, 1508, 1473, 1460, 1441, 1280, 1216 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.82 [d, J = 7.4 Hz, 18 H, CH(CH_3)$_2$], 0.94–1.09 [m, 3 H, CH(CH$_3$)$_2$], 2.59 (s, 4 H, CH_2), 4.10 (d, J = 8.3 Hz, 2 H, NCHCH), 5.74 (d, J = 8.3 Hz, 2 H, NCH), 6.83–6.97 (m, 4 H, $CH_{Ar,m}$), 7.03–7.17 (m, 4 H, $CH_{Ar,o}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5 [d, 3 C, *C*H(CH$_3$)$_2$], 17.6 [q, 6 C, CH(*C*H$_3$)$_2$], 42.3 (s, 1 C, NCHCH*C*), 50.8 (t, 2 C, CH_2), 105.4 (d, 2 C, NCH*C*H), 114.2 (d, J_{CF} = 21.1 Hz, 4 C, $CH_{Ar,m}$), 129.7 (d, 2 C, NCH), 132.7 (d, J_{CF} = 7.0 Hz, 4 C, $CH_{Ar,o}$), 135.9 (d, J_{CF} = 3.0 Hz, 2 C, C_{Ar}), 161.8 (d, J_{CF} = 242.3 Hz, 2 C, CF).

MS (CI, CH_5^+): *m*/*z* (%) = 344 (66), 454 (100) [M + H]$^+$.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{38}F_2NSi$: 454.2742; found: 454.2733.

Anal. Calcd for $C_{28}H_{37}F_2NSi$: C, 74.13; H, 8.22; N, 3.09. Found: C, 74.02; H, 7.96; N, 3.04.

4-Allyl-4-ethyl-1-triisopropylsilyl-1,4-dihydropyridine (5f)

The title product was prepared in analogy to the literature[8] starting from 4-ethylpyridine (1.00 g, 1.06 mL, 9.33 mmol) and TIPSOTf (3.14 g, 2.76 mL, 10.3 mmol) in CH_2Cl_2 (8 mL) and 0.5 M allyl$_2$Mg in THF (37.3 mL); allyl$_2$Mg was prepared according to the literature[13] from 1.0 M allylMgCl solution in THF (50.0 mL), and 1,4-dioxane (4.84 g, 55.0 mmol, 4.69 mL). Work-up of the crude product was performed with 1.0 M phosphate buffer (20 mL, pH 7) and extraction with CH_2Cl_2 (4 × 20 mL). Purification by flash chromatography (alumina, *n*-pentane) gave the desired product.

Yield: 704 mg (25%); colorless oil; R_f = 0.97 (alumina, *n*-pentane).

IR (film): 3074, 3042, 2959, 2894, 2868, 1668, 1639, 1600, 1463, 1384, 1370, 1287cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.07 [d, J = 7.3 Hz, 18 H, CH(CH_3)$_2$], 1.17 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 1.23 [m, 3 H, CH(CH$_3$)$_2$], 1.97 (dt, J = 7.2, 1.2 Hz, 2 H, CH_2CHCH$_2$), 4.05 (d, J = 8.3 Hz, 2 H, NCHCH), 4.88–5.03 (m, 2 H, CH$_2$CHCH_2), 5.87 (ddt, J = 17.4, 10.3, 7.2 Hz, 1 H, CH$_2$CHCH$_2$), 6.06 (d, J = 8.3 Hz, 2 H, NCH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0 (q, 1 C, CH_2CH_3), 11.7 [d, 3 C, *C*H(CH$_3$)$_2$], 18.1 [q, 6 C, CH(*C*H$_3$)$_2$], 36.4 (t, 1 C, CH_2CH_3), 38.5 (s, 1 C, NCHCH*C*), 50.1 (t, 1 C, *C*H$_2$CHCH$_2$), 106.0 (d, 2 C, NCH*C*H), 115.7 (t, 1 C, CH$_2$CH*C*H$_2$), 129.4 (d, 2 C, NCH), 137.0 (d, 1 C, CH$_2$*C*HCH$_2$).

MS (CI, CH_5^+): *m*/*z* (%) = 264 (100), 306 (37) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{19}H_{35}NSi$: 305.2539; found: 305.2535.

4-Allyl-4-(2-phenylethyl)-1-triisopropylsilyl-1,4-dihydropyridine (5i)

The title product was prepared in analogy to the literature[8] starting from 4-(2-phenylethyl)pyridine (840 mg, 4.58 mmol) and TIPSOTf (1.54 g, 1.35 mL, 5.04 mmol) in CH_2Cl_2 (5 mL) and 0.5 M allyl$_2$Mg

in THF (18.3 mL); allyl$_2$Mg was prepared according to the literature[13] from 1.0 M allylMgCl solution in THF (50.0 mL), and 1,4-dioxane (4.84 g, 55.0 mmol, 4.69 mL). Work-up of the crude product was performed with 1.0 M phosphate buffer (10 mL, pH 7) and extraction with CH_2Cl_2 (4 × 10 mL). Purification by flash chromatography (alumina, *n*-pentane) gave the desired product.

Yield: 329 mg (19%); colorless crystals; mp 34–35 °C; R_f = 0.70 (alumina, *n*-pentane).

IR (KBr): 3072, 3027, 2946, 2867, 1668, 1604, 1496, 1463, 1454, 1287 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.09 [d, *J* = 7.4 Hz, 18 H, CH(C*H*$_3$)$_2$], 1.22–1.33 [m, 3 H, C*H*(CH$_3$)$_2$], 1.41–1.47 (m, 2 H, C*H*$_2$CH$_2$Ph), 2.02 (d, *J* = 7.2 Hz, 2 H, C*H*$_2$CHCH$_2$), 2.52–2.67 (m, 2 H, CH$_2$C*H*$_2$Ph), 4.19 (d, *J* = 8.3 Hz, 2 H, NCHC*H*), 4.88–5.05 (m, 2 H, CH$_2$CHC*H*$_2$), 5.89 (ddt, *J* = 17.4, 10.3, 7.2 Hz, 1 H, CH$_2$C*H*CH$_2$), 6.13 (d, *J* = 8.3 Hz, 2 H, NCH), 7.10–7.15 (m, 1 H, CH$_{Ar,p}$), 7.15–7.19 (m, 2 H, CH$_{Ar,o}$), 7.21–7.26 (m, 2 H, CH$_{Ar,m}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.8 [d, 3 C, *C*H(CH$_3$)$_2$], 18.0 [q, 6 C, CH(*C*H$_3$)$_2$], 33.4 (t, 1 C, CH$_2$*C*H$_2$Ph), 38.5 (s, 1 C, NCHCH*C*), 46.7 (t, 1 C, *C*H$_2$CH$_2$Ph), 50.6 (t, 1 C, *C*H$_2$CHCH$_2$), 106.1 (d, 2 C, NCH*C*H), 115.9 (t, 1 C, CH$_2$CH*C*H$_2$), 125.6 (d, 1 C, CH$_{Ar,p}$), 128.5 (d, 2 C, CH$_{Ar,m}$), 128.8 (d, 2 C, CH$_{Ar,o}$), 129.8 (d, 2 C, NCH), 136.9 (d, 1 C, CH$_2$*C*HCH$_2$), 144.6 (s, 1 C, C$_{Ar}$).

MS (CI, CH_5^+): *m*/*z* (%) = 340 (51), 382 (100) [M + H]$^+$.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{40}NSi$: 382.2930; found 382.2921.

10,10-Diethyl-8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (6a)

The title product was prepared according to GP1 from **5a** (393 mg, 1.34 mmol) and cyclopentadiene (442 mg, 501 μL, 6.69 mmol) in 1.25 M ethanolic HCl (10 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 10 mL). Purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 97:3) gave the desired product.

Yield: 216 mg (80%); light yellow oil; R_f = 0.24 (silica gel, CH_2Cl_2–MeOH, 97:3).

IR (film): 3047, 2962, 2925, 2877, 1617, 1458, 1441, 1379, 1344 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 0.82 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.10 (dq, *J* = 14.7, 7.4 Hz, 1 H, C*H*$_2$CH$_3$), 1.15 (dd, *J* = 13.2, 1.9 Hz, 1 H, NCHC*H*$_2$), 1.22–1.33 (m, 2 H, C*H*$_2$CH$_3$, NCHC*H*$_2$), 1.40 (dq, *J* = 14.7, 7.4 Hz, 1 H, C*H*$_2$CH$_3$), 1.52 (dq, *J* = 14.7, 7.4 Hz, 1 H, C*H*$_2$CH$_3$), 2.20–2.27 (m, 1 H, CH=CHC*H*$_2$), 2.43–2.53 (m, 2 H, CH=CHC*H*$_2$, CH=CHCH$_2$C*H*), 2.57 (dd, *J* = 4.2, 2.6 Hz, 1 H, N=CHC*H*), 3.10–3.24 (m, 1 H, CH=CHC*H*), 4.16–4.28 (m, 1 H, NC*H*CH$_2$), 5.36–5.48 (m, 1 H, CH=C*H*CH$_2$), 5.53–5.64 (m, 1 H, C*H*=CHCH$_2$), 8.22 (d, *J* = 4.3 Hz, 1 H, N=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9 (q, 1 C, CH$_2$*C*H$_3$), 8.3 (q, 1 C, CH$_2$*C*H$_3$), 28.6 (t, 1 C, *C*H$_2$CH$_3$), 31.0 (t, 1 C, *C*H$_2$CH$_3$), 38.4 (t, 2 C, CH=CH*C*H$_2$, NCH*C*H$_2$), 38.7 (d, 1 C, CH=CHCH$_2$*C*H), 39.5 (s, 1 C, N=CHCH*C*), 44.5 (d, 1 C, N=CH*C*H), 45.6 (d, 1 C, CH=CH*C*H), 60.4 (d, 1 C, N*C*HCH$_2$), 131.9 (d, 1 C, CH=*C*HCH$_2$), 132.9 (d, 1 C, *C*H=CHCH$_2$), 176.1 (d, 1 C, N=CH).

MS (CI, CH_5^+): *m*/*z* (%) = 138 (35), 204 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{14}H_{21}N$: 203.1674; found: 203.1662.

10,10-Dibenzyl-8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (6b)

The title product was prepared according to GP1 starting from **5b** (400 mg, 0.960 mmol) and cyclopentadiene (317 mg, 360 μL, 4.80 mmol) in 1.25 M ethanolic HCl (10 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 10 mL). Purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 97:3) gave the desired product.

Yield: 262 mg (84%); light yellow oil; R_f = 0.26 (silica gel, CH_2Cl_2–MeOH, 97:3).

IR (film): 3085, 3057, 3027, 3001, 2927, 2848, 1617, 1602, 1494, 1453 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.74 (m, 2 H, NCHC*H*$_2$), 2.23–2.31 (m, 1 H, CH=CHC*H*$_2$), 2.44 (d, *J* = 14.2 Hz, 1 H, CH$_2$Ph), 2.47–2.60 (m, 2 H, CH=CHC*H*$_2$, CH=CHCH$_2$C*H*), 2.63 (dd, *J* = 4.1, 2.5 Hz, 1 H, N=CHC*H*), 2.70 (d, *J* = 14.2 Hz, 1 H, CH$_2$Ph), 2.81 (d, *J* = 14.8 Hz, 1 H, CH$_2$Ph), 3.00 (d, *J* = 14.8 Hz, 1 H, CH$_2$Ph), 3.42–3.50 (m, 1 H, CH=CHC*H*), 4.30 (dd, *J* = 4.6, 2.3 Hz, 1 H, NC*H*CH$_2$), 5.35–5.45 (m, 1 H, CH=C*H*CH$_2$), 5.55–5.65 (m, 1 H, C*H*=CHCH$_2$), 7.03–7.10 (m, 2 H, CH$_{Ar,o}$), 7.18–7.22 (m, 1 H, CH$_{Ar,p}$), 7.22–7.37 (m, 7 H, CH$_{Ar}$), 8.10 (d, *J* = 4.1 Hz, 1 H, N=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.97 (t, 1 C, NCH*C*H$_2$), 38.04 (t, 1 C, CH=CH*C*H$_2$), 39.0 (d, 1 C, CH=CHCH$_2$*C*H), 41.7 (s, 1 C, N=CHCH*C*), 43.3 (t, 1 C, CH$_2$Ph), 44.5 (d, 1 C, N=CH*C*H), 45.2 (t, 1 C, CH$_2$Ph), 45.8 (d, 1 C, CH=CH*C*H), 59.8 (d, 1 C, N*C*HCH$_2$), 126.27 (d, 1 C, CH$_{Ar,p}$), 126.30 (d, 1 C, CH$_{Ar,p}$), 128.1 (d, 2 C, CH$_{Ar,m}$), 128.3 (d, 2 C, CH$_{Ar,m}$), 130.3 (d, 2 C, CH$_{Ar,o}$), 130.6 (d, 2 C, CH$_{Ar,o}$), 131.3 (d, 1 C, CH=*C*HCH$_2$), 133.0 (d, 1 C, *C*H=CHCH$_2$), 138.5 (s, 1 C, C$_{Ar}$), 138.8 (s, 1 C, C$_{Ar}$), 175.1 (d, 1 C, N=CH).

MS (CI, CH_5^+): *m*/*z* (%) = 236 (24), 328 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{24}H_{25}N$: 327.1987; found: 327.1944.

10,10-Bis(4-methoxybenzyl)-8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (6c)

The title product was prepared according to GP1 starting from **5c** (53.1 mg, 0.111 mmol) and cyclopentadiene (36.7 mg, 41.7 μL, 0.555 mmol) in 1.25 M ethanolic HCl (2 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 4 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 70:30:3) gave the desired product.

Yield: 37.4 mg (87%); light yellow oil; R_f = 0.48 (alumina, *n*-pentane–MeOH, 97:3).

IR (film): 3046, 2999, 2930, 2836, 1612, 1581, 1512, 1463, 1455, 1442 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.76 (m, 2 H, NCHC*H*$_2$), 2.21–2.31 (m, 1 H, CH=CHC*H*$_2$), 2.37 (d, *J* = 14.2 Hz, 1 H, CH$_2$Ph), 2.44–2.65 (m, 3 H, N=CHC*H*, CH=CHC*H*$_2$, CH=CHCH$_2$C*H*), 2.60 (d, *J* = 14.2 Hz, 1 H, CH$_2$Ph), 2.74 (d, *J* = 14.7 Hz, 1 H, CH$_2$Ph), 2.91 (d, *J* = 14.7 Hz, 1 H, CH$_2$Ph), 3.41–3.51 (m, 1 H, CH=CHC*H*), 3.78 (s, 3 H, OCH$_3$), 3.83 (s, 3 H, OCH$_3$), 4.24–4.36 (m, 1 H, NC*H*CH$_2$), 5.37–5.44 (m, 1 H, CH=C*H*CH$_2$), 5.57–5.63 (m, 1 H, C*H*=CHCH$_2$), 6.76–6.83 (m, 2 H, CH$_{Ar,m}$), 6.84–6.92 (m, 2 H, CH$_{Ar,m}$), 6.94–7.02 (m, 2 H, CH$_{Ar,o}$), 7.16–7.23 (m, 2 H, CH$_{Ar,o}$), 8.05 (d, *J* = 4.1 Hz, 1 H, N=CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.7 (t, 1 C, NCH*C*H$_2$), 38.0 (t, 1 C, CH=CH*C*H$_2$), 38.9 (d, 1 C, CH=CHCH$_2$*C*H), 41.9 (s, 1 C, NCHCH$_2$*C*), 42.6 (t, 1 C, CH$_2$Ph), 44.2 (t, 1 C, CH$_2$Ph), 44.4 (d, 1 C, N=CH*C*H), 45.8 (d, 1 C, CH=CH*C*H), 55.1 (q, 1 C, OCH$_3$), 55.2 (q, 1 C, OCH$_3$), 59.8 (d, 1 C, N*C*HCH$_2$), 113.5 (d, 2 C, CH$_{Ar,m}$), 113.6 (d, 2 C, CH$_{Ar,m}$), 130.5 (s, 1 C, C$_{Ar}$), 130.6 (s, 1 C, C$_{Ar}$), 131.2 (d, 2 C, CH$_{Ar,o}$), 131.3 (d, 1 C, *C*H=CHCH$_2$), 131.5 (d, 2 C, CH$_{Ar,o}$), 133.0 (d, 1 C, CH=*C*HCH$_2$), 158.0 (s, 1 C, C$_{Ar,p}$), 158.1 (s, 1 C, C$_{Ar,p}$), 175.2 (d, 1 C, N=CH).

MS (FAB, NBA): *m*/*z* (%) = 200.2 (28), 266.2 (23), 322.2 (5), 388.1 (100) [M + H]$^+$.

HRMS (FAB, NBA): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}NO_2$: 388.2277; found: 388.2280.

10,10-Bis(4-fluorobenzyl)-8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (6d)

The title product was prepared according to GP1 starting from **5d** (30.7 mg, 0.0677 mmol) and cyclopentadiene (22.4 mg, 25.4 μL,

0.339 mmol) in 1.25 M ethanolic HCl (2 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 4 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 70:30:3) gave the desired product.

Yield: 18.9 mg (77%); light yellow oil; R_f = 0.60 (alumina, *n*-pentane–MeOH, 97:3).

IR (film): 3048, 3000, 2926, 2853, 1621, 1604, 1509, 1445, 1223 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.63–1.72 (m, 2 H, NCHCH_2), 2.23–2.31 (m, 1 H, CH=CHCH_2), 2.39 (d, *J* = 14.4 Hz, 1 H, CH_2Ph), 2.48–2.65 (m, 4 H, CH_2Ph, CH=CHCH_2, N=CHC*H*, CH=CHCH$_2$C*H*), 2.76 (d, *J* = 14.9 Hz, 1 H, CH_2Ph), 2.95 (d, *J* = 14.9 Hz, 1 H, CH_2Ph), 3.41–3.48 (m, 1 H, CH=CHC*H*), 4.30–4.33 (m, 1 H, NC*H*CH_2), 5.39–5.43 (m, 1 H, CH=C*H*CH_2), 5.59–5.64 (m, 1 H, C*H*=$CHCH_2$), 6.90–7.06 (m, 6 H, $CH_{Ar,o}$, $CH_{Ar,m}$), 7.17–7.23 (m, 2 H, $CH_{Ar,o}$), 8.07 (d, *J* = 4.1 Hz, 1 H, N=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.9 (t, 1 C, NCH*C*H$_2$), 38.0 (t, 1 C, CH=CH*C*H$_2$), 38.9 (d, 1 C, CH=CHCH$_2$*C*H), 41.7 (s, 1 C, NCHCH$_2$*C*), 42.7 (t, 1 C, CH_2Ph), 44.3 (t, 1 C, CH_2Ph), 44.4 (d, 1 C, N=CH*C*H), 45.8 (d, 1 C, CH=CH*C*H), 59.7 (d, 1 C, N*C*HCH$_2$), 115.0 (d, J_{CF} = 21.0 Hz, 2 C, $CH_{Ar,m}$), 115.2 (d, J_{CF} = 21.0 Hz, 2 C, $CH_{Ar,m}$), 131.0 (d, 1 C, CH=*C*HCH$_2$), 131.5 (d, J_{CF} = 7.7 Hz, 2 C, $CH_{Ar,o}$), 131.8 (d, J_{CF} = 7.7 Hz, 2 C, $CH_{Ar,o}$), 133.2 (d, 1 C, *C*H=CHCH$_2$), 133.9 (d, J_{CF} = 3.4 Hz, 1 C, C_{Ar}), 134.1 (d, J_{CF} = 3.4 Hz, 1 C, C_{Ar}), 161.5 (d, J_{CF} = 245.2 Hz, 1 C, $C_{Ar,p}$), 161.6 (d, J_{CF} = 245.2 Hz, 1 C, $C_{Ar,p}$), 174.8 (d, 1 C, N=CH).

MS (FAB, NBA): *m*/*z* (%) = 188.1 (32), 254.2 (20), 298.3 (11), 364.2 (100) $[M + H]^+$.

HRMS (FAB, NBA): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{24}F_2N$: 364.1877; found: 364.1875.

10,10-Bis(2-phenylethyl)-8-azatricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (6e)

The title product was prepared according to GP1 starting from **5e** (95.5 mg, 0.214 mmol) and cyclopentadiene (70.7 mg, 80.3 µL, 1.07 mmol) in 1.25 M ethanolic HCl (2.5 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 70:30:3) gave the desired product.

Yield: 64.6 mg (85%); light yellow oil; R_f = 0.35 (silica gel, $CHCl_3$–MeOH, 97:3).

IR (film): 3057, 3024, 2999, 2927, 2860, 1616, 1602, 1495, 1453 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (dd, *J* = 13.4, 1.7 Hz, 1 H, NCHCH_2), 1.44 (ddd, *J* = 13.9, 12.3, 4.3 Hz, 1 H, CH_2CH$_2$Ph), 1.47 (dd, *J* = 13.4, 3.8 Hz, 1 H, NCHCH_2), 1.71 (ddd, *J* = 13.9, 12.7, 5.5 Hz, 1 H, CH_2CH$_2$Ph), 1.76–1.91 (m, 2 H, CH_2CH$_2$Ph), 2.21–2.32 (m, 1 H, CH=CHCH_2), 2.46–2.67 (m, 6 H, CH$_2$CH_2Ph, CH=CHCH_2, CH=CHCH$_2$C*H*), 2.71 (dd, *J* = 4.2, 2.6 Hz, 1 H, N=CHC*H*), 3.25–3.33 (m, 1 H, CH=CHC*H*), 4.27–4.31 (m, 1 H, NC*H*CH$_2$), 5.40–5.48 (m, 1 H, CH=C*H*CH$_2$), 5.59–5.65 (m, 1 H, C*H*=CHCH$_2$), 7.11–7.38 (m, 10 H, CH_{Ar}), 8.25 (d, *J* = 4.2 Hz, 1 H, N=CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.1 (t, 1 C, CH$_2$*C*H$_2$Ph), 30.5 (t, 1 C, CH$_2$*C*H$_2$Ph), 38.2 (t, 1 C, CH=CH*C*H$_2$), 38.4 (d, 1 C, CH=CHCH$_2$*C*H), 38.7 (t, 1 C, NCH*C*H$_2$), 39.2 (t, 1 C, *C*H$_2$CH$_2$Ph), 39.4 (s, 1 C, NCHCH$_2$*C*), 41.6 (t, 1 C, *C*H$_2$CH$_2$Ph), 44.7 (d, 1 C, N=CH*C*H), 45.5 (d, 1 C, CH=CH*C*H), 60.1 (d, 1 C, N*C*HCH$_2$), 125.9 (d, 1 C, $CH_{Ar,p}$), 126.0 (d, 1 C, $CH_{Ar,p}$), 128.2 (d, 2 C, $CH_{Ar,o}$), 128.3 (d, 2 C, $CH_{Ar,o}$), 128.5 (d, 2 C, $CH_{Ar,m}$), 128.6 (d, 2 C, $CH_{Ar,m}$), 131.3 (d, 1 C, CH=*C*HCH$_2$), 133.0 (d, 1 C, *C*H=CHCH$_2$), 142.27 (s, 1 C, C_{Ar}), 142.32 (s, 1 C, C_{Ar}), 175.6 (d, 1 C, N=CH).

MS (CI, CH_5^+): *m*/*z* (%) = 250 (18), 290 (19), 356 (100) $[M + H]^+$.

HRMS (EI^+): *m*/*z* $[M]^+$ calcd for $C_{26}H_{29}N$: 355.2300; found: 355.2310.

1-[8-Benzyl-12-aza-10(1,2)-benzenatetracyclo[6.4.1.0^{2,6}.0^{7,11}]tridecaphan-4-en-12-yl]ethanone (7a)

The title product was prepared according to GP2 starting from **6b** (90.9 mg, 0.278 mmol) and AcCl (33.0 mg, 30.0 µL, 0.420 mmol) in CH_2Cl_2 (4 mL). Work-up was performed with phosphate buffer (5 mL) and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–EtOAc, 50:50) gave the desired product.

Yield: 94.3 mg (92%); colorless crystals; mp 96–98 °C; R_f = 0.44 (silica gel, *n*-pentane–EtOAc, 50:50).

IR (KBr): 3039, 2981, 2964, 2926, 2914, 2850, 1637, 1489, 1446, 1402 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.72 (dd, *J* = 14.0, 2.8 Hz, 1 H, NCHCH_2), 1.95 (dd, *J* = 14.0, 3.1 Hz, 1 H, NCHCH_2), 2.02 (s, 3 H, $COCH_3$), 2.05 (t, *J* = 3.8 Hz, 1 H, NCHC*H*C), 2.28–2.34 (m, 1 H, CH=CHCH_2), 2.51 (d, *J* = 17.0 Hz, 1 H, NCHCHCCH_2), 2.62–2.67 (m, 1 H, CH=CHCH$_2$C*H*), 2.72–2.79 (m, 1 H, CH=CHCH_2), 2.81 (d, *J* = 17.0 Hz, 1 H, NCHCHCCH_2), 2.92 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 2.98 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 3.61–3.75 (m, 2 H, CH=CHC*H*, NC*H*CH$_2$), 5.13 (d, *J* = 3.8 Hz, 1 H, NC*H*CHC), 5.67–5.73 (m, 1 H, CH=C*H*CH$_2$), 5.82–5.88 (m, 1 H, C*H*=CHCH$_2$), 6.99 (br d, *J* = 7.3 Hz, 1 H, NCHCCC*H*), 7.06–7.14 (m, 2 H, NCHCCHC*H*, NCHCCCHC*H*), 7.22–7.37 (m, 5 H, CH_{Bn}), 7.93 (dd, *J* = 7.6, 1.4 Hz, 1 H, NCHCC*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5 (q, 1 C, CO*C*H$_3$), 34.0 (s, 1 C, NCHCH*C*), 37.1 (d, 1 C, NCH*C*HC), 37.4 (t, 1 C, CH=CH*C*H$_2$), 38.1 (d, 1 C, CH=CHCH$_2$*C*H), 39.2 (t, 1 C, NCH*C*H$_2$), 41.9 (t, 1 C, NCHCHC*C*H$_2$), 44.2 (d, 1 C, CH=CH*C*H), 47.2 (t, 1 C, CH_2Ph), 50.7 (d, 1 C, N*C*HCHC), 53.4 (d, 1 C, N*C*HCH$_2$), 125.6 (d, 1 C, NCHCCH*C*H), 126.7 (d, 1 C, $CH_{Ar,p}$), 127.7 (d, 1 C, NCHCCCH*C*H), 128.4 (d, 2 C, $CH_{Ar,m}$), 129.1 (d, 1 C, NCHCC*C*H), 130.8 (d, 2 C, $CH_{Ar,o}$), 131.2 (d, 1 C, *C*H=CHCH$_2$), 131.6 (d, 1 C, CH=*C*HCH$_2$), 132.2 (d, 1 C, NCHC*C*H), 134.6 (s, 1 C, C_{Ar}), 136.9 (s, 1 C, C_{Ar}), 138.1 (s, 1 C, C_{Bn}), 169.0 (s, 1 C, C=O).

MS (CI, CH_5^+): *m*/*z* (%) = 219 (25), 370 (100) $[M + H]^+$.

HRMS (EI^+): *m*/*z* $[M]^+$ calcd for $C_{26}H_{27}NO$: 369.2093; found: 369.2085.

1-[8-(4-Methoxybenzyl)-12-aza-10(1,2)-benzenatetracyclo[6.4.1.0^{2,6}.0^{7,11}]tridecaphan-4-en-12-yl]ethanone (7b)

The title product was prepared according to GP2 starting from **6c** (13.6 mg, 0.0351 mmol) and AcCl (8.3 mg, 7.5 µL, 0.11 mmol) in CH_2Cl_2 (2 mL). Work-up was performed with phosphate buffer (2 mL) and extraction with CH_2Cl_2 (4 × 2 mL). Purification by flash chromatography (alumina, *n*-pentane–EtOAc, 60:40) gave the desired product.

Yield: 14.1 mg (94%); colorless crystals; mp 196–198 °C; R_f = 0.49 (alumina, *n*-pentane–EtOAc, 50:50).

IR (KBr): 3055, 3027, 2982, 2954, 2936, 2902, 2882, 2833, 1631, 1608, 1508, 1462, 1440, 1409, 1240 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (dd, *J* = 14.0, 2.8 Hz, 1 H, NCHCH_2), 1.91 (dd, *J* = 14.0, 3.2 Hz, 1 H, NCHCH_2), 2.01 (br t, *J* = 3.8 Hz, 1 H, NCHC*H*C), 2.04 (s, 3 H, C=OCH_3), 2.27–2.35 (m, 1 H, CH=CHCH_2), 2.42 (d, *J* = 16.7 Hz, 1 H, NCHCHCCH_2), 2.60–2.66 (m, 1 H, CH=CHCH$_2$C*H*), 2.73 (d, *J* = 16.7 Hz, 1 H, NCHCHCCH_2), 2.72–2.80 (m, 1 H, CH=CHCH_2), 2.86 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 2.90 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 3.62–3.68 (m, 1 H, CH=CHC*H*), 3.68–3.72 (m, 1 H, NC*H*CH$_2$), 3.75 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 5.09 (d, *J* = 3.8 Hz, 1 H, NC*H*CHC), 5.67–5.73 (m, 1 H, CH=C*H*CH$_2$), 5.81–5.87 (m, 1 H, C*H*=CHCH$_2$), 6.73 (dd, *J* = 8.4, 2.8 Hz, 1 H, NCHCCCHC*H*), 6.85–6.92 (m, 3 H, NCHCCC*H*, $CH_{Bn,m}$), 7.16–7.22 (m, 2 H, $CH_{Ar,o}$), 7.56 (d, *J* = 2.8 Hz, 1 H, NCHCC*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3 (q, 1 C, C=O*C*H$_3$), 33.9 (s, 1 C, NCHCH*C*), 36.9 (d, 1 C, NCH*C*HC), 37.2 (t, 1 C, CH=CH*C*H$_2$), 37.9 (d, 1 C, CH=CHCH$_2$*C*H), 38.6 (t, 1 C,

NCH*C*H$_2$), 40.9 (t, 1 C, NCHCHC*C*H$_2$), 44.0 (d, 1 C, CH=CH*C*H), 46.1 (t, 1 C, CH$_2$Ph), 50.7 (d, 1 C, N*C*HCHC), 53.3 (d, 1 C, N*C*HCH$_2$), 55.25 (q, 1 C, OCH$_3$), 55.29 (q, 1 C, OCH$_3$), 113.6 (d, 2 C, CH$_{Bn,m}$), 115.2 (d, 1 C, NCHCCCH*C*H), 115.5 (d, 1 C, NCHC*C*H), 126.4 (s, 1 C, NCHC*C*), 129.8 (d, 1 C, NCHCC*C*H), 129.9 (s, 1 C, C$_{Bn}$), 130.9 (d, 1 C, *C*H=CHCH$_2$), 131.5 (d, 3 C, CH$_{Ar,o}$, CH=*C*HCH$_2$), 137.7 (s, 1 C, NCH*C*), 157.2 (s, 1 C, NCHC-CH*C*), 158.3 (s, 1 C, C$_{Bn,p}$), 168.8 (s, 1 C, C=O).

MS (FAB, NBA): *m*/*z* (%) = 430.3 (100) [M + H]$^+$.

HRMS (FAB, NBA): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{32}NO_3$: 430.2382; found: 430.2376.

1-[8-(4-Fluorobenzyl)-12-aza-10(1,2)-benzenatetracyclo[6.4.1.0^{2,6}.0^{7,11}]tridecaphan-4-en-12-yl]ethanone (7c)

The title product was prepared according to GP2 starting from **6d** (13.0 mg, 0.0358 mmol) and AcCl (8.4 mg, 7.7 µL, 0.11 mmol) in CH_2Cl_2 (2 mL). After a reaction time of 4 h, the work-up was performed with phosphate buffer (2 mL) and extraction with CH_2Cl_2 (4 × 2 mL). Purification by flash chromatography (alumina, gradient *n*-pentane–CH_2Cl_2, 60:40, then 50:50) gave the desired product.

Yield: 12.5 mg (86%); colorless crystals; mp 171–173 °C; R_f = 0.09 (alumina, *n*-pentane–CH_2Cl_2, 60:40).

IR (KBr): 3050, 2987, 2929, 2854, 1635, 1622, 1508, 1498, 1407 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (dd, *J* = 14.0, 2.8 Hz, 1 H, NCHC*H*$_2$), 1.92 (dd, *J* = 14.0, 3.2 Hz, 1 H, NCHC*H*$_2$), 2.01 (t, *J* = 3.8 Hz, 1 H, NCHC*H*C), 2.04 (s, 3 H, COCH$_3$), 2.27–2.35 (m, 1 H, CH=CHC*H*$_2$), 2.44 (d, *J* = 16.6 Hz, 1 H, NCHCHCC*H*$_2$), 2.63 (tt, *J* = 9.6, 1.8 Hz, 1 H, CH=CHCH$_2$C*H*), 2.71 (d, *J* = 16.6 Hz, 1 H, NCHCHCC*H*$_2$), 2.73–2.81 (m, 1 H, CH=CHC*H*$_2$), 2.90 (d, *J* = 13.6 Hz, 1 H, CH$_2$Ph), 2.94 (d, *J* = 13.6 Hz, 1 H, CH$_2$Ph), 3.61–3.67 (m, 1 H, CH=CHC*H*), 3.68–3.72 (m, 1 H, NC*H*CH$_2$), 5.09 (d, *J* = 3.8 Hz, 1 H, NC*H*CHC), 5.63–5.72 (m, 1 H, CH=C*H*CH$_2$), 5.83–5.89 (m, 1 H, C*H*=CHCH$_2$), 6.84 (td, *J* = 8.4, 2.8 Hz, 1 H, NCHCCCHC*H*), 6.93 (dd, *J* = 8.4, 5.8 Hz, 1 H, NCHCCC*H*), 7.00–7.06 (m, 2 H, CH$_{Bn,m}$), 7.20–7.26 (m, 2 H, CH$_{Bn,o}$), 7.69 (dd, *J* = 10.3, 2.8 Hz, 1 H, NCHCC*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2 (q, 1 C, CO*C*H$_3$), 33.8 (s, 1 C, NCHCH*C*), 36.7 (d, 1 C, NCH*C*HC), 37.2 (t, 1 C, CH=CH*C*H$_2$), 37.8 (d, 1 C, CH=CHCH$_2$*C*H), 38.7 (t, 1 C, NCH*C*H$_2$), 40.9 (t, 1 C, NCHCHC*C*H$_2$), 43.9 (d, 1 C, CH=CH*C*H), 46.1 (t, 1 C, CH$_2$Ph), 50.2 (d, 1 C, N*C*HCHC), 53.1 (d, 1 C, N*C*HCH$_2$), 114.8 (d, J_{CF} = 21.8 Hz, 1 C, NCHCCCH*C*H), 115.1 (d, J_{CF} = 21.1 Hz, 2 C, CH$_{Bn,m}$), 118.3 (d, J_{CF} = 21.8 Hz, 1 C, NCHCC*C*H), 129.7 (d, J_{CF} = 2.9 Hz, 1 C, NCHC*C*), 130.1 (d, J_{CF} = 7.6 Hz, 1 C, NCHCCC*C*H), 131.1 (d, 1 C, CH=*C*HCH$_2$), 131.2 (d, 1 C, *C*H=CHCH$_2$), 131.9 (d, J_{CF} = 7.8 Hz, 2 C, CH$_{Bn,o}$), 133.4 (d, J_{CF} = 3.1 Hz, 1 C, C$_{Bn}$), 138.3 (d, J_{CF} = 7.6 Hz, 1 C, NCH*C*), 160.6 (d, J_{CF} = 243.5 Hz, 1 C, NCHCCH*C*), 161.7 (d, J_{CF} = 245.3 Hz, 1 C, C$_{Bn,p}$), 168.8 (s, 1 C, CO).

MS (CI, CH_5^+): *m*/*z* (%) = 406 (100) [M + H]$^+$.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{26}F_2NO$: 406.1982; found: 406.1977.

1-Ethyl-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene (8a)

The title product was prepared according to GP3 starting from **5f** (108 mg, 0.355 mmol) in 1.25 M ethanolic HCl (3 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2) gave the desired product.

Yield: 50.6 mg (95%); colorless oil; R_f = 0.69 (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:3).

IR (film): 2958, 2935, 2876, 2854, 1613, 1462, 1442, 1378, 1346, 1334, 1269 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.5 Hz, 3 H, CH$_2$C*H*$_3$), 0.92 (ddd, *J* = 12.4, 4.5, 2.1 Hz, 1 H, NCHC*H*$_2$C), 1.01–1.08 (m, 1 H, NCHC*H*$_2$CH), 1.13–1.23 (m, 2 H, C*H*$_2$CH$_3$, NCHCH$_2$CHC*H*$_2$), 1.30 (dq, *J* = 14.9, 7.5 Hz, 1 H, C*H*$_2$CH$_3$), 1.60–1.68 (m, 2 H, NCHC*H*$_2$C, NCHC*H*$_2$CH), 1.99 (ddt, *J* = 8.9, 6.6, 2.1 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 2.06–2.13 (m, 1 H, NCHCH$_2$C*H*), 2.84–2.90 (m, 1 H, NCHC*H*), 4.52–4.57 (m, 1 H, NC*H*CH$_2$), 8.10 (d, *J* = 3.4 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.5 (q, 1 C, CH$_2$*C*H$_3$), 27.3 (d, 1 C, NCHCH$_2$*C*H), 31.1 (t, 1 C, NCH*C*H$_2$CH), 32.7 (t, 1 C, *C*H$_2$CH$_3$), 36.1 (t, 1 C, NCH*C*H$_2$C), 41.2 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 42.4 (d, 1 C, NCH*C*H), 43.1 (s, 1 C, NCHCH*C*), 55.7 (d, 1 C, N*C*HCH$_2$), 167.2 (d, 1 C, N*C*HCH).

MS (ESI$^+$): *m*/*z* (%) = 150.1 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{10}H_{15}N$: 149.1204; found: 149.1203.

1-Phenyl-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene (8b)

The title product was prepared according to GP3 starting from **5g** (136 mg, 0.383 mmol) in 1.25 M ethanolic HCl (4 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2) gave the desired product.

Yield: 47.5 mg (63%); colorless oil; R_f = 0.40 (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2).

IR (film): 3082, 3059, 3026, 2994, 2936, 2863, 1608, 1494, 1446, 1343, 1333 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14–1.21 (m, 1 H, NCHC*H*$_2$CH), 1.24 (ddd, *J* = 12.7, 4.4, 2.1 Hz, 1 H, NCHC*H*$_2$C), 1.61 (d, *J* = 9.1 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 1.79 (dd, *J* = 12.7, 3.1 Hz, 1 H, NCHC*H*$_2$CH), 2.02 (dd, *J* = 12.7, 2.9 Hz, 1 H, NCHC*H*$_2$C), 2.20–2.26 (m, 1 H, NCHCH$_2$C*H*), 2.54 (ddt, *J* = 9.1, 6.9, 2.1 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 3.27–3.32 (m, 1 H, NCHC*H*), 4.62–4.68 (m, 1 H, NC*H*CH$_2$), 6.94–7.01 (m, 2 H, CH$_{Ar,o}$), 7.14–7.19 (m, 1 H, CH$_{Ar,p}$), 7.24–7.31 (m, 2 H, CH$_{Ar,m}$), 8.35 (d, *J* = 2.9 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5 (d, 1 C, NCHCH$_2$*C*H), 30.8 (t, 1 C, NCH*C*H$_2$CH), 40.9 (t, 1 C, NCH*C*H$_2$C), 41.2 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 43.3 (d, 1 C, NCH*C*H), 45.8 (s, 1 C, NCHCH*C*), 55.9 (d, 1 C, N*C*HCH$_2$), 124.8 (d, 2 C, CH$_{Ar,o}$), 126.0 (d, 1 C, CH$_{Ar,p}$), 128.4 (d, 2 C, CH$_{Ar,m}$), 147.7 (s, 1 C, C$_{Ar}$), 166.9 (d, 1 C, N*C*HCH).

MS (CI, CH_5^+): *m*/*z* (%) = 198 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{14}H_{15}N$: 197.1204; found: 197.1198.

1-Benzyl-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene (8c)

The title product was prepared according to GP3 starting from **5h** (71.7 mg, 0.195 mmol) in 1.25 M ethanolic HCl (3 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2) gave the desired product.

Yield: 37.8 mg (92%); colorless crystals; mp 94 °C; R_f = 0.66 (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:3).

IR (KBr): 3079, 3060, 3023, 2993, 2972, 2948, 2922, 2856, 1605, 1494, 1453, 1435, 1348, 1343, 1329 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.08 (m, 2 H, NCHC*H*$_2$C, NCHC*H*$_2$CH), 1.16 (d, *J* = 9.0 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 1.59 (dd, *J* = 12.6, 3.1 Hz, 1 H, NCHC*H*$_2$C), 1.62 (dd, *J* = 12.5, 2.9 Hz, 1 H, NCHC*H*$_2$CH), 2.04–2.10 (m, 1 H, NCHCH$_2$C*H*), 2.13 (ddt, *J* = 9.0, 6.6, 2.1 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 2.47 (d, *J* = 13.3 Hz, 1 H, CH$_2$Ph), 2.55 (d, *J* = 13.3 Hz, 1 H, CH$_2$Ph), 2.96–3.05 (m, 1 H, NCHC*H*), 4.47–4.54 (m, 1 H, NC*H*CH$_2$), 7.00–7.09 (m, 2 H, CH$_{Ar,o}$), 7.16–7.23 (m, 1 H, CH$_{Ar,p}$), 7.23–7.31 (m, 2 H, CH$_{Ar,m}$), 8.05 (d, *J* = 3.7 Hz, 1 H, NC*H*CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 (d, 1 C, NCHCH$_2$*C*H), 31.1 (t, 1 C, NCH*C*H$_2$CH), 36.8 (t, 1 C, NCH*C*H$_2$C), 41.1 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 42.2 (d, 1 C, NCH*C*H), 43.0 (s, 1 C, NCHCH*C*), 46.3 (t, 1 C, CH$_2$Ph), 55.7 (d, 1 C, N*C*HCH$_2$), 126.1 (d, 1 C, CH$_{Ar,p}$), 128.2 (d, 2 C, CH$_{Ar,m}$), 129.5 (d, 2 C, CH$_{Ar,o}$), 138.0 (s, 1 C, C$_{Ar}$), 166.8 (d, 1 C, N*C*HCH).

MS (CI, CH_5^+): *m*/*z* (%) = 212 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{15}H_{17}N$: 211.1361; found: 211.1366.

1-(2-Phenylethyl)-4-azatricyclo[3.3.1.0^{2,7}]non-3-ene (8d)
The title product was prepared according to GP3 starting from **5i** (114 mg, 0.297 mmol) in 1.25 M ethanolic HCl (3 mL). Work-up was performed with phosphate buffer and extraction with CH_2Cl_2 (4 × 5 mL). Purification by flash chromatography (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2) gave the desired product.

Yield: 55.6 mg (83%); colorless crystals; mp 61–63 °C; R_f = 0.49 (alumina, *n*-pentane–CH_2Cl_2–MeOH, 90:10:2).

IR (KBr): 3047, 3025, 3000, 2960, 2930, 2850, 1608, 1495, 1453, 1346 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99–1.10 (m, 2 H, NCHC*H*$_2$C, NCHC*H*$_2$CH), 1.21 (d, *J* = 9.0 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 1.50 (ddd, *J* = 13.4, 11.1, 5.9 Hz, 1 H, C*H*$_2$CH$_2$Ph), 1.59–1.69 (m, 2 H, NCHC*H*$_2$CH, C*H*$_2$CH$_2$Ph), 1.75 (dd, *J* = 12.6, 3.0 Hz, 1 H, NCHC*H*$_2$C), 2.04 (ddt, *J* = 9.0, 6.6, 1.9 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 2.10–2.15 (m, 1 H, NCHCH$_2$C*H*), 2.35–2.49 (m, 2 H, CH$_2$C*H*$_2$Ph), 2.90–2.94 (m, 1 H, NCHC*H*), 4.55–4.60 (m, 1 H, NC*H*CH$_2$), 7.11–7.19 (m, 3 H, CH$_{Ar,o}$, CH$_{Ar,p}$), 7.23–7.29 (m, 2 H, CH$_{Ar,m}$), 8.08 (d, *J* = 3.6 Hz, 1 H, NC*H*CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 (d, 1 C, NCHCH$_2$*C*H), 30.9 (t, 1 C, CH$_2$*C*H$_2$Ph), 31.0 (t, 1 C, NCH*C*H$_2$CH), 36.5 (t, 1 C, NCH*C*H$_2$C), 41.8 (t, 1 C, NCHCH$_2$CHCH$_2$), 42.31 (t, 1 C, *C*H$_2$CH$_2$Ph), 42.33 (s, 1 C, NCHCH*C*), 43.0 (d, 1 C, NCH*C*H), 55.8 (t, 1 C, N*C*HCH$_2$), 125.8 (d, 1 C, CH$_{Ar,p}$), 128.2 (d, 2 C, CH$_{Ar,o}$), 128.3 (d, 2 C, CH$_{Ar,m}$), 142.2 (s, 1 C, C$_{Ar}$), 167.1 (d, 1 C, N*C*HCH).

MS (CI, CH_5^+): *m*/*z* (%) = 226 (100) [M + H]$^+$.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{16}H_{19}N$: 225.1517; found: 225.1517.

1-Ethyl-4-azatricyclo[3.3.1.0^{2,7}]nonane Hydrochloride (9a)
The title product was prepared according to GP4 starting from **8a** (22.7 mg, 0.152 mmol) and $NaBH_3CN$ (23.9 mg, 0.380 mmol) in MeOH (2 mL) and 1.0 M ethereal HCl solution (0.760 mL). Work-up was performed with H_2O and K_2CO_3 followed by extraction with CH_2Cl_2 (10 × 3 mL) to give the desired product.

Yield: 22.8 mg (80%); colorless oil.

IR (film): 2958, 2934, 2875, 2794, 2657, 2519, 2474, 1745, 1626, 1601, 1460, 1440 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 0.86 (t, *J* = 7.5 Hz, 3 H, CH$_2$C*H*$_3$), 1.33–1.52 (m, 3 H, C*H*$_2$CH$_3$, NCHCH$_2$CHC*H*$_2$), 1.86–1.93 (m, 1 H, NCHC*H*$_2$C), 1.93–2.02 (m, 2 H, NCHCH$_2$CHC*H*$_2$, NCHC*H*$_2$CH), 2.05 (dd, *J* = 14.2, 3.5 Hz, 1 H, NCHC*H*$_2$C), 2.09–2.22 (m, 2 H, NCHC*H*$_2$CH, NCH$_2$C*H*), 2.41–2.48 (m, 1 H, NCHCH$_2$C*H*), 3.21–3.25 (m, 2 H, NC*H*$_2$CH), 3.69–3.74 (m, 1 H, NC*H*CH$_2$).

^{13}C NMR (125 MHz, CD_3OD): δ = 8.2 (q, 1 C, CH$_2$*C*H$_3$), 30.4 (d, 1 C, NCHCH$_2$*C*H), 31.4 (t, 1 C, NCH*C*H$_2$CH), 32.3 (t, 1 C, *C*H$_2$CH$_3$), 35.3 (d, 1 C, NCH$_2$*C*H), 36.5 (t, 1 C, NCH*C*H$_2$C), 39.0 (t, 1 C, N*C*H$_2$CH), 41.5 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 43.2 (s, 1 C, NCH$_2$CH*C*), 48.0 (d, 1 C, N*C*HCH$_2$).

MS (CI, CH_5^+): *m*/*z* (%) = 152 (100) [M – Cl]$^+$.

HRMS (EI$^+$): *m*/*z* [M – HCl]$^+$ calcd for $C_{10}H_{17}N$: 151.1361; found: 151.1356.

1-Phenyl-4-azatricyclo[3.3.1.0^{2,7}]nonane Hydrochloride (9b)
The title product was prepared according to GP4 starting from **8b** (29.7 mg, 0.151 mmol) and $NaBH_3CN$ (10.4 mg, 0.166 mmol) in MeOH (2 mL) and 1.0 M ethereal HCl solution (0.753 mL). Work-up was performed with H_2O and K_2CO_3 followed by extraction with CH_2Cl_2 (10 × 3 mL) to give the desired product.

Yield: 29.7 mg (84%); colorless crystals; mp 241–246 °C (dec.).

IR (KBr): 3024, 2941, 2858, 2752, 2653, 2471, 1604, 1495, 1442 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.80 (d, *J* = 9.4 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 2.11 (dd, *J* = 14.6, 3.3 Hz, 1 H, NCHC*H*$_2$CH), 2.20–2.30 (m, 2 H, NCHC*H*$_2$C, NCHC*H*$_2$CH), 2.36–2.46 (m, 2 H, NCHC*H*$_2$C, NCHCH$_2$CHC*H*$_2$), 2.54–2.61 (m, 1 H, NCHCH$_2$C*H*), 2.67–2.74 (m, 1 H, NCH$_2$C*H*), 3.42 (br d, *J* = 13.5 Hz, 1 H, NC*H*$_2$CH), 3.54 (br d, *J* = 13.5 Hz, 1 H, NC*H*$_2$CH), 3.80–3.86 (m, 1 H, NC*H*CH$_2$), 7.18–7.27 (m, 3 H, CH$_{Ar,o}$, CH$_{Ar,p}$), 7.30–7.38 (m, 2 H, CH$_{Ar,m}$).

^{13}C NMR (125 MHz, CD_3OD): δ = 30.4 (d, 1 C, NCHCH$_2$*C*H), 30.9 (t, 1 C, NCH*C*H$_2$CH), 36.2 (d, 1 C, NCH$_2$*C*H), 39.5 (t, 1 C, NCH*C*H$_2$C), 39.8 (t, 1 C, N*C*H$_2$CH). 43.0 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 45.6 (s, 1 C, NCH$_2$CH*C*), 48.1 (d, 1 C, N*C*HCH$_2$), 125.7 (d, 2 C, CH$_{Ar,o}$), 127.6 (d, 1 C, CH$_{Ar,p}$), 129.8 (d, 2 C, CH$_{Ar,m}$), 147.9 (s, 1 C, C$_{Ar}$).

MS (CI, CH_5^+): *m*/*z* (%) = 122 (50), 200 (100) [M – Cl]$^+$.

HRMS (EI$^+$): *m*/*z* [M – HCl]$^+$ calcd for $C_{14}H_{17}N$: 199.1361; found: 199.1332.

1-Benzyl-4-azatricyclo[3.3.1.0^{2,7}]nonane Hydrochloride (9c)
The title product was prepared according to GP4 starting from **8c** (20.6 mg, 0.0975 mmol) and $NaBH_3CN$ (15.3 mg, 0.244 mmol) in MeOH (2 mL) and 1.0 M ethereal HCl solution (0.487 mL). Work-up was performed with H_2O and K_2CO_3 followed by extraction with CH_2Cl_2 (10 × 3 mL) to give the desired product.

Yield: 21.4 mg (89%); colorless crystals; mp 170–172 °C (dec.).

IR (KBr): 3061, 2956, 2930, 2837, 2810, 2783, 2753, 2726, 2669, 2537, 2509, 2475, 1598, 1495, 1451, 1432 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 1.35 (d, *J* = 9.5 Hz, 1 H, NCHCH$_2$CHC*H*$_2$), 1.90 (dd, *J* = 14.5, 3.8 Hz, 1 H, NCHC*H*$_2$C), 1.94 (dd, *J* = 14.6, 3.9 Hz, 1 H, NCHC*H*$_2$CH), 1.95–2.01 (m, 1 H, NCHC*H*$_2$C), 2.06–2.14 (m, 2 H, NCHC*H*$_2$CH, NCHCH$_2$CHC*H*$_2$), 2.26–2.31 (m, 1 H, NCH$_2$C*H*), 2.40–2.46 (m, 1 H, NCHCH$_2$C*H*), 2.70 (s, 2 H, CH$_2$Ph), 3.10 (dd, *J* = 13.4, 1.7 Hz, 1 H, NC*H*$_2$CH), 3.19 (dd, *J* = 13.4, 2.2 Hz, 1 H, NC*H*$_2$CH), 3.63–3.68 (m, 1 H, NC*H*CH$_2$), 7.12–7.18 (m, 2 H, CH$_{Ar,o}$), 7.19–7.24 (m, 1 H, CH$_{Ar,p}$), 7.26–7.33 (m, 2 H, CH$_{Ar,m}$).

^{13}C NMR (125 MHz, CD_3OD): δ = 30.8 (d, 1 C, NCHCH$_2$*C*H), 31.6 (t, 1 C, NCH*C*H$_2$CH), 35.0 (d, 1 C, NCH$_2$*C*H), 36.7 (t, 1 C, NCH*C*H$_2$C), 38.9 (t, 1 C, N*C*H$_2$CH), 42.2 (t, 1 C, NCHCH$_2$CH*C*H$_2$), 43.2 (s, 1 C, NCH$_2$CH*C*), 45.6 (t, 1 C, CH$_2$Ph), 48.0 (d, 1 C, N*C*HCH$_2$), 127.5 (d, 1 C, CH$_{Ar,p}$), 129.5 (d, 2 C, CH$_{Ar,m}$), 130.8 (d, 2 C, CH$_{Ar,o}$), 138.6 (s, 1 C, C$_{Ar}$).

MS (CI, CH_5^+): *m*/*z* (%) = 214 (100) [M – Cl]$^+$.

HRMS (EI$^+$): *m*/*z* [M – HCl]$^+$ calcd for $C_{15}H_{19}N$: 213.1517; found: 213.1496.

1-(2-Phenylethyl)-4-azatricyclo[3.3.1.0^{2,7}]nonane Hydrochloride (9d)
The title product was prepared according to GP4 starting from **8d** (20.0 mg, 0.0888 mmol) and $NaBH_3CN$ (13.9 mg, 0.222 mmol) in MeOH (2 mL) and 2.0 M ethereal HCl solution (0.222 mL). Work-up was performed with H_2O and K_2CO_3 followed by extraction with CH_2Cl_2 (10 × 3 mL) to give the desired product.

Yield: 21.5 mg (92%); colorless crystals; mp 170–172 °C (dec.).

IR (KBr): 3024, 2945, 2932, 2859, 2829, 2800, 2757, 2716, 2652, 2521, 2469, 1600, 1495, 1454, 1435 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 1.38 (d, *J* = 9.5 Hz, 1 H, $NCHCH_2CHCH_2$), 1.68 (ddd, *J* = 13.6, 9.8, 7.1 Hz, 1 H, CH_2CH_2Ph), 1.78 (ddd, *J* = 13.6, 9.8, 7.1 Hz, 1 H, CH_2CH_2Ph), 1.94–2.01 (m, 2 H, $NCHCH_2C$, $NCHCH_2CH$), 2.02–2.08 (m, 1 H, NCH_2CHCH_2), 2.09–2.18 (m, 2 H, $NCHCH_2C$, $NCHCH_2CH$), 2.20–2.25 (m, 1 H, NCH_2CH), 2.43–2.50 (m, 1 H, $NCHCH_2CH$), 2.52–2.64 (m, 2 H, CH_2CH_2Ph), 3.21–3.25 (m, 2 H, NCH_2CH), 3.69–3.75 (m, 1 H, $NCHCH_2$), 7.11–7.17 (m, 1 H, $CH_{Ar,p}$), 7.17–7.22 (m, 2 H, $CH_{Ar,o}$), 7.22–7.28 (m, 2 H, $CH_{Ar,m}$).

^{13}C NMR (125 MHz, CD_3OD): δ = 30.6 (d, 1 C, $NCHCH_2CH$), 31.2 (t, 1 C, CH_2CH_2Ph or $NCHCH_2CH$), 31.3 (t, 1 C, CH_2CH_2Ph or $NCHCH_2CH$), 35.9 (d, 1 C, NCH_2CH), 36.7 (t, 1 C, $NCHCH_2C$), 38.9 (t, 1 C, NCH_2CH), 42.0 (t, 1 C, CH_2CH_2Ph or $NCHCH_2CHCH_2$), 42.1 (t, 1 C, CH_2CH_2Ph or $NCHCH_2CHCH_2$), 42.7 (s, 1 C, NCH_2CHC), 47.9 (d, 1 C, $NCHCH_2$), 126.9 (d, 1 C, $CH_{Ar,p}$), 129.3 (d, 2 C, CH_{Ar}), 129.4 (d, 2 C, CH_{Ar}), 143.5 (s, 1 C, C_{Ar}).

MS (CI, CH_5^+): *m*/*z* (%) = 228 (100) $[M - Cl]^+$.

HRMS (EI^+): *m*/*z* $[M - HCl]^+$ calcd for $C_{16}H_{21}N$: 227.1674; found: 227.1648.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Popik, P.; Layer, R. T.; Skolnick, P. *Pharmacol. Rev.* **1995**, *47*, 235. (b) Levi, M. S.; Borne, R. F. *Curr. Med. Chem.* **2002**, *9*, 1807. (c) Khan, M. O. F.; Levi, M. S.; Clark, C. R.; Ablorderrey, S. Y.; Law, S.-J.; Wilson, N. H.; Borne, R. F. In Attr-ur-Rahman *Studies in Natural Product Chemistry*; Vol. 34; Elsevier: Amsterdam, **2008**, 753.

(2) Graham, P. M.; Delafuente, D. A.; Liu, W.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **2005**, *127*, 10568.

(3) (a) Passarella, D.; Favia, R.; Giardini, A.; Lesma, G.; Martinelli, M.; Silvani, A.; Danieli, B.; Efange, S. M.; Mash, D. C. *Bioorg. Med. Chem.* **2003**, *11*, 1007. (b) Okamura, H.; Nagaike, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 8317.

(4) (a) Maia, A. A.; Freitas-Gil, R. P.; Gil, L. F.; Marazano, C. *Lett. Org.Chem.* **2004**, *1*, 168. (b) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973. (c) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299. (d) Matsumura, Y.; Nakamura, Y.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 7685.

(5) (a) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009. (b) Lamy-Schelkens, H.; Giomi, D.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 5887.

(6) (a) Craig, D.; Schaefgen, L.; Tyler, W. P. *J. Am. Chem. Soc.* **1948**, *70*, 1624. (b) Craig, D.; Kuder, A. K.; Efroymson, J. *J. Am. Chem. Soc.* **1950**, *72*, 5236.

(7) (a) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1985**, *50*, 2427. (b) Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1985**, *50*, 2423. (c) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1986**, *51*, 142. (d) Hartman, G. D.; Phillips, B. T.; Halczenko, W. *J. Org. Chem.* **1987**, *52*, 1136. (e) Hartman, G. D.; Phillips, B. T.; Halczenko, W.; Pitzenberger, S. M. *J. Org. Chem.* **1989**, *54*, 4134.

(8) (a) Bräckow, J.; Wanner, K. T. *Tetrahedron* **2006**, *62*, 2395. (b) Bräckow, J. *PhD Thesis*; Ludwig-Maximilians-Universität München: Germany, **2006**.

(9) (a) Schmaunz, C. E.; Pabel, J.; Wanner, K. T. *Synthesis* **2010**, 2147. (b) Schmaunz, C. E.; Wanner, K. T. *Synthesis* **2011**, 3332. (c) Schmaunz, C. E. *PhD Thesis*; Ludwig-Maximilians-Universität München: Germany, **2012**.

(10) The crystallographic data for compounds **7a** and **8c** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 918295 and CCDC 918294, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk]. ORTEP (Burnett, M. N.; Johnson, C. K. *ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations*, Oak Ridge National Laboratory Report ORNL-6895, 1996); Windows version (Farrugia, L. J., Univ. Glasgow) used.

(11) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: New York, **1988**.

(12) Ágai, B.; Proszenyák, A.; Tárkányi, G.; Vida, L.; Faigl, F. *Eur. J. Org. Chem.* **2004**, *17*, 3623.

(13) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: New York, **1995**, 65–67.

