Synthesis of 1,2,2a,3-Tetrahydro-1,4,7b-triazacyclopenta[*cd*]indenes

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Abstract: 1,2,2a,3-Tetrahydro-1,4,7b-triazacyclopenta[*cd*]indenes **12** were obtained from 3-halomethyl-5-chloro-6- or 8-nitropyridines in a novel reaction sequence which comprises a nucleophilic aromatic substitution followed by an intramolecular nucleophilic substitution. The starting material for this reaction (**9a**) can be prepared in good yields by halocyclization of the easily accessible 2-allylamino-6-chloro-3-nitropyridine (**4a**). Aliphatic as well as aromatic amines are suitable unless they are strongly deactivated. The tricyclic compounds are relatively reactive electrophiles and may serve as interesting intermediates for combinatorial syntheses.

Key words: polycycles, ring closure, nucleophilic aromatic substitutions, halogenation, amines

For an investigation of structure-conformation relationships of 2,6-bis-anilino-3-nitropyridines (**1**, Figure 1) we needed conformationally rigid analogues in which either R^1 or R^2 form a bridge between their aniline nitrogen atoms and the pyridine nitrogen (**2**, **3**, Figure 1).

The main objective, however, was using these compounds as new, non-planar scaffolds and intermediates for combinatorial syntheses of potential new drug molecules. Therefore, we were interested in compounds of type **2** or **3** in which the R^1 or R^2 bridges carry reactive groups that can be further structurally modified with readily accessible reagents.

Under these considerations, halocyclization of allylamino pyridines **4** to **5** followed by nucleophilic replacement of the chlorine in 6-position (6-Cl) (**6**) seemed to us an attractive synthetic approach to compounds of type **2** (Scheme 1).

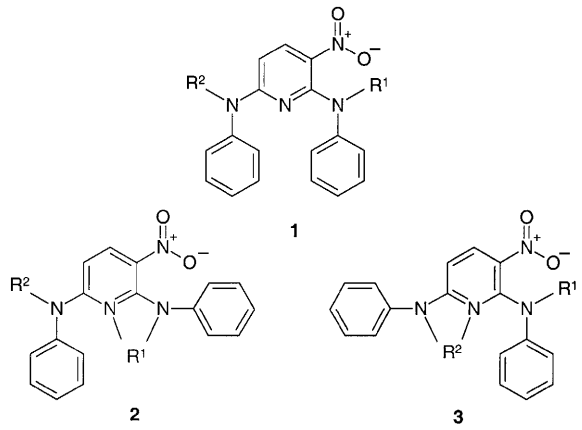
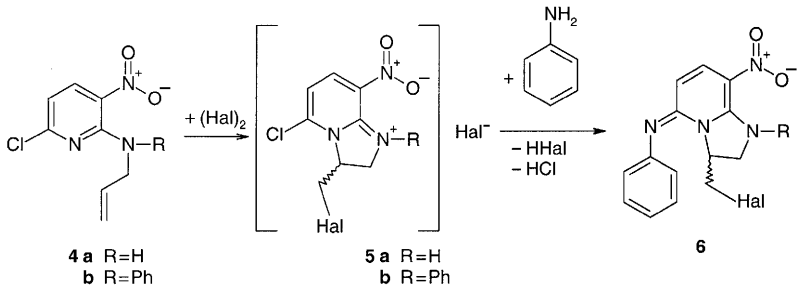


Figure 1

The halomethyl sidechain formed in the halocyclization offers a further possibility of increasing structural diversity, e.g., via nucleophilic replacement of the halogen atom by amines.

Halocyclizations have been successfully applied to the synthesis of a great variety of (partially) saturated heterocycles. Thus, allyl ureas[2–6] or *O*-alkyl isoureas[7] were converted to the corresponding imidazole derivatives with iodine, 3-allyl-2-amino-3,5-dihydroimidazol-4-ones to 2-iodomethyltetrahydroimidazo[1,2-*a*]imidazolones,[8] 3-acylamino-4-methallyl-1,2,4-triazoles to the corresponding 2-bromomethylimidazo[2,1-*c*]-1,2,4-triazoles,[9] 3-allylamino-5-phenyl-1,2,4-triazine to 3-bromomethyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]-1,2,4-triazinium bromide,[10] 3-allyl-4-imino-3,4-dihydroquinazoline-



Scheme 1 Halocyclization as an approach to compounds of type **2** with a chemically reactive side chain

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2(1*H*)-ones and -thiones to imidazo[1,2-*c*]quinazoline-5(6*H*)-ones and -thiones,[11] 4-allylamino-2-methylthioquinazoline to 3-bromomethyl-5-methylthio-2,3-dihydroimidazo[1,2-*c*]quinazoline,[11,12] 3-allylamino-4*H*-1,2,4-benzothiadiazine-1,1-dioxide to 3-bromomethyl-2,3-dihydro-1*H*-imidazo[1,2-*b*]-1,2,4-benzothiadiazine-5,5-dioxide,[13] 2-allylaminopteridin-4(3*H*)-ones to 1-iodomethyl-1,2-dihydroimidazo[1,2-*a*]pteridin-5(4*H*)-ones,[14] and 3-allyl-2-anilinopteridin-4(3*H*)-ones to 7,8-dihydro-7-iodomethyl-6-phenylimidazo[2,1-*b*]pteridin-10(6*H*)-ones.[15] There is also one report on the successful application to 2-allylaminopyridine to give 3-bromomethyl-2,3-dihydroimidazo[1,2-*a*]pyridine.[16]

The starting material in ref.[16] differs from the one that is needed for the present purpose (**4b**) by the absence of electron-withdrawing groups, which may seriously impede halocyclization. As a means of clarifying this point, we applied the reaction in a first attempt to **4a**, which covers the electronic effects of the nitro group and the chlorine but not yet the electron-withdrawing mesomeric effect of the phenyl group.

When **4a** was treated with bromine in anhydrous CH_2Cl_2 or chlorobenzene a precipitate formed the ^1H NMR spectrum of which in DMSO-d_6 indicated the presence of mainly two components (**7**, **8**, Figure 2) in variable ratios.

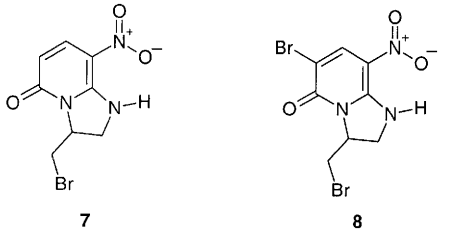
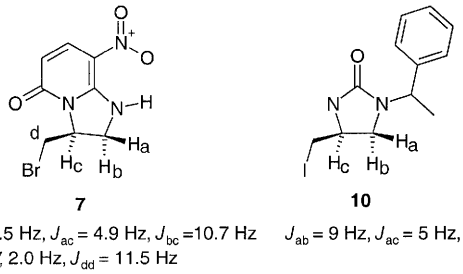


Figure 2

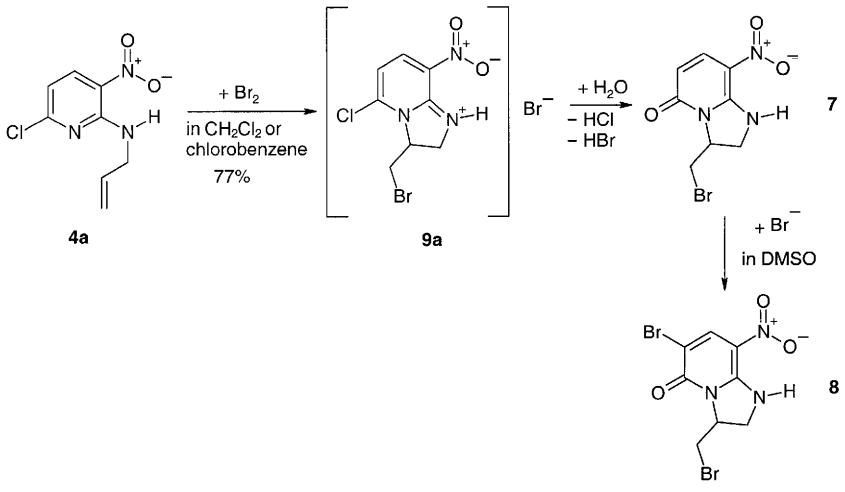
However, a spectrum of the same precipitate in DMF-d_7 shows only signals of **7**. Therefore, the observed bromination must be attributed to an oxidation of the bromide ions present in the precipitate by DMSO.[17] A spectrum recorded in $CDCl_3$ [the precipitate itself is insoluble but addition of some *N*,*N*-diisopropylethylamine (DIPEA) gives a sufficiently concentrated solution] as well as a mass spectrum and the elemental analysis indicated clearly that the precipitate is in fact the primary cyclization product **9a** (Scheme 2). The lactam **7** originates from a hydrolysis by the water content of the solvents used to prepare the NMR samples.

Considering the apparent ease of nucleophilic replacement of the chlorine, a great variety of 6-(substituted anilino) derivatives of type **2** ought to be readily accessible from **9a** or **9b**. However, when **9a** was treated with aniline in CH_2Cl_2 in the presence of DIPEA, a product precipitated which in the ^1H NMR spectrum showed coupling patterns of the aliphatic hydrogen atoms that differed remarkably from those of the imidazo[1,2-*a*]pyridines discussed above (e.g., **7**) and from those reported in the literature for the related imidazolidinone **10**[7] both of which show very similar coupling patterns (Scheme 3).



Scheme 3 Correspondence between the coupling pattern of **7** (DMSO) and a reference compound **10** ($CDCl_3$)[7]

Except for H_b each of these hydrogen atoms has only one coupling constant in the area of 10 Hz (for **10** J_{cd} and J_{dd} were not given). On the contrary, the coupling constants of the aliphatic hydrogen atoms of the new product all ranged from 9.1 to 12.5 Hz (DMSO). Taking this pattern together with mechanistic aspects leaves **12a** as the only

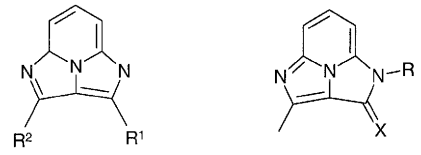


Scheme 2 Halocyclization of **4a** and origin of products **7** and **8**

plausible structure for the new product. Conceivably, the expected nucleophilic aromatic substitution had taken place (**11a**) but was rapidly followed by ring closure (Scheme 4).

To our knowledge, neither 1,2,2a,3-tetrahdro-1,4,7b-triaza-cyclopent[*cd*]indenes nor the present synthetic approach to the parent tricyclic system or its hydrogenated analogs have so far been reported in the literature. The unsubsituted[18] and the 2,3-dimethylated[19] fully aromatic tricyclic system (**13**, Figure 3) and the 1,2-dihydro- and 2-oxo-1*H*-derivatives of the former[18] have, however, been synthesized previously from 5-amino-3-ethoxycarbonylimidazo[1,2-*a*]pyridine[18] and 3-acetyl-5-acetylamino-2-methylimidazo[1,2-*a*]pyridine respectively. Variously 1-substituted 3-methyl-1,2-dihydro-1,4,7b-triazacyclopent[*cd*]indenes (**14a**, Figure 3)[20] and their 2-oxo-derivatives (**14b**, Figure 3)[20,21] have been synthesized and exerted kinase inhibiting,[21a] chemokine receptor antagonist,[21b] and platelet-derived growth factor inhibiting[20,21c,d] activities.

In order to examine the scope of the new reaction, a number of diverse aromatic amines as well as some aliphatic amines were reacted with **9a** (Scheme 5). The tricyclic system forms readily with aromatic amines including sterically hindered ones. However, there seem to be limitations with respect to the electron-withdrawing character of the aromatic system. 2-Nitro-aniline did not react whereas 2-aminopyridine and 4-aminobenzamide yielded



13 **a** $R^1 = R^2 = H$
b $R^1 = R^2 = Me$

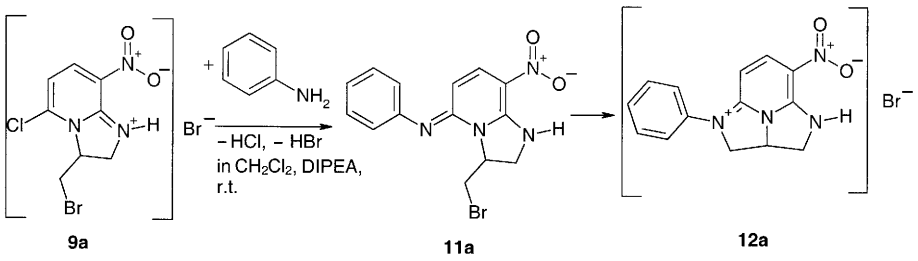
14 **a** X = H_2
b X = O

Figure 3

mainly the expected products but we were unable to purify them sufficiently.

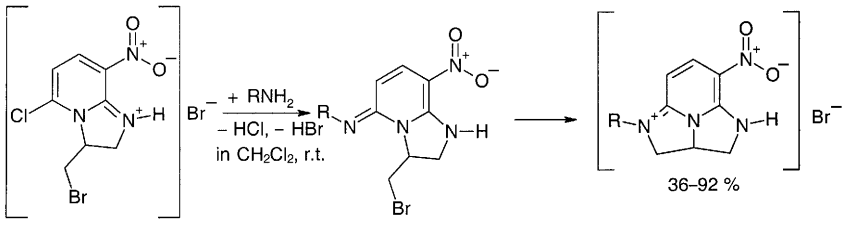
With aliphatic amines, the second step of the reaction seems to be rate limiting which made it possible to determine the more or less complete ^{1}H NMR spectra of the intermediates **11h–j**. Secondary amines **15a**,**b** also reacted with **9a** but in this case the intermediates **16a**,**b** did not undergo ring formation (Scheme 6).

Solutions of **4b** in CH_2Cl_2 or chlorobenzene also reacted with bromine but no precipitation formed in CH_2Cl_2, whilst in chlorobenzene an oily lower phase appeared. On evaporation of the solvent a glassy material remained which is most likely **9b** (Scheme 7). Attempts to characterize the material spectroscopically at least in crude form failed because DMSO solutions decomposed rapidly while in $CDCl_3$; only the aryl hydrogens gave well-resolved signals. However, on treatment of a sample of the material with aniline a solid product was obtained, which according to the ^{1}H NMR spectrum was a 9:1 mixture of



9a **11a** **12a**

Scheme 4

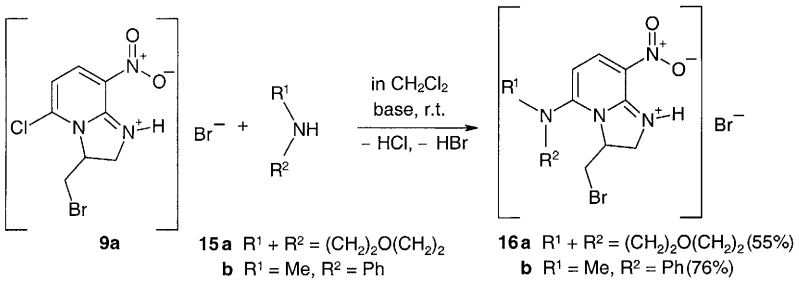


9a

11 **h** R = CH_2Ph
i R = $(CH_2)_3Ph$
j R = cyclohexyl

12 **a** R = Ph
b R = 2-MePh
c R = 2,6-(di-Me)Ph
d R = 2-(OMe)Ph
e R = 3-(OMe)Ph
f R = 3-($CONH_2$)Ph
g R = 3-pyridyl
h R = CH_2Ph
i R = $(CH_2)_3Ph$
j R = cyclohexyl

Scheme 5



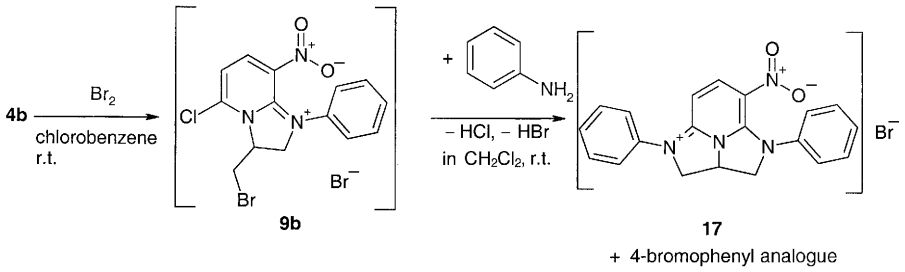
Scheme 6

the tricyclic compound **17** and a derivative of it in which one of the phenyl rings is brominated in *para* position (Scheme 7).

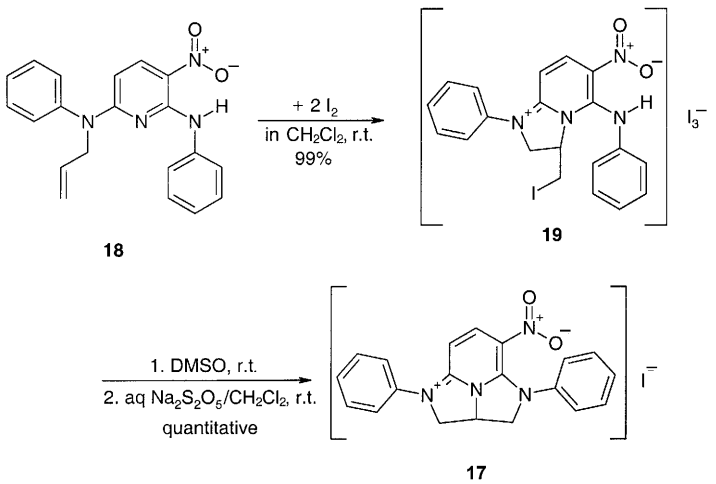
This side product may arise from bromine that remains absorbed in the crude **9b** probably in the form of a tribromide.

Since separation from the side product turned out to be very difficult, we looked for a more satisfactory alternative. We found that the easily accessible 2-anilino-6-(*N*-allylanilino)-3-nitropyridine (**18**) can be cyclized with iodine without formation of halogenated side products. The intermediate **19** cyclizes when dissolved in DMSO whilst the subsequent reduction of the triiodide to the iodide was necessary to obtain a product with a reproducible salt form (Scheme 8).

The reaction of **9a** with amines gives good results only if the latter are added in equimolar amounts. Excess amine leads to product mixtures due to nucleophilic ring opening. This limitation makes it inconvenient to synthesize the unsubstituted 5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopenta[*cd*]indene **20** from **9a** and NH_3. Therefore, an alternative synthesis strategy was developed. An obvious possibility consists of exchanging the chlorine in 6-position of **4a** prior to halocyclization, i.e., starting the synthesis of **20** from the 6-amino derivative **21** (Scheme 9). Unfortunately, such an approach always led to side products due to 5-bromination of the pyridine. Acylation of the amino groups would solve this problem provided the acylation products still undergo halocyclization. In the present case double acylation (**22**) was required in order to avoid the side reaction. Treatment of



Scheme 7



Scheme 8

this product with bromine in CH_2Cl_2 resulted in a mixture the ^1H NMR spectrum of which suggested that it is mainly composed of the addition product **23** and the imidazo[1,2-*a*]pyridine **24** in a ratio of 2:1 (Scheme 9). Apparently, the double acylation reduced the nucleophilicity of the ring nitrogen to such an extent that bromine addition to the double bond was now able to compete successfully with ring formation.

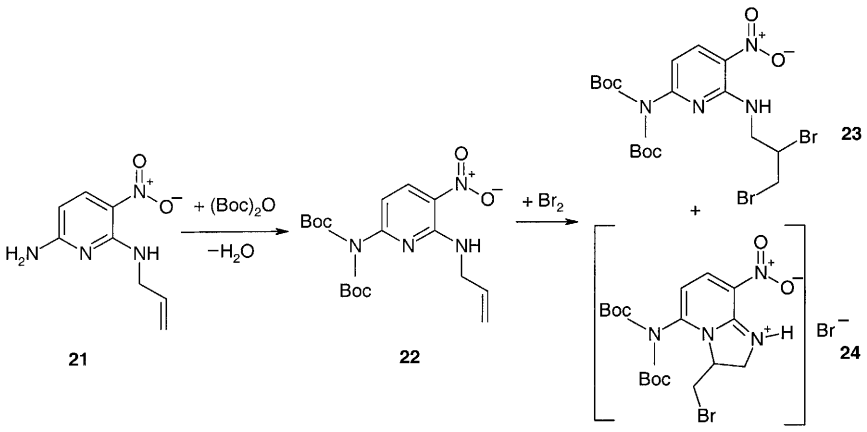
In principle, it is possible to solve this latter problem by using iodine as a cyclization reagent. The Boc groups can be removed by heating the resulting imidazo[1,2-*a*]pyridine **25** to 60 °C for 12 hours to afford the fully deprotected amino derivative **26** (Scheme 10).

The temperature at which this deprotection occurs is surprisingly low considering reports on the thermal cleavage of Boc groups in which much higher temperatures (refluxing quinoline or diphenyl,[22] or heating at 185 °C[23]) were necessary.

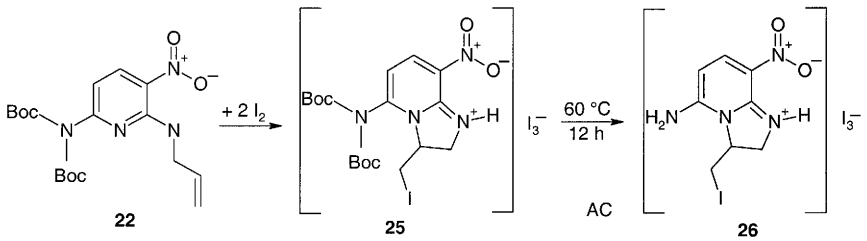
However, the procedure was still not ideal because the intermediate **25** is not stable enough to be isolated in pure form and therefore would have to be used as crude material in the next step. In addition, it turned out to be important to reduce the triiodide to iodide before ring closure to **20**.

A more satisfactory way of synthesizing **20** became possible when we found that **26** can be obtained directly and without side reactions from **21** with 1.5 equivalents of iodine (Scheme 11). The excess iodine was removed by heating with DMF to 60 °C. Treatment of **26** with base afforded the *N*-unsubstituted tricyclic system **20** (Scheme 11).

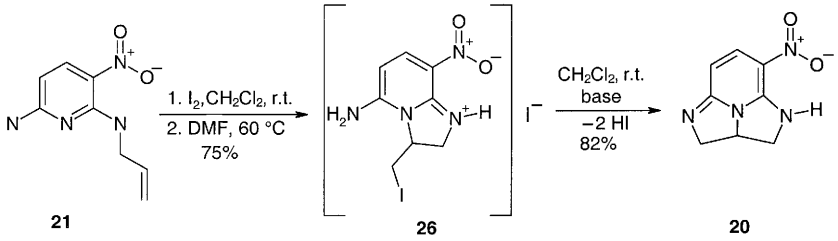
This latter route turned out to be also the most suitable one for the preparation of the 7-nitro-1-phenyl-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopenta[*cd*]indene (**27**) from 6-allylamino-2-anilino-3-nitropyridine (**28**; Scheme 12). In the first step it was, however, necessary to use two equivalents of iodine. Due to the higher lipophilicity of the intermediate **29** it was possible to reduce the excess iodine with aqueous sodium disulfite.



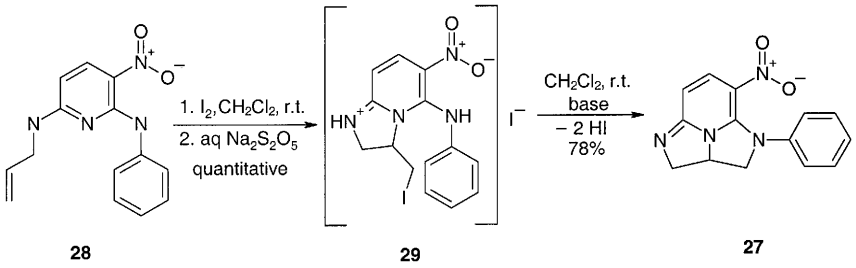
Scheme 9



Scheme 10



Scheme 11



Scheme 12

Despite the presence of two electronegative groups, 2-allylamino-6-chloro-3-nitropyridine can undergo a halocyclization reaction with bromine. If the electron-withdrawing character of the substituents increases (e.g. **22**) the competing addition of bromine to the allylic double bond becomes more important and can even gain the upper hand. A clean halocyclization may, however, still be achieved if iodine is used as a cyclization reagent.

The imidazo[1,2-*a*]pyridines formed in the reaction contain two electrophilic centers, one in 5-position and the other one in the side chain. The former one is considerably more reactive but when primary amines are used as nucleophiles the second center can undergo a subsequent intramolecular nucleophilic substitution to form a new tricyclic structure, i.e., a 1,2,2a,3-tetrahydro-1,4,7b-triaza-cyclopenta[*cd*]indene. The sensitivity to nucleophiles such as water and amines could make these compounds interesting candidates for intermediates in combinatorial syntheses.

For chromatography, silica gel 60 (230–400 mesh) from Fluka was used. Melting points were measured on a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer, in DMSO-d_6 (400 MHz for ^{1}H, 100 MHz for ^{13}C) unless stated otherwise. Chemical shifts are expressed in ppm with δ (DMSO-d_6) = 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C as internal standards. 2D-NMR spectra were recorded in DMSO at 303 K on a Bruker DPX400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C; internal reference: TMS δ = 0.00 ppm for ^{1}H and ^{13}C-DMSO δ = 39.5 ppm for ^{13}C). CI and EI mass spectra were recorded on a Finnigan SSQ7000 mass spectrometer. High-resolution ESI mass spectra were recorded on a Micromass QTOF-2 instrument. Elemental analyses were done with an Elementar Analysensysteme Vario EL analyzer. Petroleum ether used had a boiling range of 35–60 °C.

2-Allylamino-6-chloro-3-nitropyridine (4a)

To a solution of 2,6-dichloro-3-nitropyridine (4.82 g, 25 mmol) in CH_2Cl_2 (100 mL) were added at –15 °C Et_3N (2.63 g, 3.60 mL, 26 mmol) and subsequently dropwise within 8 h allyl amine (1.48 g, 1.95 mL, 26 mmol). After another 8 h at r.t., the solution was washed with 0.2 M aq citric acid and sat. aq $NaHCO_3$ and evaporated. The crude product was crystallized from EtOH.

Yield: 4.90 g (92%); yellow needles; mp 58–59 °C.

^{1}H NMR: δ = 4.14 (t, J = 5.3 Hz, 2 H, CH_2), 5.10 (m, 1 H, H3′ *trans* to CH_2), 5.17 (m, 1 H, H3′ *cis* to CH_2), 5.93 (ddt, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 5.1 Hz, 1 H, H2′), 6.78 (d, J = 8.6 Hz, 1 H, H5), 8.43 (d, J = 8.6 Hz, 1 H, H4), 8.78 (br t, J = 5 Hz, 1 H, NH).

^{13}C NMR: δ = 155.0, 151.4, 138.6, 134.4, 126.8, 115.8, 111.6, 43.1.

MS (CI): m/z = 214 $[M + H]^+$, 216.

Anal. Calcd for $C_8H_8ClN_3O_2$: C, 44.99; H, 3.77; N, 19.67. Found: C, 45.07; H, 3.79; N, 19.70.

2-*N*-Allylanilino-6-chloro-3-nitropyridine (4b)

A mixture of 2-anilino-6-chloro-3-nitropyridine[24] (1000 mg, 4 mmol), ally bromide (725 mg, 0.51 mL, 6 mmol), K_2CO_3 (702 mg, 6 mmol) and DMF (5 mL) was stirred at r.t. After 1 d another portion of allyl bromide (72 mg, 0.05 mL, 0.6 mmol) was added and stirring continued for 1 d. Water was added and the resulting mixture was extracted with EtOAc. In order to separate the product from unreacted starting material, the solvent was evaporated and the residue dissolved in EtOH (3 mL). *o*-Phenylenediamine (20 mg) and DIPEA (0.02 mL) were added and the solution was warmed to 40 °C for 2 d. After evaporation of the solvent the residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 4:1).

Yield: 701 mg (60%); orange solid; mp 36 °C.

^{1}H NMR: δ = 4.66 (dt, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 2 H, CH_2), 5.12 (dq, J_1 = 10.4 Hz, J_2 = 1.5 Hz, 1 H, H3′ *trans* to CH_2), 5.23 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1 H, H3′ *cis* to CH_2), 5.96 (ddt, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 5.2 Hz, 1 H, H2′), 7.08 (d, J = 8.3 Hz, 1 H, H5), 7.09 (m, 2 H, *ortho*-H), 7.12 (m, 1 H, *para*-H), 7.28 (m, 2 H, *meta*-H), 8.16 (d, J = 8.3 Hz, 1 H, H4).

^{13}C NMR: δ = 150.9, 149.4, 144.3, 138.7, 133.6, 133.5, 129.6, 125.6, 122.4, 117.2, 114.8, 54.4.

MS (CI): m/z = 290 $[M + H]^+$, 292.

Anal. Calcd for $C_{14}H_{12}ClN_3O_2$: C, 58.04; H, 4.17; N, 14.50. Found: C, 58.03; H, 4.22; N, 14.44.

3-Bromomethyl-8-nitro-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-5-one (7)

Compound **9a** (150 mg, 0.4 mmol) was added to a stirred mixture of EtOAc (50 mL) and sat. aq $NaHCO_3$ solution (50 mL). After 3 h at r.t., the organic phase was concentrated in vacuo and the residue crystallized from toluene.

Yield: 87 mg (89%); pale yellow crystals; mp 172 °C.

^{1}H NMR: δ = 3.67 (ddd, J_1 = 11.6 Hz, J_2 = 4.8 Hz, J_3 = 1.0 Hz, 1 H, H2 *trans* to H3), 3.83 (dd, J_1 = 10.6 Hz, J_2 = 2.0 Hz, 1 H, CH_2), 4.03 (t, J = 11.1 Hz, 1 H, H2 *cis* to H3), 4.13 (dd, J_1 = 10.6 Hz, J_2 = 4.6 Hz, 1 H, CH_2), 5.03 (dtd, J_1 = 10.6 Hz, J_2 = 4.8 Hz, J_3 = 2.0 Hz, 1 H, H3), 5.70 (d, J = 10.1 Hz, 1 H, H6), 7.96 (d, J = 10.1 Hz, 1 H, H7), 9.52 (br s, 1 H, NH).

^{13}C NMR: δ = 160.2, 151.6, 135.8, 112.3, 107.0, 56.0, 47.8, 34.7.

MS (CI): m/z = 274 $[M + H]^+$, 276.

Anal. Calcd for $C_8H_8BrN_3O_3$: C, 35.06; H, 2.94; N, 15.33. Found: C, 34.85; H, 2.94; N, 15.19.

6-Bromo-3-bromomethyl-8-nitro-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-5-one (8)

To a suspension of **7** (240 mg, 0.87 mmol) in CH_2Cl_2 (5 mL) was added dropwise at r.t. a solution of bromine (139 mg, 0.044 mL, 0.87 mmol) in CH_2Cl_2 (5 mL). After the addition was completed the mixture was stirred for 4 h and evaporated. The residue was crystallized from *n*-hexane–EtOAc (4:1).

Yield: 200 mg (65%); pale yellow powder; mp 220 °C (decomp.).

^{1}H NMR: δ = 3.70 (ddd, J_1 = 11.6 Hz, J_2 = 5.1 Hz, J_3 = 1.0 Hz, 1 H, H2 *trans* to H3), 3.84 (dd, J_1 = 10.9 Hz, J_2 = 2.0 Hz, 1 H, CH_2), 4.05 (t, J = 11.2 Hz, 1 H, H2 *cis* to H3), 4.11 (dd, J_1 = 10.8 Hz, J_2 = 4.8 Hz, 1 H, CH_2), 5.07 (dtd, J_1 = 10.8 Hz, J_2 = 4.9 Hz, J_3 = 2.0 Hz, 1 H, H3), 8.32 (s, 1 H, H7), 9.65 (s, 1 H, NH).

^{13}C NMR: δ = 156.3, 151.0, 136.8, 112.4, 99.1, 57.0, 48.2, 34.3.

MS (CI): *m*/*z* = 352 $[M + H]^+$, 354, 356.

Anal. Calcd for $C_8H_8Br_2N_3O_3$: C, 27.22; H, 2.00; N, 11.90. Found: C, 27.07; H, 1.99; N, 11.89.

3-Bromomethyl-5-chloro-8-nitro-2,3-dihydroimidazo[1,2-*a*]pyridine Hydrobromide (9a)

To a solution of **4a** (4.62 g, 23 mmol) in chlorobenzene (100 mL) was added dropwise within 2 h a solution of bromine (3.44 g, 23 mmol) in chlorobenzene (20 mL). The mixture from which a solid precipitated was stirred for 15 h at r.t. and then treated with cyclohexene (0.6 mL). Stirring was continued for 2 h and the precipitate was collected by filtration, washed with CH_2Cl_2 and dried over paraffin.

Yield: 6.58 g (77%); yellowish crystals; mp 217–219 °C (decomp.).

^{1}H NMR ($CDCl_3$ + 9 equiv DIPEA): δ = 3.53 (dd, J_1 = 10.6 Hz, J_2 = 2.8 Hz, 1 H, CH_2Br), 3.62 (dd, J_1 = 10.6 Hz, J_2 = 7.6Hz, 1 H, CH_2Br), 4.11 (dd, J_1 = 15.7 Hz, J_2 = 3.9 Hz, 1 H, H2 *trans* to H3), 4.25 (dd, J_1 = 15.7 Hz, J_2 = 10.0 Hz, 1 H, H2 *cis* to H3), 4.76 (dddd, J_1 = 10.0 Hz, J_2 = 7.6 Hz, J_3 = 3.9 Hz, J_4 = 2.8 Hz, 1 H, H3), 5.79 (d, J = 8.1 Hz, 1 H, H6), 8.06 (d, J = 8.1 Hz, 1 H, H7); the assignment of the H-atoms in position 2 is based on the coupling constants and is in agreement with the assignment reported for equivalent protons in iodomethylimidazolinones (ref.[7]).

MS (EI): *m*/*z* = 291 $[M]^+$, 293, 295; due to a replacement of chlorine by bromine which (considering the analytical data) occurs during recording of the MS data [*m*/*z* = 335 $[M(Br)]^+$, 337, 339].

Anal. Calcd for $C_8H_7BrClN_3O_2$·HBr: C, 25.73; H, 2.16; N, 11.25. Found: C, 25.51; H, 2.28; N, 11.03.

5-Nitro-1-phenyl-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12a)

To a mixture of **9a** (1.50 g, 4.0 mmol) in CH_2Cl_2 (40 mL) and DIPEA (1.03 g, 1.37 mL, 8.0 mmol) was added a solution of aniline (0.37 g, 4.0 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at r.t. for 24 h, the precipitate collected by filtration, washed with CH_2Cl_2 and dried.

Yield: 1.17 g (84%); yellow solid; mp 275–277 °C.

^{1}H NMR: δ = 4.26 (dd, J_1 = 12.2 Hz, J_2 = 10.6 Hz, 1 H, H3 *cis* to H2a), 4.37 (dd, J_1 = 10.4 Hz, J_2 = 9.3 Hz, 1 H, H3 *trans* to H2a), 4.65 (dd, J_1 = 9.7 Hz, 9.2 Hz, 1 H, H2 *trans* to H2a), 4.96 (dd, J_1 = 12.5 Hz, J_2 = 10.0 Hz, 1 H, H2 *cis* to H2a), 5.51 (tt, J_1 = 12.3 Hz, J_2 = 9.2 Hz, 1 H, H2a), 6.49 (d, J = 9.4 Hz, 1 H, H7), 7.41 (m, 1 H, H4′), 7.48 (m, 2 H, H2′), 7.58 (m, 2 H, H3′), 8.39 (d, J = 9.4 Hz, 1 H, H6), 10.16 (br s, 1 H, NH).

^{13}C NMR: δ = 153.3, 149.8, 143.2, 136.3, 130.0, 127.4, 120.7, 120.3, 95.4, 60.9, 55.6, 54.2. In an HC–HMBC experiment cross peaks were observed between 3-H (*trans* to 2a-H) and C-4a and between 2-H (*trans* to 2a-H) and C-7a but not between these two carbon atoms and 2a-H, 2-H (*cis*), or 3-H (*cis*).

MS (CI): *m*/*z* = 269 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{12}N_4O_2$·HBr: C, 48.16; H, 3.75; N, 16.04. Found: C, 48.05; H, 3.81; N, 16.12.

Analogously were prepared:

1-(2-Methylphenyl)-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide, Hydrochloride (12b)

Prepared from **9a** (187 mg, 0.5 mmol) and 2-methylaniline (54 mg, 0.5 mmol) with DIPEA (65 mg, 0.5 mmol).

Yield: 175 mg (69%); yellow solid; mp 225 °C (decomp.).

^{1}H NMR: δ = 2.33 (s, 3 H, CH_3), 4.28 (t, J = 11 Hz, 1 H, H3 *cis* to H2a), 4.36 (t, J = 10 Hz, 1 H, H3 *trans* to 2a-H), 4.57 (dd, J_1 = 10.2 Hz, J_2 = 9.6 Hz, 1 H, H2 *trans* to H2a), 4.73 (dd, J_1 = 12.3 Hz, J_2 = 10.2 Hz, 1 H, H2 *cis* to H2a), 5.54 (m, 1 H, H2a), 5.84 (d, J = 9.2 Hz, 1 H, H7), 7.43 (m, 4 H, H4′, H5′, H6′), 8.30 (d, J = 9.2 Hz, 1 H, H6), 10.15 (br s, 1 H, NH).

^{13}C NMR: δ = 155.4, 150.0, 143.1, 135.1, 134.4, 131.8, 129.7, 127.5, 119.7, 95.0, 62.6, 55.8, 54.5 17.2.

MS (CI): *m*/*z* = 283 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{14}N_4O_2$·HBr·HCl: C, 45.08; H, 4.04; N, 14.02. Found: C, 45.21; H, 3.88; N, 14.23.

1-(2,6-Dimethylphenyl)-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12c)

Prepared from **9a** (94 mg, 0.25 mmol) and 2,6-dimethylaniline (30 mg, 0.25 mmol) with 2,4,6-trimethylpyridine (61 mg, 0.5 mmol) in chlorobenzene (2.5 mL).

Yield: 89 mg (92%); yellow solid; mp 225 °C (decomp.).

^{1}H NMR: δ = 2.26 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 4.34 (m, 2 H, H3), 4.48 (dd, J_1 = 10.5 Hz, J_2 = 9.2 Hz, 1 H, H2 *trans* to H2a), 4.65 (dd, J_1 = 12.8 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H2a), 5.62 (m, 1 H, H2a), 5.76 (d, J = 9.4 Hz, 1 H, H7), 7.24 (br d, J = 7.6 Hz, 1 H, H3′), 7.28 (br d, J = 7.6 Hz, 1 H, H5′), 7.35 (t, J = 7.6 Hz, 1 H, H4′), 8.32 (d, J = 9.4 Hz, 1 H, H6), 10.14 (br s, 1 H, NH).

^{13}C NMR: δ = 153.7, 149.4, 143.4, 136.8, 135.9, 132.1, 130.0, 129.2, 129.0, 120.1, 94.2, 60.4, 56.2, 54.4 17.48, 17.45.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}N_4O_2$: 297.1352; found: 297.1348.

Anal. Calcd for $C_{16}H_{16}N_4O_2$·HBr·0.25HCl: C, 49.74; H, 4.50; N, 14.50. Found: C, 49.79; H, 4.74; N, 14.38.

1-(2-Methoxyphenyl)-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12d)

Prepared from **9a** (187 mg, 0.5 mmol) and 2-methoxyaniline (62 mg, 0.5 mmol) with DIPEA (129 mg, 1.0 mmol).

Yield: 162 mg (85%); yellow solid; mp from 140 °C (decomp.).

^{1}H NMR: δ = 3.89 (s, 3 H, OCH_3), 4.26 (dd, J_1 = 12.2 Hz, J_2 = 10.6 Hz, 1 H, H3 *cis* to H2a), 4.34 (dd, J_1 = 10.4 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 4.55 (dd, J_1 = 9.9 Hz, J_2 = 9.1 Hz, 1 H, H2 *trans* to H2a), 4.91 (dd, J_1 = 12.6 Hz, J_2 = 10.2 Hz, 1 H, H2 *cis* to H2a), 5.51 (tt, J_1 = 12.3 Hz, J_2 = 9.1 Hz, 1 H, H2a), 6.02 (d, J = 9.4 Hz, 1 H, H7), 7.12 (m, 1 H, H5′), 7.30 (m, 1 H, H3′), 7.45 (m, 1 H, H6′), 7.47 (m, 1 H, H4′), 8.32 (d, J = 9.3 Hz, 1 H, H6), 10.11 (br s, 1 H, NH).

^{13}C NMR: δ = 154.5, 152.9, 149.9, 142.6, 130.0, 124.3, 124.1, 121.0, 119.8, 113.2, 96.1, 61.7, 55.9, 55.7, 54.3. In an HC–HMBC experiment strong cross peaks were observed between 3-H (*trans* to 2a-H) and C-4a and between 2-H (*trans* to 2a-H) and C-7a; weak cross peaks between these two carbon atoms and 2-H (*cis*) or 3-H (*cis*) respectively; no cross peak between the two carbons and 2a-H.

MS (CI): *m*/*z* = 299 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{14}N_4O_3$·HBr: C, 47.51; H, 3.99; N, 14.77. Found: C, 47.43; H, 4.04; N, 14.83.

1-(3-Methoxyphenyl)-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12e)

Prepared from **9a** (187 mg, 0.5 mmol) and 3-methoxyaniline (62 mg, 0.5 mmol) with DIPEA (129 mg, 1.0 mmol).

Yield: 157 mg (83%); yellow solid; mp 302–303 °C.

^{1}H NMR: δ = 3.82 (s, 3 H, OCH_3), 4.21 (dd, J_1 = 12.0 Hz, J_2 = 10.5 Hz, 1 H, H3 *cis* to H2a), 4.35 (dd, J_1 = 10.5 Hz, J_2 = 9.3 Hz, 1 H, 3-H *trans* to 2a-H), 4.62 (dd, J_1 = 9.9 Hz, J_2 = 9.3 Hz, 1 H, H2 *trans* to H2a), 4.90 (dd, J_1 = 12.4 Hz, J_2 = 9.9 Hz, 1 H, H2 *cis* to H2a), 5.46 (m, 1 H, H2a), 6.50 (d, *J* = 9.4 Hz, 1 H, H7), 6.98 (m, 2 H, H2′, H6′), 7.02 (m, 1 H, H4′), 7.47 (m, 1 H, H5′), 8.36 (d, *J* = 9.4 Hz, 1 H, H6), 10.15 (br s, 1 H, NH).

^{13}C NMR: δ = 160.2, 153.4, 149.8, 143.2, 137.5, 131.0, 120.4, 113.0, 112.9, 106.8, 95.6, 61.0, 55.6, 55.6, 54.2.

MS (CI): *m*/*z* = 299 $[M+H]^+$.

Anal. Calcd for $C_{15}H_{14}N_4O_3$·HBr: C, 47.51; H, 3.99; N, 14.77. Found: C, 47.49; H, 4.08; N, 14.83.

1-(3-Aminocarbonylphenyl)-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12f)

Prepared from **9a** (374 mg, 1.0 mmol) and 3-aminobenzamide (137 mg, 1.0 mmol) with DIPEA (260 mg, 2.0 mmol). The precipitate was separated by filtration, immediately transferred into a glass dish, triturated after drying and stirred at 42 °C for 18 h in CH_2Cl_2 to which one drop of DIPEA was added.

Yield: 143 mg (36%); yellow solid; mp 200 °C (decomp.).

^{1}H NMR: δ = 4.24 (dd, J_1 = 12.1 Hz, J_2 = 10.5 Hz, 1 H, H3 *cis* to H2a), 4.36 (dd, J_1 = 10.5 Hz, J_2 = 9.6 Hz, 1 H, H3 *trans* to H2a), 4.66 (t, *J* = 10.1 Hz, 1 H, H2 *trans* to H2a), 4.96 (dd, J_1 = 12.5 Hz, J_2 = 10.1 Hz, 1 H, H2 *cis* to H2a), 5.50 (m, 1 H, H2a), 6.51 (d, *J* = 9.4 Hz, 1 H, H7), 7.57 (br s, 1 H, CONH), 7.60–7.67 (m, 2 H, H2′, H6′), 7.86–7.90 (m, 2 H, H4′, H6′), 8.19 (br s, 1 H, CONH), 8.40 (d, *J* = 9.4 Hz, 1 H, H6), 10.17 (br s, 1 H, NH).

^{13}C NMR: δ = 166.7, 153.4, 149.8, 143.5, 136.6, 136.0, 130.2, 126.2, 123.6, 120.6, 119.8, 95.5, 61.1, 55.8, 54.3.

MS (CI): *m*/*z* = 312 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{13}N_5O_3$·HBr: C, 45.94; H, 3.60; N, 17.86. Found: C, 45.61; H, 3.80; N, 17.65.

5-Nitro-1-(3-pyridyl)-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12g)

To a suspension of **9a** (150 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) were added 2,4-dimethylpyridine (86 mg, 0.05 mL, 0.4 mmol) and subsequently dropwise a solution of 3-aminopyridine (38 mg, 0.4 mmol) and 2,4-dimethylpyridine (86 mg, 0.05 mL, 0.4 mmol) in CH_2Cl_2 (2 mL). After stirring at r.t. for 24 h 2,4-dimethylpyridine (0.1 mL) was added and stirring was continued for 24 h. The precipitate was collected by filtration.

Yield: 89 mg (63%); yellow solid; mp 200–210 °C.

^{1}H NMR: δ = 4.24 (dd, J_1 = 12.3 Hz, J_2 = 10.6 Hz, 1 H, H3 *cis* to H2a), 4.37 (dd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 4.70 (dd, J_1 = 9.6 Hz, J_2 = 9.2 Hz, 1 H, H2 *trans* to H2a), 4.96 (dd, J_1 = 12.4 Hz, J_2 = 10.0 Hz, 1 H, H2 *cis* to H2a), 5.51 (tt, J_1 = 12.3 Hz, J_2 = 9.1 Hz, 1 H, H2a), 6.57 (d, *J* = 9.4 Hz, 1 H, H7), 7.60 (ddd, J_1 = 8.3 Hz, J_2 = 4.7 Hz, J_3 = 0.5 Hz, 1 H, 5′-H′), 7.95 (ddd, J_1 = 8.3 Hz, J_2 = 2.8 Hz, J_3 = 1.3 Hz, 1 H, H4′), 8.41 (d, *J* = 9.4 Hz, 1 H, H6), 8.59 (dd, J_1 = 4.7 Hz, J_2 = 1.3 Hz, 1 H, H6′), 8.75 (br d, *J* = 2.5 Hz, 1 H, H2′) 10.21 (br d, 1 H, NH).

^{13}C NMR: δ = 151.8, 149.7, 148.1, 143.6, 142.2, 133.5, 128.7, 124.6, 120.8, 95.3, 60.9, 56.0, 54.2.

MS (CI): *m*/*z* = 270 $[M + H]^+$, 135.5 $[M + 2 H]^{2+}$.

Anal. Calcd for $C_{13}H_{11}N_5O_2$·HBr: C, 44.59; H, 3.45; N, 20.00. Found: C, 44.49; H, 3.63; N, 19.85.

1-Benzyl-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12h)

To a suspension of **9a** (748 mg, 2.0 mmol) in CH_2Cl_2 (25 mL) were added dropwise DIPEA (412 mg, 0.545 mL; 3.2 mmol) and subsequently benzylamine (214 mg, 0.229 mL; 2.0 mmol). The mixture was stirred at r.t. for 16 h, DIPEA (0.02 mL, 0.12 mmol) was added and stirring was continued at 30 °C for 2 h. The precipitate was collected by filtration.

Yield: 359 mg (51%, based on a 2:1 mixture of hydrobromide and hydrochloride); light yellow solid; mp 271 °C (decomp.).

^{1}H NMR: δ = 4.12 (dd, J_1 = 12.1 Hz, J_2 = 10.5 Hz, 1 H, H3 *cis* to H2a), 4.13 (dd, J_1 = 12.3 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H2a), 4.18 (dd, J_1 = 10.6 Hz, 9.5 Hz, 1 H, H2 *trans* to H2a), 4.22 (dd, J_1 = 10.5 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 4.81 (s, 2 H, CH_2), 5.30 (dddd, J_1 = 12.3 Hz, J_2 = 12.1 Hz, J_3 = 9.5 Hz, J_4 = 9.4 Hz, 1 H, H2a), 6.56 (d, *J* = 9.5 Hz, 1 H, H7), 7.34–7.43 (m, 5 H, Ph), 8.35 (d, *J* = 9.5 Hz, 1 H, H6), 9.97 (br s, 1 H, NH).

^{13}C NMR: δ = 156.1, 150.1, 142.4, 133.8, 128.8, 128.3, 118.8, 94.9, 58.7, 55.5, 54.6, 44.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_4O_2$: 283.1195; found: 283.1194.

Anal. Calcd for $C_{15}H_{14}N_4O_2$·0.67HBr·0.33HCl: C, 51.66; H, 4.43; N, 16.07. Found: C, 51.51; H, 4.45; N, 16.00.

^{1}H NMR [intermediate **11h** (protonated) from a reaction mixture]: δ = 3.91 (m, 1 H, H2 *trans* to H3), 3.93 (m, 1 H, CH_2Br), 4.16 (dd, J_1 = 11.9 Hz, 4.0 Hz, 1 H, CH_2Br), 4.24 (dd, J_1 = 11.4 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H3), 4.74 (s, 2 H, CH_2), 5.69 (m, 1 H, H3), 6.32 (d, *J* = 9.9 Hz, 1 H, H6), 7.28 (m, 1 H, H4′), 7.35 (m, 2 H, H3′), 7.41 (m, 2 H, H2′), 8.33 (d, *J* = 9.9 Hz, 1 H, H7), 10.21 (br s, 1 H, NH1).

5-Nitro-1-(3-phenyl-1-propyl)-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12i)

Prepared from **9a** (374 mg, 1.0 mmol) and 3-phenyl-1-propylamine (135 mg, 1.0 mmol) with DIPEA (220 mg, 1.7 mmol).

Yield: 165 mg (42%); light yellow solid; mp 215–216 °C.

^{1}H NMR: δ = 1.91 [m, 2 H, CH_2(2)], 2.66 [m, 2 H, CH_2(3)], 3.54 [dt, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 1 H, CH_2(1)], 3.63 [dt, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 1 H, CH_2(1)], 4.15 (dd, J_1 = 12.1 Hz, J_2 = 10.6 Hz, 1 H, H3 *cis* to H2a), 4.24 (dd, J_1 = 12.1 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H2a), 4.28 (dd, J_1 = 10.6, J_2 = 9.4 Hz, 1 H, H2 *trans* to H2a), 4.30 (dd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 5.25 (tt, J_1 = 12.3 Hz, J_2 = 9.4, 1 H, H2a), 6.40 (d, *J* = 9.4 Hz, 1 H, H7), 7.19 (m, 1 H, H4′), 7.23 (m, 2 H, H2′), 7.29 (m, 2 H, H3′), 8.28 (d, *J* = 9.6 Hz, 1 H, H6), 9.94 (br s, 1 H, NH).

^{13}C NMR: δ = 156.2, 150.3, 141.9, 141.0, 128.4, 128.2, 125.9, 118.3, 95.0, 58.6, 55.4, 54.6, 44.8, 31.8, 28.3.

MS (CI): *m*/*z* = 311 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{18}N_4O_2$·HBr: C, 52.19; H, 4.89; N, 14.32. Found: C, 52.20; H, 4.91; N, 14.29.

^{1}H NMR [intermediate **11i** (protonated) which in one case precipitated in crude form]: δ = 1.91 [m, 2 H, CH_2(2)], 2.66 [m, 2 H, CH_2(3)], 3.53 [br m, 2 H, CH_2(1)], 3.87 (m, 2 H, H2 *trans* to H3, CH_2Br), 4.04 (dd, J_1 = 11.8 Hz, J_2 = 4.7 Hz, 1 H, CH_2Br), 4.19 (dd, J_1 = 11.4, J_2 = 10.5 Hz, 1 H, H2 *cis* to H3), 5.48 (m, 1 H, H3), 6.45 (d, *J* = 10.0 Hz, 1 H, H6), 7.18 (m, 1 H, H4′), 7.21 (m, 2 H, H2′),

7.29 (m, 2 H, H3′), 8.28 (d, J = 9.9 Hz, 1 H, H7), 9.48 [br t, J = 5.5 Hz, 1 H, NH (5)], 10.19 (br s, 1 H, NH1).

1-Cyclohexyl-5-nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydrobromide (12j)

Prepared from **9a** (748 mg, 2.0 mmol) and cyclohexyl amine (198 mg, 0.23 mL, 2.0 mmol) with DIPEA (439 mg, 0.58 mL, 3.4 mmol); 3 d; crystallized from CH_2Cl_2.

Yield: 281 mg (39%); light yellow solid; mp 225 °C (decomp.).

^{1}H NMR: δ = 1.12 (qt, J_1 = 12.8 Hz, J_2 = 3.5 Hz, 1 H, H4a-cy), 1.28–1.90 (m, 9 H, cy), 3.86 (tt, J_1 = 11.5 Hz, J_2 = 3.7 Hz, 1 H, H1-cy), 4.13 (dd, J_1 = 11.9 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H2a), 4.18 (dd, J_1 = 12.4 Hz, J_2 = 10.6 Hz, 1 H, H3 *cis* to H2a), 4.26 (dd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, 1 H, H2 *trans* to H2a), 4.29 (dd, J_1 = 10.6 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 5.22 (tt, J_1 = 12.3 Hz, J_2 = 9.4 Hz, 1 H, H2a), 6.47 (d, J = 9.4 Hz, 1 H, H7), 8.26 (d, J = 9.4 Hz, 1 H, H6), 9.94 (br s, 1 H, NH).

^{13}C NMR: δ = 155.3, 150.5, 141.6, 118.2, 95.4, 55.1, 55.0, 54.6, 30.6, 28.6, 24.5, 24.4, 24.3.

MS (CI): m/z = 275 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{18}N_4O_2$·HBr: C, 47.34; H, 5.39; N, 15.77. Found: C, 47.63; H, 5.71; N, 15.40.

^{1}H NMR [characteristic signals of the intermediate **11j** (protonated) from a reaction mixture]: δ = 5.73 (br m, 1 H, H3), 6.58 (d, J = 9.9 Hz, 1 H, H6), 8.36 (d, J = 9.9 Hz, 1 H, H7), 9.05 [br d, J = 7.8 Hz, 1 H, NH (5)], 10.21 (br s, 1 H, NH1).

3-Bromomethyl-5-morpholino-8-nitro-2,3-dihydroimidazo[1,2-*a*]pyridine Hydrobromide (16a)

To a suspension of **9a** (374 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (152 mg, 0.207 mL, 1.5 mmol), and subsequently **15a** (87 mg, 0.87 mL, 1.0 mmol). The mixture was stirred at r.t. for 16 h and the precipitate was collected by filtration.

Yield: 235 mg (55%); yellow solid; mp 212–218 °C (decomp.).

^{1}H NMR: δ = 3.59–3.84 (m, 8 H, morph.), 3.87 (dd, J_1 = 11.9 Hz, J_2 = 2.8 Hz, 1 H, H2 *trans* to H3), 3.90 (dd, J_1 = 11.9 Hz, J_2 = 2.5 Hz, 1 H, one of CH_2), 4.05 (dd, J_1 = 11.9 Hz, J_2 = 4.6 Hz, 1 H, CH_2), 4.20 (dd, J_1 = 11.9 Hz, J_2 = 9.9 Hz, 1 H, H2 *cis* to H3), 5.70–5.77 (m, 1 H, H3), 6.71 (d, J = 9.6 Hz, 1 H, H6), 8.55 (d, J = 9.6 Hz, 1 H, H7), 10.38 (s, 1 H, NH).

^{13}C NMR: δ = 156.0, 150.7, 140.0, 119.5, 102.9, 65.4, 62.2, 50.0, 47.9, 33.1.

MS (CI): m/z = 343 $[M + H]^+$, 345, 423$[M + HBr + H]^+$, 425, 427.

Anal. Calcd for $C_{12}H_{15}BrN_4O_3$·HBr: C, 33.99; H, 3.80; N, 13.21. Found: C, 33.86; H, 3.90; N, 13.33.

3-Bromomethyl-5-(*N*-methylanilino)-8-nitro-2,3-dihydroimidazo[1,2-*a*]pyridine Hydrobromide (16b)

To a suspension of **9a** (150 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) was added DIPEA (83 mg, 0.11 mL, 0.64 mmol) upon which a dark red solution was formed. Compound **15** (43 mg, 0.043 mL, 0.4 mmol) was added and the mixture was left at r.t. for 24 h. The precipitate was collected by filtration.

Yield: 111 mg (76%); yellow solid; mp 205 °C.

^{1}H NMR: δ = 3.64 (s, 3 H, Me), 3.67 (dd, J_1 = 11.9 Hz, J_2 = 3.0 Hz, 1 H, H2 *trans* to H3), 3.69 (dd, J_1 = 11.4 Hz, J_2 = 2.3 Hz, 1 H, CH_2), 3.90 (dd, J_1 = 11.9 Hz, J_2 = 9.9 Hz, 1 H, H2 *cis* to H3), 3.90 (dd, J_1 = 11.4 Hz, J_2 = 5.6 Hz, 1 H, CH_2), 4.02 (m, 1 H, H3), 6.78 (d, J = 9.6 Hz, 1 H, H6), 7.48 (m, 1 H, H4′), 7.56 (m, 2 H, H3′), 7.59 (m, 2 H, H2′), 8.67 (d, J = 9.6 Hz, 1 H, H7), 10.37 (s, 1 H, NH).

^{13}C NMR: δ = 154.2, 150.8, 142.3, 140.7, 130.7, 128.8, 125.0, 120.3, 103.1, 60.9, 47.5, 44.6, 32.5.

MS (CI): m/z = 363 $[M + H]^+$, 365, 443 $[M + HBr + H]^+$, 445, 447.

Anal. Calcd for $C_{15}H_{15}BrN_4O_2$·HBr: C, 40.57; H, 3.63; N, 12.62. Found: C, 40.69; H, 3.71; N, 12.64.

5-Nitro-1,4-diphenyl-2,2a,3,4-tetrahydro-4,7b-diaza-1-azoniacyclopent[*cd*]indene Iodide (17)

Compound **19** (80 mg, 0.09 mmol) of was dissolved in DMSO (2 mL). After 20 min at r.t. water (10 mL) was added and the solution was extracted with CH_2Cl_2 (10 mL). The organic phase was washed with water (10 mL) and was then stirred with a 0.2 M aq solution of sodium disulfite (15 mL) for 30 min at r.t. The organic layer was separated and evaporated, the residual material crystallized from CH_2Cl_2–petroleum ether.

Yield: 55 mg (100%); yellow solid; mp 250 °C.

^{1}H NMR: δ = 4.67 (t, J = 9.6 Hz, 1 H, H2 *trans* to H2a), 4.71 (dd, J_1 = 12.6 Hz, J_2 = 9.9 Hz, 1 H, H3 *cis* to H2a), 4.76 (dd, J_1 = 9.9 Hz, J_2 = 9.6 Hz, 1 H, H3 *trans* to H2a), 4.97 (dd, J_1 = 12.6 Hz, J_2 = 9.6 Hz, 1 H, H2 *cis* to H2a), 5.68 (m, 1 H, H2a), 6.68 (d, J = 9.4 Hz, 1 H, H7), 7.35 (m, 2 H, H2″), 7.40 (m, 1 H, H4″), 7.42 (m, 1 H, H4′), 7.48 (m, 2 H, H3″), 7.51 (m, 2 H, H2′), 7.59 (m, 2 H, H3′), 8.46 (d, J = 9.4 Hz, 1 H, H6).

^{13}C NMR: δ = 152.7, 145.8, 144.9, 139.4, 136.4, 130.1, 129.1, 128.0, 127.4, 122.3, 120.7, 96.6, 64.3, 60.2, 55.4.

MS (CI): m/z = 345 $[M^+]$, 473 $[M + HI]^+$.

Anal. Calcd for $C_{20}H_{17}N_4O_2I$: C, 50.86; H, 3.63; N, 11.86. Found: C, 50.73; H, 3.61; N, 11.69.

2-Anilino-6-(*N*-allylanilino)-3-nitropyridine (18)

To a solution of 2,6-bisanilino-3-nitropyridine[22] (495 mg, 1.5 mmol) in DMF (3 mL) were added K_2CO_3 (270 mg, 2.0 mmol) and allyl bromide (240 mg, 0.17 mL, 2.0 mmol). The mixture was stirred at r.t. for 16 h. Another portion of allyl bromide (240 mg) was added and stirring was continued for 16 h. Water (75 mL) was added and the mixture was extracted with EtOAc (45 mL). The organic layer was separated and concentrated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 4:1).

Yield: 407 mg (64%); orange crystals; mp 104–105 °C.

^{1}H NMR: δ = 4.51 (dt, J_1 = 5.3 Hz, J_2 = 1.4 Hz, 2 H, H1-allyl), 5.11 (dq, J_1 = 16.4 Hz, J_2 = 1.4 Hz, 1 H, H3-allyl-*cis*), 5.12 (dq, J_1 = 10.6 Hz, J_2 = 1.4 Hz, 1 H, H3-allyl-*trans*), 5.90 (br, 1 H, H5), 5.91 (ddt, J_1 = 16.4 Hz, J_2 = 10.6 Hz, J_3 = 5.3 Hz, 1 H, H2-allyl), 7.09 (m, 1 H, H4′), 7.28 (m, 2 H, H3′), 7.35 (m, 2 H, H2″), 7.41 (m, 1 H, H4″), 7.51 (m, 2 H, H3″), 7.59 (m, 2 H, H2′9), 8.17 (d, J = 9.5 Hz, 1 H, H4), 10.60 (s, 1 H, NH).

^{13}C NMR: δ = 159.3, 150.4, 142.7, 138.1, 136.3, 132.9, 130.0, 128.5, 127.8, 124.0, 122.2, 119.3, 117.3, 101.0, 53.6.

MS (EI): m/z = 346 $[M]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.27; H, 5.28; N, 16.05.

3-Iodomethyl-6-nitro-1-phenyl-5-phenylimino-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridine Hydrotriiodide (19)

To a solution of **18** (162 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) was added iodine (119 mg, 0.47 mmol). The solution was stirred at r.t. for 2 h and another portion of iodine (119 mg, 0.47 mmol) was added. After another 4 h at r.t. the dark colored crystalline product was collected by filtration.

Yield: 400 mg (99%); mp 78 °C.

^{1}H NMR ($CDCl_3$): δ = 3.23 (dd, J_1 = 11.9 Hz, J_2 = 2 Hz, 1 H, CH_2), 3.69 (dd, J_1 = 11.9 Hz, J_2 = 4.6 Hz, 1 H, CH_2), 3.92 (dd, J_1 = 11.6 Hz, J_2 = 3.3 Hz, 1 H, H2 *trans* to H3), 4.77 (br, 1 H, H3), 5.16 (dd,

J_1 = 11.6 Hz, J_2 = 10.9 Hz, 1 H, H2 *cis* to H3), 6.32 (d, J = 9.9 Hz, 1 H, H8), 7.51–7.70 (m, 10 H, Ph), 8.68 (d, J = 9.9 Hz, 1 H, H6), 11.41 (br, 1 H, NH).

MS (CI): m/z = 473 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{17}IN_4O_2 \cdot HI_3$: C, 28.13; H, 2.12; N, 6.56. Found: C, 28.08; H, 2.28; N, 6.54.

2-Allylamino-6-amino-3-nitropyridine (21)

Concd aq NH_3 (15 mL) was added to a concd solution of **4a** (5.0 g, 23.4 mmol) in EtOH and the mixture was heated in a closed vessel to 50 °C for 5 d. The solution was evaporated to dryness and the residue was distributed between water and EtOAc. Evaporation of the organic phase gave **21** (4.53 g, 100%).

Yellow crystals; mp 118–120 °C.

^{1}H NMR: δ = 4.14 (tt, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 2 H, CH_2), 5.10 (dq, J_1 = 10.4 Hz, J_2 = 1.5 Hz, 1 H, H3-allyl-*trans*), 5.17 (dq, J_1 = 17.2 Hz, J_2 = 1.8 Hz, 1 H, H3-allyl-*cis*), 5.91 (d, J = 9.4 Hz, 1 H, H5), 5.96 (ddt, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 5.3 Hz, 1 H, H2-allyl), 7.39 (br, 1 H, NH_2), 7.50 (br, 1 H, NH_2), 8.00 (d, J = 9.1 Hz, 1 H, H4), 8.93 (br t, J = 5.7 Hz, 1 H, NH).

^{13}C NMR: δ = 162.4, 154.1, 135.7, 135.2, 117.8, 115.6, 101.2, 42.3.

MS (CI): m/z = 195 $[M + H]^+$.

Anal. Calcd for $C_8H_{10}IN_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.58; H, 5.25; N, 28.85.

2-Allylamino-6-(bis-*tert.*-butoxycarbonylamino)-3-nitropyridine (22)

To a solution of **21** (2.0 g, 10.3 mmol) in CH_2Cl_2 (25 mL) were added di-*tert*-butyldicarbonate (4.8 g, 22.0 mmol) and 4-(*N,N*-dimethylamino)pyridine (DMAP, 50 mg). After 20 min at r.t. the mixture was evaporated to dryness and the residue crystallized from *n*-hexane–EtOAc (6:1).

Yield: 2.45 g (69%); yellow crystals; mp 104–107 °C.

^{1}H NMR: δ = 1.48 (s, 18 H, *t*-Bu) 4.08 (tt, J_1 = 5.7 Hz, J_2 = 1.5 Hz, 2 H, CH_2), 5.08 (dq, J_1 = 10.4 Hz, J_2 = 1.5 Hz, 1 H, H3-allyl-*trans*), 5.15 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1 H, H3-allyl-*cis*), 5.91 (ddt, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 5.3 Hz, 1 H, H2-allyl), 6.95 (d, J = 9.1 Hz, 1 H, H5), 8.46 (d, J = 9.1 Hz, 1 H, H4), 8.69 (br t, J = 5.8 Hz, 1 H, NH).

^{13}C NMR: δ = 154.7, 151.1, 149.8, 138.0, 134.7, 124.2, 115.8, 104.2, 84.2, 42.7, 27.3.

MS (CI): m/z = 395 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{26}N_4O_6$: C, 54.81; H, 6.64; N, 14.20. Found: C, 54.74; H, 6.61; N, 14.36.

5-Imino-3-iodomethyl-8-nitro-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridine Hydroiodide (26)

To a solution of **21** (360 mg, 1.8 mmol) in CH_2Cl_2 (15 mL) was added iodine (683 mg, 2.7 mmol). The mixture was stirred at r.t. for 2 d. The dark precipitate was dissolved in DMF (2.5 mL) and kept at 60 °C for 2 h. The solvent was removed under vacuum and the remaining material was triturated with boiling CH_2Cl_2 (15 mL). The yellow precipitate was collected by filtration.

Yield: 610 mg (75%); mp 155 °C (decomp.).

^{1}H NMR: δ = 3.59 (dd, J_1 = 11.4 Hz, J_2 = 2.5 Hz, 1 H, CH_2), 3.73 (m, 2 H, H2 *trans* to H3, CH_2), 4.17 (dd, J_1 = 11.9 Hz, J_2 = 10.1 Hz, 1 H, H2 *cis* to H3), 5.03 (m, 1 H, H3), 6.19 (d, J = 9.6 Hz, 1 H, H6), 8.32 (d, J = 9.6 Hz, 1 H, H7), 9.14 (br, 1 H, NH_2^+), 9.72 (br, 1 H, NH_2^+), 10.16 (br, 1 H, H1).

^{13}C NMR: δ = 153.7, 149.3, 138.5, 116.1, 100.1, 57.5, 54.9, 50.4.

HRMS: m/z $[M + H]^+$ calcd for $C_8H_9IN_4O_2$: 320.9849; found: 320.9851.

Anal. Calcd for $C_8H_9IN_4O_2 \cdot HI$: C, 21.45; H, 2.25; N, 12.51. Found: C, 21.53; H, 2.27; N, 12.50.

5-Nitro-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopent[*cd*]indene Hydroiodide (20)

A mixture of **26** (40 mg, 0.09 mmol), CH_2Cl_2 (1.8 mL), and DIPEA (18 mg, 0.024 mL, 0.14 mmol) was stirred at r.t. for 4 d. The precipitate was collected and washed with CH_2Cl_2.

Yield: 23 mg (82%); amorphous orange solid; mp 140 °C (decomp.).

^{1}H NMR: δ = 4.13 (dd, J_1 = 12.1 Hz, J_2 = 10.4 Hz, 1 H, H2 *cis* to H2a), 4.15 (dd, J_1 = 12.4 Hz, J_2 = 10.9 Hz, 1 H, H3 *cis* to H2a), 4.24 (dd, J_1 = 10.4 Hz, J_2 = 9.4 Hz, 1 H, H2 *trans* to H2a), 4.28 (dd, J_1 = 10.9 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 5.26 (tt, J_1 = 12.3 Hz, J_2 = 9.4 Hz, 1 H, H2a), 6.19 (d, J = 9.4 Hz, 1 H, H7), 8.23 (d, J = 9.4 Hz, 1 H, H6), 9.89 (s, 1 H, NH).

^{13}C NMR: δ = 157.6, 150.1, 141.9, 118.3, 96.0, 56.4, 54.7, 54.5.

HRMS: m/z $[M + H]^+$ calcd for $C_8H_9N_4O_2$: 193.0726; found: 193.0729.

6-Allylamino-2-anilino-3-nitropyridine (28)

A solution of 2-anilino-6-chloro-3-nitropyridine[22] (1000 mg, 4 mmol), allyl amine (286 mg, 0.375 mL, 5 mmol), and DIPEA (542 mg, 0.854 mL, 5 mmol) in CH_2Cl_2 (2 mL) was refluxed for 2 h. The mixture was washed with 0.2 M aq citric acid (15 mL) and aq $NaHCO_3$ and evaporated. The residue was crystallized from *n*-hexane–EtOAc (4:1).

Yield: 800 mg (74%); light orange crystals; mp 146–148 °C.

^{1}H NMR: δ = 3.98 (br t, J = 5.3 Hz, 2 H, CH_2), 5.11 (dq, J_1 = 10.2 Hz, J_2 = 1.5 Hz, 1 H, H-allyl-3 *trans* to CH_2), 5.17 (dq, J_1 = 17.2 Hz, J_2 = 1.5 Hz, 1 H, H-allyl-3 *cis* to CH_2), 5.90 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 5.3 Hz, 1 H, H-allyl-2), 6.16 (d, J = 8.4 Hz, 1 H, H5), 7.11 (m, 1 H, H4′), 7.34 (m, 2 H, H3′), 7.70 (m, 2 H, H2′), 8.10 (d, J = 8.4 Hz, 1 H, H4), 8.44 (br t, J = 5.2 Hz, 1 H, 6-NH) 10.82 (br s, 1 H, 2-NH).

^{13}C NMR: δ = 160.1, 152.2, 138.2, 135.0, 134.5, 128.5, 123.8, 121.9, 118.1, 115.9, 103.2, 43.3.

MS (CI): m/z = 271 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.36; H, 5.29; N, 20.85.

3-Iodomethyl-5-phenylimino-6-nitro-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridine Hydroiodide (29)

To a solution of **28** (108 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) was added iodine (200 mg, 0.8 mmol). The mixture was stirred at r.t. for 1 d. The dark precipitate was collected by filtration and stirred with a 0.2 M aq sodium disulfite solution (3 mL) for 30 min. The solid material was separated by filtration and washed with acetone and CH_2Cl_2.

Yield: 210 mg (100%); yellow solid; mp 143 °C.

^{1}H NMR (500 MHz, CD_3OD internal standard CD_3 = 3.31 ppm): δ = 3.39 (dd, J_1 = 11.4 Hz, J_2 = 2.3 Hz, 1 H, CH_2), 3.61 (dd, J_1 = 11.4 Hz, J_2 = 6.6 Hz, 1 H, CH_2), 3.77 (dd, J_1 = 12.1 Hz, J_2 = 3.3 Hz, 1 H, H2 *trans* to H3), 4.07 (dd, J_1 = 12.1 Hz, J_2 = 9.9 Hz, 1 H, H2 *cis* to H3), 4.43 (m, 1 H, H3), 6.54 (d, J = 9.6 Hz, 1 H, H8), 7.43 (m, 2 H, *ortho*-H), 7.44 (m, 1 H, *para*-H), 7.55 (m, 2 H, *meta*-H), 8.67 (d, J = 9.9 Hz, 1 H, H7).

^{13}C NMR [CD_3OD (internal standard 49.00 ppm)]: δ = 159.4, 147.0, 143.4, 137.5, 131.6, 129.2, 125.2, 99.2, 63.4, 50.5, 49.5.

MS (CI) under the experimental conditions reduction to a de-iodinated species occurs: 271 $[M + H]^+$ and a peak for I_2: 255 $[I_2 + H]^+$ appears.

Anal. Calcd for $C_{14}H_{13}IN_4O_2 \cdot HI$: C, 32.08; H, 2.69; N, 10.69. Found: C, 31.97; H, 2.63 N, 10.59.

7-Nitro-1-phenyl-1,2,2a,3-tetrahydro-1,4,7b-triazacyclopenta[*cd*]indene Hydroiodide (27)

To a solution of **29** (105 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added DIPEA (32.3 mg, 0.042 mL, 0.25 mmol) and the mixture was stirred at r.t. for 1 h. The precipitate was collected by filtration.

Yield: 62 mg (78%); pale yellow crystals; mp 240 °C (decomp.).

^{1}H NMR: δ = 4.22 (dd, J_1 = 12.6 Hz, J_2 = 10.9 Hz, 1 H, H3 *cis* to H2a), 4.32 (dd, J_1 = 10.9 Hz, J_2 = 9.4 Hz, 1 H, H3 *trans* to H2a), 4.64 (m, 2 H, H2), 5.47 (m, 1 H, H2a), 6.38 (d, J = 9.4 Hz, 1 H, H5), 7.32 (m, 2 H, *ortho*-H), 7.35 (m, 1 H, *para*-H), 7.44 (m, 2 H, *meta*-H), 8.33 (d, J = 9.4 Hz, 1 H, H7), 9.90 (br, 1 H, NH).

^{13}C NMR: δ = 156.9, 145.8, 143.7, 139.6, 128.9, 127.8, 120.4, 97.2, 64.5, 56.2, 54.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}N_4O_2$: 269.1039; found: 269.1034.

Bromination of 2-Allylamino-6-(bis-*tert*-butoxycarbonylamino)-3-nitropyridine

To a solution of **22** (394 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added dropwise at r.t. a solution of bromine (160 mg, 0.051 mL, 1 mmol). After 20 min the solvent was removed under vacuum and a ^{1}H NMR spectrum (DMSO) of the residue was taken which showed the signals of a 2:1 mixture of **23** and **24**.

^{1}H NMR (DMSO): δ = 1.44 (s, 9 H, *t*-Bu), 3.65 (dd, J_1 = 12.1 Hz, J_2 = 3.8 Hz, 1 H, CH_2), 3.97 (dd, J_1 = 12.1 Hz, J_2 = 2.0 Hz, 1 H, CH_2), 4.02 (dd, J_1 = 12.4 Hz, J_2 = 3.8 Hz, 1 H, H2 *trans* to H3), 4.34 (dd, J_1 = 12.4 Hz, J_2 = 10.6 Hz, 1 H, H2 *cis* to H3), 5.48 (m, 1 H, H3), 7.50 (d, J = 8.6 Hz, 1 H, H6), 9.12 (d, J = 8.6 Hz, 1 H, H7), 10.78 (br s, 1 H, NH)].

Through chromatography on silica (*n*-hexane–EtOAc, 4:1) of half of the material **23** (80 mg) was obtained as an orange solid.

^{1}H NMR (DMSO): δ = 1.50 (s, 9 H, *t*-Bu), 3.86 (dd, J_1 = 11.4 Hz, J_2 = 6.3 Hz, 1 H, CH_2Br), 3.94 (dd, J_1 = 11.4 Hz, J_2 = 5.6 Hz, 1 H, CH_2Br), 3.95 (m, 2 H, CH_2), 4.66 [m (slightly distorted pent.), 1 H, CHBr], 6.97 (d, J = 9.1 Hz, 1 H, H5), 8.48 (d, J = 9.1 Hz, 1 H, H4), 8.74 (t, J = 5.8 Hz, 1 H, NH).

^{13}C NMR (DMSO): δ = 154.5, 151.0, 149.9, 138.1, 124.9, 105.5, 84.3, 51.9, 45.7, 36.2, 27.4.

Anal. Calcd for $C_{18}H_{26}Br_2N_4O_6$: C, 39.01; H, 4.73; N, 10.11. Found: C, 39.22; H, 4.85; N, 9.88.

Attempt to Prepare 17 via 9b

A solution of bromine (320 mg, 0.1 mL, 2.0 mmol) in chlorobenzene (1 mL) was added dropwise at r.t. to a solution of **4b** (580 mg) in chlorobenzene (5 mL). An oily material precipitated which adopted a glassy state. After 1 h cyclohexene (0.1 mL) was added and after 20 min the solvent was decanted and the residue was washed with petroleum ether and dissolved in CH_2Cl_2 (10 mL). The solution was evaporated to dryness yielding a yellow material (867 mg).

MS (CI): 368 $[M]^+$, 370, 372, 448 $[M + HBr]^+$, 450, 452.

A replacement of chlorine by bromine takes place, which most likely occurs on recording of the MS.

MS: 412 $[M(Br)]^+$, 414, 416, 492 $[M(Br) + HBr]^+$, 494, 496.

This material (450 mg) was dissolved in CH_2Cl_2 (4 mL) and aniline (93 mg, 0.09 mL, 1 mmol) was added dropwise followed by DIPEA (129 mg, 0.171 mL, 1 mmol). The mixture was stirred for 4 h and the formed precipitate (370 mg) was collected by filtration. The ^{1}H NMR spectrum of this product was identical with that of the iodide of **17** (see above) except that it was contaminated with 10% of a 4-bromophenyl analogue.

^{1}H NMR: δ = 6.70 (d, J = 9.4 Hz, 1 H, H7), 7.77 (part of an AA′BB′ system, 2 H, BrPh), 8.50 (d, J = 9.4 Hz, 1 H, H6).

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