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Stereoselective Synthesis of *cis*,*cis*-Configured Vicinal Triamines

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The first stereoselective synthesis of a *cis*,*cis*-configured vicinal triamine was achieved, starting from *N*-cyclohexenylpyrrolidone (**10**). The reaction sequence consists of the stereoselective construction of the *trans*-configured 1,3-diamide **14**, *trans*-to-*cis* isomerization via enols or enamines, and subsequent highly stereoselective reduction of the intermediate imine **17D** to the amine **18A**. The postulated reaction pathway explains the observed stereoconvergence and is supported by calculation of the heats of formation of its intermediates at the PM3 level. $LiAlH_4$ reduction of **18A** yielded the tetracyclic aminal **19**, which was converted into the pyrrolidinylquinoxaline **7**, which showed low to moderate affinity towards κ and σ_1 receptors.

Introduction

Vicinal triamines on alicyclic systems are found in various types of compounds including sugars, amino acids, natural products, and pharmacologically active agents. The structural motif is prominent within triaminoglucose **1**[1,2] and tetraaminoglucose,[3] as well as in galactose[4] and pyroglutamate derivatives. These amino sugars and amino acid derivatives exhibit antibacterial activity.[5] A great effort has been invested in the stereoselective synthesis of naphthyridinomycins **2**,[6] which contain a 1,2,3-triamine fragment and display high antibacterial and anticancer activities.[7] The saxitoxins **3** are vicinal triamines that block voltage-gated sodium channels and have been discussed in the context of pain control.[8] A considerable effort has been devoted to the stereoselective synthesis of agelastatins **4**,[9] which exhibit strong antitumor and GSK-3β-inhibiting activities.[10] Alicyclic vicinal triamines have also been found in the very potent neuraminidase inhibitors **5**[11] and κ agonists **6**[12] (Figure 1).

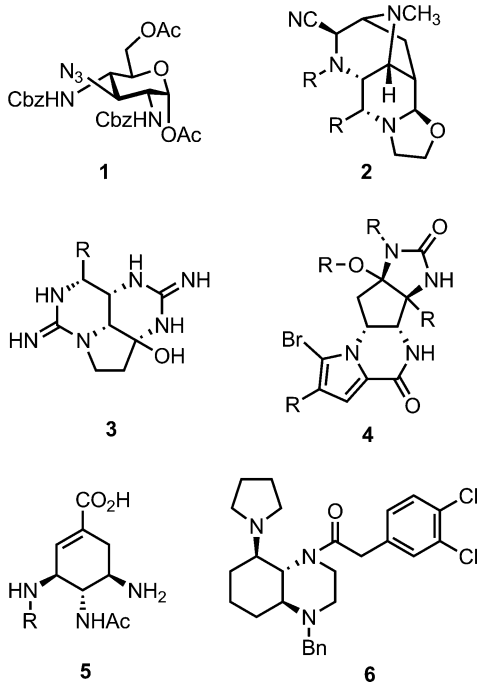

Figure 1. Examples of vicinal triamines with biological activity.

The aim of this work was to produce **7**, the *cis*,*cis*-configured analogue of the κ agonist **6**. The modified relative configuration of the center of chirality in the 4a-position should give insight into the relationship between the relative configuration of the cyclohexane-1,2,3-triamine framework and the κ receptor affinity. This entailed the development of a strategy to provide *cis*,*cis*-configured cyclohexane-1,2,3-triamines stereoselectively and, moreover, a method for the transformation of these triamines into the target dichlorophenylacetamide **7** (Figure 2).

The stereoselective synthesis of alicyclic vicinal triamines is to date restricted to the construction of *trans*,*trans*- and *cis*,*trans*-configured derivatives, such as 1,2,3-triaminocyclopropanes,[13] -cyclobutanes,[14] and -cycloheptanes.[15]

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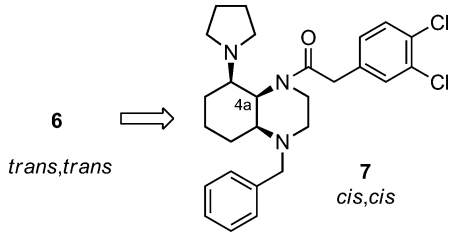
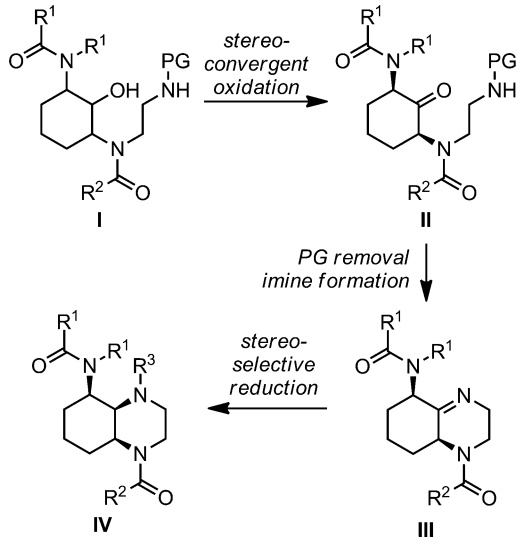


Figure 2. Production of *cis,cis*-configured aminoquinoxaline **7** from *trans,trans*-configured κ agonist **6**.

Various methods have been established for cyclopentane-1,2,3-triamines, which are found as precursors of the agelastatines **4**.[9] One method uses a *syn*-selective, intramolecular aziridination of an allylamine derivative catalyzed by the Du Bois catalyst [Rh_2esp_2].[16a] The same method was also applied to prepare the analogous cyclohexane derivatives.[16b] However, terminal opening of the aziridine ring led to decomposition, whereas nucleophilic attack at the 2-position exclusively produced *trans,trans*-configured cyclohexane-1,2,3-triamines.[17] A *cis,trans*-configured cyclohexane derivative was obtained on use of *cis*-3-bromo-1,2-epoxycyclohexane as a starting material. The authors also reported that neighboring-group participation of vicinal amino groups prevented inversion of sp^3-centered electrophiles and promoted formation of *cis,trans*- instead of *cis,cis*-configured triamines.[18] No conversion was observed when 1,2-diamido-3-bromides bearing the leaving group conformationally locked in an equatorial orientation were combined with strong nucleophiles such as sodium azide.[19] The synthesis of the triamine **6** was enabled by use of sp^2-centered electrophiles under thermodynamic control, thus leading to the stereoselective formation of *trans,trans*-configured triamines.[20,12]

Therefore, a synthetic route using 1,3-diamides **I** as deactivated diamines was envisaged. To circumvent the disadvantages associated with a *trans*-configured leaving group in the 2-position locked into an equatorial orientation by large substituents in the 1- and 3-positions, we reasoned that the third amino moiety between the two amide groups should be installed by reductive amination. Oxidation of the alcohol in **I** would produce planar ketones of type **II**. Tautomeric equilibration could enable isomerization to the thermodynamically most favored *cis*-configured diamides, thus producing stereoconvergence. Deprotection would give intermediate primary amines that would undergo formation of imines of type **III**, in which the *cis* configuration would be favored due to 1,3-allylic strain. Finally, the imines **III** would be reduced diastereoselectively under kinetic control to provide *cis,cis*-configured amidoquinoxalines of type **IV** (Scheme 1).



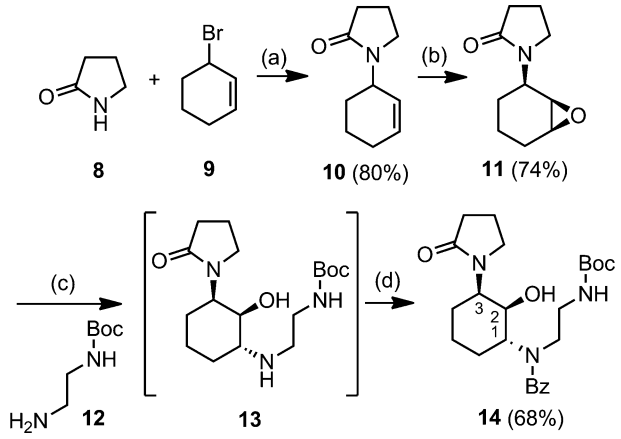
Scheme 1. Concept for the stereoselective synthesis of *cis,cis*-configured amidoquinoxalines of type **IV**. Only one enantiomer of the racemic mixture is shown.

Results and Discussion

To carry out this plan, pyrrolidin-2-one (**8**) was deprotonated with NaH and allylated with 3-bromocyclohex-1-ene (**9**) to give the alkene **10** in 80% yield. The alkene **10** had previously been prepared by acylation and alkylation of cyclohex-2-en-1-amine with 4-chlorobutyryl chloride.[21] The alkene **10** reacted diastereoselectively with *m*-chloroperbenzoic acid (*m*CPBA) in a Prileshaev reaction to afford the *cis*-configured epoxide **11** exclusively, in 74% yield. A comparable result was obtained in the epoxidation of *N*-(cyclohex-2-en-1-yl)-2-nitrobenzenesulfonamides, which gave exclusively *cis*-configured products.[22] The observed diastereoselectivity can be explained by a Bartlett-type mechanism,[23] which involves H-bond interactions between the peroxy acid and H-bond acceptor substituents on the cyclohexene ring. Mono-Boc-protected ethylenediamine (**12**)[24] was combined with the epoxide **11** to yield the amine **13** through regioselective ring-opening. The amine **13** was converted into the benzamide **14** with benzoyl chloride under Schotten–Baumann conditions in 68% yield (Scheme 2).

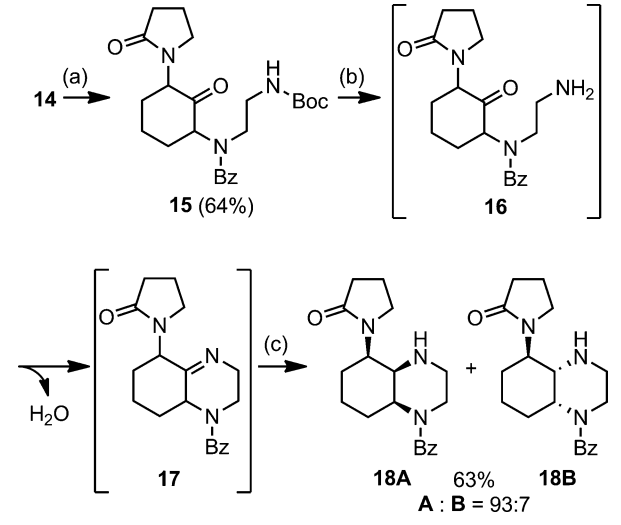
The relative configuration of the alcohol **14** was determined by analysis of the coupling constants of the methyne protons, which are J(1-*H*/2-*H*) = 9.9 Hz and J(2-*H*/3-*H*) = 4.2 Hz. These values indicate a diaxial and an equatorial/axial orientation of the respective protons and overall *trans,cis* configuration. This result was confirmed by a differential NOE experiment in which the intensity of the signal at δ = 3.75 ppm (2-*H*) was increased upon saturation of the signal at δ = 4.52 ppm (3-*H*).

The alcohol **14** did not react under Swern oxidation conditions.[25] However, oxidation with PCC immobilized on neutral alumina[26] provided the ketone **15** in 64% yield and as a 9:1 mixture of isomers according to LC/MS analysis. The determination of the relative configuration of the major isomer was, however, inhibited by signal broadening, probably caused by slow rotation of the amide *N*–*C*=O bond. The Boc group was subsequently removed with trifluoroacetic acid, giving the intermediate primary amine **16**. Monitoring of the transformation by LC/MS showed com-



Scheme 2. Synthesis of the alcohol **14**. Reagents and reaction conditions: (a) (i) NaH, THF, room temp., 3 h, (ii) **9**, DMSO, room temp., 19 h; (b) *m*CPBA, CH_2Cl_2, room temp., 2 d; (c) **12**, H_2O, room temp., 1 d; (d) BzCl, NaOH (1 M, aq.), CH_2Cl_2, room temp., 18 h. For the racemic mixtures only one enantiomer is shown in each case.

plete conversion after 3 h at ambient temperature, resulting in the imine or enamine species **17**. After removal of the solvent, the intermediate imine/enamine **17** was reduced. Interestingly, use of L-Selectride (Li[*sec*-Bu_3BH]) did not result in any conversion of **17**, but $NaBH_4$ reduced the octahydroquinoxaline derivative **17** to afford the diastereomeric decahydroquinoxalines **18A** and **18B** in 63% yield and in a ratio of 93:7 according to HPLC and ^1H NMR analysis (Scheme 3).



Scheme 3. Oxidation of the alcohol **14** and intramolecular reductive amination to the amines **18A** and **18B**. Reagents and reaction conditions: (a) PCC/Al_2O_3 (25%-w/w), CH_2Cl_2, room temp., 2 d; (b) TFA, mol. sieves (4 Å), CH_2Cl_2, room temp., 3 h; (c) $NaBH_4$, THF, 0 °C, 11 h. For the racemic mixtures only one enantiomer is shown in each case.

The heats of formation of the intermediates in the intramolecular reductive amination pathway were calculated to clarify the *trans*-to-*cis* isomerization of the ketones **15** and **16** and/or the imine **17**. The semiempirical parametrized model 3 (PM3)[27] was applied to determine differences in energy of structurally related compounds, thus minimizing the known discrepancies between calculated and experimentally determined values (Figure 3).[28]

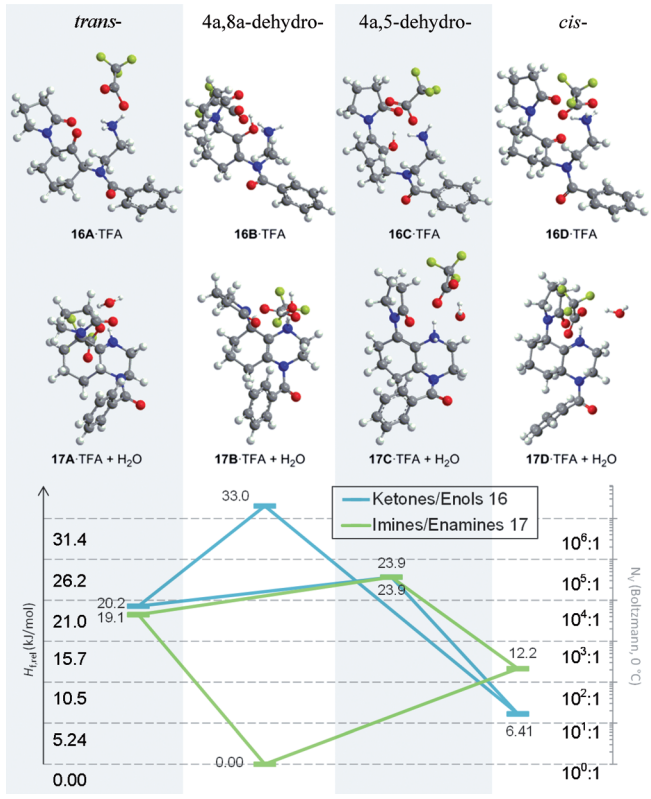


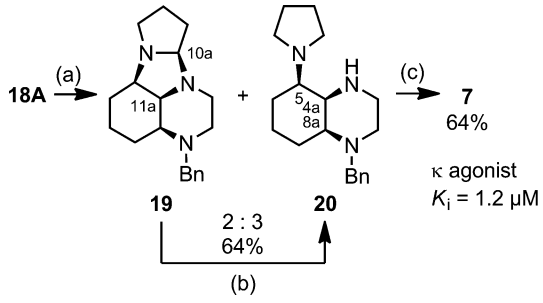
Figure 3. Relative heats of formation ($H_{f,rel}$) of the diastereomers and tautomers of **16**·TFA (blue) and **17**·TFA (green), calculated at the PM3 level and displayed with the aid of Chem3D, together with the resulting Boltzmann distributions at 0 °C.

The results show that the *cis*-configured diamido ketone **16D**·TFA is more stable than the *trans*-configured diastereomer **16A**·TFA by 13.8 kJ mol^{-1}. Although the activation energy for tautomerization strongly depends on the solvent,[29] the results calculated in vacuo suggest that the isomerization of **16A** to **16D** occurs via the enol tautomer **16C** rather than via the enol tautomer **16B**, which is energetically less stable by 9.1 kJ mol^{-1}. The thermodynamic equilibrium of **16A** to **16D** lies at 436:1 in favor of **16D** with the assumption of a Boltzmann distribution at 0 °C.

Subsequent ring-closure yielded the iminium or enammonium salts **17**·TFA and a stoichiometric amount of water with an exothermic reaction enthalpy of –6.41 kJ mol^{-1}. The 4a,8a-dehydro enammonium tautomer **17B** is more stable than its 4a,5-dehydro isomer **17C** by 23.9 kJ mol^{-1}. This observation is in good agreement with the preference seen in octalins for the double bond in the 4a,8a- over the 4,4a-position by 16.3 kJ mol^{-1}.[30] The *cis*-configured iminium salt **17D** is more stable than the *trans*-configured diastereomer **17A** by 6.9 kJ mol^{-1}, corresponding to a Boltzmann distribution of 146:7 (**17D**/**17A**) at 0 °C. Because the iminium salts **17D** and **17A** have the same configurations of the 1,3-propylenediamine fragment as the amines **18A** and **18B**, respectively, it is assumed that the predominance

of **17D** in the tautomeric equilibria led to the preferred formation of **18A** by selective backside reduction of the imine **17D**. The ratio of 93:7 (**18A/18B**) is in good accordance with the calculated ratio of the diastereomeric iminium salts **17D** and **17A** (146:7), and this supports the discussed pathway. It is known that TFA and $NaBH_4$ form trifluoroacetoxyborohydride species in THF,[31,32] so these are the probable reducing agents in this reaction. The enammonium salt **17B** is more stable than the iminium salt **17D** by 12.2 kJ mol^{-1}; however, initially formed enammonium species are known to undergo H-shift towards the iminium tautomer.[33]

Reduction of the diamide **18** with $LiAlH_4$ provided a mixture of the tetracyclic aminal **19** and the triamine **20** in a ratio of 2:3 as determined by LC/MS. The mixture was separated after acetylation of **20** under Schotten–Baumann conditions with 3,4-dichlorophenylacetyl chloride (**21**),[34] to provide the acetamide **7** and the aminal **19** in 24% and 59% yields, respectively. The aminal **19** was reduced with $NaBH_4$ in the presence of TFA to give the triamine **20** in 28% yield. Acetylation of **20** with the chloride **21** gave the identical amide **7** in 64% yield (Scheme 4).



Scheme 4. Synthesis of the κ agonist **7**. Reagents and reaction conditions: (a) $LiAlH_4$, THF, reflux, 11 h; (b) TFA, $NaBH_4$, CH_2Cl_2/DMSO (2:1), 0 °C, 2 h, 28%; (c) 2-(3,4-dichlorophenyl)acetyl chloride (**21**), NaOH (1 M, aq.), CH_2Cl_2, room temp., 14 h. Only one enantiomer of each racemic mixture is shown.

The signal broadening observed in the ^{1}H NMR spectrum of **7** was prominent within a temperature range from –30 to 100 °C. Therefore, differential NOE experiments failed to provide information on relative configuration.

The relative configuration of the tetracyclic aminal **19**, however, was clearly determined from the coupling constants of the methyne protons. The proton 11a-*H* produces a triplet (J = 5.1 Hz), which indicates a *cis*,*cis* configuration of the substituents on the cyclohexane ring. Furthermore, saturation of the signal at δ = 4.25 ppm (10a-*H*) in a differential NOE spectrum led to an increased intensity of the signal at δ = 1.98 ppm (11a-*H*); this is attributed to a *cis* configuration of these protons in the imidazolidine ring.

Moreover, the relative configuration of the triamine **20** was determined from the coupling of the methyne protons 4a-*H*, 5-*H*, and 8a-*H* on the cyclohexane ring with J = 3.0 Hz, resulting in a triplet for the signal of the 4a-*H* and indicating a *cis*,*cis* configuration of the vicinal triamine. This assignment was confirmed by two differential NOE spectra in which the signals of 4a-*H* and 8a-*H* were saturated and the intensities of the signals of the vicinal protons were increased. The results unequivocally confirmed the *cis*,*cis* configuration of the vicinal triamine fragment in **7**, **18A**, **19**, and **20**.

The affinities of **7** towards the κ, δ, σ_1, and σ_2 receptors were determined by competition experiments with the radioligands [^{3}H]-U-69,593, [^{3}H]-DPDPE, [^{3}H]-(+)-pentazocine, and [^{3}H]-DTG, respectively. Membrane preparations from guinea pig brain (κ, σ_1 receptors), rat brain (δ receptor), and rat livers (σ_2 receptor) were used as receptor materials.

The acetamide **7** showed a κ receptor affinity of 1.2 μM. Additionally, a σ_1 receptor affinity of 0.5 μM was determined, but interactions with σ_2 and δ receptors could not be observed. The decreased κ affinity in comparison with the κ affinity of the *trans*,*trans*-configured stereoisomer **6** (K_i = 9.4 nM) is consistent with the results found for U-50,488 and its *cis*-configured diastereomer: the *trans* configuration corresponded with high κ affinity, whereas the *cis*-configured diastereomer preferred the σ_1 receptor.[35]

Conclusions

The stereoselective construction of vicinal triamines was made possible by use of 2-hydroxy-1,3-diamides as precursors. The synthesis strategy made use of the hydrogen borrowing concept, which was split into its components oxidation, imine formation, and reduction. Steric shielding of the leaving group in the central position was overcome by oxidation of the alcohol **14** with PCC. Deprotection provided the primary amine **16**, which underwent intramolecular imine formation directly. Calculations on the intermediate ketone and imine forms **16** and **17**, respectively, showed that tautomeric equilibria were responsible for the stereoconvergent formation of 1,3-*cis*-configured α,α′-diamidoimines, which were stereoselectively reduced with $NaBH_4$ to give the *cis*,*cis*-configured perhydroquinoxaline **18A**. Diamide reduction and acylation transformed the quinoxaline **18** into the *cis*,*cis*-configured dichlorophenylacetamide **7**. The low κ receptor affinity of **7** showed that the relative *trans*,*trans* configuration of **6** is crucial for high κ affinity. However, the moderate σ_1 affinity of **7** confirmed the observation that changing of the configuration in potent κ agonists leads to σ_1 ligands.

Experimental Section

General Information: All commercially available reagents were used without further purification. CH_2Cl_2 and THF were dried by distillation over CaH_2 and sodium, respectively. DMSO was dried with molecular sieves (4 Å). All reactions were carried out under nitrogen. The reactions were monitored by thin layer chromatography (tlc) with silica gel-coated aluminum plates (Merck 60 F254) and visualized with $KMnO_4$ or cerium molybdate stain (Hanessian's stain), yields refer to chromatographically purified or distilled compounds. Flash column chromatography (fc) was carried out with silica gel (400–630 μm mesh) at medium pressure (1.5 bar). Parentheses include diameter (d) of the column, stationary phase length

(*l*), fraction size (*V*), eluent, and R_f value. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were recorded with a 400 MHz or a 600 MHz spectrometer. ^{1}H NMR spectra were recorded at 400 MHz or 600 MHz and are reported in parts per million (δ) relative to TMS calculated from the residual solvent signals. Data for ^{1}H NMR spectra are as follows: chemical shift δ (ppm), multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant *J* [Hz], and relative integration. ^{13}C NMR spectra were recorded at 100 MHz or 150 MHz and are reported in parts per million (δ) relative to TMS calculated from the residual solvent signal. High-resolution mass spectra (HRMS) were obtained with a TOF-Q instrument. Infrared (IR) spectra were recorded with an FTIR spectrometer by the attenuated total reflection (ATR) technique or by transmission through NaCl plates and are reported as wave numbers υ (cm^{-1}). Melting points were measured in capillary tubes sealed on one side and are uncorrected.

1-[(4a*RS*,8*SR*,8a*SR*)-4-Benzyl-8-(pyrrolidin-1-yl)perhydroquinoxalin-1-yl]-2-(3,4-dichlorophenyl)ethan-1-one (7): The amine **20** (25 mg, 84 μmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL). 3,4-Dichlorophenylacetic acid (26 mg, 120 μmol, 1.4 equiv.) was added. After 1 h, aqueous NaOH (2 M, 7 μL, 0.1 mmol, 1.7 equiv.) was added. The mixture was stirred for 48 h and washed with a mixture of aqueous NaOH (2 M, 2 mL) and brine (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc [*d* = 2 cm, *l* = 5 cm, *V* = 20 mL, cyclohexane/ethyl acetate 1:0 → 1:1 → ethyl acetate/methanol 1:0 → 19:1 → 7:1, R_f = 0.25 (tlc, ethyl acetate/methanol 1:1, detection: $KMnO_4$)] to afford the acetamide **7** (WMS-36–01) as a brown oil, yield 26 mg (64%). LC/MS (ESI$^+$): 1.18 min (100%, 486 {$C_{27}H_{34}{}^{35}Cl_2N_3O$ [M + H]$^+$}, 488 {$C_{27}H_{34}{}^{35}Cl^{37}ClN_3O$ [M + H]$^+$}, 490 [$C_{27}H_{34}{}^{37}Cl_2N_3O$ [M + H]$^+$}). Purity (HPLC): 96.1%, t_R = 16.39 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.40 (dt, *J* = 13.4, 5.0 Hz, 1 H, 6-C$H_{2,eq,bicycl}$), 1.43–1.51 (m, 1 H, 5-C$H_{2,bicycl}$), 1.61–1.82 (m, 6 H, 6-C$H_{2,ax,bicycl}$, 7-C$H_{2,bicycl}$, 3-C$H_{2,py}$, 4-C$H_{2,py}$), 1.87 (td, ^2J = 11.5, ^3J = 11.5, 3.7 Hz, 1 H, 2-C$H_{2,ax,bicycl}$), 2.09–2.13 (m, 1 H, 7-CH_2), 2.14–2.22 (m, 1 H, 5-C$H_{2,bicycl}$), 2.43–2.49 (m, 1 H, 4a-CH_{bicycl}), 2.62–2.67 (m, 1 H, 2-C$H_{2,eq,bicycl}$), 2.75–2.88 (m, 2 H, 2-C$H_{2,py}$, 5-C$H_{2,py}$), 2.94 [d, ^2J = 12.7 Hz, 1 H, (Ar2)-CH_2], 3.13–3.29 (m, 2 H, 2-C$H_{2,py}$, 5-C$H_{2,py}$), 3.34–3.48 (m, 2 H, 3-C$H_{2,bicycl}$, 8-CH_{bicycl}), 3.60 (d, ^2J = 15.4 Hz, 1 H, CH_2-C=O), 3.68–3.78 (m, 2 H, CH_2-C=O, 3-C$H_{2,bicycl}$), 4.06–4.10 (m, 1 H, 8a-CH_{bicycl}), 4.09 [d, ^2J = 13.3 Hz, 1 H, (Ar2)-CH_2], 7.06 (dd, ^3J = 8.2, ^4J = 1.5 Hz, 1 H, 6-CH_{ar1}), 7.23–7.27 (m, 3 H, 2-CH_{ar1}, 3-CH_{ar2}, 5-CH_{ar2}), 7.29 (t, *J* = 5.0 Hz, 1 H, 4-CH_{ar2}), 7.31 (dd, ^3J = 7.2, ^4J = 1.1 Hz, 2 H, 2-CH_{ar2}, 6-CH_{ar2}), 7.35 (d, *J* = 8.2 Hz, 1 H, 5-CH_{ar1}) ppm. ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 18.0 (C-6_{bicycl}), 23.6 (C-3_{py}, C-4_{py}), 23.9 (C-7_{bicycl}), 25.5 (C-5_{bicycl}), 40.1 (*C*H$_2$-C=O), 45.2 (C-3_{bicycl}), 50.8 (C-2_{bicycl}), 52.0 (C-2_{py}, C-5_{py}), 53.6 (C-8a$_{bicycl}$), 58.1 [C-8_{bicycl}, (Ar2)-*C*H$_2$], 59.1 (C-4a$_{bicycl}$), 127.3 (C-4_{ar2}), 128.5 (C-3_{ar2}, C-5_{ar2}), 128.6 (C-6_{ar1}), 129.1 (C-2_{ar2}, C-6_{ar2}), 130.5 (C-5_{ar1}), 131.1 (C-2_{ar1}), 131.4 (C-4_{ar1}), 132.5 (C-3_{ar1}), 135.6 (C-1_{ar1}), 138.4 (C-1_{ar2}), 149.6 (*C*=O) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2947 (s, C–H), 2796 (s, C–H), 1631 (s, C=O), 732 (C=C$_{ar,oop}$) cm^{-1}. HRMS (APCI): *m*/*z* calcd. for $C_{27}H_{34}{}^{35}Cl_2N_3O$ [M + H]$^+$ 486.2079; found 486.2081, calcd. for $C_{27}H_{34}{}^{35}Cl^{37}ClN_3O$ [M + H]$^+$ 488.2049; found 488.2081, calcd. for $C_{27}H_{34}{}^{37}Cl_2N_3O$ [M + H]$^+$ 490.2020; found 490.2073.

3-Bromocyclohex-1-ene (9):[36] *N*-Bromosuccinimide (20.0 g, 112 mmol, 1.0 equiv.) was suspended in cyclohexene (90 mL, 964 mmol, 8.6 equiv.) and AIBN (250 mg) was added. The vigorously stirred suspension was heated to reflux for 2 h. The mixture was concentrated by distillation. After cooling to ambient temperature, the mixture was filtered (glass frit, no. 3) and the residue was washed with cyclohexene. Excess cyclohexene was removed by distillation under ambient pressure. Distillation under reduced pressure afforded the desired bromide **9** as a colorless oil, b.p. (7 mbar) 90 °C, yield 12.6 g (70%). Spectroscopic data are identical to the reported data.[37]

1-[(1*RS*)-Cyclohex-2-enyl]-pyrrolidin-2-one (10):[21] NaH (60%-w/w suspension in mineral oil, 6.46 g, 161 mmol, 4.0 equiv.) was suspended in abs. THF (200 mL). Pyrrolidin-2-one (**8**, 15.5 mL, 201 mmol, 5.0 equiv.) was added dropwise and the mixture was stirred for 3 h until no more evolution of gas was observed. It was then concentrated under reduced pressure and the residue was suspended in dry DMSO (100 mL). 3-Bromocyclohex-1-ene (**9**, 6.50 g, 40.4 mmol, 1.0 equiv.) was added dropwise and the resulting mixture was stirred for 19 h and then diluted with H_2O (100 mL) and extracted with ethyl acetate (5 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by fc [*d* = 8 cm, *l* = 15 cm, *V* = 100 mL, cyclohexane/ethyl acetate 1:0 → 7:1 → 3:1 → 7:3, R_f = 0.83 (tlc, ethyl acetate/methanol 1:1, detection: $KMnO_4$)] to afford the olefin **10** as a colorless oil, yield 5.36 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.58 (m, 1 H, 6-C$H_{2,cycl}$), 1.58–1.71 (m, 1 H, 5-C$H_{2,cycl}$), 1.71–1.84 (m, 2 H, 5-C$H_{2,cycl}$, 6-C$H_{2,cycl}$), 1.88–2.03 (m, 4 H, 4-C$H_{2,cycl}$, 4-C$H_{2,py}$), 2.38 (t, *J* = 8.1 Hz, 2 H, 3-C$H_{2,py}$), 3.31 (t, *J* = 7.0 Hz, 2 H, 5-C$H_{2,py}$), 4.72 (ddd, *J* = 11.4, 5.5, 2.7 Hz, 1 H, 1-CH_{cycl}), 5.43–5.35 [dtdd, $^3J(H/H)$ = 10.2, 2.3, ^4J = 2.3, 2.0, $^3J(H/N)$ = 1.1 Hz, 1 H, 2-CH_{cycl}], 5.88 [dtdd, ^3J = 10.2, 3.4, $^4J(H/H)$ = 2.4, $^4J(H/N)$ = 0.9 Hz, 1 H, 3-CH_{cycl}] ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 18.3 (C-4_{py}), 21.2 (C-5_{cycl}), 24.6 (C-4_{cycl}), 26.6 (C-6_{cycl}), 31.6 (C-3_{py}), 43.5 (C-5_{py}), 47.5 (C-1_{cycl}), 127.4 (C-2_{cycl}), 131.5 (C-3_{cycl}), 174.8 (C-2_{py}) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2940 (m, C–H), 2862 (m, C–H), 1678 (s, C=O), 1420 (m, C=C) cm^{-1}. HRMS (APCI): *m*/*z* calcd. for $C_{10}H_{16}NO$ [M + H]$^+$ 166.1232; found 166.1248.

1-[(1*RS*,2*RS*,6*SR*)-7-Oxabicyclo[4.1.0]heptan-2-yl]pyrrolidin-2-one (11): The olefin **10** (1.34 g, 8.10 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (100 mL) and 3-chloroperbenzoic acid (77%, 2.72 g, 12.1 mmol, 1.5 equiv.) was added. The mixture was stirred for 2 d and was then washed with a saturated aqueous solution of $NaHSO_3$ (10 mL) and a saturated aqueous solution of K_2CO_3 (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by fc [*d* = 8 cm, *l* = 12 cm, *V* = 100 mL, cyclohexane/ethyl acetate 1:0 → 7:1 → 13:7 → 1:3, R_f = 0.13 (tlc, cyclohexane/ethyl acetate 1:1, detection: $KMnO_4$)] to afford the epoxide **11** as a colorless oil, yield 1.09 g (74%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 2 H, 3-C$H_{2,bicycl}$, 4-C$H_{2,bicycl}$), 1.54 (tdd, ^2J = 12.9, ^3J = 12.9, 11.0, 2.1 Hz, 1 H, 3-C$H_{2,bicycl}$), 1.57–1.61 (m, 1 H, 4-C$H_{2,bicycl}$), 1.70–1.76 (m, 1 H, 5-C$H_{2,bicycl}$), 1.90 (dddd, *J* = 11.7, 6.9, 4.8, 2.1 Hz, 1 H, 5-C$H_{2,bicycl}$), 1.96–2.07 (m, 2 H, 4-C$H_{2,py}$), 2.34–2.43 (m, 2 H, 3-C$H_{2,py}$), 3.09 (dd, *J* = 1.8, 1.4 Hz, 1 H, 1-CH_{bicycl}), 3.18 (td, *J* = 4.8, 1.4 Hz, 1 H, 6-CH_{bicycl}), 3.40–3.45 (m, 1 H, 5-C$H_{2,py}$), 3.54–3.58 (m, 1 H, 5-C$H_{2,py}$), 4.46 (ddd, *J* = 11.0, 6.2, 1.8 Hz, 1 H, 2-CH_{bicycl}) ppm. ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 18.4 (C-4_{py}), 21.0 (C-4_{bicycl}), 22.1 (C-3_{bicycl}), 23.0 (C-5_{bicycl}), 31.3 (C-3_{py}), 44.6 (C-5_{py}), 49.0 (C-2_{bicycl}), 52.6 (C-6_{bicycl}), 54.4 (C-1_{bicycl}), 175.1 (C-2_{py}) ppm. FT-IR (NaCl): $\tilde{\nu}$ = 3472 (br. s, O–H), 2934 (s, C–H), 2877 (s, C–H), 1686 (s, C=O) cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd. for $C_{10}H_{15}NO_2Na$ [M + Na]$^+$ 204.1000; found 204.1058.

***tert*-Butyl *N*-(2-Aminoethyl)carbamate (12):**[24] A solution of di-*tert*-butyl dicarbonate (16 mL, 70 mmol, 1.0 equiv.) in CH_2Cl_2

(500 mL) was added dropwise at 0 °C over a period of 1 h to a solution of ethylenediamine (29 mL, 427 mmol, 6.1 equiv.) in CH_2Cl_2 (140 mL). The resulting mixture was stirred for 12 h with slow warming to ambient temperature and concentrated under reduced pressure. The residue was dissolved in aqueous $NaHCO_3$ (20% w/w, 150 mL) and extracted with CH_2Cl_2 (3× 150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the amine **12** as a colorless oil, yield 11 g (98%). Spectroscopic data are identical to the reported data.[24]

***tert*-Butyl *N*-(2-{*N*-[(1*RS*,2*RS*,3*RS*)-2-Hydroxy-3-(2-oxopyrrolidin-1-yl)cyclohexyl]benzamido}ethyl)carbamate (14):** A solution of the amine **12** (332 mg, 2.07 mmol, 1.5 equiv.) in H_2O (5 mL) was added dropwise to a solution of the epoxide **11** (250 mg, 1.38 mmol, 1.0 equiv.) in H_2O (5 mL). The resulting mixture was stirred at ambient temperature for 1 d and then concentrated under reduced pressure. The residue was dissolved in toluene and concentrated under reduced pressure. This process was repeated. The residue was dissolved in CH_2Cl_2 (3 mL). Benzoyl chloride (0.18 mL, 1.6 mmol, 1.2 equiv.) and, after 30 min, aqueous NaOH (1 M, 2.30 mL, 2.30 mmol, 1.7 equiv.) were carefully added to the stirred solution. Stirring was continued for 18 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc [d = 3 cm, l = 10 cm, V = 20 mL, cyclohexane/ethyl acetate 1:0→7:3→0:1→ ethyl acetate/methanol 7:1, R_f = 0.84 (tlc, ethyl acetate/methanol 1:1, detection: $KMnO_4$)] to afford the alcohol **14** as a colorless solid, m.p. 63–66 °C, yield 419 mg (68%). LC/MS (ESI^+): 1.12 min (100%, 346 {$C_{19}H_{28}N_3O_3$ [M + H – CH_2=C(CH_3)$_2CO_2$]$^+$}, 390 {$C_{20}H_{28}N_3O_5$ [M + H – CH_2=C(CH_3)$_2$]$^+$}, 446 {$C_{24}H_{36}N_3O_5$ [M + H]$^+$}, 468 {$C_{24}H_{35}N_3NaO_5$ [M + Na]$^+$}). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.28–1.36 (m, 1 H, 5-C$H_{2,cycl}$), 1.44 [s, 9 H, C(CH_3)$_3$], 1.58–1.78 (m, 6 H, 4-C$H_{2,cycl}$, 5-C$H_{2,cycl}$, 6-C$H_{2,cycl}$, 4-C$H_{2,py}$), 1.78–1.88 (m, 1 H, 4-C$H_{2,py}$), 2.30 (t, J = 7.7 Hz, 2 H, 3-C$H_{2,py}$), 2.74 (dt, ^2J = 6.3, ^3J = 6.1 Hz, 1 H, 5-C$H_{2,py}$), 3.19 (dt, ^2J = 6.3, ^3J = 5.1 Hz, 1 H, 5-C$H_{2,py}$), 3.39–3.48 (m, 3 H, CH_2-CH_2-NH, CH_2-NH), 3.51–3.58 (m, 1 H, CH_2-CH_2-NH), 3.72 (dt, J = 11.1, 9.9 Hz, 1 H, 1-CH_{cycl}), 3.75 (dd, J = 9.9, 4.2 Hz, 1 H, 2-CH_{cycl}), 4.52 (td, J = 4.2, 2.1 Hz, 1 H, 3-CH_{cycl}), 5.55 (br. s, 1 H, NH), 7.34–7.37 (m, 3 H, 3-CH_{ar}, 4-CH_{ar}, 5-CH_{ar}), 7.41–7.45 (m, 2 H, 2-CH_{ar}, 6-CH_{ar}) ppm. No signal for the OH proton is seen in the spectrum. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 18.4 (C-4$_{py}$), 21.2 (C-5$_{cycl}$), 26.6 (C-4$_{cycl}$), 28.6 [C(*C*H$_3$)$_3$], 29.5 (C-6$_{cycl}$), 30.5 (C-3$_{py}$), 39.9 (*C*H$_2$-NH), 41.0 (*C*H$_2$-CH$_2$-NH), 48.0 (C-5$_{py}$), 53.1 (C-3$_{cycl}$), 59.1 (C-1$_{cycl}$), 73.1 (C-2$_{cycl}$), 79.3 [*C*(CH$_3$)$_3$], 127.3 (C-2$_{ar}$, C-6$_{ar}$), 128.2 (C-3$_{ar}$, C-5$_{ar}$), 128.9 (C-4$_{ar}$), 137.7 (C-1$_{ar}$), 156.7 (O-*C*=O), 173.7 (Ph-*C*=O), 178.8 (C-2$_{py}$) ppm. FT-IR (ATR): $\tilde{\nu}$ = 3329 (br. s, O–H, N–H), 2974 (s, C–H), 2936 (s, C–H), 2870 (m, C–H), 1705 [s, O(C=O)NH], 1655 (s, Ph–C=O), 1620 (s, CH_2C=O), 702 (m, C=C$_{ar,oop}$) cm^{-1}. HRMS (APCI): m/z calcd. for $C_{19}H_{28}N_3O_3$ [M + H -CH_2=C(CH_3)$_2CO_2$]$^+$ 346.2131; found 346.2168.

***tert*-Butyl *N*-(2-{*N*-[2-Oxo-3-(2-oxopyrrolidin-1-yl)cyclohexyl]benzamido}ethyl)carbamate (15):** The alcohol **14** (1.80 g, 4.040 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (180 mL). Pyridinium chlorochromate adsorbed on neutral alumina (25%-w/w, 5.57 g, 6.46 mmol, 1.6 equiv.) was added and the resulting mixture was stirred at ambient temperature for 2 d, filtered, and concentrated under reduced pressure. The residue was purified by fc [d = 5 cm, l = 10 cm, V = 100 mL, cyclohexane/ethyl acetate 1:0→0:1→ethyl acetate/methanol 19:1, R_f = 0.16 (tlc, ethyl acetate, detection: Hanessian's stain)] to afford the ketone **15** as a colorless solid, m.p. 50–52 °C, yield 1.15 g (64%). Purity (HPLC): 80.3%, t_R = 17.30 min; 13.7%, t_R = 17.07 min. LC/MS (ESI^+): 0.78 min (100%, 344 {$C_{19}H_{26}N_3O_3$ [M + H – CH_2=C(CH_3)$_2CO_2$]$^+$}, 388 {$C_{20}H_{26}N_3O_5$ [M + H – CH_2=C(CH_3)$_2$]$^+$}, 444 {$C_{24}H_{34}N_3O_5$ [M + H]$^+$}, 466 {$C_{24}H_{33}N_3NaO_5$ [M + Na]$^+$}). Three sets of signals (^1H NMR intensity ratio **A1**/**A2**/**B** = 6:3:1) are seen in the ^1H NMR spectrum, originating from two diastereomers (**A**, **B**) and rotational isomers observed for the major diastereomer (**A1**, **A2**). Rotational isomerism of the minor diastereomer is not observed. Rotational isomerism is not seen in the ^{13}C NMR spectrum due to low signal intensity. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.39 [s, 0.6×9 H, C(CH_3)$_3$], 1.44 [s, 0.3×9 H, 0.1×9 H, C(CH_3)$_3$], 1.77–1.89 (m, 1 H, 5-C$H_{2,cycl}$), 1.93–2.20 (m, 5 H, 4-C$H_{2,cycl}$, 5-C$H_{2,cycl}$, 4-C$H_{2,py}$), 2.22–2.32 (m, 1 H, 6-C$H_{2,cycl}$), 2.35–2.55 (m, 3 H, 6-C$H_{2,cycl}$, 3-C$H_{2,py}$), 2.92–3.05 (m, 0.6×1 H, CH_2-NH), 3.12–3.32 (m, 0.6×1 H, 0.4×3 H, CH_2-NH, CH_2-CH$_2$-NH), 3.32–3.47 (m, 0.6×1 H, 1 H, CH_2-CH$_2$-NH, 5-C$H_{2,py}$), 3.47–3.63 (m, 0.6×1 H, 1 H, CH_2-CH$_2$-NH, 5-C$H_{2,py}$), 3.84–3.95 (m, 0.4×1 H, CH_2-CH$_2$-NH), 3.95–4.07 (m, 0.6×1 H, 0.1×1 H, 1-CH_{cycl}), 4.30–4.38 (m, 0.3×1 H, 1-CH_{cycl}), 4.42–4.51 (m, 0.3×1 H, 3-CH_{cycl}), 4.64–4.68 (m, 0.1×1 H, 3-CH_{cycl}), 4.69–4.82 (m, 0.6×1 H, 3-CH_{cycl}), 5.19 (br. s, 0.3×1 H, NH), 5.30 (br. s, 0.1×1 H, NH), 5.34 (br. s, 0.6×1 H, NH), 7.32–7.50 (m, 5 H, CH_{ar}) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ = 18.3 (C-4$_{py}$, both), 22.5 (C-5$_{cycl}$, both), 28.1 (C-4$_{cycl}$, both), 28.6 [C(*C*H$_3$)$_3$, both], 29.5 (C-6$_{cycl}$, both), 30.9 (C-3$_{py}$, both), 39.1 (*C*H$_2$-NH, both), 44.2 (*C*H$_2$-CH$_2$-NH, both), 51.0 (C-5$_{py}$, both), 59.3 (C-3$_{cycl}$, both), 63.8 (C-1$_{cycl}$, both), 79.5 [*C*(CH$_3$)$_3$, both], 126.2 (C-2$_{ar}$, C-6$_{ar}$, minor), 126.9 (C-2$_{ar}$, C-6$_{ar}$, major), 128.5 (C-3$_{ar}$, C-5$_{ar}$, minor), 128.7 (C-3$_{ar}$, C-5$_{ar}$, major), 129.1 (C-4$_{ar}$, minor), 129.7 (C-4$_{ar}$, major), 130.2 (C-1$_{ar}$, both), 162.8 (O-*C*=O, both), 171.8 (Ph-*C*=O, both), 176.3 (C-2$_{py}$, both), 200.2 (C-2$_{cycl}$, both) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2970 (s, N–H), 2932 (s, C–H), 2878 (m, C–H), 1705 (s, 2–C=O), 1674 (s, C$_{ar,q}$–C=O), 1624 (s, CH_2C=O) cm^{-1}. HRMS (APCI): m/z calcd. for $C_{24}H_{34}N_3O_5$ [M + H]$^+$ 444.2498; found 444.2499.

1-[(4a*RS*,5*RS*,8a*SR*)-1-Benzoyldecahydroquinoxalin-5-yl]pyrrolidin-2-one (18A) and 1-[(4a*RS*,5*SR*,8a*SR*)-1-Benzoyldecahydroquinoxalin-5-yl]pyrrolidin-2-one (18B): The ketone **15** (88 mg, 0.198 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (4 mL). TFA (1.0 mL) was added. The mixture was stirred at ambient temperature for 3 h and concentrated under reduced pressure. The residue was dissolved in abs. THF (25 mL) and cooled to 0 °C. Sodium borohydride (8.0 mg, 0.21 mmol, 1.05 equiv.) was added. The resulting mixture was allowed to warm slowly to ambient temperature while being stirred for 11 h. The mixture was concentrated under reduced pressure, immobilized on SiO_2 (200 mg), and purified by fc [d = 2 cm, l = 5 cm, V = 20 mL, cyclohexane/ethyl acetate 1:0→1:1→0:1→ ethyl acetate/methanol 7:1→7:3, R_f = 0.28 (tlc, ethyl acetate/methanol 1:1, detection: $KMnO_4$)] to afford a mixture of the diastereomers **18A** and **18B** (dr = 93:7) as a colorless solid, m.p. 65–67 °C, yield 31 mg (63%). Two sets of signals (^1H NMR intensity ratio = 9:1) are observed, originating from two diastereomers. LC/MS (ESI^+): 0.75 min (B, 7%, 328 {$C_{19}H_{26}N_3O_2$ [M + H]$^+$}, 346 {$C_{19}H_{28}N_3O_3$ [M + H + H_2O]$^+$}, 350 {$C_{19}H_{25}N_3NaO_2$ [M + Na]$^+$}, 368 {$C_{19}H_{27}N_3NaO_3$ [M + Na + H_2O]$^+$}), 0.86 min (A, 93%, 328 {$C_{19}H_{26}N_3O_2$ [M + H]$^+$}, 346 {$C_{19}H_{28}N_3O_3$ [M + H + H_2O]$^+$}, 368 {$C_{19}H_{27}N_3NaO_3$ [M + Na + H_2O]$^+$}). ^1H NMR (600 MHz, CD_3OD): δ = 1.51–1.96 (m, 6 H, 6-C$H_{2,bicycl}$, 7-C$H_{2,bicycl}$, 8-C$H_{2,bicycl}$), 2.09–2.19 (m, 2 H, 4-C$H_{2,py}$), 2.32–2.53 (m, 2 H, 3-C$H_{2,py}$), 3.13–3.25 [m, 0.9×2 H, 3-C$H_{2,bicycl}$(A)], 3.34–3.41 [m, 0.9×1 H, 0.1×2 H, 5-C$H_{2,py}$(A), 5-C$H_{2,py}$(B)], 3.43–3.56 [m, 0.9×1 H, 1 H, 5-C$H_{2,py}$(A), 2-C$H_{2,bicycl}$], 3.57–3.66 [m, 1 H, 0.1×1 H, 2-C$H_{2,bicycl}$, 3-C$H_{2,bicycl}$(B)], 3.70–3.82 [m, 0.1×2 H, 3-C$H_{2,bicycl}$(B), 8a-CH_{bicycl}(B)], 3.92–3.95 [m, 0.9×1 H, 4a-

CH_{bicycl}(A)], 4.01–4.07 [m, 0.9 × 1 H, 8a-CH_{bicycl}(A)], 4.13 [dd, J = 11.2, 3.6 Hz, 0.1 × 1 H, 4a-CH_{bicycl}(B)], 4.18 [td, J = 11.2, 5.6 Hz, 0.1 × 1 H, 5-CH_{bicycl}(B)], 4.66 (br. s, 1 H, NH), 4.90–4.99 [m, 0.9 × 1 H, 5-CH_{bicycl}(A)], 7.42–7.56 (m, 5 H, CH_{ar}) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, CD_3OD): δ = 18.5 (C-4_{py}, minor, B), 18.8 (C-4_{py}, major, A), 23.2 (C-7_{bicycl}, minor, B), 23.3 (C-7_{bicycl}, major, A), 23.4 (C-8_{bicycl}, both), 23.6 (C-6_{bicycl}, both), 32.0 (C-3_{py}, minor, B), 32.1 (C-3_{py}, major, A), 40.9 (C-3_{bicycl}, major, A), 41.4 (C-3_{bicycl}, minor, B), 45.2 (C-5_{py}, minor, B), 45.3 (C-5_{py}, major, A), 48.2 (C-2_{bicycl}, both), 49.0 (C-5_{bicycl}, major, A), 53.1 (C-5_{bicycl}, minor, B), 54.5 (C-$8a_{bicycl}$, minor, B), 54.9 (C-$8a_{bicycl}$, major, A), 57.5 (C-$4a_{bicycl}$, minor, B), 57.7 (C-$4a_{bicycl}$, major, A), 128.0 (C-2_{ar}, C-6_{ar}, major, A), 128.2 (C-2_{ar}, C-6_{ar}, minor, B), 129.9 (C-3_{ar}, C-5_{ar}, both), 131.6 (C-4_{ar}, major, A), 131.8 (C-4_{ar}, minor, B), 135.8 (C-1_{ar}, both), 163.0 (Ph-*C*=O, minor, B), 163.2 (Ph-*C*=O, major, A), 179.4 (C-2_{py}, both) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2959 (s, N–H), 2800 (s, C–H), 1627 (br. s, C=O), 729 (s, C=$C_{ar,oop}$) cm^{-1}. HRMS (APCI): *m*/*z* calcd. for $C_{19}H_{26}N_3O_2$ $[M + H]^+$ 328.2025; found 328.2036.

(3a*RS*,6a*SR*,10a*SR*,11a*RS*)-3-Benzylperhydropyrrolo[1′,2′:1,2]imidazo[3,4,5-*de*]quinoxaline (19): The ketone **15** (1.05 g, 2.37 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (41 mL). TFA (10.2 mL) and molecular sieves (4 Å, 200 mg) were added. The mixture was stirred at ambient temperature for 3 h, decanted, and concentrated under reduced pressure. The residue was dissolved in abs. THF (60 mL) and cooled to 0 °C. $NaBH_4$ (131 mg, 3.46 mmol, 1.46 equiv.) was added. The resulting mixture was allowed to warm slowly to ambient temperature while being stirred for 11 h. Lithium aluminum hydride (677 mg, 17.8 mmol, 7.5 equiv.) was added, and the resulting mixture was heated under reflux for 24 h. After the system had cooled to ambient temperature, H_2O (20 mL) was carefully added. The mixture was filtered and concentrated under reduced pressure. The residue was suspended in CH_2Cl_2 (20 mL), filtered, and concentrated under reduced pressure to give a crude mixture of the triamine **20** and the aminal **19** (yield 294 mg, 42%). 3,4-Dichlorophenylacetyl chloride (**21**, 689 mg, 3.08 mmol, 1.3 equiv.) was added. After 1 h, aqueous NaOH (1 M, 3.56 mL, 3.56 mmol, 1.5 equiv.) was added and the resulting mixture was stirred at ambient temperature for 14 h. The layers were separated and the aqueous layer was diluted with brine (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with a mixture of aqueous NaOH (1 M, 5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc [d = 3 cm, l = 10 cm, V = 20 mL, cyclohexane/ethyl acetate 1:0 → 1:1 → 0:1 → ethyl acetate/methanol 19:1 → 7:1 → 7:3, R_f(**19**) = 0.01 (tlc, ethyl acetate/methanol 1:1, detection: $KMnO_4$)] to afford the acetamide **7**, yield 48 mg (4%), and the triamine **19**, yield 172 mg (24%) as a colorless solid; m.p. could not be determined due to decomposition before melting. LC/MS (ESI^+): 0.75 min (100%, 298 $\{C_{19}H_{28}N_3$ $[M + H]^+\}$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (ddt, J = 18.4, 13.7, 3.1 Hz, 1 H, 5-C$H_{2,ax}$), 1.41–1.53 (m, 1 H, 6-CH_2), 1.54–1.68 (m, 2 H, 4-CH_2), 1.72–1.80 (m, 1 H, 6-CH_2), 1.86–1.93 (m, 1 H, 5-C$H_{2,eq}$), 1.94–2.01 (m, 3 H, 9-CH_2, 10-CH_2), 2.01–2.10 (m, 1 H, 9-CH_2), 2.34 (ddd, ^2J = 10.3, ^3J = 11.1, 3.2 Hz, 1 H, 1-C$H_{2,ax}$), 2.57 (ddd, ^2J = 11.8, ^3J = 3.2, 2.5 Hz, 1 H, 2-C$H_{2,eq}$), 2.71 (ddd, ^2J = 11.8, ^3J = 11.1, 2.5 Hz, 1 H, 2-C$H_{2,ax}$), 2.80 (dt, ^2J = 10.3, ^3J = 2.5 Hz, 1 H, 1-C$H_{2,eq}$), 2.95 (dt, J = 11.2, 5.1 Hz, 1 H, 3a-CH), 3.01 (t, J = 5.1 Hz, 1 H, 11a-CH), 3.17–3.34 (m, 2 H, 8-CH_2), 3.64 (d, ^2J = 13.6 Hz, 1 H, Ph-CH_2), 3.74 (d, ^2J = 13.6 Hz, 1 H, Ph-CH_2), 3.89–3.98 (m, 1 H, 6a-CH), 4.25 (dd, J = 5.0, 3.5 Hz, 1 H, 10a-CH), 7.29–7.32 (m, 4 H, 2-CH_{ar}, 3-CH_{ar}, 5-CH_{ar}, 6-CH_{ar}), 7.37–7.45 (m, 1 H, 4-CH_{ar}) ppm. NOE (400 MHz, $CDCl_3$): irradiation at δ = 4.22–4.28 (10a-CH) ppm, increase in signal intensity at δ = 1.94–2.01 (10-CH_2), 2.34 (1-C$H_{2,ax}$), 3.01 (11a-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 17.5 (C-4), 21.5 (C-5), 23.1 (C-6), 24.7 (C-9), 28.2 (C-10), 44.6 (C-2), 46.7 (C-8), 48.8 (C-1), 56.0 (C-3a), 58.0 (Ph-*C*H$_2$), 60.8 (C-6a), 63.2 (C-11a), 86.9 (C-10a), 127.4 (C-4_{ar}), 128.6 (C-2_{ar}, C-3_{ar}, C-5_{ar}, C-6_{ar}), 130.5 (C-1_{ar}) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2940 (s, C–H), 740 (C=$C_{ar,oop}$). HRMS (APCI): *m*/*z* calcd. for $C_{19}H_{28}N_3$ $[M + H]^+$ 298.2283; found 298.2271.

(4a*RS*,5*RS*,8a*SR*)-1-Benzyl-5-(pyrrolidin-1-yl)decahydroquinoxaline (20): The aminal **19** (100 mg, 0.336 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5 mL) and DMSO (2.5 mL). At 0 °C, TFA (26 μL, 0.34 mmol, 1.0 equiv.) and $NaBH_4$ (15 mg, 0.40 mmol, 1.2 equiv.) were added. The mixture was stirred for 12 h while being allowed to warm slowly to ambient temperature. It was washed with a mixture of aqueous NaOH (2 M, 2 mL) and brine (4 mL) and extracted twice with a mixture of aqueous HCl (2 M, 1.5 mL) and brine (2 mL). The combined acidic aqueous layers were adjusted to pH > 12 with aqueous NaOH (2 M, 3.5 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc [d = 2 cm, l = 3 cm, V = 20 mL, cyclohexane/ethyl acetate 1:0 → 7:1 → ethyl acetate/methanol 1:0 → 7:1 → 7:3 → 1:1, R_f = 0.00 (tlc, methanol, detection: $KMnO_4$)] to afford the decahydroquinoxaline **20** as a colorless oil, yield 28 mg (28%). LC/MS (ESI^+): 0.60 min (100%, 300 $\{C_{19}H_{30}N_3$ $[M + H]^+\}$). Purity (HPLC): 74.5%, t_R = 5.14 min. ^1H NMR (400 MHz, $CDCl_3$): δ = = 1.09 (qt, ^2J = 13.3, ^3J = 13.3, 4.0 Hz, 1 H, 7-C$H_{2,ax,bicycl}$), 1.49 (ddd, ^2J = 12.4, ^3J = 7.6, 4.0 Hz, 1 H, 6-C$H_{2,eq,bicycl}$), 1.59–1.69 (m, 2 H, 8-C$H_{2,bicycl}$), 1.75–1.86 (m, 5 H, 7-C$H_{2,eq,bicycl}$, 3-C$H_{2,py}$, 4-C$H_{2,py}$), 1.98 (dtd, ^3J = 13.3, ^2J = 12.4, ^3J = 12.4, 3.9 Hz, 1 H, 6-C$H_{2,ax,bicycl}$), 2.04 (s, 1 H, NH), 2.06–2.12 (m, 1 H, 8a-CH_{bicycl}), 2.43 (ddd, ^2J = 11.3, ^3J = 3.2, 1.8 Hz, 1 H, 3-C$H_{2,eq,bicycl}$), 2.57–2.69 (m, 6 H, 2-C$H_{2,py}$, 5-C$H_{2,py}$, 3-C$H_{2,ax,bicycl}$, 5-CH_{bicycl}), 2.83 (td, ^2J = 11.3, ^3J = 11.3, 3.4 Hz, 1 H, 2-C$H_{2,ax,bicycl}$), 3.00 (ddd, ^2J = 11.3, ^3J = 3.1, 1.8 Hz, 1 H, 2-C$H_{2,eq,bicycl}$), 3.17 (t, J = 3.0 Hz, 1 H, 4a-CH_{bicycl}), 3.56 (d, ^2J = 13.5 Hz, 1 H, Ph-CH_2), 3.70 (d, J = 13.5 Hz, 1 H, Ph-CH_2), 7.21 (tt, ^3J = 7.1, ^4J = 1.5 Hz, 1 H, 4-CH_{ar}), 7.36–7.27 (m, 4 H, 2-CH_{ar}, 3-CH_{ar}, 5-CH_{ar}, 6-CH_{ar}) ppm. NOE (400 MHz, $CDCl_3$): irradiation at δ = 2.04–2.14 (8a-CH_{bicycl}) ppm, increase in signal intensity at δ = 1.59–1.69 (8-C$H_{2,bicycl}$), 2.57–2.69 (3-C$H_{2,ax,bicycl}$, 5-CH_{bicycl}), 3.17 (4a-CH_{bicycl}); irradiation at δ = 3.15–3.20 (4a-CH_{bicycl}), increase in signal intensity at δ = 2.06–2.12 (8a-CH_{bicycl}), 2.57–2.69 (2-C$H_{2,py}$, 5-C$H_{2,py}$, 5-CH_{bicycl}), 2.83 (2-C$H_{2,ax,bicycl}$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 16.4 (C-6_{bicycl}), 23.1 (C-7_{bicycl}), 23.3 (C-3_{py}, C-4_{py}), 26.1 (C-8_{bicycl}), 46.6 (C-3_{bicycl}), 46.7 (C-2_{bicycl}), 51.9 (C-2_{py}, C-5_{py}), 57.8 (C-4a), 59.0 (Ph-*C*H$_2$), 59.3 (C-5), 67.0 (C-8a), 126.9 (C-4_{ar}), 128.3 (C-3_{ar}, C-5_{ar}), 128.9 (C-2_{ar}, C-6_{ar}), 139.5 (1-*C*$_{ar}$) ppm. FT-IR (ATR): $\tilde{\nu}$ = 2940 (s, N–H), 2799 (s, C–H), 729 (C=$C_{ar,oop}$) cm^{-1}. HRMS (APCI): *m*/*z* calcd. for $C_{19}H_{30}N_3$ $[M + H]^+$ 300.2440; found 300.2456.

2-(3,4-Dichlorophenyl)acetyl Chloride (21):[34] 2-(3,4-Dichlorophenyl)acetic acid (10.3 g, 50.0 mmol, 1.0 equiv.) was suspended in abs. Et_2O (100 mL). At 0 °C, oxalyl chloride (5.1 mL, 60 mmol, 1.2 equiv.) and DMF (0.5 mL) were carefully added. The resulting mixture was stirred for 14 h. It was then concentrated under reduced pressure. The acid chloride **21** was isolated by distillation under reduced pressure as a pale yellow oil, $b.p._{0.012\ mbar}$ = 98 °C, yield 9.22 g (83%). Spectroscopic data are identical to the reported data.[34]

Supporting Information (see footnote on the first page of this article): Methods and results of theoretical calculations, chromatog-

raphy methods, starting materials synthesis protocols, pharmacological methods and results, ^{1}H and ^{13}C NMR spectra.

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