Stereoselective Synthesis of *cis*,*cis*-Configured Perhydroquinoxaline-5-Carbonitrile from Cyclohex-2-en-1-ol

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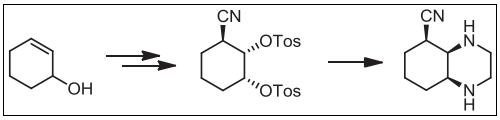

cis,*cis*-Configured perhydroquinoxaline-5-carbonitrile **10** was synthesized stereoselectively by ditosylation of *trans*,*cis*-2,3-dihydroxycyclohexane-1-carbonitrile **4** and subsequent reaction with ethylenediamine. The diol precursor **4** was stereoselectively obtained by regioselective opening of the epoxide **3** with KCN in water avoiding hazardous Et_2AlCN.

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INTRODUCTION

Perhydroquinoxalines have been widely employed in medicinal chemistry, e.g. as δ opioid receptor [1] and 5-HT_1 receptor ligands [2], cholinesterase inhibitors [3], and P2X7 receptor antagonists [4]. Compounds with this heterocycle have also been used for the treatment of depression [5], type 2 diabetes [6], *Alzheimer*'s disease and *Down*'s syndrome [7], as well as autoimmune diseases [8]. Recently, the *trans*,*trans*-configured 5-pyrrolidinyl-substituted perhydroquinoxaline derivative **1** was demonstrated to exhibit high κ opioid receptor affinity ($K_i = 9.3$ nM) [9].

This result motivated us to investigate type **I** compounds by variation of, first, the relative configuration of the 5-aminoquinoxaline scaffold and, second, the nature of the substituent in 5-position. Whereas the *cis*,*cis*-configuration of the scaffold could give insight into the dependence of the κ affinity on the relative configuration, the introduction of a pyrrolidinone or a cyano moiety in 5-position could allow late-stage diversification of the substrates.

The perhydroquinoxalines **I** are retrosynthetically derived from *trans*,*cis*-configured ditosylates **II** and ethylenediamine and **II** is further traced back to *trans*,*cis*-configured diols **III**. The synthesis of piperazines by reaction of ethylene ditosylates with ethylenediamine has not yet been reported (Fig. 1).

SYNTHESIS

Cyclohex-2-en-1-ol (**2**) reacted with monoperoxyphthalic acid (MPPA) in aqueous solution applying the method of *Ye et al.* [10] to stereoselectively afford the *cis*-configured epoxyalcohol **3** in 73% yield. *Benedetti et al.* reported the conversion of the epoxide **3** into the diol **4** using Et_2AlCN at rt with 65% yield [11]. Furthermore amines are able to open epoxides regioselectively when promoted with $Ti(O^iPr)_4$ [12].

Epoxide ring-opening in water is an established method with similar regioselectivity as under *Lewis* acid-promoted conditions [13]. We thus aimed at replacing the hazardous organometallic reagent Et_2AlCN with KCN in water. Performing the epoxide opening with amines in water should also avoid the Ti(IV)-species. The reaction of epoxide **3** with pyrrolidine in water gave a quantitative yield of aminodiol **5** with high regio- and diastereoselectivity as well as high reproducibility. However, synthesis of the nitrile **4** required some optimization. Finally it was found that a biphasic mixture of water and ethyl acetate at a slightly elevated temperature (40°C) provided the cyanodiol **4** in 62% yield, which is close to the yield reported by *Benedetti et al.* using Et_2AlCN.

Despite a broad screening of reaction conditions and in contrast to other epoxides [14], deprotonated pyrrolidin-2-one did not react with the epoxide **3**, even after addition of the *Lewis* acid $Ti(Oi\text{-}Pr)_4$. However, the synthesis of the diol **6** was achieved by dihydroxylation of the alkene **7**, which was prepared by deprotonation of pyrrolidin-2-one with NaH and subsequent reaction with 3-bromocyclohex-1-ene [15]. Reaction of **7** with $KMnO_4$ and $MgSO_4$ at −25°C, similar to the method of *Kresze* and *Kysela* [16], furnished the diol **6** with 51% yield as a 7:3 mixture of the *trans*,*cis*- (**6A**) and *cis*, *cis*-configured (**6B**) diastereomers (Scheme 1).

Conversion of the diol **5** with *p*-toluenesulfonyl (tosyl) chloride was complete after 2.5 d as monitored by tlc. However, after aqueous work-up, the diol **5** was reisolated with 96% yield. It is therefore postulated that an intermediate N-tosylammonium salt was formed [17], which is probably due to the high nucleophilicity of the pyrrolidine N-atom.

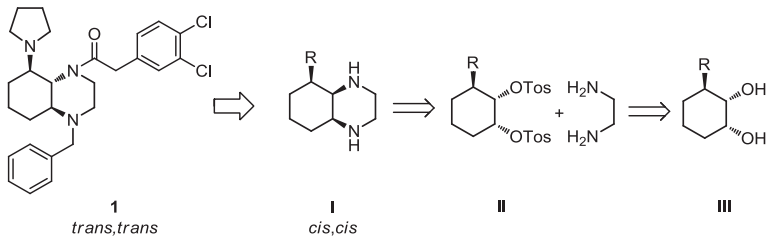
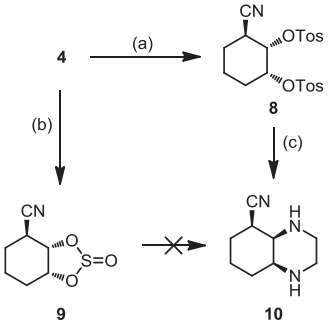


Figure 1. Development of target compounds **I** from the κ agonist **1** and retrosynthetic analysis.

The diol **6** reacted with tosyl chloride to give the epoxide **3** stereospecifically in 75% yield. This reverse transformation of the diol **6** into the epoxide **3** is explained by tosylation of the lactam O-atom, followed by intramolecular nucleophilic substitution of the pyrrolidone group by the vicinal OH group. Reaction of the diol **6** with other electrophiles, e.g. intermediate sulfonium ylides generated under conditions of a *Swern* oxidation, also led to stereospecific formation of the epoxide **3**, which was isolated in high yields. This result indicates the high reactivity of the pyrrolidin-2-one moiety against electrophiles.

The cyanodiol **4** reacted with thionyl chloride to give the cyclic sulfite **9** in 69% yield. However, reaction of cyclic sulfite **9** with ethylenediamine only led to decomposition. Therefore, the cyanodiol **4** was treated with tosyl chloride to afford the ditosylate **8** in 38% yield, which was reacted with ethylenediamine in refluxing THF to give the desired *cis*,*cis*-configured perhydroquinoxaline-5-carbonitrile (**10**) in 42% yield (Scheme 2).

Scheme 2. Synthesis of the perhydroquinoxaline **10** from the diol **4**.

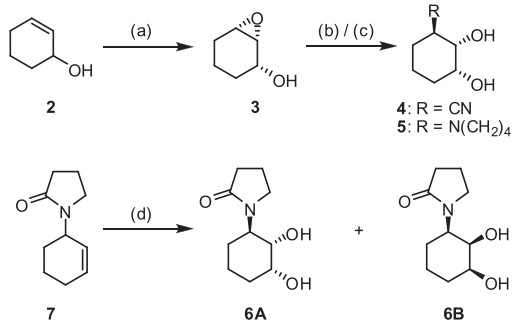


Reagents and conditions: (a) *p*-TosCl, pyridine, 0 °C → rt, 2 d, 38%; (b) $SOCl_2$, NEt_3, THF, 0 °C, 2 h, 69%; (c) ethylenediamine, THF, *reflux*, 5.5 h, 42%. Only one enantiomer of the racemic mixtures is shown.

CONCLUSION

The successful synthesis of the quinoxalinecarbonitrile **10** demonstrates that *cis,cis*-configured 5-substituted perhydroquinoxalines are accessible by double nucleophilic substitution of 1,2-ditosylates with ethylenediamine. However, the synthesis depends strongly on the nature of the substituent in 3-position of the cyclohexane-1,2-diol. Whereas pyrrolidine and pyrrolidin-2-one substituted cyclohexanediols **5** and **6** react with electrophiles under N-tosylation (desactivation) and actam tosylation (pyrrolidone elimination), respectively, the cyano group allowed the transformation of both OH-groups of **4** into tosyloxy leaving groups. Thus, *cis*,*cis*-configured perhydroquinoxaline-5-carbonitrile (**10**) was prepared stereoselectively, which will be used as a precursor in the synthesis of new quinoxaline-based κ agonists.

Scheme 1. Synthesis of the diols **4**, **5**, and **6**.



Reagents and conditions: (a) MPPA, NaOH (1 M, aq.), rt, 18 h, 73%; (b) KCN, $NaHCO_3$, EtOAc:H_2O (5:2), 40 °C, 24 h, 62% (**4**); (c) pyrrolidine, H_2O, rt, 3 d, 100% (**5**); (d) $KMnO_4$, $MgSO_4$, EtOH:H_2O (1:1), −25 °C, 2 h, rt, 16 h, 51%, **6A**:**6B** = 7:3. Only one enantiomer of the racemic mixtures is shown.

EXPERIMENTAL

General. All commercially available reagents were used without further purification. THF was dried by distillation over sodium. All reactions were carried out under nitrogen atmosphere. The reactions were monitored by thin layer chromatography (tlc) using silica gel-coated aluminium plates (Merck KGaA, 60F254) and visualized with $KMnO_4$. Yields refer to chromatographically purified or distilled compounds. Flash column chromatography (fc) was carried out using silica gel (Merck KGaA, 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, and HRMS). NMR spectra were recorded on a 400-MHz spectrometer (Varian Mercury® Plus 400) and on a 600-MHz spectrometer (Jeol ECA 600). ^{1}H NMR spectra 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, b = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet), coupling constant *J* (Hz), and relative integration. ^{13}C NMR spectra are reported in parts per million (δ) relative to TMS calculated from the residual solvent signal. High-resolution mass spectra (HRMS) were obtained on a Bruker® Daltonics microTOF-QII™ (APCI, ESI). Fragmentation mass spectra (EI) were obtained on a Thermo Finnigan GCQ Finnigan MAT. Infrared (IR) spectra were recorded on an FT-IR spectrometer (Jasco® FT/IR-480 plus) using attenuated total reflection (ATR) technique or by transmission through NaCl plates (Jasco FT/IR-6100) and are reported as wave numbers υ (cm^{-1}). Melting points were measured using a Stuart™ SMP3 apparatus in capillary tubes sealed on one side and are uncorrected.

(1RS,2RS,3SR)-2,3-Dihydroxycyclohexane-1-carbonitrile (4). KCN (251 mg, 3.85 mmol, 4.0 equiv.) and $NaHCO_3$ (323 mg, 3.85 mmol, 4.0 equiv.) were dissolved in H_2O (5 mL), and a solution of the epoxide **3** (110 mg, 0.964 mmol, 1.0 equiv.) in ethyl acetate (2 mL) was added. The mixture was stirred at 40°C for 24 h. The layers were separated. The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (4 × 7 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc (*d* = 5 cm, *l* = 5 cm, *V* = 20 mL, cyclohexane:ethyl acetate = 1:0 ➔ 7:1 ➔ 7:3 ➔ 0:1, R_f = 0.22 (tlc, cyclohexane:ethyl acetate = 1:1, detection: *Hanessian*'s stain)) to afford the diol **4** (84 mg, 62%) as a colorless solid, mp 82–83°C. See supplementary information and report [18] for spectroscopic data.

(1RS,2RS,3RS)-3-(Pyrrolidin-1-yl)cyclohexane-1,2-diol (5). The epoxide **3** (795 mg, 6.97 mmol, 1.0 equiv.) was dissolved in H_2O (5 mL). Pyrrolidine (5.7 mL, 70 mmol, 10 equiv.) was added, and the mixture was stirred for 3 d. The solvent and excess pyrrolidine were removed under reduced pressure, and the residue was dissolved in methanol. The solution was dried (Na_2SO_4), immobilized on silica gel, and purified by fc (*d* = 8 cm, *l* = 2 cm, *V* = 65 mL, cyclohexane: ethyl acetate = 1:0 ➔ 7:1 ➔ 1:1 ➔ 0:1 ➔ ethyl acetate: methanol = 19:1 ➔ 7:1, R_f = 0.10 (tlc, methanol, detection: iodine chamber)) to afford the diol **5** (1.27 g, 98%) as a red oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.26 (td, *J* = 13.3/3.5 Hz, 1H, 4-C$H_{2,cycl,eq}$), 1.41 (tdd, *J* = 13.3/3.8/2.8 Hz, 1H, 6-C$H_{2,cycl,eq}$), 1.59 (tt, *J* = 13.3/3.4 Hz, 1H, 5-C$H_{2,cycl}$), 1.69 (tt, *J* = 13.3/3.8 Hz, 1H, 5-C$H_{2,cycl}$), 1.80–1.88 (m, 5H, 3-C$H_{2,py}$, 4-C$H_{2,py}$, 4-C$H_{2,cycl,ax}$), 1.91 (dd, ^{2}*J* = 16.8 Hz, ^{3}*J* = 14.5 Hz, 1H, 6-C$H_{2,cycl,ax}$), 2.84–2.92 (m, 4H, 2-C$H_{2,py}$, 5-C$H_{2,py}$), 3.14 (ddd, *J* = 12.0/10.5/3.5 Hz, 1H, 3-CH_{cycl}), 3.52 (dd, *J* = 10.5/3.0 Hz, 1H, 2-CH_{cycl}), 4.16 (d, *J* = 3.0 Hz, 1H, 1-CH_{cycl}), 4.96 (s, 2H, O*H*). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ [ppm] = 19.2 (C-5$_{cycl}$), 22.4 (C-4$_{cycl}$), 23.7 (C-3$_{py}$, C-4$_{py}$), 29.9 (C-6$_{cycl}$), 48.5 (C-2$_{py}$, C-5$_{py}$), 60.0 (C-3$_{cycl}$), 69.0 (C-1$_{cycl}$), 72.4 (C-2$_{cycl}$). FT-IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3368 (bs, O–H), 2934 (s, C–H), 2871 (s, C–H), 2819 (s, C–H). Exact mass (APCI): *m/z* = 186.1546 (calcd. 186.1494 for $C_{10}H_{20}NO_2$ $[MH]^+$).

1-[(1RS,2SR,3RS)- and (1RS,2RS,3SR)-2,3-Dihydroxycyclohex-1-yl]pyrrolidin-2-one (6A and 6B). The alkene **7** (100 mg, 0.605 mmol, 1.0 equiv.) was dissolved in ethanol (1.5 mL), and the solution was cooled to −25°C. A solution of $MgSO_4$ (124 mg, 1.03 mmol, 1.7 equiv.) and $KMnO_4$ (172 mg, 1.09 mmol, 1.8 equiv.) in H_2O (4.0 mL) was added dropwise over a period of 2 h. The resulting mixture was stirred under slow warming to ambient temperature for 16 h, then diluted with *iso*-propanol (2 mL) and filtered (paper, grade 388). The residue was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was 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 ➔ 7:1 ➔ 1:1 ➔ 0:1 ➔ ethyl acetate:methanol = 19:1, R_f = 0.50 (tlc, ethyl acetate:methanol = 1:1, detection: $KMnO_4$)) to afford a 7:3 mixture of the diastereomers **6A** and **6B** (61 mg, 51%) as a pale yellow oil. Two sets of signals (^{1}H NMR intensity ratio **6A**:**6B** = 7:3) are seen in the spectra originating from two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.32–1.55 (m, 3H, 4-C$H_{2,cycl}$, 5-C$H_{2,cycl}$, 6-C$H_{2,cycl}$), 1.56–1.87 (m, 2H, 5-C$H_{2,cycl}$, 6-C$H_{2,cycl}$), 1.90–2.10 (m, 3H, 4-C$H_{2,py}$, 4-C$H_{2,cycl}$), 2.35–2.43 (m, 1H, 3-C$H_{2,py}$), 2.42–2.49 (m, 1H, 3-C$H_{2,py}$), 3.40 (t, *J* = 7.1 Hz, 2H, 5-C$H_{2,py}$), 3.49 (dd, *J* = 10.8/3.3 Hz, 0.7x1H, 2-CH_{cycl}, **A**), 3.62 (dd, *J* = 5.8/2.1 Hz, 0.3x1H, 2-CH_{cycl}, **B**), 3.97 (ddd, *J* = 5.8/5.6/4.6 Hz, 0.3x1H, 1-CH_{cycl}, **B**), 4.06 (t, *J* = 2.1 Hz, 0.3x1H, 3-CH_{cycl}, **B**), 4.15 (dd, *J* = 5.6/3.3 Hz, 0.7x1H, 3-CH_{cycl}, **A**), 4.25 (ddd, *J* = 12.2/10.8/4.1 Hz, 0.7x1H, 1-CH_{cycl}, **A**). Signals for the O*H* protons are not seen in the spectrum. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ [ppm] = 18.1 (C-4$_{py}$, **A**), 18.2 (C-4$_{py}$, **B**), 18.6 (C-5$_{cycl}$, **B**), 18.7 (C-5$_{cycl}$, **A**), 27.6 (C-6$_{cycl}$, **B**), 28.7 (C-6$_{cycl}$, **A**), 30.2 (C-4$_{cycl}$, **B**), 30.9 (C-4$_{cycl}$, **A**), 31.5 (C-3$_{py}$, **B**), 31.8 (C-3$_{py}$, **A**), 43.4 (C-5$_{py}$, **A**), 43.6 (C-5$_{py}$, **B**), 51.7 (C-1$_{cycl}$, **A**), 58.1 (C-1$_{cycl}$, **B**), 70.1 (C-3$_{cycl}$, **A**), 71.2 (C-2$_{cycl}$, **B**), 72.4 (C-2$_{cycl}$, **A**), 72.7 (C-3$_{cycl}$, **B**), 175.3 (C-2$_{py}$, **B**), 177.2 (C-2$_{py}$, **A**). FT-IR (ATR): $\tilde{\upsilon}$[cm^{-1}] = 3410 (bs, O–H), 2936 (s, C–H), 2866 (s, C–H), 1690 (s, C = O). Exact mass (APCI): *m/z* = 200.1289 (calcd. 200.1287 for $C_{10}H_{18}NO_3$ $[MH]^+$).

(1RS,2SR,3SR)-3-Cyanocyclohexane-1,2-diyl bis(4-methylbenzenesulfonate) (8). The diol **4** (132 mg, 0.935 mmol, 1.0 equiv.) was dissolved in pyridine (1 mL), and, at 0°C, 4-methylbenzenesulfonyl chloride (178 mg, 0.935 mmol, 1.0 equiv.) was added. The mixture was warmed to ambient temperature under stirring for 2 d. The mixture was diluted with an aqueous solution of HCl (2 M, 5 mL) and extracted with ethyl acetate (3 × 10 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 ➔ 39:1 ➔ 19:1 ➔ 7:1, R_f = 0.66 (tlc, cyclohexane:ethyl acetate = 1:1, detection: *Hanessian* stain)) to afford the ditosylate **8** (160 mg, 38%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.57–1.73 (m, 4H, 4-CH_2, 5-CH_2, 6-CH_2), 2.00–2.13 (m, 2H, 4-CH_2, 6-CH_2), 2.44 (s, 6H, CH_3), 3.17 (bs, 1H, 3-C*H*), 4.43 (d, *J* = 8.2 Hz, 1H, 2-C*H*), 4.86 (bs, 1H, 1-C*H*), 7.33 (d, *J* = 8.9 Hz, 2H, 3-CH_{ar}, 5-CH_{ar}), 7.34 (d, *J* = 8.6 Hz, 2H, 3-CH_{ar}, 5-CH_{ar}), 7.70 (d, *J* = 8.9 Hz, 2H, 2-CH_{ar}, 6-CH_{ar}), 7.76 (d, *J* = 8.6 Hz, 2H, 2-CH_{ar}, 6-CH_{ar}). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ [ppm] = 18.6 (C-4), 21.8 (*C*H$_3$x2), 27.0 (C-5), 28.1 (C-6), 30.7 (C-3), 76.1 (C-1), 76.6 (C-2), 119.1 (*C*≡N), 128.0 (C-2$_{ar}$, C-6$_{ar}$), 128.5 (C-2$_{ar}$, C-6$_{ar}$), 130.1 (C-3$_{ar}$x2, C-5$_{ar}$x2), 132.0 (C-4$_{ar}$), 133.1 (C-4$_{ar}$), 145.3 (C-1$_{ar}$), 145.8 (C-1$_{ar}$). FT-IR (NaCl plates): $\tilde{\upsilon}$ [cm^{-1}] = 2960 (m, C–H), 2256 (m, C≡N). Exact mass (ESI^+): *m/z* = 472.0876 (calcd. 472.0864 for $C_{21}H_{23}NNaO_6S_2$ $[MNa]^+$).

(2RS,3aRS,4RS,7aSR)-2-Oxo-3a,4,5,6,7,7a-hexahydrobenzo[d]-[1,3,2λ⁴]dioxathiol-4-carbonitrile (9). The diol **4** (100 mg, 0.708 mmol, 1.0 equiv.) and NEt_3 (0.22 mL, 1.6 mmol, 2.2 equiv.) were dissolved in abs. THF (10 mL). At 0°C, thionyl chloride (77 µL, 1.1 mmol, 1.5 equiv.) was added dropwise, and the mixture was stirred for 2 h at 0°C. H_2O (3 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 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 ➔ 19:1 ➔ 7:1, R_f = 0.65 (tlc, cyclohexane:ethyl acetate = 1:1, detection: $KMnO_4$)) to afford a 7:3 mixture of the diastereomers **9A** and **9B** (92 mg, 69%) as a colorless oil. Two sets of signals (^{1}H NMR intensity ratio **A**:**B** = 7:3) are seen in the NMR spectra originating from two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.49–1.66 (m, 2H, 5-CH_2, 6-CH_2), 1.66–1.82 (m, 1H, 6-CH_2), 1.86 (ddd, ^2J = 16.9 Hz, ^3J = 10.6/4.4 Hz, 0.3x1H, 7-CH_2, **B**), 1.98 (ddd, ^2J = 15.9 Hz, ^3J = 12.2/3.9 Hz, 0.7x1H, 7-CH_2, **A**), 2.10 (d, J = 11.6 Hz, 0.7x1H, 5-CH_2, **A**), 2.19 (d, ^2J = 14.3 Hz, 0.3x1H, 5-CH_2, **B**), 2.32 (d, ^2J = 15.9 Hz, 0.7x1H, 7-CH_2, **A**), 2.39 (d, ^2J = 16.9 Hz, 0.3x1H, 7-CH_2, **B**), 2.58 (ddd, J = 12.4/8.9/3.3 Hz, 0.7x1H, 4-CH, **A**), 3.39 (ddd, J = 12.5/9.4/3.8 Hz, 0.3x1H, 4-CH, **B**), 4.57 (dd, J = 9.4/4.4 Hz, 0.3x1H, 3a-CH, **B**), 4.71 (d, J = 4.4 Hz, 0.3x1H, 7a-CH, **B**), 4.82 (dd, J = 8.9/4.0 Hz, 0.7x1H, 3a-CH, **A**), 5.15 (d, J = 4.0 Hz, 0.7x1H, 7a-CH, **A**). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ [ppm] = 18.4 (C-6, both), 25.3 (C-7, major, **A**), 26.3 (C-5, major, **A**), 26.8 (C-5, minor, **B**), 27.0 (C-7, minor, **B**), 32.9 (C-4, major, **A**), 33.5 (C-4, minor, **B**), 76.0 (C-3a, major, **A**), 78.2 (C-3a, minor, **B**), 79.1 (C-7a, major, **A**), 81.2 (C-7a, minor, **B**), 119.4 (C≡N, major, **A**), 119.7 (C≡N, minor, **B**). FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (s, C–H), 2236 (m, C≡N), 1203 (s, S=O). MS (EI$^+$): m/z = 188 ([M + H], 9.7%), 139 ([M − SO], 9.4%), 123 ([M − SO_3], 21%), 110 ([M − SO_2 − CH], 39%), 106 ([M − SO_2 − OH], 37%), 95 ([M − SO_2 − CO], 55%), 94 ([M − SO_2 − CHO], 67%), 80 ([M − SO_2 − CHO − CH_2], 78%), and 67 ([M − SO_2 − CHO − CH_2 − CH], 100%).

(4aRS,5RS,8aSR)-Decahydroquinoxaline-5-carbonitrile (10). The ditosylate **8** (130 mg, 0.289 mmol, 1.0 equiv.) was dissolved in abs. THF (5 mL) and ethylenediamine (38 µL, 0.58 mmol, 2.0 equiv.) was added. The mixture was heated under reflux for 5.5 h. After cooling to ambient temperature, the mixture was filtered. Silica gel (100 mg) was added, and the mixture was concentrated under reduced pressure. The residue was purified by fc (d = 3 cm, l = 3 cm, V = 100 mL, cyclohexane:ethyl acetate = 1:0 ➔ 7:1 ➔ 0:100 ➔ ethyl acetate:methanol = 3:1 (500 mL), product not detected by TLC, collection of the ethyl acetate:methanol mixture is necessary) to afford the quinoxaline **10** (20 mg (42%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.56–1.62 (m, 1H, 6-CH_2), 1.68–1.72 (m, 1H, 8-CH_2), 1.80–1.88 (m, 2H, 7-CH_2), 1.92–1.94 (m, 2H, 6-CH_2, 8-CH_2), 2.88 (dd, J = 4.8/5.5 Hz, 1H, 4a-CH), 2.97 (d, J = 5.7 Hz, 1H, 8a-CH), 3.25–3.31 (m, 1H, 5-CH), 3.42 (t, J = 6.6 Hz, 1H, 2-CH), 3.45 (t, J = 6.8 Hz, 1H, 2-CH), 3.57 (t, J = 6.8 Hz, 1H, 3-CH), 3.67 (t, J = 6.6 Hz, 1H, 3-CH), 4.9 (bs, 2H, 1-NH, 4-NH). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ [ppm] = 19.6 (C-8), 23.1 (C-7), 27.6 (C-6), 39.8 (C-8a), 44.2 (C-2), 45.0 (C-4a), 52.9 (C-5), 62.0 (C-3), 119.2 (C≡N). FT-IR (NaCl plates): $\tilde{\nu}$ [cm^{-1}] = 3274 (bs, NH), 2951 (s, C–H), 2214 (m, C≡N). Exact mass (ESI$^+$): m/z = 166.1352 (calcd. 166.1344 for $C_9H_{16}N_3$ [MH]$^+$).

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