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Asymmetric synthesis of 3-substituted tetrahydro-2-benzazepines

Matthias P. Quick, Roland Fröhlich, Dirk Schepmann, Bernhard Wünsch

a Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität
Münster, Corrensstraße 48, D-48149 Münster, Germany
Tel.: +49-251-8333311; Fax: +49-251-8332144; E-mail: wuensch@uni-muenster.de

b Organisch-chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstr. 40,
D-48149 Münster, Germany

c Cells-in-Motion Cluster of Excellence (EXC 1003 – CiM), Westfälische Wilhelms-Universität
Münster, Germany

Abstract

The enantiomerically and diastereomerically pure tricyclic oxazolidine cis-10 was prepared in a five step synthesis starting with 1-bromo-2-iodobenzene. Me3SiCN and allylSiMe3 reacted with cis-10 in the presence of TiCl4 to form the nitrile (3S)-11 and the allyl derivative (3S)-12 with high diastereoselectivity. The hydrogenolytic removal of the chiral auxiliary failed, since the endocyclic benzyl-N-bond was cleaved simultaneously. Therefore the N-(hydroxyethyl)amide of (3S)-12 was transformed into the enamide 27, which was hydrolyzed to afford the secondary amide 28. The enamide strategy to remove the chiral auxiliary from (3S)-11 led to complete racemization due to fast deprotonation in α-position of the cyano moiety. Two pairs of enantiomers 30a-b/ent-30a-b with prototypical σ substituents at the N-atom were prepared. The low σ1 affinity of the tetrahydro-2-benzazepines (ent-30b, Ki = 407 nM) is attributed to the short distance between the two lipophilic aromatic moieties.
Key words
Asymmetric synthesis; tetrahydro-2-benzazepines; 3-(2-bromophenyl)propionaldehyde derivatives; chiral oxazolidines; diastereoselective ring opening; enamide hydrolysis; radioligand receptor binding studies; $\sigma$ receptors

1. Introduction
Tetrahydro-2-benzazepines can be regarded as regioisomers (constitutional isomers) of tetrahydro-3-benzazepines and ring homologs of tetrahydroisoquinolines. Both tetrahydro-3-benzazepines$^{1-7}$ and tetrahydroisoquinolines$^{8,9}$ are found in several pharmacological active compounds and are therefore regarded as privileged heterocycles. Despite its similarity to these heterocycles, the tetrahydro-2-benzazepine ring system is less abundant in pharmacological active compounds. The most prominent drug with a tetrahydro-2-benzazepine scaffold is the natural product galanthamine ($Galanthus nivalis$), which inhibits the acetylcholine esterase and is therefore clinically used for the treatment of Alzheimer’s disease.$^{10,11}$ Very recently we have reported on a novel synthetic approach to racemic tetrahydro-2-benzazepines $1$ which allows the introduction of various substituents in 5-position.$^{12-14}$ (Figure 1) In particular 5-benzyltetrahydro-2-benzazepines $1a$ with a linear N-butyl moiety ($K_i = 8.5$ nM) and $1b$ with a N-(4-fluorobenzyl) moiety ($K_i = 7.1$ nM) show high $\sigma_1$ receptor affinity and selectivity over the $\sigma_2$ subtype.$^{13}$

Figure 1

Comparison of the envisaged 2-benzazepines $2$ with regioisomeric 2-benzazepines $1$ (position of $R^1$) and 3-benzazepines $3$ (position of ring N-atom), which show promising $\sigma_1$ affinity.
The $\sigma_1$ receptor represents a unique receptor, which differs considerably from known mammalian ligand-gated ion channel receptors, G-protein-coupled receptors, tyrosine kinase receptors and nuclear receptors. $^{15-18}$ $\sigma_1$ receptor agonists were reported to be beneficial for the treatment of Alzheimer’s disease and depression. On the contrary, $\sigma_1$ antagonists could be used for the treatment of pain, in particular neuropathic pain, schizophrenia, addiction (ethanol, cocaine, methamphetamine) and cancer. $^{19-22}$ Although an X-ray crystal structure is not yet available, a 3D homology model of the $\sigma_1$ receptor protein was recently published. $^{23}$ The intracellularly located ligand binding site of the $\sigma_1$ receptor was analyzed in detail using this model. $^{24}$ According to various pharmacophore models, a protonated amino group flanked by two hydrophobic moieties in defined distances is required for high $\sigma_1$ receptor affinity. $^{25}$ Introduction of appropriate substituents at the tetrahydro-2-benzazepine scaffold resulted in compounds, which fit nicely into the reported pharmacophore models explaining the high $\sigma_1$ affinity of $1a$ and $1b$. $^{13}$

In addition to $1$, tetrahydro-3-benzazepines $3$, which are in accordance with these pharmacophore models, show also very high $\sigma_1$ affinity. $^{26,27}$ Recently we have reported a very short and efficient asymmetric synthesis of tetrahydro-3-benzazepines $3$, which gave access to enantiomerically pure $\sigma_1$ ligands of type $3$. $^{28,29}$ It was shown that the $(R)$-configured enantiomer $(R)-3a$ ($K_i(\sigma_1) = 3.2$ nM) has four-fold higher $\sigma_1$ affinity than the $(S)$-configured enantiomer $(S)-3a$ ($K_i(\sigma_1) = 12$ nM). Both enantiomers display high selectivity over the $\sigma_2$ subtype. $^{27}$

Since the tetrahydro-2-benzazepines $2$ are regioisomers of 2-benzazepines $1$ (position of the substituent $R^1$) and 3-benzazepines $3$ (position of the ring N-atom), which display promising $\sigma_1$ affinity, the development of an asymmetric synthesis of tetrahydro-2-benzazepines $2$ with different
substituents in 2- and 3-position was envisaged. Moreover, the $\sigma_1$ and $\sigma_2$ affinities of 2-benzazepines 2 with appropriate substituents R$_1$ and R$_2$ will be reported herein.

Scheme 1

Plan for the synthesis of enantiomerically pure 3-substituted tetrahydro-2-benzazepines 2.

According to our plan, 1-bromo-2-iodobenzene (4) will be converted into 2-bromophenylpropionaldehyde acetal 5. After introduction of a carboxylic acid, an enantiomerically pure $\beta$-aminoalcohol will be used to establish the key tricyclic N/O-acetal 6. The stereochemistry during the ring opening of the cyclic N/O-acetal by different nucleophiles will be investigated. After reductive removal of the N-bound chiral auxiliary, the resulting secondary amines will be provided with substituents, which give rise to high $\sigma_1$ receptor affinity of the final 2-benzazepines 2. The synthesis of the central tricyclic N/O-acetal has already been reported in a short communication.$^{34}$ (Scheme 1)

2. Synthesis

In the first step Pd(OAc)$_2$ catalyzed Heck reaction$^{30}$ of 1-bromo-2-iodobenzene (4) with allyl alcohol$^{31,32}$ afforded 3-(2-bromophenyl)propionaldehyde upon coupling and subsequent double bond isomerization.$^{33}$ Treatment of the unpurified aldehyde with ethylene glycol led to the ethylene acetal 7 in 75 % yield over two reaction steps.$^{33-35}$ (Scheme 2) Bromine/lithium exchange of 7 with n-BuLi at -78 °C and subsequent trapping of the aryllithium intermediate with CO$_2$ provided the carboxylic acid 8, which was coupled with (R)-phenylglycinol to form the amide 9. The highest
yields of 9 were achieved using the coupling agent EDC·HCl in the presence of 1-hydroxybenzotriazole (HOBt). Thus the corresponding ester consisting of the acid 8 and HOBt could be isolated as side product.

Scheme 2

Preparation of cis-10 and trans-10 as key intermediate for asymmetric synthesis of 3-substituted tetrahydro-2-benzazepines. Reagents and reaction conditions: (a) 1. H₂C=CHCH₂OH, Pd(OAc)₂, NaHCO₃, Et₃BnNCl, DMF, 45 °C, 5.5 h; 2. ethylene glycol, TosOH, CHCl₃, reflux, 75 % over two steps.³⁵ (b) n-BuLi, THF, -80 °C, 10 min, then CO₂, -78 °C, 75 min, 93 %. (c) (R)-phenylglycinol, EDC·HCl, HOBt, CH₂Cl₂, rt, 5.25 h, 74 %. (d) CHCl₃, HCl, rt, 16 h, cis-10 (76 %), trans-10 (10 %). The stereodescriptors cis and trans reflect the relative orientation of the methine protons of the oxazolidine ring, i.e. the protons in 3- and 11a-position of the ring system.

Unexpectedly, the transformation of the hydroxyamide 9 into the tricyclic N/O-acetals 10 turned out to be very difficult. Initial experiments with p-toluenesulfonic acid in protic or aprotic solvents at low or high temperature did not yield the expected tricyclic compounds 10. However, stirring a solution of hydroxyamide 9 in CHCl₃ and concentrated HCl at room temperature for 16 h led to complete transformation of 9 into the tricyclic N/O-acetals 10.³⁴ Separation by flash chromatography provided cis-10 and trans-10 in 76 % and 10 % yields, respectively.
The relative configuration of cis-10 and trans-10 was determined by NOE difference spectroscopy. At first the NOE experiment was performed with cis-10. Irradiation at 5.22 ppm (3-H) increased the signal at 5.27 ppm (11a-H). This nuclear Overhauser effect indicates cis-orientation of 3-H and 11a-H at the five-membered oxazolidine ring. Since the absolute configuration of the chiral center in 3-position is known from the starting material (R)-phenylglycinol, (R)-configuration is attributed to the newly formed center of chirality at 11a-position. The same experiment performed with the diastereomer trans-10 did not increase the signal at 5.05 ppm (11a-H) after irradiation at 5.47 ppm (3-H). These protons are on opposite sides of the oxazolidine ring and therefore (S)-configuration is attributed to the newly formed center of chirality in 11a-position of trans-10.

Scheme 3

Stereoselective opening of the oxazolidine ring of cis-10.

Reagents and reaction conditions: (a) Me₃SiCN, TiCl₄, CH₂Cl₂, microwave irradiation, 44 % ((3S)-11, 19 % ((3R)-11). (b) allylSiMe₃, TiCl₄, CH₂Cl₂, microwave irradiation, 64 % ((3S)-12, 5 % ((3R)-12).

The stereoselective ring opening of bicyclic lactams prepared by cyclocondensation of (R)-phenylglycinol and γ- or δ-oxoalkanoic acids has been reported to result in enantiomerically pure substituted pyrrolidine and piperidine derivatives. For this purpose the bicyclic N/O-acetals were
reacted with different C-nucleophiles (e.g. Grignard reagents, cuprates, trimethylsilyl reagents) to produce substituted pyrrolidine and piperidine derivatives. Activation of the bicyclic lactams with a Lewis acid (e.g. TiCl$_4$, BF$_3$) to form an N-acyliminium intermediate often improved the conversion. Usually this transformation resulted in high diastereoselectivities (>9:1).$^{36-41}$

As described for bicyclic lactams the tricyclic lactam cis-$10$ (main diastereomer) was reacted with different C-nucleophiles. However, reaction of cis-$10$ with Grignard reagents (PhMgBr, MeMgBr, EtMgBr) or cuprates (Me$_2$CuCNLi$_2$) at -78 °C to +20 °C did not provide the corresponding alkylated products. Moreover, the trimethylsilyl enol ether of acetophenone in the presence of different Lewis acids (TiCl$_4$, SnCl$_4$, BF$_3$OEt$_2$) did not transform cis-$10$ into the desired alkylated products. Finally it was found that Me$_3$SiCN and allylSiMe$_3$ in the presence of a Lewis acid converted the tricyclic N/O-acetal cis-$10$ into the nitriles $11$ and the allyl derivatives $12$, respectively. (Scheme 3)

The reaction of cis-$10$ with Me$_3$SiCN was carefully optimized with respect to the Lewis acid (TiCl$_4$, AlCl$_3$, ZnCl$_2$, BF$_3$OEt$_2$, SnCl$_4$), solvent (CH$_2$Cl$_2$, THF), temperature (-78 °C to +60 °C including microwave irradiation) and the stoichiometry of the reagents. It turned out that the reaction of cis-$10$ with excess of Me$_3$SiCN (15 equiv.) and TiCl$_4$ (8 equiv.) in CH$_2$Cl$_2$ under microwave irradiation led to the best transformation allowing the isolation of the diastereomeric nitriles (3$S$)-$11$ and (3$R$)-$11$ in 44 % and 19 % yields, respectively. A reduced amount of Me$_3$SiCN (3 equiv.) led to partial epimerization of cis-$10$ to trans-$10$. Experiments with the analogous tin reagent Bu$_3$SnCN did not afford the nitriles $11$.

After crystallization, X-ray crystal structure analyses of the diastereomerically pure nitriles (3$S$)-$11$ and (3$R$)-$11$ were recorded. The X-ray crystal structures clearly show ($S$)-configuration in 3-position of (3$S$)-$11$ (Figure 2) and ($R$)-configuration in 3-position of (3$R$)-$11$. (Figure 3) The elemental unit of both structures contains only one conformer. Both structures reveal pseudoaxial
orientation of the cyano moiety within the seven-membered azepine ring due to the allylic strain of the lactam group. However, the orientation of the 2-hydroxy-1-phenylethyl side chain at the N-atom differs in the structures of the diastereomers. Whereas in (3S)-11 the phenyl moiety is oriented towards the cyano moiety, in (3R)-11 it is oriented to the opposite side.

Figure 2

Crystal structure of compound (3S)-11. Thermal ellipsoids are shown at 15% probability.

Figure 3

Crystal structure of compound (3R)-11. Thermal ellipsoids are shown at 15% probability.
Transferring the optimized conditions on the reaction of cis-10 with allylSiMe₃ led to the diastereomeric allyl derivatives (3S)-12 and (3R)-12, which were separated by flash chromatography and isolated in 64 % and 5 %, respectively. The main diastereomer (3S)-12 was crystallized from methanol giving crystals suitable for X-ray crystal structure analysis. The elemental unit of (3S)-12 contains two conformers. In the first conformer the allyl moiety adopts a pseudoaxial and in the second conformer a pseudoequatorial orientation relative to the benzazepine ring. In both conformers the phenyl moiety of the chiral auxiliary points towards the lipophilic allyl moiety.

Scheme 4

Postulated mechanism of oxazolidine ring opening explaining the preferred formation of (3S)-configured products.

The reaction of cis-10 with both Me₃SiCN and allylSiMe₃ in the presence of TiCl₄ provided diastereoselectively the (3S)-configured diastereomers (3S)-11 and (3S)-12 as main products. This diastereoselectivity is explained by attack of TiCl₄ at the oxazolidine O-atom, opening the oxazolidine ring and formation of chelate 13, in which TiCl₄ is additionally coordinated with the carbonyl O-atom. (Scheme 4) In the chelate 13 the phenyl moiety of the chiral auxiliary is fixed below the benzazepine ring plane shielding the Si-face at the C-atom of the intermediate N-acyliminium ion 13. Thus the Re-face attack of the nucleophiles Me₃SiCN, allylSiMe₃ is favored leading predominantly to products with (3S)-configuration.
In order to obtain enantiomerically pure products at the end, the diastereomeric purity of the main diastereomers (3S)-11 and (3S)-12 was determined by HPLC analysis. The diastereomeric purity of both isolated compounds (3S)-11 and (3S)-12 was greater than 99:1.

Scheme 5

Removal of the chiral auxiliary from (3S)-11 by hydrogenolysis.
Reagents and reaction conditions: (a) LiAlH₄, AlCl₃, THF, 0 °C, 30 min. (b) 1,4-diiodobutane, NaHCO₃, CH₃CN, reflux, 2 h, 49 % (over two steps). (c) H₂ (1 bar), Pd/C, CH₃OH, rt, 6 h. (d) 2-(3,4-dichlorophenyl)acetyl chloride, NEt₃, rt, 48 h, 31 % (over two steps). The enantiomer ent-15 was prepared in the same manner starting from (S)-phenylglycinol.

Next the main diastereomer (3S)-11 was reduced with AlH₃, which was generated by mixing of three equivalents of LiAlH₄ and one equivalent of AlCl₃. Without purification the formed primary amine 14 was alkylated with 1,4-diiodobutane to afford the pyrrolidine 15. (Scheme 5) Stirring the pyrrolidine 15 under a H₂ atmosphere in the presence of Pd/C did not only cleave the exocyclic benzyl-N-bond but also the endocyclic benzyl-N-bond resulting in the phenylpropylamine 16. The structure of the very polar primary amine 16 was confirmed after acylation with 2-(3,4-dichlorophenyl)acetyl chloride to give the amide 17. The same result was obtained by transfer hydrogenolysis of 15 using ammonium formate instead of H₂.
Scheme 6

(3S)-11 \(\rightarrow\) \(\xrightarrow{(a)}\) \(\xrightarrow{(b)}\) 18

\(\xrightarrow{(c)}\) 19 \(\xrightarrow{(d)}\) 20 \(\xrightarrow{(d)}\) 21

Removal of the chiral auxiliary from (3S)-11 by hydrolysis of the enamide 19.

Reagents and reaction conditions: (a) SOCl₂, THF, 0 °C, 1 h, 64 %. (b) DBU, THF, reflux, 1.5 h, 53 %, (c) HCl, THF, reflux, 16 h, 76 % (racemic mixture). (d) LiAlH₄, AlCl₃, THF, 0 °C, 40 min; 2. PhCH=O, NaBH(OAc)₃, CH₂Cl₂, rt, 1 h, 36 %.

Since the hydrogenolytic cleavage of the endocyclic benzyl-N-bond appeared to be a general problem associated with the 2-benzazepine ring system, the chiral auxiliary should be removed by hydrolysis of the enamide 19.⁴³ (Scheme 6) Thus, reaction of (3S)-11 with SOCl₂ led to the chloride 18, which yielded the enamide 19 upon treatment with DBU in refluxing THF. Then aqueous HCl in refluxing THF converted the enamide 19 into the secondary lactam 20 (76 % yield) together with acetophenone. After selective AlH₃ reduction of the nitrile 20, reductive alkylation of the resulting primary amine with benzaldehyde and NaBH(OAc)₃ provided the dibenzylamine 21. Reaction of 20 with AlH₃ reduced chemoselectively the cyano moiety but not the lactam function, which is probably due to anion formation by fast deprotonation of the secondary amide.

The dibenzylamine 21 was easily isolated in pure form and subsequently its enantiomeric purity was analyzed. Recording of the optical rotation even at different wave lengths led to a specific rotation close to 0.0. A chiral HPLC showed two peaks in the ratio 1:1 indicating complete
racemization. Analyzing the reaction sequence starting with (3S)-11 revealed that the racemization took place during the reaction of the nitrile 18 with the base DBU. Obviously, the base DBU is able to remove the proton in α-position to the cyano moiety of 18 or 19 leading to racemization.

Scheme 7

Attempts to remove the chiral auxiliary from the allyl derivative (3S)-12 hydrogenolytically, Reagents and reaction conditions: (a) LiAlH4, AlCl3, THF, 0 °C, 30 min, rt, 30 min, 54 %. (b) H2 (1 bar), Pd/C, CH3OH, rt, 30 min, (c) H2 (5 bar), Pd/C, CH3OH, rt, 30 min, 99 %. (d) LiAlH4, AlCl3, THF, 0 °C, 1 h, 82 %. The enantiomers ent-22 and ent-25 were prepared in the same manner starting from (S)-phenylglycinol.

Next the allyl derivative (3S)-12 should be transformed into enantiomerically pure tetrahydro-2-benzazepines. The tertiary amine 22 was obtained by reduction of the lactam group of (3S)-12 with AlH3. Reaction of the 2-benzazepine 22 with H2 and Pd/C in methanol again led to cleavage of the endocyclic benzyl-N-bond. (Scheme 7) According to LC-MS data the secondary amine 23 is the main product still bearing the 2-hydroxy-1-phenylethyl residue originating from the chiral auxiliary. The same result was obtained upon hydrogenolysis of the propyl derivative 25, which was prepared by hydrogenation of the allyl moiety of (3S)-12 and subsequent AlH3 reduction.
It can be concluded that during hydrogenolysis the endocyclic benzyl-N-bond of the prepared tetrahydro-2-benzazepines 15, 22 and 25 is at least as reactive as the exocyclic benzyl-N-bond towards the chiral auxiliary.

Scheme 8

Conversion of the propyl derivative 24 into the \( \sigma_1 \) ligands 30.

Reagents and reaction conditions: (a) SOCl\(_2\), THF, 0 °C, 0.5 h. (b) LDA, THF, -78 °C, 1.5 h, 34 % (over two steps). (c) HCl, H\(_2\)O, Et\(_2\)O, 38 °C, 4.5 h, 95 %. (d) LiAlH\(_4\), AlCl\(_3\), THF, 0 °C, 1 h, 100 %. (e) PhCH=O or C\(_6\)H\(_{11}\)CH=O, NaBH(OAc)\(_3\), CH\(_2\)Cl\(_2\), rt, 4-8 h, 31 % (30a), 45 % (30b). The enantiomers \textit{ent}-30a and \textit{ent}-30b were prepared in the same manner starting from (S)-phenylglycinol.

The conversion of (3S)-12 into an enamide failed, probably due to the reactivity of the allyl moiety in 3-position. Therefore the propyl derivative 24 was reacted with SOCl\(_2\) to give the chloro derivative 26, which was treated with LDA at -78 °C to produce the enamide 27. In contrast to the cyano derivatives 18/19, the strong base LDA can be used in this case, since the acidity of the proton at the center of chirality in 3-position is very low. Hydrolysis of the enamide 27 with 20 % HCl in boiling Et\(_2\)O led to the secondary amide 28 in 95 % yield. (Scheme 8)
Finally the lactam 28 was reduced with AlH₃ to afford the secondary amine 29. During work-up the high volatility of the amine 29 has to be taken into account, in particular the removal of the solvents has to be performed very carefully. In the last step the secondary amine 29 was reductively alkylated with benzaldehyde or cyclohexanecarbaldehyde and NaBH(OAc)₃ to give the tertiary amines 30a and 30b. The benzyl and cyclohexylmethyl moieties were selected, since potent σ₁ ligands often contain these N-substituents.

Compounds with a basic amino group should be tested pharmacologically. For this purpose the enantiomers ent-15, ent-22, ent-25, ent-30a and ent-30b were prepared as described above using (S)-phenylglycinol as chiral auxiliary.

With the pairs of enantiomers 30a/ent-30a and 30b/ent-30b in hand a chiral HPLC system was established to prove the enantiomeric purity of the ligands. One column alone did not lead to a sufficient separation of the enantiomers. Therefore, two columns, a Chiralcel OD® and a ChiralPak IB® column were employed sequentially. Since the compounds 30 are rather lipophilic, a rather lipophilic mobile phase (isohexane:isopropanol 99:1) was used to achieve a separation of both pairs of enantiomers allowing the determination of the ratio of enantiomers. Analysis of the products revealed the existence of only small amounts of the corresponding enantiomers in the samples: 30a (13 %), ent-30a (1.7 %), 30b (3.6 %), ent-30b (2.5 %). The benzyl derivative 30a was the first compound of this series. For its preparation several conditions were explored until the optimal conditions had been found. The particular sample of 30a containing a rather high amount of its enantiomer resulted from a non-optimized reaction sequence.

3. Receptor affinity

The affinity of basic tetrahydro-2-benzazepines towards σ₁ and σ₂ receptors was investigated. Since ligands for σ, κ-opioid and NMDA receptors are often very similar differing only in a N-substituent
or the configuration, \(^{44-47}\) the affinity towards \(\kappa\)-opioid receptors and the phencyclidine (PCP) and ifenprodil binding sites of the NMDA receptor was also included into this study. The affinity towards the above mentioned receptors was determined in competition experiments using radioligands with high affinity and selectivity for the respective receptor. The following radioligands were used: \([^{3}\text{H}](+)-\text{pentazocine} (\sigma_1),^{48,49} [^{3}\text{H}]\text{ditolylguanidine} (\sigma_2),^{48,49} [^{3}\text{H}]\text{-U-69,593} (\kappa),^{50} [^{3}\text{H}](+)-\text{MK-801} (\text{PCP binding site})^{51,52} \text{ and } [^{3}\text{H}]\text{ifenprodil (ifenprodil binding site).}^{53,54}\) The results of the receptor binding studies are summarized in Table 1.

Table 1. Affinities of tetrahydro-2-benzazepines towards various receptors.

<table>
<thead>
<tr>
<th>compd.</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>(K_i \pm \text{SEM (nM)})</th>
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<td></td>
<td></td>
<td></td>
<td>(\sigma_1)</td>
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<tr>
<td>15</td>
<td>CH(_2)-pyr</td>
<td>PhCHCH(_2)OH</td>
<td>28 %</td>
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<tr>
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<td>22</td>
<td>CH(_2)CH=CH(_2)</td>
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<td>0 %</td>
</tr>
<tr>
<td>ent-22</td>
<td>CH(_2)CH=CH(_2)</td>
<td>PhCHCH(_2)OH</td>
<td>0 %</td>
</tr>
<tr>
<td>25</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>PhCHCH(_2)OH</td>
<td>27 %</td>
</tr>
<tr>
<td>ent-25</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>PhCHCH(_2)OH</td>
<td>44 %</td>
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<tr>
<td>30b</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>CH(_2)C(<em>6)H(</em>{11})</td>
<td>48 %</td>
</tr>
<tr>
<td>ent-30b</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>CH(_2)C(<em>6)H(</em>{11})</td>
<td>407 nM</td>
</tr>
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<td>(+)-pentazocine</td>
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<td>5.7 ± 2.2</td>
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<tr>
<td>Haloperidol</td>
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<td></td>
<td>6.3 ± 1.6</td>
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<tr>
<td>di-o-tolylguanidine</td>
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<td>89 ± 29</td>
</tr>
<tr>
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</tr>
<tr>
<td>Ifenprodil</td>
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<td>Naloxone</td>
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Most of the compounds of this series show rather low affinities. Therefore the radioligand displacement at a test compound concentration of 1 µM is given in %.

The basic tetrahydro-2-benzazepines show only very low affinity towards $\sigma_1$, $\sigma_2$ and $\kappa$-opioid receptors as well as the PCP and ifenprodil binding site of the NMDA receptor. Therefore the reduction of the radioligand binding (in %) in the presence of 1 µM of the test compound is given for most of the compounds. Since this value is below 50 %, the IC$_{50}$-value of the test compounds is higher than 1 µM indicating low interactions. The only exception is the (S)-configured cyclohexylmethyl derivative ent-30b with a $\sigma_1$ affinity of 407 nM. However, this $\sigma_1$ affinity is also close to 1 µM indicating moderate $\sigma_1$ affinity.

Pharmacophore models for $\sigma_1$ and $\sigma_2$ receptor ligands are characterized by a basic amino group flanked by two lipophilic moieties. The distances of these lipophilic moieties towards the basic amino group differ considerably: The shorter distance is in the range of 2.5 - 4 Å ($\sigma_1$, $\sigma_2$) and the longer distance in the range of 6 - 10 Å ($\sigma_1$) and 11.6 – 13.6 Å ($\sigma_2$).

In case of the tetrahydro-2-benzazepines of this work the distances of the lipophilic phenyl moieties towards the central basic amino group are identical and rather short (3.7 Å). It is postulated that one distance is too short to bring the lipophilic substituent into the corresponding binding pocket of the $\sigma$ receptors. The high $\sigma_1$ affinity of the analogous tetrahydro-2-benzazepines 1a and 1b (Figure 1) is explained by the lipophilic benzyl moiety in 5-position occupying the more distal second hydrophobic region of the $\sigma_1$ receptor. The distance between the rather small allyl and propyl moieties in 3-position of the tetrahydro-2-benzazepines 22, 25 and 30 and the basic amino moiety appears to be too short to result in high binding energy.

4. Conclusion
Herein a novel asymmetric synthesis of enantiomerically pure 3-substituted tetrahydro-2-benzazepines is reported. The key building block cis-10 was prepared stereoselectively in a five-step synthesis starting with 1-bromo-2-iodobenzene. The diastereoselective ring opening of the tricyclic oxazolidine cis-10 with nucleophiles was investigated very carefully. Me_3SiCN and allylSiMe_3 were found to open the oxazolidine ring in the presence of an excess of TiCl_4. The reaction with allylSiMe_3 led to high diastereoselectivity (93:7), whereas moderate diastereoselectivity (70:30) was observed with Me_3SICN. The removal of the chiral auxiliary turned out to be problematic due to the fast hydrogenolytic cleavage of the endocyclic benzyl-N-bond. Therefore the N-substituent was removed via a three step enamide hydrolysis sequence. In receptor binding studies with radioligands only the (S)-configured cyclohexylmethyl substituted 2-benzazepine ent-30b showed moderate σ_1 affinity (K_i = 407 nM). It is assumed that the second hydrophobic pocket of the σ receptors cannot be addressed by the 3-substituted 2-benzazepines due to too short distances between the lipophilic structural elements.

5. Experimental Part

5.1. General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, length of column, fraction size, eluent, R_f value. Melting point: melting point apparatus SMP 3 (Stuart Scientific), uncorrected. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). \(^1\)H NMR (400 MHz), \(^13\)C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Optical rotation: Polarimeter 341 (Perkin Elmer); 1.0 dm tube; concentration c in g/100 mL; T = 20 °C; wavelength 589 nm (D-line of Na light); the unit of the specific rotation (\([\alpha]_D^T\) grad mL dm\(^{-1}\) g\(^{-1}\)) is omitted for clarity. MS: EI = electron impact, ESI =
electro spray ionization: MicroTof (Bruker Daltronics, Bremen), calibration with sodium formate clusters before measurement. Microwave apparatus: CEM Discover LabMate Synthesiser, single mode cavity; Discover-PC-software (CEM Corporation, NC); reactions were performed in glass vessels (capacity 10 mL) sealed with corresponding pressure adaptor; pressure was controlled using a piezo-electric pressure sensor; temperature of the vessel contents was monitored by using an external infrared temperature control. Alternatively an 80 mL open vessel was used.

5.2. HPLC methods

5.2.1. Method 1: Purity of compounds
Merck Hitachi equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method A: column: LiChrospher® 60 RP-select B (5 µm), 250-4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection $\lambda = 210$ nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid: gradient elution: (A %): 0-4 min: 90 %, 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %.

5.2.2. Method 2: Purity of compounds
The same apparatus as describe for method 1, but another gradient for the elution of the compounds was used: solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid: gradient elution: (A %): 0-1 min: 80 %, 1-22 min: gradient from 80 % to 0 %, 22-31 min: 0 %, 31-31.5 min: gradient from 0 % to 80 %, 31.5-40 min: 80 %.

5.2.3. Method 3: Ratio of diastereomers (3S)-12:(3R)-12
Merck Hitachi equipment; UV-DAD detector: L-7455; rheodyne 7125; pump: L6200A; data acquisition: HSM-software. Column: Daicel Chiralpak AD-H, 5 µm, 250 mm / 4.6 mm; guard column: Daicel Chiralpak AD-H, 5 µm, 10 mm / 4 mm; flow rate: 1.00 mL/min; injection: volume:
7.0 µL; detection \( \lambda = 210 \) nm; eluent: isohexane / isopropanol / ethanol = 80 / 8 / 12.

### 5.2.4. Method 4: Preparative HPLC for purification of 30b and ent-30b

Merck Hitachi equipment; UV detector: L-7400; autosampler: L-7200; pump: L-6200A; data acquisition: HSM-software; column: Phenomenex Gemini, 5 µm, C18, 110A, 250 mm / 21.2 mm; guard column: Phenomenex Gemini, 5 µm, C18, 110A, 50 mm / 21.2 mm; flow rate: 9.99 mL/min; injection: volume: 180 µL (THF); detection \( \lambda = 210 \) nm; eluent: acetonitrile / water / NH3 conc. = 90 / 9.5 / 0.5.

### 5.2.5. Method 5: Chiral HPLC to determine the enantiomeric purity of dibenzylamine 21

Merck Hitachi equipment; UV-DAD detector: L-7455; rheodyne 7125; pump: L-6200A; data acquisition: HSM-software; column: Daicel Chiralpak AD-H, 5 µm, 250 mm / 4.6 mm; guard column: Daicel Chiralpak AD-H, 5 µm, 10 mm / 4 mm; flow rate: 1.00 mL/min; injection: volume: 5.0 µL; detection \( \lambda = 210 \) nm; eluent: isohexane / isopropanol = 9 / 1.

### 5.2.6. Method 6: Chiral HPLC to determine the enantiomeric purity 2-benzazepines 30

Merck Hitachi equipment; UV-DAD detector: L-7455; rheodyne 7125; pump: L-6200A; data acquisition: HSM-software; column 1: Daicel Chiralcel OD, 10 µm, 250 mm / 4.6 mm; guard column: Daicel Chiralpak IB, 5 µm, 10 mm / 4 mm; column 2: Daicel Chiralpak IB, 5 µm, 250 mm / 4.6 mm; flow rate: 1.00 mL/min; injection: volume: 3.0 µL; detection \( \lambda = 210 \) nm; eluent: isohexane / isopropanol = 99 / 1.

### 5.2. General procedures

#### 5.3.1. General procedure 1: Preparation of 0.67 M (AlH3) solution

Under N\(_2\) LiAlH\(_4\) (1 M, in THF, 5 mL) was transferred into a dried Schlenk-tube and cooled to 0 °C. HCl (2 M, in Et\(_2\)O, 2.5 mL) was added dropwise and the resulting clear solution was stirred
for 1 h at 0 °C.

5.3.2. General procedure 2: Preparation of 0.36 M (AlH₃) solution

Under N₂ AlCl₃ (0.239 g, 1.80 mmol) was dissolved in THF (14.5 mL) at 0 °C. LiAlH₄ (1 M, in THF, 5.4 mL, 5.4 mmol) was carefully added to the solution of AlCl₃ under stirring. The resulting clear solution was slowly brought to rt and stirred for 20 min.

5.4. Synthetic procedures

2-[2-(1,3-Dioxolan-2-yl)ethyl]benzoic acid (8)

Under N₂ aryl bromide 7 (7.78 g, 30.27 mmol) was dissolved in THF (151 mL) and cooled to -80 °C. n-BuLi (1.6 M in hexanes, 19.0 mL, 31.27 mmol) was added (1 mL/min) and the resulting clear solution was stirred for 10 min at -80 °C. CO₂ gas was dried carefully by bubbling through concentrated H₂SO₄ before it was passed into the reaction mixture via a glass tube (inner diameter = 0.5 cm) for 75 min. It was essential to prevent plugging of the glass pipe and to install a Bunsen valve! A colour change from yellow to red to colorless occurred during this procedure. After removing the gas inlet, the reaction mixture was brought to -5 °C and water was added until a separation of layers occurred. Aqueous NaOH (2 M) was added until a pH value of 11-14 and the mixture was extracted with Et₂O to remove starting material and byproducts. The benzoic acid 72 was precipitated from the aqueous layer by addition of aqueous HCl (1 M). To prevent cleavage of the acetal, the amount of HCl was controlled. The aqueous layer was extracted several times with Et₂O, the combined organic layers were dried (Na₂SO₄) and the solvent and valeric acid were removed under reduced pressure. Colourless solid, mp 71-72 °C, yield 6.26 g (93 %). C₁₂H₁₄O₄, Mᵣ = 222.2. MS (EI): m/z [%] = 222 (M, 18), 177 (M – CO₂, 24), 149 (M – CH(OCH₂)₂, 100), 73 (CH(OCH₂)₂, 88). ¹H NMR (CDCl₃): δ [ppm] = 1.93 – 1.98 (m, 2H, ArCH₂CH₂CH), 3.08 – 3.12 (m, 2H, ArCH₂), 3.73 – 3.99 (m, 4H, CH(OC₂H₅)₂), 4.88 (t, J = 4.9 Hz, 1H, ArCH₂CH₂CH), 7.21 – 7.27 (m, 2H, Ar-H), 7.41 (t, J = 7.5 Hz, 1H, 4-H₅), 7.98 (dd, J = 7.8/1.3 Hz, 1H, 6-H₅). A signal for
the CO$_2$H proton is not seen in the spectrum. IR (neat): $\nu$ [cm$^{-1}$] = 2985 (OH), 1675 (C=O). HPLC (method 1): $t_R$ = 14.26 min, purity 86.3 %.

2-[2-(1,3-Dioxolan-2-yl)ethyl]-N-[(1R)-2-hydroxy-1-phenylethyl]benzamide (9)

Under N$_2$ benzoic acid 8 (0.300 g, 1.35 mmol) was dissolved in CH$_2$Cl$_2$ (15 mL). HOBt · H$_2$O (0.182 g, 1.35 mmol) and EDC · HCl (0.260 g, 1.35 mmol) were added and the mixture was stirred for 5 min., then (R)-(−)-2-phenylglycinol (0.185 g, 1.35 mmol) was added. The reaction mixture was stirred at rt for 5.25 h and then heated to reflux for 15 h. Under vigorous stirring the mixture was cooled down to rt, then HCl (1 M) was added until no more precipitate was formed. The precipitate was filtered off, washed thoroughly with CH$_2$Cl$_2$ and the layers of the filtrate were separated. The organic layer was washed several times with HCl and the precipitate filtered off again. The combined acidic aqueous layers were reextracted with CH$_2$Cl$_2$. The combined organic layers were washed several times with NaOH (2 M). The combined basic aqueous layers were reextracted with CH$_2$Cl$_2$, then the combined organic layers were washed with brine (1x), dried (Na$_2$SO$_4$) and filtered.

Silica gel was added and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 3 cm, h = 14 cm, cyclohexane : ethyl acetate = 1 : 1, V = 14 mL, $R_f$ = 0.31 (cyclohexane : ethyl acetate = 1 : 3)). Colorless solid, mp 94.5 °C, 0.331 g, (74 %). C$_{20}$H$_{23}$NO$_4$, Mr = 341.4. MS (EI): $m/z$ [%] = 341 (M, 8), 310 (M-CH$_2$OH, 58), 117 (ArC$_3$H$_5$, 100), 73 (CH(OCH$_2$)$_2$), 87. $^1$H NMR (CDCl$_3$): $\delta$ [ppm] = 1.93 – 2.07 (m, 2H, ArCH$_2$CH$_2$CH), 2.92 (t, J = 8.0 Hz, 2H, ArCH$_2$CH$_2$CH), 3.05 (s, broad, 1H, CH$_2$OH), 3.76 – 3.85 (m, 2H, CH(OC$_2$H$_5$)$_2$, 3.89 – 4.05 (m, 4H, CH(OC$_2$H$_5$)$_2$, CH$_2$OH), 4.83 (t, J = 4.6 Hz, 1H, ArCH$_2$CH$_2$CH), 5.25 – 5.29 (m, 1H, NHCHPh), 6.65 (d, 7.3 Hz, 1H, NH), 7.19 – 7.40 (m, 9H, Ar-H). IR (neat): $\nu$ [cm$^{-1}$] = 3291 (OH / NH), 1634 (O=CNHR, amide I), 1525 (O=CNHR, amide II). Specific rotation: $[\alpha]_D^{20}$ = -8.2 (c = 1.60; CH$_2$Cl$_2$). HPLC (method 1): $t_R$ = 15.58 min, purity 96.1 %.
2-(2-(1,3-Dioxolan-2-yl)ethyl)-N-[(1S)-2-hydroxy-1-phenylethyl]benzamide (ent-9)

As described for the synthesis of amide 9 benzoic acid 8 (5.56 g, 25.0 mmol) was dissolved in CH$_2$Cl$_2$ (275 mL) and treated with HOBT · H$_2$O (3.39 g, 25.0 mmol), EDC · HCl (4.79 g, 25 mmol) and (S)-(+-)2-phenylglycinol (3.77 g, 27.5 mmol). After work-up, the residue was purified by fc (Ø = 8 cm, h = 10 cm, cyclohexane : ethyl acetate = 7 : 3, V = 65 mL, R$_f$ = 0.31 (cyclohexane : ethyl acetate = 1 : 3)). Colorless solid, yield 6.9 g (80 %). Specific rotation: [α]$_D^{20}$ = +8.5 (c = 0.62; CH$_2$Cl$_2$). HPLC (method 1): t$_R$ = 15.60 min, purity 92.1 %.

(3R,11aR)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10H)-one (cis-10) and (3R,11aS)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10H)-one (trans-10)

HCl$_{conc}$ (8.39 g) was added to an ice-cooled solution of benzamide 9 (5.03 g, 14.7 mmol) in CHCl$_3$ (590 mL). The solution was vigorously stirred overnight at rt. The reaction mixture was added to a saturated aqueous solution of NaHCO$_3$. After the formation of CO$_2$ had finished, the aqueous layer was separated and extracted with CHCl$_3$ (2x). The organic layer was washed with water (1x) and a saturated aqueous solution of NaCl resulting in a clear, colourless organic layer. The combined aqueous layers were reextracted with CHCl$_3$. The combined organic layers were dried (Na$_2$SO$_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 6 cm, h = 17, cyclohexane : ethyl acetate = 7 : 3, V = 30 mL).

cis-10 (R$_f$ = 0.25): Colorless solid, mp 128 ºC, yield 3.12 g (76 %). C$_{18}$H$_{17}$NO$_2$, M$_r$ = 279.3. MS (EI): m/z [%] = 279 (M, 90), 159 (M-PhCHCH$_2$O, 10), 104 (PhCHCH$_2$, 100). $^1$H NMR (CDCl$_3$): δ [ppm] = 2.10 – 2.20 (m, 1H, ArCH$_2$CH$_2$CH), 2.27 – 2.38 (tt, J = 12.3/6.9 Hz, 1H, ArCH$_2$CH$_2$CH), 2.67 – 2.76 (ddd, J = 13.9/6.9/1.0 Hz, 1H, ArCH$_2$CH$_2$CH), 2.94 – 3.04 (m, 1H, ArCH$_2$CH$_2$CH), 3.94 (d, J = 8.8 Hz, 1H, OCH$_2$CH), 4.40 (dd, J = 8.8/5.7 Hz, 1H, OCH$_2$CH), 5.22 (d, J = 5.7 Hz, 1H, OCH$_2$CH), 5.27 (dd, J = 9.5/5.7 Hz, 1H, ArCH$_2$CH$_2$CH), 7.12 – 7.16 (d, J = 7.4 Hz, 1H, 9-H$_{aren}$).
7.17 – 7.34 (m, 7H, Ar-H), 7.49 – 7.53 (dd, J = 7.6/1.3 Hz, 1H, 6-H_arom.). 13C NMR (CDCl3): δ (ppm) = 29.4 (C-10), 35.3 (C-11), 60.1 (C-3), 72.6 (C-2), 88.7 (C-11a), 126.2 (C-Ar), 127.4 (C-Ar), 127.8 (C-Ar), 128.8 (C-Ar), 128.9 (C-Ar), 131.4 (C-Ar), 136.3 (C-Ar_q), 137.6 (C-Ar_q), 140.9 (C-Ar_q), 166.0 (C=O). IR (neat): v [cm⁻¹] = 1645 (O=CNR₂). Specific rotation: [α]D²⁰ = +100 (c = 1.00; CH₂Cl₂). HPLC (method 1): tᵣ = 18.20 min, purity 99.3 %.

trans-10 (R_f = 0.40): Pale yellow, viscous oil, yield 0.492 g (10 %). C₁₈H₁₇NO₂, M_r = 279.3. MS (EI): m/z [%] = 279 (M, 100), 120 (PhCHCH₂O, 90), 104 (PhCH₂, 86). ¹H NMR (CDCl₃): δ [ppm] = 2.25 (dddd, J = 13.0/9.3/7.9/1.4 Hz, 1H, ArCH₂CH₂CH), 2.49 (tt, J = 12.7/6.2 Hz, 1H, ArCH₂CH₂CH), 2.75 (dd, J = 13.0/6.6 Hz, 1H, ArCH₂CH₂CH), 3.14 (td, J = 13.2/7.9 Hz, 1H, ArCH₂CH₂CH), 4.21 – 4.27 (m, 2H, OCH₂CH₂), 5.05 (dd, J = 9.3/5.7 Hz, 1H, ArCH₂CH₂CH), 5.47 (dd, J = 5.6/4.0 Hz, 1H, OCH₂CH₂), 7.18 – 7.40 (m, 7H, Ar-H), 7.49 (d, J = 8.1 Hz, 1H, 9-H_arom.), 7.76 (d, J = 7.6 Hz, 1H, 6-H_arom.). ¹³C NMR (CDCl₃): δ (ppm) = 29.9 (C-10), 36.1 (C-11), 59.8 (C-3), 73.7 (C-2), 89.5 (C-11a), 126.9 (C-Ar), 127.4 (C-Ar), 127.9 (C-Ar), 128.9 (C-Ar), 129.3 (C-Ar), 129.6 (C-Ar), 131.8 (C-Ar), 135.0 (C-Ar_q), 138.9 (C-Ar_q), 140.6 (C-Ar_q), 168.1 (C=O). IR (neat): v [cm⁻¹] = 1645 (O=CNR₂). Specific rotation: [α]D²⁰ -164 (c = 0.14; CH₂Cl₂). HPLC (method 1): tᵣ = 18.90 min, purity 97.4 %.

(3S,11aS)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10H)-one (ent-cis-10) and (3S,11aR)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10H)-one (ent-trans-10)

As described for the synthesis of cis-10 and trans-10 benzamide ent-9 (5.023 g, 14.71 mmol) was treated with HCl_conc. (8.39 g) in CHCl₃ (588 mL). After work-up the residue was purified by fc (Ø = 5 cm, h = 17 cm, cyclohexane : ethyl acetate = 7 : 3, V = 30 mL).

ent-cis-10 (R_f = 0.25): Colorless solid, yield 2.93 (71 %). Specific rotation: [α]D²⁰ = -103 (c = 1.00; CH₂Cl₂). HPLC (method 2): tᵣ = 15.85 min, purity 99.6 %.
ent-trans-10 (Rf = 0.40): Pale yellow, viscous oil, yield 0.216 g (6.3 %). Specific rotation: $[\alpha]_D^{20} = +163$ (c = 0.14; CH$_2$Cl$_2$). HPLC (method 1): $t_R = 18.59$ min, purity 98.7 %.

(3S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-1-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carbonitrile ((3S)-11) and (3R)-2-[(1R)-2-Hydroxy-1-phenylethyl]-1-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carbonitrile ((3R)-11)

A solution of cis-10 (0.600 g, 2.15 mmol) in CH$_2$Cl$_2$ (17 mL) was transferred into a 80 mL microwave reaction vessel and purged with N$_2$. Me$_3$SiCN (4 mL, 3.16 g, 31 mmol) and TiCl$_4$ (1 M in CH$_2$Cl$_2$, 17 mL, 17.0 mmol) were added. After purging again with N$_2$, the vessel was sealed and reacted in the microwave apparatus (55-60 °C, 60 W, ramp 5 min, hold 1 min). The black reaction mixture was slowly transferred into a separation funnel filled with cold water (50 mL). The aqueous layer was extracted several times with CH$_2$Cl$_2$. The organic layers where combined, washed with water, dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure. The residue was purified by fc ($\varnothing = 4$ cm, h = 15 cm, cyclohexane : ethyl acetate = 7 : 3, after cis-10 and (3R)-11 had eluted, cyclohexane : ethyl acetate = 1 : 3, V = 25 mL).

(3S)-11 (Rf = 0.06, cyclohexane : ethyl acetate = 7 : 3): Colorless crystals, mp 164 °C, yield 0.291 g (44 %). C$_{19}$H$_{18}$N$_2$O$_2$, M$_r = 306.4$. MS (EI): $m/z$ [%] = 306 (M, 2), 275 (M – CH$_2$OH, 20). $^1$H NMR (CDCl$_3$): $\delta$ [ppm] = 2.11 – 2.19 (m, 1H, ArCH$_2$CH$_2$CH), 2.53 – 2.60 (m, 1H, ArCH$_2$CH$_2$CH), 2.66 (dd, J = 13.8/6.2 Hz, 1H, ArCH$_2$CH$_2$CH), 2.94 – 3.02 (m, 2H, ArCH$_2$CH$_2$CH and CHCH$_2$OH), 4.07 – 4.13 (m, 1H, CHCH$_2$OH), 4.28 (dd, J = 11.7/4.4 Hz, 1H, CHCH$_2$OH), 4.39 (dd, J = 11.7/1.8 Hz, 1H, ArCH$_2$CH$_2$CH), 6.12 – 6.20 (s, broad, 1H, CH$_2$OH), 7.14 – 7.6 (m, 1H, 6-H$_{arom}$), 7.28 – 7.47 (m, 7H, Ar-H), 7.74 – 7.77 (m, 1H, 9-H$_{arom}$). $^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) = 29.8 (C-4), 36.3 (C-5), 60.6 (Ph-CHN), 73.0 (CH$_2$OH), 89.1 (C-3), 118.2 (CN), 126.6 (C-Ar), 127.3 (C-Ar), 127.8 (C-Ar), 128.2 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 128.7 (C-Ar), 129.0 (C-Ar), 129.1 (C-Ar), 129.2 (C-Ar), 129.3 (C-Ar), 129.4 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 130.0 (C-Ar), 130.2 (C-Ar), 130.3 (C-Ar),
131.8 (C-Ar), 132.3 (C-Ar), 132.8 (C-Ar), 136.7 (C-Ar<sub>q</sub>), 138.1 (C-Ar<sub>q</sub>), 141.0 (C-Ar<sub>q</sub>), 166.5 (C=O). IR (neat): ν [cm<sup>-1</sup>] = 2249 (CN), 1624 (O=CNR<sub>2</sub>). Specific rotation: [α]<sub>D</sub><sup>20</sup> = -46 (c = 1.00; CH<sub>2</sub>Cl<sub>2</sub>). HPLC (method 1): t<sub>R</sub> = 16.59, purity 99.7 %.

(3R)-11 (R<sub>f</sub> = 0.12, cyclohexane : ethyl acetate = 7 : 3): Colorless solid, mp 182 – 184 °C, yield 0.251 g (19 %). C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, M<sub>r</sub> = 306.4. MS (ESI): m/z [%] = 307 (M + H, 100). ¹H NMR (CDCl<sub>3</sub>): δ [ppm] = 1.57 – 1.69 (m, 1H, ArCH<sub>2</sub>CH<sub>2</sub>CH), 1.96 (tdd, J = 12.5/6.3/1.0 Hz, 1H, ArCH<sub>2</sub>CH<sub>2</sub>CH), 2.44 (s, 1H, CHCH<sub>2</sub>O), 2.67 (ddd, J = 13.8/6.3/1.6 Hz, 1H, ArCH<sub>2</sub>CH<sub>2</sub>CH), 2.91 (td, J = 13.7/7.4 Hz, 1H, ArCH<sub>2</sub>CH<sub>2</sub>CH), 4.28 – 4.40 (m, 2H, CHCH<sub>2</sub>O), 4.62 (dd, J = 8.1/1.1 Hz, 1H, ArCH<sub>2</sub>CH<sub>2</sub>CH), 5.98 (t, J = 4.9 Hz, 1H, CHCH<sub>2</sub>OH), 7.20 (m, 1H, ArH), 7.36 – 7.56 (m, 7H, ArH), 7.80 (d, J = 7.2/1.9 Hz, 1H, 9-H<sub>arom</sub>). ¹³C NMR (CDCl<sub>3</sub>): δ [ppm] = 29.3 (C-5), 35.6 (C-4), 43.9 (C-3), 58.8 (PhCN), 62.5 (CH<sub>2</sub>OH), 118.2 (CN), 128.3 (C-Ar), 128.6 (C-Ar), 128.8 (C-Ar), 129.3 (C-Ar), 130.2 (C-Ar), 132.5 (C-Ar), 134.8 (C-Ar<sub>q</sub>), 136.3 (C-Ar<sub>q</sub>), 136.9 (C-Ar<sub>q</sub>), 171.8 (C=O). IR (neat): ν [cm<sup>-1</sup>] = 2251 (-CN), 1639 (O=CNR<sub>2</sub>). Specific rotation: [α]<sub>D</sub><sup>20</sup> = -17 (c = 0.10; CH<sub>2</sub>Cl<sub>2</sub>). HPLC (method 1): t<sub>R</sub> = 16.95 min, purity 99.7 %.

(3R)-2-[(1S)-2-Hydroxy-1-phenylethyl]-1-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carbonitrile (ent-(3S)-11)

As described for the synthesis of (3S)-11/(3R)-11, ent-cis-10 (0.600 g, 2.15 mmol) was treated with Me₃SiCN (4 mL, 3.16 g, 31.0 mmol) and TiCl<sub>4</sub> (1 M in CH₂Cl₂, 17 mL, 17.0 mmol) in CH₂Cl₂. After work-up, the residue was purified by fc (Ø = 4 cm, h = 15 cm, cyclohexane : ethyl acetate = 7 : 3, V = 25 mL, R<sub>f</sub> = 0.06 (cyclohexane : ethyl acetate = 7 : 3)). Colorless solid, yield 0.301 g (46 %). Specific rotation: [α]<sub>D</sub><sup>20</sup> = +45 (c = 1.00; CH₂Cl₂). HPLC (method 2): t<sub>R</sub> = 13.28 min, purity 99.6 %.
(3S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-2-benzazepin-1-one ((3S)-12) and (3R)-2-[(1R)-2-Hydroxy-1-phenylethyl]-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-2-benzazepin-1-one ((3R)-12)

Under N\textsubscript{2} cis-10 (0.30 g, 1.07 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (6 mL). Me\textsubscript{3}Siallyl (2.9 mL, 2.08 g, 18.2 mmol) and TiCl\textsubscript{4} (1M in CH\textsubscript{2}Cl\textsubscript{2}, 6.4 mL, 6.4 mmol) were added. After purging with N\textsubscript{2}, the 80-mL-reaction vessel was sealed and reacted in the microwave apparatus (70 °C, 80 W, ramp 5 min, hold 10 min). The dark orange colored reaction mixture was slowly transferred into a separation funnel filled with ice-cold water (50 mL). The layers were separated and the aqueous layer was extracted several times with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with water, dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and the solvent was removed under reduced pressure. The residue was purified by fc (Ø= 3 cm, h = 16 cm, n-hexane : ethyl acetate= 8 : 2, V = 25 mL).

(3S)-12 (R\textsubscript{f} = 0.08, cyclohexane : ethyl acetate 7 : 3): Colorless needles, mp 156 °C, yield 0.222 g (64 %). C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2}, M\textsubscript{r} = 321.4. MS (ESI): m/z [%] = 665 (2M + Na, 100), 322 (M + H, 10). MS (EM): m/z = 322.1802 (calcd. 322.1801 for C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2}H\textsuperscript{+} [M+H+]); m/z = 344.1621 (calcd. 344.1621 for C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2}Na [M+Na+]; m/z = 665.3350 (calcd. 665.3349 for (C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2})\textsubscript{2}Na\textsuperscript{2+} [2M+Na+]. \textsuperscript{1}H NMR (D\textsubscript{5}-nitrobenzene, 110 °C): δ [ppm] = 1.14 – 1.24(m, 2H, C\textsubscript{2}H\textsubscript{2}CH=CH\textsubscript{2}), 1.46 – 1.57 (m, 1H, ArCH\textsubscript{2}CH\textsubscript{2}CH), 1.82 – 1.93 (m, 1H, ArCH\textsubscript{2}CH\textsubscript{2}CH), 2.29 – 2.38 (m, 1H, ArCH\textsubscript{2}CH\textsubscript{2}CH), 2.39 – 2.40 (m, 1H, CH\textsubscript{2}O\textsubscript{H}), 2.63 – 2.73 (m, 1H, ArCH\textsubscript{2}CH\textsubscript{2}CH), 3.16 – 3.24 (m, 1H, ArCH\textsubscript{2}CH\textsubscript{2}CH), 3.88 – 3.93 (m, 1H, CH\textsubscript{2}OH), 3.96 – 4.07 (m, 2H, CH\textsubscript{2}OH and CH\textsubscript{2}OH), 4.20 (d, J = 10.2 Hz, 1H, CH\textsubscript{2}OH), 4.58 – 4.65 (m, 1H, CH\textsubscript{2}OH and CH\textsubscript{2}OH), 5.54 (s, broad, 1H, CH\textsubscript{2}OH), 6.84 – 7.35 (m, 9H, Ar-H). The correct assignment of the signals was performed by high temperature COSY experiments. IR (neat): ν [cm\textsuperscript{-1}] = 3347 (OH), 1608 (O=CN\textsubscript{2}R\textsubscript{2}), 916 (C=CH\textsubscript{2}). Specific rotation: [α]\textsubscript{D}\textsuperscript{20} = +7.9 (c = 1.04; CH\textsubscript{2}Cl\textsubscript{2}). HPLC (method 2): t\textsubscript{R} = 17.97 min, purity 99.6 %. HPLC (method 3): t\textsubscript{R} = 10.66 min, purity 98.5 %.

(3R)-12 (R\textsubscript{f} = 0.10, cyclohexane : ethyl acetate 7 : 3): Colorless resin, yield 0.017 g (5 %).
C₂₁H₂₃NO₂, Mr = 321.4. MS (ESI): m/z [%] = 665 (2M + Na, 100), 344 (M + Na, 60). ¹H NMR (D₅-nitrobenzene, 100 °C): δ [ppm] = 0.62 – 0.69 (m, 1H, ArCH₂CH₂CH), 0.74, - 0.81 (m, 1H, ArCH₂CH₂CH), 0.83 – 0.91 (m, 1H, CH₂CH=CH₂), 1.12 – 1.24 (m, 1H, CH₂CH=CH₂), 1.57 – 1.64 (m, 1H, ArCH₂CH₂CH), 1.90 – 1.98 (m, 1H, ArCH₂CH₂CH), 2.38 (s, 1H, CHCH₂OH), 2.74 – 2.81 (m, 1H, ArCH₂CH₂CH), 3.47 – 3.55 (m, 2H, CH₂CH₂OH), 3.94 (d, J = 17.0 Hz, 1H, trans-CH₂CH=CH₂), 4.06 (d, J = 10.2 Hz, 1H, cis-CH₂CH=CH₂), 4.71 – 4.82 (m, 1H, CH₂CH=CH₂), 5.14 (t, J = 6.4 Hz, 1H, CHCH₂OH), 6.22 – 6.33 (m, 1H, ArH), 6.44 – 6.55 (m, 4H, ArH), 6.71 (m, 2H, ArH), 6.92 (m, 1H, ArH), 7.23 (s, 1H, ArH). IR (neat): ν [cm⁻¹] = 3377 (O-H), 1611 (O=CNR₂), 917 (C=CH₂). Specific rotation: [α]D₂₀ = -20 (c = 0.29; CH₂Cl₂). HPLC (method 1): t_R = 19.17 min, purity 91.9 %.

(3R)-2-[(1S)-2-Hydroxy-1-phenylethyl]-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-2-benzazepin-1-one (ent-(3S)-12)

As described for the synthesis of (3S)-12/(3R)-12, ent-cis-10 (0.30 g, 1.07 mmol) was treated with Me₃Siallyl (2.9 mL, 2.08 g, 18.2 mmol) and TiCl₄ (1M in CH₂Cl₂, 6.4 mL, 6.4 mmol) in CH₂Cl₂ (6 mL). After work-up, the residue was purified by fc (Ø = 3 cm, h = 16 cm, hexane : ethyl acetate = 8 : 2, V = 25 mL, R_f = 0.08 (cyclohexane : ethyl acetate = 7 : 3)). Colorless solid, yield 0.202 g (59 %). Specific rotation: [α]D₂₀ = -7.2 (c = 1.04; CH₂Cl₂). HPLC (method 2): t_R = 18.33 min, purity 99.3 %. HPLC (method 3): t_R = 16.77 min, purity 99.8 %. The diastereomer ent-(3R)-12 was not isolated.

(2R)-2-[(3S)-3-(Aminomethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]-2-phenylethanol (14)

A solution of nitrile (3S)-11 (0.10 g, 0.326 mmol) in THF (2.6 mL) was added dropwise to a freshly prepared and cooled (0 °C) AlH₃ solution (0.67 M, 2.9 mL, 1.96 mmol, prepared according to General procedure 1) and the mixture was stirred for 30 min at 0 °C. A few drops of a solution of
glycerol/water (1/1) were added until the formation of \( \text{H}_2 \) had ceased. The formed solid was separated, washed with \( \text{Et}_2\text{O} \), dissolved in \( \text{NaOH} \) (43 %) and the aqueous solution was extracted with \( \text{Et}_2\text{O} \). Filtrate and organic extracts were combined, dried (\( \text{K}_2\text{CO}_3 \)) and concentrated under reduced pressure. Without further purification the product was used for the synthesis of pyrrolidine 15. Orange colored liquid. \( \text{C}_{19}\text{H}_{24}\text{N}_2\text{O} \), \( \text{M}_r = 296.4 \). MS (EI): \( m/\text{z} \) [%] = 266 (M - CH\(_2\)NH\(_2\), 63), 146 (2-benzazepine core, 100). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) [ppm] = 1.79 – 1.84 (m, 1H, ArCH\(_2\)CH\(_2\)CH), 1.98 – 2.08 (m, 1H, ArCH\(_2\)CH\(_2\)CH), 2.76 (dd, \( J = 16.0/10.0 \) Hz, 1H, ArCH\(_2\)CH\(_2\)CH), 2.88 (dd, \( J = 12.8/3.7 \) Hz, 1H, CH\(_2\)CH\(_2\)NH\(_2\)), 2.97 – 3.05 (m, 1H, ArCH\(_2\)CH\(_2\)CH), 3.14 (t, \( J = 11.5 \) Hz, 1H, CH\(_2\)CH\(_2\)NH\(_2\)), 3.4 (d, \( J = 16.2 \) Hz, 1H, ArCH\(_2\)N), 3.61 – 3.65 (m, 2H, PhCH\(_2\)OH and ArCH\(_2\)CH\(_2\)CH), 3.72 (t, \( J = 7.0 \) Hz, 2H, PhCH\(_2\)CH\(_2\)OH), 4.15 (d, \( J = 16.0 \) Hz, 1H, ArCH\(_2\)N), 6.40 (d, \( J = 7.4 \) Hz, 1H 6-H\(_\text{arom}\)), 7.03 – 7.10 (m, 2H, Ar-H), 7.16 – 7.25 (m, 6H, Ar-H). Signals for the OH- and NH\(_2\)-protons are not seen in the spectrum. \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) (ppm) = 29.0 (C-5), 32.0 (C-4), 42.7 (C-3), 48.1 (CH\(_2\)NH\(_2\)), 57.9 (PhCHN), 63.6 (CH\(_2\)OH), 65.8 (C-1), 125.8 (C-Ar), 127.0 (C-Ar), 127.5 (C-Ar), 128.2 (C-Ar), 128.9 (C-Ar), 129.1 (C-Ar), 130.2 (C-Ar), 138.5 (C-Ar\(_q\)), 141.28 (C-Ar\(_q\)), 141.33 (C-Ar\(_q\)).

\((2S)-2\)\-\((3R)-3-(\text{Aminomethyl})-2,3,4,5\)-tetrahydro-1\(\text{H}\)-2-benzazepin-2-yl\)-2-phenylethanol (ent-14)

As described for the synthesis of 14 a solution of nitrile ent-(3S)-11 (0.247 g, 0.806 mmol) in THF (6.45 mL) was treated with a freshly prepared AlH\(_3\) solution (0.36 M, 16.1 mL, 5.80 mmol, General procedure 1). After work-up and removal of the solvent, the residue was directly used for the synthesis of pyrrolidine ent-15.
(2R)-2-[(3S)-3-(Pyrrolidinomethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]-2-phenylethanol (15)

Primary amine 14 was dissolved in acetonitrile (12 mL) and 1,4-diiodobutane (0.402 g, 1.3 mmol) and NaHCO₃ (0.193 g, 2.3 mmol) were added. The mixture was heated to reflux for 2 h and stirred overnight at rt. The solvent was reduced to half volume under reduced pressure. The mixture was acidified with 1 M HCl. By-products and excess 1,4-diiodobutane were removed by extraction with Et₂O. Treatment of the aqueous layer with 2 M NaOH led to a precipitate, which was extracted several times with Et₂O. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and the residue was purified by fc (Ø = 2 cm, h = 17 cm, cyclohexane : ethyl acetate : N,N-dimethylethanamine = 3 : 1 : 0.04, V = 14 mL, Rₙ = 0.50). Pale yellow liquid, which solidified on cooling in the refrigerator, pale yellow solid, mp: 113 – 115 °C, yield 56 mg (49 %, two steps from (3S)-11). C₂₃H₃₀N₂O, Mᵣ = 350.5. MS (EI): m/z [%] = 266 (M – pyrrolidinomethyl), 146 (2-benzazepine core, 100). MS (ESI): m/z [%] = 351 (M + H, 100). ¹H NMR (CDCl₃): δ [ppm] = 1.77 (ddd, J = 14.4/9.1/2.2 Hz, 1H, ArCH₂CH₂CH), 1.82 – 1.86 (m, 4H, N(CH₂CH₂)₂), 1.98 (ddddd, J = 12.6/7.4/5.3/2.1 Hz, 1H, ArCH₂CH₂CH), 2.33 (dd, J = 12.8/2.6 Hz, 1H, CHCH₂N), 2.65 – 2.71 (m, 2H, N(CH₂CH₂)₂), 2.75 – 2.78 (m, 2H, N(CH₂CH₂)₂), 2.83 – 2.92 (m, 3H, ArCH₂CH₂CH and CHCH₂N), 3.43 – 3.49 (m, 1H, ArCH₂CH₂CH), 3.57 (d, J = 16.8 Hz, 1H, ArCH₂N), 3.68 (dd, J = 11.8/5.0 Hz, 1H, CHCH₂OH), 3.75 – 3.77 (m, 1H, CHCH₂OH), 4.07 (dd, J = 11.8/3.5 Hz, 1H, CHCH₂OH), 4.18 (d, J = 16.8 Hz, 1H, ArCH₂N), 6.40 (d, J = 7.5 Hz, 1H, 9-Hₐ₉), 6.86 (td, J = 7.3/1.5 Hz, 1H, 8-Hₐ₉), 6.94 – 7.01 (m, 2H, 6-Hₐ₉ and 7-Hₐ₉), 7.06 – 7.11 (m, 5H, Ar-H). A signal for the OH proton is not seen in the spectrum. ¹³C NMR (CDCl₃): δ (ppm) = 23.9 (C-3ₚₚ, C-4ₚₚ), 31.8 (C-5), 32.9 (C-4), 47.4 (C-3), 55.5 (C-2ₚₚ, C-5ₚₚ), 59.8 (PhCH₃), 60.2 (CH₂Nₚₚ), 63.6 (CH₂OH), 68.5 (C-1), 125.5 (C-Ar), 126.3 (C-Ar), 127.0 (C-Ar), 127.8 (C-Ar), 128.7 (C-Ar), 129.3 (C-Ar), 129.4 (C-Ar), 139.9 (C-Arₙ), 140.4 (C-Arₙ), 141.8 (C-Arₙ). IR (neat): ν [cm⁻¹] = 744 (1,2-disubst. benzene). Specific rotation: [α]D²⁰ = -5.7 (c = 1.11; CH₂Cl₂). HPLC (method 2): tᵣ =
(2S)-2-[3R)-3-(Pyrrolidinomethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]-2-phenylethanol (ent-15)

As described for the synthesis of 15, primary amine ent-14 (0.806 mmol) was treated with 1,4-diiodobutane (0.750 g, 2.42 mmol) and NaHCO₃ (0.496 g, 5.90 mmol) in acetonitrile (32 mL). After work-up, the residue was purified by fc (Ø = 3 cm, h = 15 cm, cyclohexane : ethyl acetate : N,N-dimethylethanamine= 3 : 1 : 0.04, V = 14 mL, Rₖ = 0.50). Pale yellow liquid, which solidified on cooling in the refrigerator, pale yellow solid, yield 0.127 g (45 %, two steps from ent-(3S)-11). Specific rotation: \([\alpha]_D^{20} = +5.8 (c = 1.11; \text{CH}_2\text{Cl}_2)\). HPLC (method 2): \(t_R = 14.95\) min, purity 99.6 %.

(S)-2-(3,4-Dichlorophenyl)-N-(1-(pyrrolidin-1-yl)-4-(o-tolyl)butan-2-yl)acetamide (17)

A mixture of pyrrolidine 15 (48 mg, 0.137 mmol), MeOH (1.5 mL) and Pd/C (10 %, 17 mg) was stirred under a H₂ atmosphere (1 bar) at 0 °C for 6 h. After addition of 1 M HCl (1.5 mL), hydrogenation was continued overnight, then conc. HCl (1 drop) was added and the reaction mixture was stirred for additional 32 h under H₂. The catalyst was filtered off. The mixture was alkalized with NaOH and extracted several times with Et₂O. The combined organic layers were dried (Na₂SO₄), filtered, the solvent was removed under reduced pressure and the residue (16, 33 mg) was dissolved in CH₂Cl₂. After cooling to 0 °C in an ice-bath, 3,4-dichlorophenylacetyl chloride (0.1 mL) and NEt₃ (0.1 mL) were added. The mixture was slowly brought to rt and stirred at rt fo 48 h. NaOH was added and the mixture was extracted several times with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaCl solution, dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure. The residue was purified twice by fc (Ø = 2 cm, h = 15 cm, cyclohexane : ethyl acetate : dimethylethylamine= 1 : 6 : 0.04, V = 10 mL, Rₖ = 0.30). Colorless oil, yield 18 mg (31 %). C₂₃H₂₈Cl₂N₂O, \(M_r = 419.4\). MS (EI): \(m/z\) [%] = 418
(M, 6), 84 (pyrrolidinomethyl, 100). $^1$H NMR (CDCl$_3$): $\delta$ [ppm] = 1.66 – 1.75 (m, 5H, ArCH$_2$CH$_2$CH, CH$_2$N(CH$_2$CH$_2$)$_2$), 1.77 – 1.86 (m, 1H, ArCH$_2$CH$_2$CH), 2.24 (s, 3H, ArCH$_3$), 2.40 – 2.50 (m, 5H, CH$_2$N(CH$_2$CH$_2$)$_2$, ArCH$_2$CH$_2$CH), 2.55 – 2.62 (m, 3H, CH$_2$N(CH$_2$CH$_2$)$_2$, 3.50 (s, 2H, HNC(=O)CH$_2$Ar), 3.96 – 4.05 (m, 1H, ArCH$_2$CH$_2$CH), 5.85 (d, J = 6.7 Hz, 1H, HNC(=O)CH$_2$Ar), 7.06 – 7.15 (m, 5H, ArH), 7.39 – 7.41 (m, 2H, ArH). IR (neat): $\nu$ [cm$^{-1}$] = 3284 (N-H), 1638 (O=CNHR, amide I), 1552 (O=CNHR, amide II), 741 (Ar-Cl). HPLC (method 1): $t_R$ = 18.56 min, purity 93.1%.

(3S)-2-[(1R)-2-Chloro-1-phenylethyl]-1-oxo-2,3,4,5-tetrahydro-1$H$-2-benzazepine-3-carbonitrile (18)

Under N$_2$, a solution of nitrile (3S)-11 (0.20 g, 0.653 mmol) in THF (12 mL) was cooled to 0 °C. A solution of SOCl$_2$ (2 M in THF, 0.327 mL, 0.653 mmol) was added and the mixture was stirred at 0 °C for 1 h. A saturated aqueous solution of NaHCO$_3$ was added and the mixture was stirred for 10 min. The solution was extracted with ethyl acetate, the combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was purified by fc ($Ø = 3$ cm, h = 14 cm, cyclohexane : ethyl acetate = 2 : 1, V = 14 mL, $R_f$ = 0.38). Colorless liquid, yield 0.135 g (64 %). C$_{19}$H$_{17}$ClN$_2$O, M$_r$ = 324.8. MS (EM): $m/z = 325.1090$ (calcd. 325.1102 for C$_{19}$H$_{17}^{35}$ClN$_2$OH$^+$ [M+H$^+$]). $^1$H NMR (CDCl$_3$): $\delta$ [ppm] = 2.22 – 2.31 (m, 1H, ArCH$_2$CH$_2$CH), 2.53 – 2.60 (m, 1H, ArCH$_2$CH$_2$CH), 2.87 – 2.92 (m, 1H, ArCH$_2$CH$_2$CH), 3.13 – 3.21 (m, 1H, ArCH$_2$CH$_2$CH), 4.16 (d, J = 5.5 Hz, 2H, NCH$_2$Cl), 4.32 (dd, J = 7.6/2.7 Hz, 1H, ArCH$_2$CH$_2$CH), 6.24 – 6.32 (m, broad, 1H, PhCH$_2$Cl), 7.20 – 7.22 (m, 1H, Ar-H), 7.32 – 7.49 (m, 7H, Ar-H), 7.79 (dd, J = 7.4/1.6 Hz, 1H, 9-H$_{arom}$). $^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) = 29.3(C-5), 35.9 (C-4), 43.8 (C-3), 53.6 (PhCHN), 59.0 (CH$_2$Cl), 117.3 (CN), 127.8 (C-Ar), 128.4 (C-Ar), 128.8 (C-Ar), 129.1 (C-Ar), 129.5 (C-Ar), 130.1 (C-Ar), 132.6 (C-Ar), 135.1 (C-Ar$_q$), 135.9 (C-Ar$_q$), 136.5 (C-Ar$_q$), 171.3 (C=O). IR (neat): $\nu$ [cm$^{-1}$] = 1646 (O=CN$_2$), a signal for the CN group is not seen.
(±)-1-Oxo-2-(1-phenylvinyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carbonitrile (19)

Under N₂, DBU (0.32 mL, 2.1 mmol) was added to a solution of chloride 18 (0.135 g, 0.412 mmol) in THF (6.5 mL). The reaction mixture was heated to reflux for 1.5 h, then stirred at rt for 10 min. A sufficient amount of silica gel was added and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 3 cm, h = 17 cm, cyclohexane : ethyl acetate = 2 : 1, V = 14 mL, Rf = 0.19). Colorless viscous oil, yield 65 mg (53 %). C₁₉H₁₆N₂O, Mᵣ = 288.3. MS (EM): m/z = 289.1335 (calcd. 289.1335 for C₁₉H₁₆N₂OH⁺ [M+H⁺]); m/z = 335.1754 (calcd. 335.1754 for C₁₉H₁₆N₂OC₂H₅OH₂⁺ [M+2H⁺]). ¹H NMR (CDCl₃): δ [ppm] = 2.33 (dddd, J = 13.8/8.6/7.1/5.1 Hz, 1H, ArCH₂CH₂), 2.51 (dtd, J = 12.7/7.2/5.2 Hz, 1H, ArCH₂CH₂), 2.85 – 2.99 (m, 1H, ArCH₂CH₂CH₂), 4.57 (dd, J = 6.7/5.1 Hz, 1H, ArCH₂CH₂CH₂CH₂), 5.38 (d, J = 0.9 Hz, 1H, C=CH₂), 5.80 (d, J = 0.9 Hz, 1H, C=CH₂), 7.18 – 7.21 (m, 1H, Ar-H), 7.27 – 7.48 (m, 7H, Ar-H), 7.73 (dd, J = 7.4/1.6 Hz, 1H, 9-Hₚₐromatic). IR (neat): ν [cm⁻¹] = 1643 (O=CNR₂), a signal for the CN group is not observed.

(±)-1-Oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carbonitrile (20)

1 M HCl (5 mL) and HCl conc. (7 drops) were added to a solution of enamide 19 (65 mg, 0.22 mmol) in THF (5 mL). The mixture was heated to reflux overnight, HCl conc. (10 drops) was added and the mixture was heated to reflux for additional 18 h. The mixture was poured into a saturated solution of aqueous NaHCO₃, the mixture was extracted with ethyl acetate, the combined organic layers were dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by fc, which was performed with a gradient (Ø = 2 cm, h = 16 cm, cyclohexane : ethyl acetate = 2 : 1 until acetonaphone had been eluted, then cyclohexane : ethyl acetate = 1 : 2, V = 14 mL, Rf = 0.25 (cyclohexane : ethyl acetate = 1 : 2). Pale yellow liquid, yield 31 mg (76 %). C₁₁H₁₀N₂O, Mᵣ = 186.2. MS (EM): m/z = 187.0866 (calcd. 187.0869 for C₁₁H₁₀N₂OH⁺ [M+H⁺]).
m/z = 395.1478 (calcd. 395.1478 for (C_{11}H_{10}N_{2}O)_{2}Na^{+} [2M+Na^{+}]). ¹H NMR (CDCl₃): δ [ppm] = 2.25 – 2.46 (m, 2H, ArCH₂CH₂CH), 2.75 – 3.07 (m, 2H, ArCH₂CH₂CH), 4.21 (dt, J = 9.0/6.4 Hz, 1H, ArCH₂CH₂CH), 6.47 – 6.60 (s, broad, 1H, CONH), 7.15 – 7.17 (m, 1H, 6-Harom.), 7.32 – 7.45 (m, 2H, 7-Harom., 8-Harom.) 7.68 (dd, J = 7.5/1.5 Hz, 1H, 9-Harom.). IR (neat): ν [cm⁻¹] = 3210 (NH), 2247 (CN), 1655 (CONHR).

(±)-3-(N,N-Dibenzylaminomethyl)-2,3,4,5-tetrahydro-2-benzazepin-1-one (21)

Under N₂, a solution of nitrile 20 (68 mg, 0.365 mmol) in THF (2.9 mL) was added to a cooled (0 °C) freshly prepared solution of AlH₃ (0.67 M, 3.0 mL, 2.01 mmol, prepared according to General procedure 1) and the mixture was stirred for 40 min at 0 °C. A solution of glycerol in water (1:1) was added dropwise until the evolution of H₂ had ceased. The precipitate was filtered off, suspended in THF (1 mL), heated to reflux and filtered off. This procedure was repeated twice. The combined filtrates were dried (Na₂SO₄), filtered and the solvent was removed under reduced pressure at high vacuum yielding 63 mg of crude primary amine. The crude primary amine was dissolved in CH₂Cl₂ (75 mL). Under N₂ benzaldehyde (0.116 g, 1.09 mmol) and NaBH(OAc)₃ (0.273 g, 1.29 mmol) were added and the mixture was stirred at rt for 1 h. Under ice-cooling 1 M HCl was added, and the mixture was stirred at rt for 10 min. Then 2 M NaOH was added, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered, concentrated in vacuo and the residue was purified by fc (Ø = 3 cm, h = 17 cm, cyclohexane : ethyl acetate = 3 : 1, V = 14 mL, Rf = 0.12). Pale yellow oil, yield 48 mg (36 %, two steps from nitrile 20). C₂₅H₂₆N₂O, Mᵣ = 370.5. MS (EM): m/z = 371.2196 (calcd. 371.2118 for C₂₅H₂₆N₂O⁺ [M+H⁺]). ¹H NMR (CDCl₃): δ [ppm] = 1.57 – 1.63 (m, 1H, ArCH₂CH₂CH), 1.83 – 1.52 (m, 1H, ArCH₂CH₂CH), 2.40 (dd, J = 13.0/4.4 Hz, 1H, CHCH₂NR₂), 2.56 (dd, J = 13.0/10.5 Hz, 1H, CHCH₂NR₂), 2.64 (dd, 13.6/6.2 Hz, 1H, ArCH₂CH₂CH), 2.93 (td, J = 13.0/7.7 Hz, 1H, ArCH₂CH₂CH), 3.23 – 3.31 (m, 3H, N(CH₂Ph)₂, ArCH₂CH₂CH), 3.70 (d,
J = 13.3 Hz, 2H, N(CH₂Ph)₂), 5.97 (d, J = 2.7 Hz, 1H, CONHR), 7.13 (d, J = 7.2 Hz, 1H, ArH), 
7.23 – 7.38 (m, 12H, ArH), 7.68 (dd, J = 7.5/1.4 Hz, 1H, ArH). IR (neat): ν [cm⁻¹] = 1653 
(O=CNHR). HPLC (method 1): t_R = 17.19 min, purity 97.1 %. HPLC (method 5): t_R = 10.64 min, 
48.5 % (enantiomer 1) and t_R = 12.31 min, 48.5 % (enantiomer 2).

(2R)-2-Phenyl-2-[(3S)-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]ethanol (22)

Under N₂, a solution of AlH₃ (0.36 M in THF, 1.9 mL, 0.68 mmol, freshly prepared according to 
General procedure 2) was cooled to 0 °C. With a cannula, a solution of allylbenzazepinone (3S)-12 
(70 mg, 0.218 mmol) in THF (1.8 mL) was slowly transferred into the solution of AlH₃. The 
mixture was stirred at 0 °C for 0.5 h and at rt for 0.5 h. 1 M NaOH (2 mL) was added, the 
precipitate was removed and washed carefully with Et₂O. The layers were separated and the 
aqueous layer was washed several times with Et₂O. The combined organic layers were dried 
(Na₂SO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by 
fcc (Ø = 1 cm, h = 15 cm, cyclohexane : ethyl acetate = 8 : 2, V = 7 mL, R_f = 0.42). Colorless oil, 
yield 36 mg (54 %). C₂₁H₂₅NO, M_r = 307.4. MS (EM): m/z = see enantiomer ent-22. ¹H NMR 
(CDCl₃): δ [ppm] = 1.70 – 1.77 (m, 1H, ArCH₂CH₂CH), 1.98 – 2.06 (m, 1H, ArCH₂CH₂CH₂), 2.39 
(dt, J = 14.1/7.1 Hz, 1H, CH₂CH=CH₂), 2.62 – 2.74 (m, 2H, ArCH₂CH₂CH₂, CH₂CH=CH₂), 3.10 – 
3.17 (m, 1H, ArCH₂CH₂CH₂), 3.37 – 3.41 (m, 2H, ArCH₂N, ArCH₂CH₂CH₂), 3.66 – 3.71 (m, 2H, 
NCH₂CH₂OH, NCH₂CH₂OH), 3.82 – 3.88 (m, 1H, NCH₂CH₂OH), 4.19 (d, J = 15.7 Hz, 1H, 
ArCH₂N), 5.11 – 5.17 (m, 2H, CH₂CH=CH₂), 5.98 (ddt, J = 17.2/10.1/7.1 Hz, 1H, CH₂CH=CH₂), 
6.51 (d, J = 7.3 Hz, 1H, ArH), 6.94 – 7.00 (m, 1H, ArH), 7.10 – 7.11 (m, 2H, ArH), 7.23 – 7.35 (m, 
5H, ArH). A signal for the OH-proton is not seen in the spectrum. ¹³C NMR (CDCl₃): δ (ppm) = 
28.9 (CH₂CH=CH₂), 29.1 (C-5), 36.9 (C-4), 49.3 (C-3), 57.3 (PhCHN), 64.1 (C-1), 64.7 (CH₂OH), 
116.6 (CH=CH₂), 125.7 (C-Ar), 127.1 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.5 (C-Ar), 128.9 (C- 
Ar), 128.9 (C-Ar), 129.0 (C-Ar), 129.1 (C-Ar), 130.0 (C-Ar), 136.9 (CH=CH₂), 139.4 (C-Ar),
140.7 (C-Ar$_q$), 142.7 (C-Ar$_q$). IR (neat): $\nu$ [cm$^{-1}$] = see enantiomer $\textit{ent-22}$. Specific rotation: $[\alpha]_D^{20} = -17$ (c = 0.60; CH$_2$Cl$_2$). HPLC (method 2): $t_R = 13.53$ min, purity 97.8%.

**(2S)-2-Phenyl-2-[(3R)-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]ethanol**

($\textit{ent-22}$)

As described for the synthesis of $\textit{22}$, allylbenzazepinone $\textit{ent-(3S)-12}$ (0.10 g, 0.31 mmol) in THF (2.5 mL) was treated with a freshly prepared solution of AlH$_3$ (0.67 M in THF, 1.4 mL, 0.94 mmol, General procedure 1). The mixture was stirred at 0 °C for 0.5 h and at rt for 0.5 h. A solution of glycerol in water (1:1) was added dropwise, until the evolution of H$_2$ gas had ceased. The precipitate was filtered off, suspended in THF (1 mL), heated to reflux and filtered off. This procedure was repeated twice. The solvent of the combined filtrates was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$, washed with 2 M NaOH, dried (Na$_2$SO$_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by fc ($\varnothing = 2$ cm, h = 16 cm, cyclohexane : ethyl acetate = 9 : 1, V = 14 mL, $R_f = 0.20$). Colorless oil, yield 66 mg (69%). C$_{21}$H$_{25}$NO, M$_r = 307.4$. MS (EM): $m/z = 308.2003$ (calcd. 308.2009 for C$_{21}$H$_{25}$NOH$^+$ [M+H$^+$]). IR (neat): $\nu$ [cm$^{-1}$] = 3854 (O-H), 1638 (C-H arom.), 1491 (C-H arom.). Specific rotation: $[\alpha]_D^{20} = +16$ (c = 0.72; CH$_2$Cl$_2$). HPLC (method 1): $t_R = 15.97$ min, purity 99.7%.

**(3R)-2-[(1R)-2-Hydroxy-1-phenylethyl]-3-propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (24)**

A mixture of allylbenzazepinone $(3S)$-$12$ (0.10 g, 0.31 mmol), CH$_3$OH (12 mL) and Pd/C (10 %, 10 mg) shaken under a H$_2$ atmosphere (5 bar) at rt for 30 min. The mixture was filtered and the solvent was removed under reduced pressure. Colorless solid, mp 161 °C, yield 0.101 g (99%). C$_{21}$H$_{25}$NO$_2$, M$_r = 323.4$ MS (ESI): $m/z$ [%] = 324 (M + H, 17), 346 (M + Na, 100), 669 (2M + Na, 12). $^1$H NMR (D$_5$-nitrobenzene, 100 °C): $\delta$ [ppm] = 0.01 – 0.04 (m, 3H, CH$_3$), 0.30 – 0.42 (m, 2H, CH$_2$CH$_2$CH$_3$), 0.58 – 0.63 (m, 2H, CH$_2$CH$_2$CH$_3$), 1.60 – 1.62 (m, 1H, ArCH$_2$CH$_2$CH$_2$), 1.69 (s, 1H,
CHCH$_2$OH), 1.92 – 1.97 (m, 1H, ArCH$_2$CH$_2$CH), 2.48 – 2.52 (m, 1H, ArCH$_2$CH$_2$CH), 2.72 – 2.79 (m, 1H, ArCH$_2$CH$_2$CH), 3.19 – 3.22 (m, 1H, ArCH$_2$CH$_2$CH), 4.02 – 4.05 (m, 1H, CHCH$_2$OH), 4.12 – 4.18 (m, 1H, CHCH$_2$OH), 5.50 – 5.58 (s, broad, 1H, CHCH$_2$OH), 6.79 – 7.47 (m, 9H, Ar-H). IR (neat): ν [cm$^{-1}$] = 3356 (OH), 1619 (O=CNR$_2$). Specific rotation: $[\alpha]_{D}^{20} = +11$ (c = 1.00; CH$_2$Cl$_2$). HPLC (method 1): $t_R = 20.11$ min, purity 98.4 %.

(3S)-2-[(1S)-2-Hydroxy-1-phenylethyl]-3-propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (ent-24)

As described for the synthesis of 24 allylbenzazepinone ent-(3S)-12 (0.57 g, 1.78 mmol) was reduced with H$_2$ (5 bar) in presence of Pd/C (10 %, 57 mg) in MeOH (27 mL). After work-up, purification of the residue was not necessary. Colorless solid, yield 0.556 g (95 %). Specific rotation: $[\alpha]_{D}^{20} = -10$ (c = 1.00; CH$_2$Cl$_2$). HPLC (method 1): $t_R = 19.35$ min, purity 99.2 %.

(2R)-2-Phenyl-2-[(3R)-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]ethanol (25)

Under N$_2$, a solution of propylbenzazepinone 24 (90 mg, 0.278 mmol) in THF (2.22 mL) was added to a freshly prepared solution of AlH$_3$ (0.67 M, 1.25 mL, 0.83 mmol, General procedure 1) at 0 °C and the mixture was stirred for 1 h at 0 °C. A solution of glycerol in water (1:1) was added dropwise until the evolution of H$_2$ had ceased. The precipitate was filtered off, suspended in THF (1 mL), heated to reflux and filtered off. This procedure was repeated twice. The solvent of the combined filtrates was removed under reduced pressure. The residue was dissolved in Et$_2$O, the solution was washed with 2 M NaOH, dried (Na$_2$SO$_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by fc ($\Phi = 2$ cm, h = 15 cm, cyclohexane : ethyl acetate = 9 : 1, $V = 7$ mL, $R_f = 0.36$). Colorless oil, yield 71 mg (82 %). C$_{21}$H$_{27}$NO, $M_r = 309.4$. MS (EM): $m/z = 310.2165$ (calcd. 310.2165 for C$_{21}$H$_{27}$NOH$^+$ [M+H$^+$]). $^1$H NMR (CDCl$_3$): $\delta$ [ppm] = 1.01 (t, $J = 7.1$ Hz, 3H, CH$_2$CH$_2$CH$_3$), 1.45 – 1.69 (m, 4H, CH$_2$CH$_2$CH$_3$, ArCH$_2$CH$_2$CH), 1.95 – 2.04 (m,
2H, \(CH_2CH_2CH_3\), \(ArCH_2CH_2CH\), 2.61 (m, 1H, \(ArCH_2CH_2CH\)), 3.16 (m, 1H, \(ArCH_2CH_2CH\)), 3.28 – 3.32 (m, 2H, \(ArCH_2CH_2CH\), \(ArCH_2N\)), 3.66 – 3.70 (m, 2H, \(NCHCH_2OH\), \(NCHCH_2OH\)), 3.79 – 3.85 (m, 1H, \(NCHCH_2OH\)), 4.17 (d, \(J = 15.6\) Hz, 1H, \(ArCH_2N\)), 6.47 (d, \(J = 7.3\) Hz, 1H, \(ArH\)), 6.94 – 6.98 (m, 1H, \(ArH\)), 7.10 – 7.12 (m, 2H, \(ArH\)), 7.24 – 7.36 (m, 5H, \(ArH\)). A signal for the \(OH-\)proton is not seen in the spectrum. \(^{13}\)C NMR (\(CDCl_3\)): \(\delta\) (ppm) = 14.6 (\(CH_2CH_2CH_3\)), 20.1 (\(CH_2CH_2CH_3\)), 28.8 (C-5), 31.0 (\(CH_2CH_2CH_3\)), 34.4 (C-4), 49.3 (C-3), 56.3 (PhCHN), 64.3 (CH_2OH), 64.4 (C-1), 125.5 (C-Ar), 127.0 (C-Ar), 127.6 (C-Ar), 128.5 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 130.1 (C-Ar), 139.5 (C-Ar_q), 141.0 (C-Ar_q), 143.0 (C-Ar_q). IR (neat): \(\nu\) [cm\(^{-1}\)] = 3452 (O-H), 2927 (C-H), 1600 (C-H arom.), 1491 (C-H arom.). Specific rotation: \([\alpha]_D^{20} = -24\) (c = 0.68; \(CH_2Cl_2\)).

HPLC (method 1): \(t_R = 17.79\) min, purity 99.4 %.

\((2S)-2\text{-Phenyl-2-[(3S)-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepin-2-yl]ethanol (ent-25)}\)

As described for the synthesis of 25, propylbenzazepinone \(\text{ent-24}\) (0.10 g, 31 mmol) was dissolved in \(THF\) (2.5 mL) and treated with a freshly prepared solution of \(AlH_3\) (0.67 M, 1.39 mL, 0.93 mmol, General procedure 1). After work-up, the residue was purified by fc (\(\Theta = 2\) cm, h = 15 cm, cyclohexane : ethyl acetate = 9 : 1, \(V = 14\) mL, \(R_f = 0.36\)). Colorless oil, yield 66 mg (68 %). Specific rotation: \([\alpha]_D^{20} = +24\) (c = 1.07; \(CH_2Cl_2\)). HPLC (method 1): \(t_R = 17.32\) min, purity 99.5 %.

\((3R)-2-[(1R)-2-Chloro-1-phenylethyl]-3-propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (26)}\)

Under \(N_2\), freshly distilled \(SOCl_2\) (0.023 mL, 0.31 mmol) was added to a solution of 24 (50 mg, 0.154 mmol) in \(THF\) (3 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The solvent and excess \(SOCl_2\) were removed at rt under reduced pressure. As the colorless liquid was very unstable, the unpurified product was immediately used in the next step. \(C_{21}H_{24}ClNO\), \(M_r = 341.9\). MS (EM): \(m/z = 364.1439\) (calcd. 364.1439 for \(C_{21}H_{24}^{35}CINO Na^+ [M+Na^+]\)).
(3S)-2-[(1S)-2-Chloro-1-phenylethyl]-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (ent-26)

As described for the synthesis of 26, ent-24 (0.200 g, 0.62 mmol) was treated with freshly distilled SOCl₂ (0.093 mL, 1.24 mmol) in THF (12 mL). After removal of the solvent and SOCl₂, the colorless liquid was immediately used in the next step.

(3R)-2-(1-Phenylvinyl)-3-propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (27)

At -78 °C a freshly prepared solution of LDA (0.57 M in THF/n-hexane, 1.25 mL, 0.71 mmol) was added slowly to a solution of unpurified 26 (50 mg, 0.154 mmol) in THF (1.5 mL). The mixture was stirred at -78 °C for 1.5 h. The black reaction mixture was poured into water and the aqueous layer was extracted several times with Et₂O. The combined organic layers were washed with saturated aqueous NaCl solution, dried (Na₂SO₄), filtered, silica gel was added and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 2 cm, h = 17 cm, cyclohexane : ethyl acetate = 6 : 1, V = 12 mL, Rᵣ = 0.16 (cyclohexane : ethyl acetate = 4 : 1). Pale yellow oil, yield 16 mg (34 %, two steps from 24). C₂₁H₂₃NO, Mᵣ = 305.4 MS (EM): m/z = 306.1852 (calcd. 306.1852 for C₂₁H₂₃NOH⁺ [M+H⁺]); m/z = 328.1672 (calcd. 328.1617 for C₂₁H₂₃NONa⁺ [M+Na⁺]).

1H NMR (CDCl₃): δ [ppm] = 0.68 (t, J = 7.3 Hz, 3H, CH₂CH₂C₆H₃), 0.97 – 1.52 (m, 4H, CH₂CH₂CH₃), 1.83 – 1.95 (m, 1H, ArCH₂CH₂CH), 2.07 (ddddd, J = 13.5/11.7/6.8/5.0 Hz, 1H, ArCH₂CH₂CH), 2.82 (dddd, J = 13.7/6.9/2.4 Hz, 1H, ArCH₃CH₂CH), 3.07 (dddd, J = 13.6/11.1/7.6 Hz, 1H, ArCH₂CH₂CH), 3.58 – 3.69 (m, 1H, ArCH₂CH₂CH), 5.28 (s, 1H, C=CH₂), 5.87 (s, 1H, C=CH₂), 7.16 (dd, J = 7.0/1.5 Hz, 1H, ArH), 7.27 – 7.43 (m, 5H, ArH), 7.50 – 7.55 (m, 2H, ArH), 7.70 (dd, J = 6.8/2.1 Hz, 1H, 9-Hₐrom.). IR (neat): ν [cm⁻¹] = 2957 (C-H), 1646 (CONR₂).

HPLC (method 1): tᵣ = 21.76 min, purity 99.3 %. 
(3S)-2-(1-Phenylvinyl)-3-propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (ent-27)

As described for the synthesis of 27 unpurified ent-26 (0.212 g, 0.62 mmol) was treated with a freshly prepared solution of LiTMP (0.56 M in THF/hexanes, 5.56 mL, 3.1 mmol) in THF (6.5 mL) for 40 min. After work-up, the residue was purified by fc (Ø = 3 cm, h = 10 cm, hexane : ethyl acetate = 5 : 1, V = 14 mL, Rf = 0.40 (cyclohexane : ethyl acetate = 7 : 3). Colorless oil, yield 0.148 g (78 %; two steps from ent-24).

(3R)-3-Propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (28)

20 % HCl (0.5 mL) was added to a solution of enamide 27 (16 mg, 0.05 mmol) in Et2O (0.75 mL). The mixture was heated to reflux for 4.5 h and then poured into a saturated aqueous NaHCO3 solution. The mixture was extracted with Et2O (3x). The combined organic layers were dried (Na2SO4), filtered, silica gel was added and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 2 cm, h = 15 cm, cyclohexane : ethyl acetate = 2 : 1, V = 10 mL, Rf = 0.13). Colorless solid, yield 10 mg (95 %). C13H17NO, Mr = 203.3. MS (EM): m/z = 226.1202 (calcd. 226.1202 for C13H17NONa+ [M+Na+]); m/z = 429.2512 (calcd. 429.2513 for (C13H17NO)2Na+ [2M+Na+]). 1H NMR (CDCl3): δ [ppm] = 0.88 (t, J = 7.2 Hz, 3H, CH2CH2CH3), 1.29 – 1.55 (m, 4H, CH2CH2CH3), 1.79 – 1.87 (m, 1H, ArCH2CH2CH), 1.97 (tdd, J = 12.2/6.6/5.4 Hz, 1H, ArCH2CH2CH), 2.70 (dd, 13.6/6.6 Hz, 1H, ArCH2CH2CH), 3.00 (td, J = 13.0/8.0 Hz, 1H, ArCH2CH2CH), 3.09 – 3.19 (m, 1H, ArCH2CH2CH), 5.82 (s, 1H, NH), 7.18 (d, J = 7.3 Hz, 1H, ArH), 7.30 – 7.42 (m, 2H, ArH), 7.70 (dd, J = 7.5/1.3 Hz, 1H, ArH). 13C NMR (CDCl3): δ (ppm) = 14.0 (CH2CH2CH3), 19.6 (CH2CH2CH3), 30.8 (C-5), 36.9 (C-4), 37.3 (CH2CH2CH3), 51.1 (C-3), 127.1 (C-Ar), 128.7 (C-Ar), 128.8 (C-Ar), 131.3 (C-Ar), 135.3 (C-Arq), 138.9 (C-Arq), 172.7 (C=O). IR (neat): ν [cm⁻¹] = 3192 (N-H), 1652 (O=CNHR). Specific rotation: [α]D²⁰ = -180 (c = 1.01; CH2Cl2). HPLC (method 1): tR = 17.93 min, purity 84.1 %. 

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(3S)-3-Propyl-2,3,4,5-tetrahydro-2-benzazepin-1-one (ent-28)

As described for the synthesis of 28, ent-27 (0.148 g, 0.485 mmol) was treated with 20 % HCl (5 mL) in Et₂O (7 mL) for 2 h. After work-up, the residue was purified by fc (Ø = 2 cm, h = 15 cm, hexane : ethyl acetate = 8 : 2, V = 14 mL, Rₓ = 0.12). Pale yellow oil, yield 30 mg (30 %). MS (EM): m/z = 204.1409 (calcd. 204.1383 for C_{13}H_{17}NOH\+[M+H\+]). Specific rotation: [α]D^{20} = +200 (c = 1.00; CH₂Cl₂). HPLC (method 1): t_R = 17.45 min, purity 99.3 %.

(3R)-3-Propyl-2,3,4,5-tetrahydro-1H-2-benzazepine (29)

Under N₂, a freshly prepared AlH₃ solution (0.67 M, 1.3 mL, 0.87 mmol, prepared according to General procedure 1) was added in a cooled (0 °C) solution of lactam 28 (28 mg, 0.138 mmol) in THF (1.4 mL) and the reaction mixture was stirred at 0 °C for 1 h. The ice bath was removed, and the mixture was stirred overnight at rt. A mixture of ethylene glycol : water (1:1) was added dropwise until evolution of H₂ gas had ceased. The precipitate was filtered off, suspended in THF (1 mL), heated to reflux and filtered off. This procedure was repeated twice. The combined filtrates were evaporated with gentle heating. The residue was dissolved in CH₂Cl₂, washed with 2 M NaOH dried (Na₂SO₄), filtered and the solvent was removed under vacuum with gentle heating. (Cave! The product 29 is volatile). Colorless oil, yield 31 mg (100 %) C_{13}H_{19}N, Mₛ = 189.3. MS (ESI): m/z [%] = 190 (M + H, 100). \(^{1}\)H NMR (CDCl₃): δ [ppm] = 0.92 (t, J = 6.9 Hz, 3H, CH₂CH₂CH₃), 1.24 (qd, J = 12.2/1.6 Hz, 1H, ArCH₂CH₂CH₃), 1.34 – 1.44 (m, 4H, CH₂CH₂CH₃), 1.96 (ddt, J = 13.7/7.0/2.1 Hz, 1H, ArCH₂CH₂CH₃), 2.82 (ddd, J = 14.6/6.9/1.6 Hz, 1H, ArCH₂CH₂CH₃), 2.86 – 2.92 (m, 1H, ArCH₂CH₂CH₃), 3.01 (ddd, J = 14.1/12.2/1.6 Hz, 1H, ArCH₂CH₂CH₃), 3.83 (d, J = 14.6 Hz, 1H, ArCH₂N), 3.91 (d, J = 14.5 Hz, 1H, ArCH₂N), 7.03 – 7.08 (m, 4H, ArH). IR (neat): ν [cm⁻¹] = 2923 (C-H), 1492 (C-H₆₉), 747 (1,2-disubst. benzene).
(3S)-3-Propyl-2,3,4,5-tetrahydro-1H-2-benzazepine (ent-29)

As described for the synthesis of 29, ent-28 (30 mg, 0.148 mmol) was treated with a freshly prepared AlH₃ solution (0.67 M, 1.33 mL, 0.891 mmol. General procedure 1) in THF (1.5 mL) for 30 min. After work-up and careful evaporation of the solvent under reduced pressure, the residue was directly used for the next step. Pale yellow oil, yield 25 mg.

(3R)-2-Benzyl-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine (30a)

Under N₂, a solution of the unpurified secondary amine 29 (35 mg, 0.185 mmol), benzaldehyde (65 mg, 0.611 mmol) and NaBH(OAc)₃ (0.153 g, 0.722 mmol) in CH₂Cl₂ (3 mL) was stirred. After stirring for 4 h at rt an additional amount of NaBH(OAc)₃ (40 mg) was added and the mixture was stirred for additional 18 h. After addition of 1 M HCl, the mixture was stirred at rt for 10 min. Then 2 M NaOH was added, the layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered, concentrated in vacuo and the residue was purified by fc (Ø = 2 cm, h = 18 cm, cyclohexane : ethyl acetate = 18 : 1, V = 14 mL, Rf = 0.4). Colorless oil, yield 16 mg (31 %). C₂₀H₂₅N, Mr = 279.4. MS (ESI): m/z [%] = 280 (M + H, 100). ¹H NMR (CDCl₃): δ [ppm] = 0.88 (t, J = 7.2 Hz, 3H, CH₂CH₂C₃H₃), 1.31 – 1.43(m, 2H, C₃H₂CH₂CH₃), 1.44 – 1.56 (m, 2H, ArCH₂CH₂CH, CH₂CH₂CH₃), 1.66 – 1.77 (m, 2H, ArCH₂CH₂CH, CH₂CH₂CH₃), 2.73 – 2.79 (m, 1H, ArCH₂CH₂CH), 2.87 – 2.95 (m, 1H, ArCH₂CH₂CH), 2.97 – 3.03 (m, 1H, ArCH₂CH₂CH), 3.08 (d, J = 13.8 Hz, 1H, 1-H), 3.52 (d, J = 13.8 Hz, 1H, 1-H), 3.70 (d, J = 15.0 Hz, 1H, NCH₂Ph), 3.90 (d, J = 15.1 Hz, 1H, NCH₂Ph), 6.71 (d, J = 7.3 Hz, 1H, ArH), 6.96 – 7.02 (m, 1H, ArH), 7.08 – 7.09 (m, 2H, ArH), 7.14 – 7.25 (m, 5H, ArH). ¹³C NMR (CDCl₃): δ (ppm) = 14.43 (CH₂CH₂CH₃)), 20.2 (CH₂CH₂CH₃)), 28.4 (C-5), 34.5 (C-4), 36.7 (CH₂CH₂CH₃), 51.1 (C-3), 55.1 (PhCH₂), 65.2 (C-1), 125.6 (C-Ar), 126.7 (C-Ar), 127.1 (C-Ar), 128.2 (C-Ar), 128.9 (C-Ar), 130.5 (C-Ar), 139.5 (C-Ar,q), 140.2 (C-Ar,q), 143.1 (C-Ar,q). IR (neat): ν [cm⁻¹] = 2922 (C-H), 1602 (C-H₆₆₄), 1493 (C-H₆₆₄). Specific rotation: [α]D²⁰ = +30 (c = 0.63; CH₂Cl₂). HPLC (method 1): tᵣ = 18.25 min, purity 98.2 %. HPLC (method
6): \( t_R = 7.78 \) min, ratio of enantiomers 86.8 : 13.2.

(3S)-2-Benzyl-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine (ent-30a)

As described for the synthesis of 30a, unpurified secondary amine ent-29 (25 mg, 0.132 mmol) was treated with benzaldehyde (46 mg, 0.436 mmol), \( \text{NaBH(OAc)}_3 \) (0.109 g, 0.515 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2.5 mL). After 3 h, a further amount of \( \text{NaBH(OAc)}_3 \) (40 mg) was added. The mixture was stirred for 6.5 h. After work-up, the residue was purified by fc (\( \Omega = 2 \) cm, \( h = 18 \) cm, \( n\)-hexane : ethyl acetate = 18 : 1, \( V = 14 \) mL, \( R_f = 0.30 \)). Colorless oil, yield 15.6 mg (43 %). Specific rotation: \( [\alpha]_D^{20} = -34 \) (c = 0.53; \( \text{CH}_2\text{Cl}_2 \)). HPLC (method 1): \( t_R = 17.71 \) min, purity 98.7 %. HPLC (method 6): \( t_R = 8.07 \) min, ratio of enantiomers 98.3 : 1.7.

(3R)-2-(Cyclohexylmethyl)-3-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine (30b)

Under \( \text{N}_2 \), a solution of the unpurified secondary amine 29 (31 mg, 0.164 mmol) cyclohexanecarbaldehyde (61 mg, 0.54 mmol) and \( \text{NaBH(OAc)}_3 \) (0.136 g, 0.64 mmol) in \( \text{CH}_2\text{Cl}_2 \) (3 mL) was stirred The mixture was stirred at rt for 8 h. After addition of 1 M \( \text{HCl} \), the mixture was stirred at rt for 10 min. Then 2 M \( \text{NaOH} \) was added, the layers were separated and the aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \). The combined organic layers were dried (\( \text{Na}_2\text{SO}_4 \)), filtered, concentrated in vacuo and the residue was purified by preparative HPLC (method 4): \( t_R = 53.3 \) min to 63.2 min. Colorless oil, yield 21 mg (45 %). \( \text{C}_{20}\text{H}_{31}\text{N} \), \( M_r = 285.5 \). MS (EM): \( m/z = 286.2521 \) (calcld. 286.2529 for \( \text{C}_{20}\text{H}_{31}\text{NH}^+ \text{[M+H]}^+ \)). \( ^1\text{H NMR} \) (CDCl\(_3\)): \( \delta \) (ppm) = 0.62 – 0.73 (m, 2H, Cy), 0.87 (t, \( J = 7.2 \) Hz, 3H, \( \text{CH}_2\text{CH}_2\text{CH}_2\)), 1.01 – 1.68 (m, 14H, Cy, \( \text{CH}_2\text{CH}_2\text{CH}_2\text{H}_3\), \( \text{ArCH}_2\text{CH}_2\text{CH}_2\)), 1.71 – 1.89 (m, 2H, \( \text{NCH}_2\text{Cy} \), \( \text{CH}_2\text{Cy} \)), 1.93 – 2.06 (m, 1H, \( \text{NCH}_2\text{Cy} \)), 2.62 – 2.77 (m, 1H, \( \text{ArCH}_2\text{CH}_2\)), 2.80 – 2.93 (m, 2H, \( \text{ArCH}_2\text{CH}_2\)), 3.71 (d, \( J = 15.4 \) Hz, 1H, \( \text{ArCH}_2\text{N} \)), 4.03 (d, \( J = 15.2 \) Hz, 1H, \( \text{ArCH}_2\text{N} \)), 7.01 – 7.06 (m, 4H, ArH). \( ^13\text{C NMR} \) (CDCl\(_3\)): \( \delta \) (ppm) = 14.5(\( \text{CH}_2\text{CH}_2\text{CH}_3 \)), 20.4 (\( \text{CH}_2\text{CH}_2\text{CH}_3 \)), 26.5 (\( \text{Cyclohex} \)), 26.6 (\( \text{Cyclohex} \)), 27.2 (\( \text{Cyclohex} \)), 28.1 (C-5), 31.9 (\( \text{Cyclohex} \)), 32.1
(C_{cyclohex.}), 34.5 (C_{cyclohex.}), 35.5 (C-4), 36.8 (CH_{2}CH_{2}CH_{3}), 54.0 (CH_{2}Cyclohex.), 56.0 (C-3), 65.9 (C-1), 125.7 (C-Ar), 127.0 (C-Ar), 129.0 (C-Ar), 130.1 (C-Ar), 140.1 (C-Ar), 143.1 (C-Ar).

143.1 (C-Ar).

IR (neat): \( \nu \text{ [cm}^{-1} \text{]} = 2918 \) (C-H), 1491 (C-H arom.), 752 (1,2 disubst. benzene). Specific rotation: \([\alpha]_{D}^{20} = +21 \) (c = 0.64; CH_{2}Cl_{2}). HPLC (method 1): \( t_{R} = 20.06 \) min, purity 99.8 %. HPLC (method 6): \( t_{R} = 6.95 \) min, ratio of enantiomers 96.4 : 3.6.

**5.5. X-ray crystal structure analysis**

**5.5.1. General**

Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction Denzo-SMN;\(^{56}\) absorption correction, Denzo;\(^{57}\) structure solution SHELXS-97;\(^{58}\) structure refinement SHELXL-97\(^{59}\) and graphics, XP (Bruker AXS, 2000). Thermals ellipsoids are shown with 15% probability, \( R \)-values are given for observed reflections, and \( wR^{2} \) values are given for all reflections.

**5.5.2. X-ray crystal structure of (3S)-11**

Formula \( \text{C}_{19}\text{H}_{18}\text{N}_{2}\text{O}_{2} \), \( M = 306.35 \), colorless crystal, 0.37 x 0.07 x 0.05 mm, \( a = 7.9192(2) \), \( b = 14.3040(9) \), \( c = 14.6004(9) \) \( \AA \), \( V = 1653.9(2) \) \( \AA^{3} \), \( \rho_{\text{calc}} = 1.230 \) g cm\(^{-3} \), \( \mu = 0.647 \) mm\(^{-1} \), empirical
absorption correction \((0.795 \leq T \leq 0.968)\), \(Z = 4\), orthorhombic, space group \(P2_12_12_1\) (No. 19), \(\lambda = 1.54178\ \text{Å}, \ T = 223(2)\ K, \ \omega\) and \(\phi\) scans, 6802 reflections collected \((\pm h, \pm k, \pm l)\), \([(\sin \theta)/\lambda] = 0.60\ \text{Å}^{-1}\), 2771 independent \((R_{int} = 0.035)\) and 2607 observed reflections \([I>2\sigma(I)]\), 209 refined parameters, \(R = 0.039, \ wR^2 = 0.102\), max. (min.) residual electron density 0.11 (-0.13) e Å\(^{-3}\), the hydrogen atoms were calculated and refined as riding atoms. Flack parameter: -0.0(3). CCDC 1050885.

5.5.3. X-ray crystal structure of \((3R)-11\)

Formula \(C_{19}H_{18}N_2O_2\), \(M = 306.35\), colorless crystal, 0.47 x 0.07 x 0.02 mm, \(a = 7.4874(6)\), \(b = 7.3181(4)\), \(c = 15.1101(13)\ \text{Å}, \ \beta = 103.139(5)\)°, \(V = 806.3(1)\ \text{Å}^3\), \(\rho_{\text{calc}} = 1.262\ \text{gcm}^{-3}\), \(\mu = 0.663\ \text{mm}^{-1}\), empirical absorption correction \((0.745 \leq T \leq 0.986)\), \(Z = 2\), monoclinic, space group \(P2_1\) (No. 4), \(\lambda = 1.54178\ \text{Å}, \ T = 223(2)\ K, \ \omega\) and \(\phi\) scans, 4431 reflections collected \((\pm h, \pm k, \pm l)\), \([(\sin \theta)/\lambda] = 0.59\ \text{Å}^{-1}\), 2009 independent \((R_{int} = 0.041)\) and 1805 observed reflections \([I>2\sigma(I)]\), 209 refined parameters, \(R = 0.045, \ wR^2 = 0.116\), max. (min.) residual electron density 0.29 (-0.17) e Å\(^{-3}\), the hydrogen atoms were calculated and refined as riding atoms. Flack parameter: -0.2(4). CCDC 1050886.

5.6. Receptor binding studies

5.6.1. Affinity towards the \(\sigma_1\) receptor

The affinity towards the \(\sigma_1\) receptor was recorded as described in reference\(^{48,49}\).

5.6.2. Affinity towards the \(\sigma_2\) receptor

The affinity towards the \(\sigma_2\) receptor was recorded as described in reference\(^{48,49}\).

5.6.3. Affinity towards the \(\kappa\)-opioid receptor

The affinity towards the \(\kappa\)-opioid receptor was recorded as described in reference\(^{50}\).
5.6.4. Affinity towards the PCP binding site of the NMDA receptor

The affinity towards the PCP binding site of the NMDA receptor was recorded as described in reference\textsuperscript{51,52}.

5.6.5. Affinity towards the ifenprodil binding site of the NMDA receptor

The affinity towards the ifenprodil binding site of the NMDA receptor was recorded as described in reference\textsuperscript{53,54}.

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References


Graphical Abstract

Asymmetric synthesis of 3-substituted tetrahydro-2-benzazepines

Matthias P. Quick, a Roland Fröhlich, b Dirk Schepmann, a Bernhard Wünsch a*