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Asymmetric synthesis of 3-substitued tetrahydro-2-benzazepines

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Abstract

The enantiomerically and diastereomerically pure tricyclic oxazolidine *cis*-**10** was prepared in a five step synthesis starting with 1-bromo-2-iodobenzene. Me_3SiCN and $allylSiMe_3$ reacted with *cis*-**10** in the presence of $TiCl_4$ to form the nitrile (3*S*)-**11** and the allyl derivative (3*S*)-**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 (3*S*)-**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 (3*S*)-**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 σ_1 affinity of the tetrahydro-2-benzazepines (*ent*-**30b**, K_i = 407 nM) is attributed to the short distance between the two lipophilic aromatic moieties.

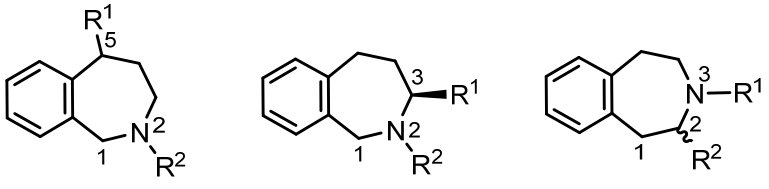
Key words

Asymmetric synthesis; tetrahydro-2-benzazepines; 3-(2-bromophenyl)propionaldehyde derivatives; chiral oxazolidines; diastereoselective ring opening; enamide hydrolysis; radioligand receptor binding studies; σ 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 σ_1 receptor affinity and selectivity over the σ_2 subtype.[13]

Figure 1



1 **2** **3**

1a: R^1 = Bn, R^2 = Bu
1b: R^1 = Bn, R^2 = 4-FBn

3a: R^1 = Bn, R^2 = CH_3

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 σ_1 affinity.

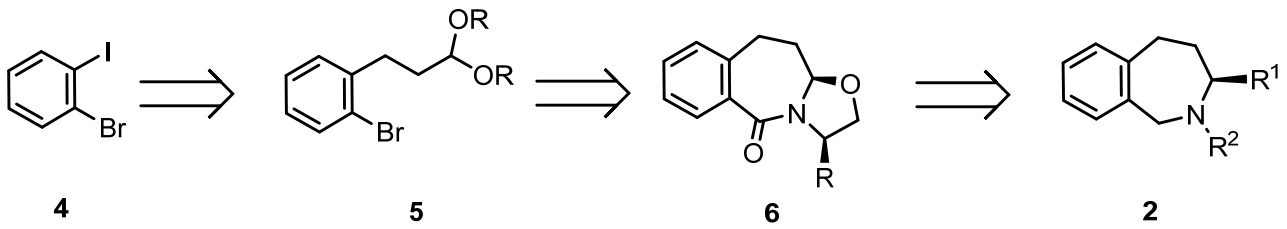
The σ_1 receptor represents an unique receptor, which differs considerably from known mammalian ligand-gated ion channel receptors, G-protein-coupled receptors, tyrosine kinase receptors and nuclear receptors.[15-18] σ_1 receptor agonists were reported to be beneficial for the treatment of Alzheimer's disease and depression. On the contrary, σ_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 σ_1 receptor protein was recently published.[23] The intracellularly located ligand binding site of the σ_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 σ_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 σ_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 σ_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 σ_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 σ_1 affinity than the (*S*)-configured enantiomer (*S*)-**3a** ($K_i(\sigma_1)$ = 12 nM). Both enantiomers display high selectivity over the σ_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 σ_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 σ_1 and σ_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**.

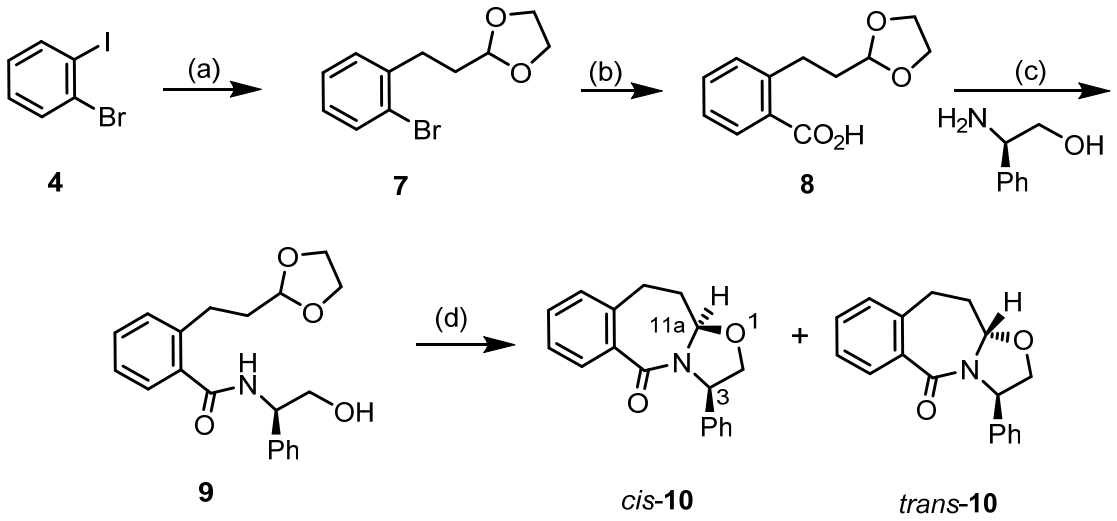
According to our plan, 1-bromo-2-iodobenzene (**4**) will be converted into 2-bromophenylpropionaldehyde acetal **5**. After introduction of a carboxylic acid, an enantiomerically pure β-aminoalcohol will be used to establish the key tricyclic N/O-acetal **6**. The stereochemistry during the ring opening 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 σ_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

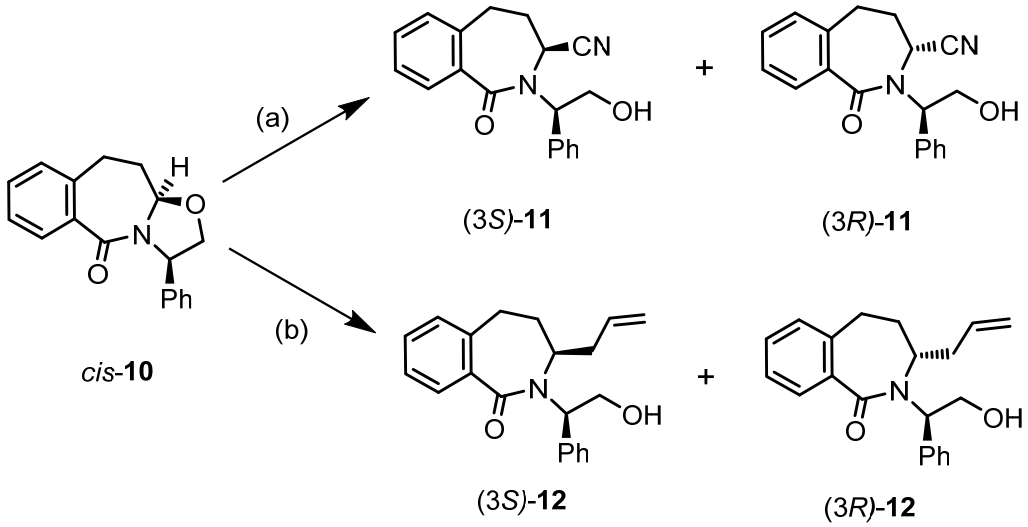


Preparation of *cis*-**10** and *trans*-**10** as key intermediate for asymmetric synthesis of 3-substituted tetrahydro-2-benzazepines. Reagents and reaction conditions: (a) 1. $H_2C{=}CHCH_2OH$, $Pd(OAc)_2$, $NaHCO_3$, Et_3BnNCl, DMF, 45 °C, 5.5 h; 2. ethylene glycol, TosOH, $CHCl_3$, reflux, 75 % over two steps.[35] (b) n-BuLi, THF, -80 °C, 10 min, then CO_2, -78 °C, 75 min, 93 %. (c) (*R*)-phenylglycinol, EDC·HCl, HOBt, CH_2Cl_2, rt, 5.25 h, 74 %. (d) $CHCl_3$, 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 $CHCl_3$ 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) Me_3SiCN, $TiCl_4$, CH_2Cl_2, microwave irradiation, 44 % ((3*S*)-**11**, 19 % ((3*R*)-**11**). (b) $allylSiMe_3$, $TiCl_4$, CH_2Cl_2, microwave irradiation, 64 % ((3*S*)-**12**, 5 % ((3*R*)-**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]

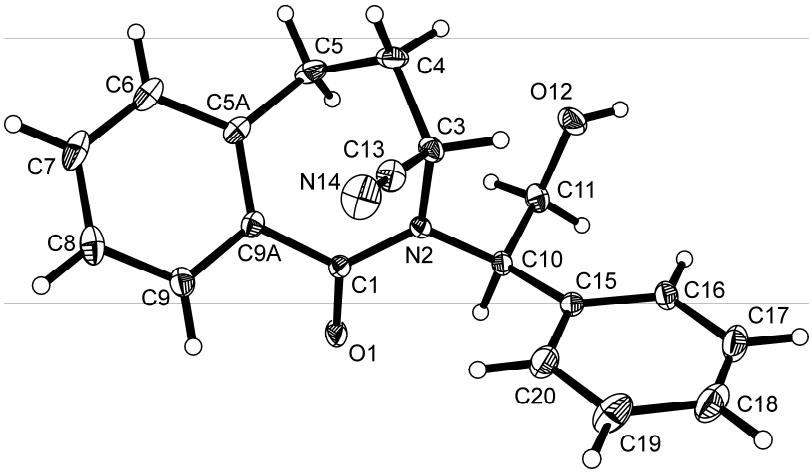
As described for bicyclic lactams the tricyclic lactam *cis*-**10** (main diastereomer) was reacted with different C-nucleophiles. However, reaction of *cis*-**10** with Grignard reagents (PhMgBr, MeMgBr, EtMgBr) or cuprates ($Me_2CuCNLi_2$) at -78 °C to +20 °C did not provide the corresponding alkylated products. Moreover, the trimethylsilyl enol ether of acetophenone in the presence of different Lewis acids ($TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$) did not transform *cis*-**10** into the desired alkylated products. Finally it was found that Me_3SiCN 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_3SiCN was carefully optimized with respect to the Lewis acid ($TiCl_4$, $AlCl_3$, $ZnCl_2$, $BF_3{\cdot}OEt_2$. $SnCl_4$), solvent (CH_2Cl_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_3SiCN (15 equiv.) and $TiCl_4$ (8 equiv.) in CH_2Cl_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_3SiCN (3 equiv,) led to partial epimerization of *cis*-**10** to *trans*-**10**. Experiments with the analogous tin reagent Bu_3SnCN 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

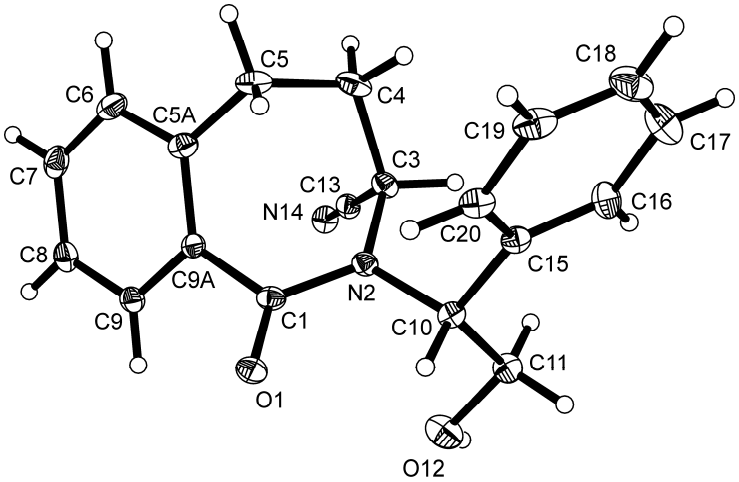
orientation of the cyano moiety within the seven-membered azepine ring due to the allylic strain of the lactam group. However, the orientation of the 2-hydroxy-1-phenylethyl side chain at the N-atom differs in the structures of the diastereomers. Whereas in (3*S*)-**11** the phenyl moiety is oriented towards the cyano moiety, in (3*R*)-**11** it is oriented to the opposite side.

Figure 2



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

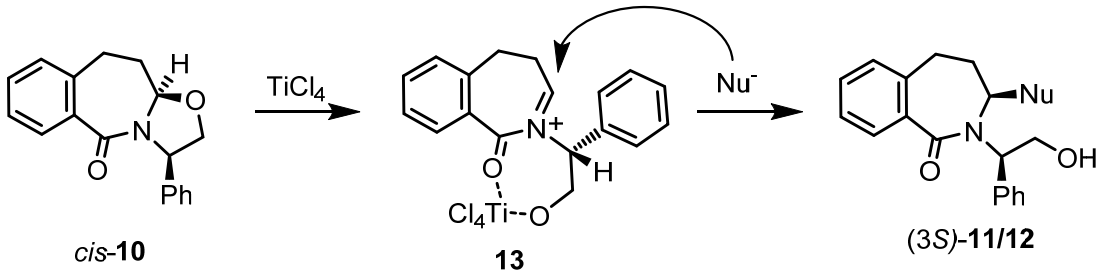
Figure 3



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

Transferring the optimized conditions on the reaction of *cis*-**10** with allylSiMe$_3$ led to the diastereomeric allyl derivatives (3*S*)-**12** and (3*R*)-**12**, which were separated by flash chromatography and isolated in 64 % and 5 %, respectively. The main diastereomer (3*S*)-**12** was crystallized from methanol giving crystals suitable for X-ray crystal structure analysis.[34] The elemental unit of (3*S*)-**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



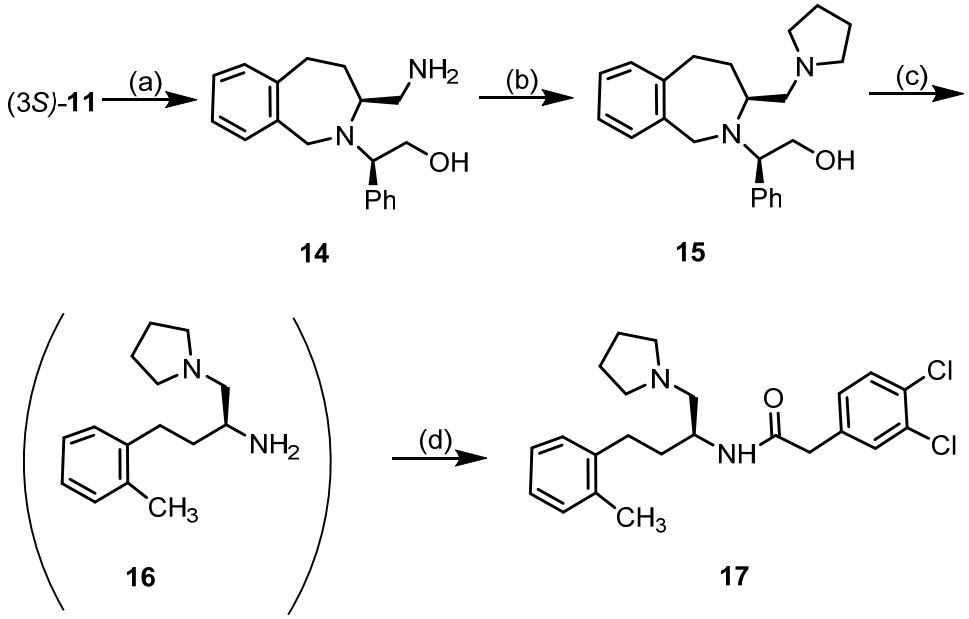
cis-**10** **13** (3*S*)-**11/12**

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

The reaction of *cis*-**10** with both Me$_3$SiCN and allylSiMe$_3$ in the presence of TiCl$_4$ provided diastereoselectively the (3*S*)-configured diastereomers (3*S*)-**11** and (3*S*)-**12** as main products. This diastereoselectivity is explained by attack of TiCl$_4$ at the oxazolidine O-atom, opening the oxazolidine ring and formation of chelate **13**, in which TiCl$_4$ 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 Me$_3$SiCN, allySiMe$_3$ is favored leading predominantly to products with (3*S*)-configuration.[34]

In order to obtain enantiomerically pure products at the end, the diastereomeric purity of the main diastereomers (3*S*)-**11** and (3*S*)-**12** was determined by HPLC analysis. The diastereomeric purity of both isolated compounds (3*S*)-**11** and (3*S*)-**12 was** greater than 99:1.

Scheme 5

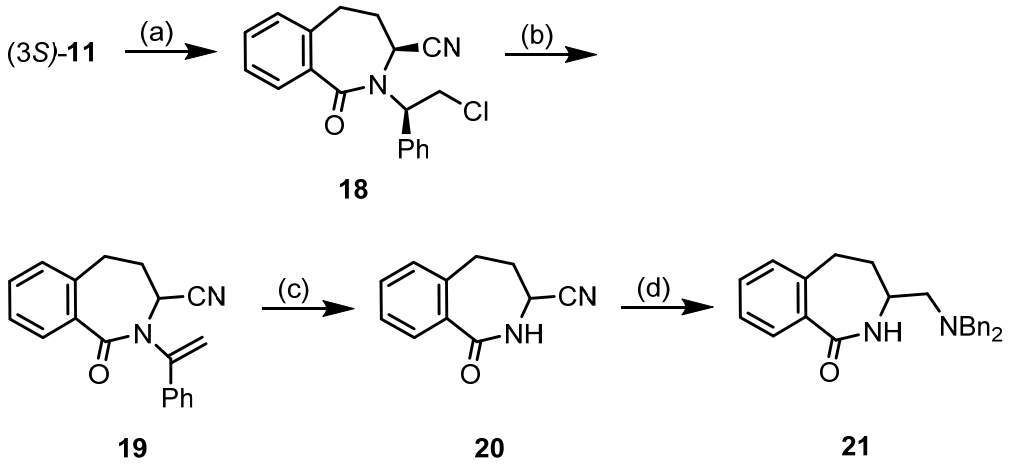


Removal of the chiral auxiliary from (3*S*)-**11** by hydrogenolysis.

Reagents and reaction conditions: (a) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 30 min. (b) 1,4-diiodobutane, $NaHCO_3$, CH_3CN, reflux, 2 h, 49 % (over two steps). (c) H_2 (1 bar), Pd/C, CH_3OH, rt, 6 h. (d) 2-(3,4-dichlorophenyl)acetyl chloride, NEt_3, 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 (3*S*)-**11** was reduced with AlH_3, which was generated by mixing of three equivalents of $LiAlH_4$ and one equivalent of $AlCl_3$.[42] 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 H_2 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 H_2.

Scheme 6



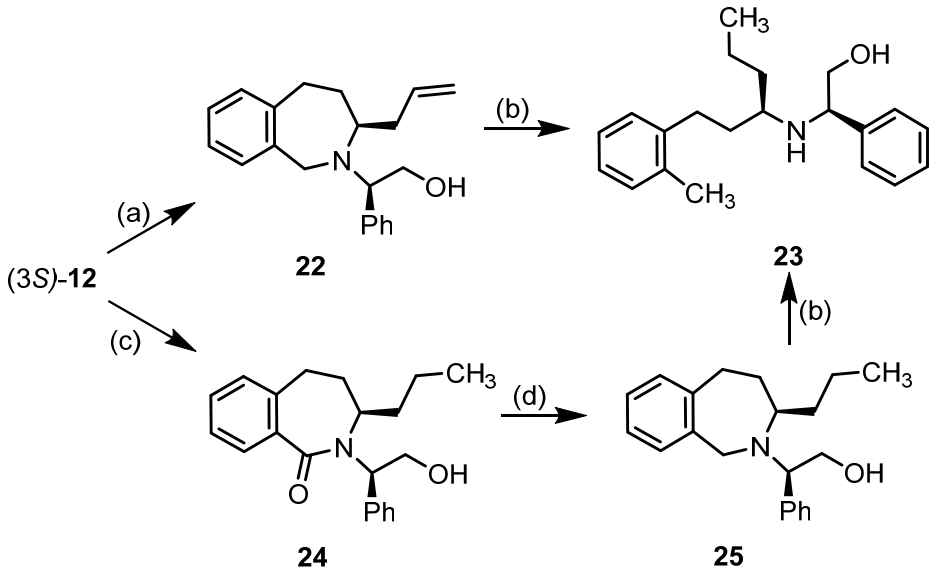
Removal of the chiral auxiliary from (3*S*)-**11** by hydrolysis of the enamide **19**.
Reagents and reaction conditions: (a) $SOCl_2$, THF, 0 °C, 1 h, 64 %. (b) DBU, THF, reflux, 1.5 h, 53 %. (c) HCl, THF, reflux, 16 h, 76 % (racemic mixture). (d) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 40 min; 2. PhCH=O, $NaBH(OAc)_3$, CH_2Cl_2, 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 (3*S*)-**11** with $SOCl_2$ 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 AlH_3 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 AlH_3 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 (3*S*)-**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

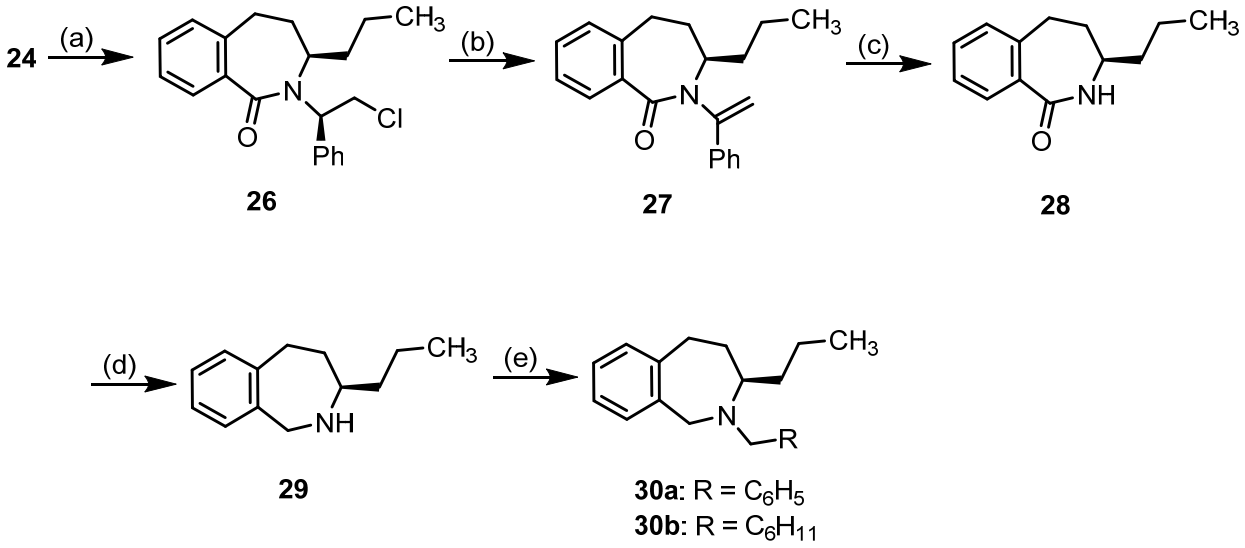


Attempts to remove the chiral auxiliary from the allyl derivative (3*S*)-**12** hydrogenolytically, Reagents and reaction conditions: (a) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 30 min, rt, 30 min, 54 %. (b) H_2 (1 bar), Pd/C, CH_3OH, rt, 30 min, (c) H_2 (5 bar), Pd/C, CH_3OH, rt, 30 min, 99 %. (d) $LiAlH_4$, $AlCl_3$, 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 (3*S*)-**12** should be transformed into enantiomerically pure tetrahydro-2-benzazepines. The tertiary amine **22** was obtained by reduction of the lactam group of (3*S*)-**12** with AlH_3. Reaction of the 2-benzazepine **22** with H_2 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 (3*S*)-**12** and subsequent AlH_3 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 σ_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_2O, Et_2O, 38 °C, 4.5 h, 95 %. (d) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 100 %. (e) PhCH=O or $C_6H_{11}CH$=O, $NaBH(OAc)_3$, CH_2Cl_2, rt, 4-8 h, 31 % (**30a**), 45 % (**30b**). The enantiomers *ent*-**30a** and *ent*-**30b** were prepared in the same manner starting from (*S*)-phenylglycinol.

The conversion of (3*S*)-**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_2O led to the secondary amide **28** in 95 % yield. (Scheme 8)

Finally the lactam **28** was reduced with AlH_3 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 σ_1 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.

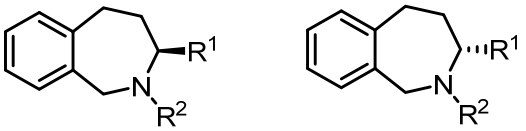
With the pairs of enantiomers **30a**/*ent*-**30a** and **30b**/*ent*-**30b** in hand a chiral HPLC system was established to prove the enantiomeric purity of the ligands. One column alone did not lead to a sufficient separation of the enantiomers. Therefore, two columns, a Chiralcel OD® and a ChiralPak 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 σ_1 and σ_2 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 κ-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}H]-(+)-pentazocine (σ_1),[48,49] [^{3}H]ditolylguanidine (σ_2),[48,49] [^{3}H]-U-69,593 (κ),[50] [^{3}H]-(+)-MK-801 (PCP binding site)[51,52] and [^{3}H]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.



ent-series

compd.	R^1	R^2	$K_i \pm$ SEM (nM)$^+$				
			σ_1	σ_2	PCP	GluN2B	κ-opioid
15	CH_2-pyr	$PhCHCH_2OH$	28 %	18 %	14 %	31 %	15 %
ent-**15**	CH_2-pyr	$PhCHCH_2OH$	0 %	9 %	26 %	24 %	18 %
22	$CH_2CH{=}CH_2$	$PhCHCH_2OH$	0 %	10 %	21 %	14 %	-
ent-**22**	$CH_2CH{=}CH_2$	$PhCHCH_2OH$	0 %	2 %	21 %	0 %	-
25	$CH_2CH_2CH_3$	$PhCHCH_2OH$	27 %	0 %	24 %	7 %	-
ent-**25**	$CH_2CH_2CH_3$	$PhCHCH_2OH$	44 %	11 %	40 %	0 %	-
30a	$CH_2CH_2CH_3$	CH_2Ph	17 %	3 %	8 %	8 %	-
ent-**30a**	$CH_2CH_2CH_3$	CH_2Ph	48 %	0 %	11 %	20 %	-
30b	$CH_2CH_2CH_3$	$CH_2C_6H_{11}$	48 %	2 %	0 %	23 %	-
ent-**30b**	$CH_2CH_2CH_3$	$CH_2C_6H_{11}$	407 nM	33 %	0 %	26 %	-
(+)-pentazocine			5.7 ± 2.2	-	-	-	-
Haloperidol			6.3 ± 1.6	78 ± 2.3	-	-	-
di-*o*-tolylguanidine			89 ± 29	58 ± 18	-	-	-
(+)-MK-801			-	-	2.8 ± 1.8	-	-
Ifenprodil			-	-	-	10 ± 0.7	-
Naloxone			-	-	-	-	7.3 ± 0.5

[+] 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 σ_1, σ_2 and κ-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 σ_1 affinity of 407 nM. However, this σ_1 affinity is also close to 1 μM indicating moderate σ_1 affinity.

Pharmacophore models for σ_1 and σ_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 (σ_1, σ_2) and the longer distance in the range of 6 - 10 Å (σ_1) and 11.6 – 13.6 Å (σ_2).[25,55] 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 σ receptors. The high σ_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 σ_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). ^1H 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 λ = 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 (3*S*)-12:(3*R*)-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 λ = 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, C_{18}, 110A, 250 mm / 21.2 mm; guard column: Phenomenex Gemini, 5 µm, C_{18}, 110A, 50 mm / 21.2 mm; flow rate: 9.99 mL/min; injection: volume: 180 µL (THF); detection λ = 210 nm; eluent: acetonitrile / water / $NH_{3\ conc.}$ = 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 λ = 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 λ = 210 nm; eluent: isohexane / isopropanol = 99 / 1.

5.2. General procedures

5.3.1. General procedure 1: Preparation of 0.67 M (AlH_3) 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_2O, 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 (AlH_3) solution

Under N_2 $AlCl_3$ (0.239 g, 1.80 mmol) was dissolved in THF (14.5 mL) at 0 °C. $LiAlH_4$ (1 M, in THF, 5.4 mL, 5.4 mmol) was carefully added to the solution of $AlCl_3$ 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 N_2 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. CO_2 gas was dried carefully by bubbling through concentrated H_2SO_4 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 Et_2O 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 Et_2O, the combined organic layers were dried (Na_2SO_4) and the solvent and valeric acid were removed under reduced pressure. Colourless solid, mp 71-72 °C, yield 6.26 g (93 %). $C_{12}H_{14}O_4$, M_r = 222.2. MS (EI): *m/z* [%] = 222 (M, 18), 177 (M – CO_2, 24), 149 (M – $CH(OCH_2)_2$, 100), 73 ($CH(OCH_2)_2$, 88). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.93 – 1.98 (m, 2H, $ArCH_2CH_2CH$), 3.08 – 3.12 (m, 2H, $ArCH_2$), 3.73 – 3.99 (m, 4H, $CH(OCH_2)_2$), 4.88 (t, J = 4.9 Hz, 1H, $ArCH_2CH_2CH$), 7.21 – 7.27 (m, 2H, Ar-H), 7.41 (t, J = 7.5 Hz, 1H, 4-H_{arom}), 7.98 (dd, J = 7.8/1.3 Hz, 1H, 6-H_{arom}). A signal for

the CO_2H proton is not seen in the spectrum. IR (neat): ν [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-[(1*R*)-2-hydroxy-1-phenylethyl]benzamide (9)

Under N_2 benzoic acid **8** (0.300 g, 1.35 mmol) was dissolved in CH_2Cl_2 (15 mL). HOBt · H_2O (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_2Cl_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_2Cl_2. The combined organic layers were washed several times with NaOH (2 M). The combined basic aqueous layers were reextracted with CH_2Cl_2, then the combined organic layers were washed with brine (1x), dried (Na_2SO_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 %). $C_{20}H_{23}NO_4$, M_r = 341.4. MS (EI): *m/z* [%] = 341 (M, 8), 310 (M-CH_2OH, 58), 117 (ArC_3H_5, 100), 73 ($CH(OCH_2)_2$, 87). ^1H NMR ($CDCl_3$): δ [ppm] = 1.93 – 2.07 (m, 2H, $ArCH_2CH_2CH$), 2.92 (t, J = 8.0 Hz, 2H, $ArCH_2CH_2CH$), 3.05 (s, broad, 1H, CH_2OH), 3.76 – 3.85 (m, 2H, $CH(OCH_2)_2$), 3.89 – 4.05 (m, 4H, $CH(OCH_2)_2$, CH_2OH), 4.83 (t, J = 4.6 Hz, 1H, $ArCH_2CH_2CH$), 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): ν [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_2Cl_2). HPLC (method 1): t_R = 15.58 min, purity 96.1 %.

2-[2-(1,3-Dioxolan-2-yl)ethyl]-N-[(1*S*)-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_2Cl_2 (275 mL) and treated with HOBt · H_2O (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: $[\alpha]_D^{20}$ = +8.5 (c = 0.62; CH_2Cl_2). HPLC (method 1): t_R = 15.60 min, purity 92.1 %.

(3*R*,11a*R*)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10*H*)-one (*cis*-10) and (*3R*,11a*S*)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10*H*)-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_2SO_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 °C, 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$_2$C*H*$_2$CH), 2.27 – 2.38 (tt, J = 12.3/6.9 Hz, 1H, ArCH$_2$C*H*$_2$CH), 2.67 – 2.76 (ddd, J = 13.9/6.9/1.0 Hz, 1H, ArC*H*$_2$CH$_2$CH), 2.94 – 3.04 (m, 1H, ArC*H*$_2$CH$_2$CH), 3.94 (d, J = 8.8 Hz, 1H, OC*H*$_2$CH), 4.40 (dd, J = 8.8/5.7 Hz, 1H, OC*H*$_2$CH), 5.22 (d, J = 5.7 Hz, 1H, OCH$_2$C*H*), 5.27 (dd, J = 9.5/5.7 Hz, 1H, ArCH$_2$CH$_2$C*H*), 7.12 – 7.16 (d, J = 7.4 Hz, 1H, 9-H$_{arom.}$,

7.17 – 7.34 (m, 7H, Ar-H), 7.49 – 7.53 (dd, J = 7.6/1.3 Hz, 1H, 6-$H_{arom.}$). ^{13}C NMR ($CDCl_3$): 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): ν [cm^{-1}] = 1645 (O=CNR_2). Specific rotation: $[\alpha]_D^{20}$ = +100 (c = 1.00; CH_2Cl_2). HPLC (method 1): t_R = 18.20 min, purity 99.3 %.

trans-**10** (R_f = 0.40): Pale yellow, viscous oil, yield 0.492 g (10 %). $C_{18}H_{17}NO_2$, M_r = 279.3. MS (EI): *m/z* [%] = 279 (M, 100), 120 (PhCHCH_2O, 90), 104 (PhCHCH_2, 86). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.25 (dddd, J = 13.0/9.3/7.9/1.4 Hz, 1H, ArCH_2CH_2CH), 2.49 (tt, J = 12.7/6.2 Hz, 1H, ArCH_2CH_2CH), 2.75 (dd, J = 13.0/6.6 Hz, 1H, ArCH_2CH_2CH), 3.14 (td, 13.2/7.9 Hz, 1H, ArCH_2CH_2CH), 4.21 – 4.27 (m, 2H, OCH_2CH), 5.05 (dd, J = 9.3/5.7 Hz, 1H, ArCH_2CH_2C*H*), 5.47 (dd, J = 5.6/4.0 Hz, 1H, OCH_2C*H*), 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-$H_{arom.}$). ^{13}C NMR ($CDCl_3$): 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): ν [cm^{-1}] = 1645 (O=CNR_2). Specific rotation: $[\alpha]_D^{20}$ -164 (c = 0.14; CH_2Cl_2). HPLC (method 1): t_R = 18.90 min, purity 97.4 %.

(3*S*,11a*S*)-3-Phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10*H*)-one (*ent-cis*-10) and (3*S*,11a*R*)-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[3,2-b][2]benzazepin-5(10*H*)-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 $CHCl_3$ (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: $[\alpha]_D^{20}$ = -103 (c = 1.00; CH_2Cl_2). HPLC (method 2): t_R = 15.85 min, purity 99.6 %.

ent-trans-**10** (R_f = 0.40): Pale yellow, viscous oil, yield 0.216 g (6.3 %). Specific rotation: $[\alpha]_D^{20}$ = +163 (c = 0.14; CH_2Cl_2). HPLC (method 1): t_R = 18.59 min, purity 98.7 %.

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

A solution of *cis*-**10** (0.600 g, 2.15 mmol) in CH_2Cl_2 (17 mL) was transferred into a 80 mL microwave reaction vessel and purged with N_2. Me_3SiCN (4 mL, 3.16 g, 31 mmol) and $TiCl_4$ (1 M in CH_2Cl_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_2Cl_2. The organic layers where combined, washed with water, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by fc (*Ø* = 4 cm, h = 15 cm, cyclohexane : ethyl acetate = 7 : 3, after *cis*-**10** and (3*R*)-**11** had eluted, cyclohexane : ethyl acetate = 1 : 3, V = 25 mL).

(3*S*)-**11** (R_f = 0.06, cyclohexane : ethyl acetate = 7 : 3): Colorless crystals, mp 164 °C, yield 0.291 g (44 %). $C_{19}H_{18}N_2O_2$, M_r = 306.4. MS (EI): *m/z* [%] = 306 (M, 2), 275 (M – CH_2OH, 20). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.11 – 2.19 (m, 1H, $ArCH_2CH_2CH$), 2.53 – 2.60 (m, 1H, $ArCH_2CH_2CH$), 2.66 (dd, J = 13.8/6.2 Hz, 1H, $ArCH_2CH_2CH$), 2.94 – 3.02 (m, 2H, $ArCH_2CH_2CH$ and $CHCH_2OH$), 4.07 – 4.13 (m, 1H, $CHCH_2OH$), 4.28 (dd, J = 11.7/4.4 Hz, 1H, $CHCH_2OH$), 4.39 (dd, J = 11.7/1.8 Hz, 1H, $ArCH_2CH_2CH$), 6.12 – 6.20 (s, broad, 1H, $CHCH_2OH$), 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 ($CDCl_3$): δ (ppm) = 29.8 (C-4), 36.3 (C-5), 60.6 (Ph-CHN), 73.0 (CH_2OH), 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),

131.8 (C-Ar), 132.3 (C-Ar), 132.8 (C-Ar), 136.7 (C-Ar_q), 138.1 (C-Ar_q), 141.0 (C-Ar_q), 166.5 (C=O). IR (neat): ν [cm^{-1}] = 2249 (CN), 1624 (O=CNR_2). Specific rotation: $[\alpha]_D^{20}$ = -46 (c = 1.00; CH_2Cl_2). HPLC (method 1): t_R = 16.59, purity 99.7 %.

(3*R*)-**11** (R_f = 0.12, cyclohexane : ethyl acetate = 7 : 3): Colorless solid, mp 182 – 184 °C, yield 0.251 g (19 %). $C_{19}H_{18}N_2O_2$, M_r = 306.4. MS (ESI): *m/z* [%] = 307 (M + H, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.57 – 1.69 (m, 1H, $ArCH_2CH_2CH$), 1.96 (tdd, J = 12.5/6.3/1.0 Hz, 1H, $ArCH_2CH_2CH$), 2.44 (s, 1H, $CHCH_2OH$), 2.67 (ddd, J = 13.8/6.3/1.6 Hz, 1H, $ArCH_2CH_2CH$), 2.91 (td, J = 13.7/7.4 H, 1H, $ArCH_2CH_2CH$), 4.28 – 4.40 (m, 2H, $CHCH_2OH$), 4.62 (dd, J = 8.1/1.1 Hz, 1H, $ArCH_2CH_2CH$), 5.98 (t, J = 4.9 Hz, 1H, $CHCH_2OH$), 7.20 (m, 1H, ArH), 7.36 – 7.56 (m, 7H, ArH), 7.80 (d, J = 7.2/1.9 Hz, 1H, 9-$H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 29.3 (C-5), 35.6 (C-4), 43.9 (C-3), 58.8 (PhCHN), 62.5 (CH_2OH), 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_q), 136.3 (C-Ar_q), 136.9 (C-Ar_q), 171.8 (C=O). IR (neat): ν [cm^{-1}] = 2251 (-CN), 1639 (O=CNR_2). Specific rotation: $[\alpha]_D^{20}$ = -17 (c = 0.10; CH_2Cl_2). HPLC (method 1): t_R = 16.95 min, purity 99.7 %.

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

As described for the synthesis of (3*S*)-**11**/(3*R*)-**11**, *ent-cis*-**10** (0.600 g, 2.15 mmol) was treated with Me_3SiCN (4 mL, 3.16 g, 31.0 mmol) and $TiCl_4$ (1 M in CH_2Cl_2, 17 mL, 17.0 mmol) in CH_2Cl_2. After work-up, the residue was purified by fc (Ø = 4 cm, h = 15 cm, cyclohexane : ethyl acetate = 7 : 3, V = 25 mL, R_f = 0.06 (cyclohexane : ethyl acetate = 7 : 3)). Colorless solid, yield 0.301 g (46 %). Specific rotation: $[\alpha]_D^{20}$ = +45 (c = 1.00; CH_2Cl_2). HPLC (method 2): t_R = 13.28 min, purity 99.6 %.

(3*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-2-benzazepin-1-one ((3*S*)-12) and (3*R*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(prop-2-en-1-yl)-2,3,4,5-tetrahydro-2-benzazepin-1-one ((3*R*)-12)[34]

Under N_2 *cis*-**10** (0.30 g, 1.07 mmol) was dissolved in CH_2Cl_2 (6 mL). Me_3Siallyl (2.9 mL, 2.08 g, 18.2 mmol) and $TiCl_4$ (1M in CH_2Cl_2, 6.4 mL, 6.4 mmol) were added. After purging with N_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_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_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).

(3*S*)-**12** (R_f = 0.08, cyclohexane : ethyl acetate 7 : 3): Colorless needles, mp 156 °C, yield 0.222 g (64 %). $C_{21}H_{23}NO_2$, M_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 $C_{21}H_{23}NO_2H^+$ [M+H$^+$]); *m/z* = 344.1621 (calcd. 344.1621 for $C_{21}H_{23}NO_2Na$ [M+Na$^+$]; *m/z* = 665.3350 (calcd. 665.3349 for $(C_{21}H_{23}NO_2)_2Na^+$ [2M+Na$^+$]. ^{1}H NMR (D_5-nitrobenzene, 110 °C): δ [ppm] = 1.14 – 1.24(m, 2H, CH_2CH=CH$_2$), 1.46 – 1.57 (m, 1H, ArCH$_2$CH_2CH), 1.82 – 1.93 (m, 1H, ArCH$_2$CH_2CH), 2.29 – 2.38 (m, 1H, ArCH_2CH$_2$CH), 2.39 – 2.40 (m, 1H, CH$_2$O*H*), 2.63 – 2.73 (m, 1H, ArCH_2CH$_2$CH), 3.16 – 3.24 (m, 1H, ArCH$_2$CH$_2$C*H*), 3.88 – 3.93 (m, 1H, CHCH_2OH), 3.96 – 4.07 (m, 2H, CHCH_2OH and CH$_2$CH=CH_2), 4.20 (d, J = 10.2 Hz, 1H, CH$_2$CH=CH_2), 4.58 – 4.65 (m, 1H, CH$_2$C*H*=CH$_2$), 5.54 (s, broad, 1H, C*H*CH$_2$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^{-1}] = 3347 (OH), 1608 (O=CNR$_2$), 916 (C=CH$_2$). Specific rotation: $[\alpha]_D^{20}$ = +7.9 (c = 1.04; CH_2Cl_2). HPLC (method 2): t_R = 17.97 min, purity 99.6 %. HPLC (method 3): t_R = 10.66 min, purity 98.5 %.

(3*R*)-**12** (R_f = 0.10, cyclohexane : ethyl acetate 7 : 3): Colorless resin, yield 0.017 g (5 %).

$C_{21}H_{23}NO_2$, M_r = 321.4. MS (ESI): *m/z* [%] = 665 (2M + Na, 100), 344 (M + Na, 60). ^{1}H NMR (D_5-nitrobenzene, 100 °C): δ [ppm] = 0.62 – 0.69 (m, 1H, $ArCH_2CH_2CH$), 0.74, - 0.81 (m, 1H, $ArCH_2CH_2CH$), 0.83 – 0.91 (m, 1H, $CH_2CH=CH_2$), 1.12 – 1.24 (m, 1H, $CH_2CH=CH_2$), 1.57 – 1.64 (m, 1H, $ArCH_2CH_2CH$), 1.90 – 1.98 (m, 1H, $ArCH_2CH_2CH$), 2.38 (s, 1H, $CHCH_2OH$), 2.74 – 2.81 (m, 1H, $ArCH_2CH_2CH$), 3.47 – 3.55 (m, 2H, $CHCH_2OH$), 3.94 (d, J = 17.0 Hz, 1H, *trans*-$CH_2CH=CH_2$), 4.06 (d, J = 10.2 Hz, 1H, *cis*-$CH_2CH=CH_2$), 4.71 – 4.82 (m, 1H, $CH_2CH=CH_2$), 5.14 (t, J = 6.4 Hz, 1H, $CHCH_2OH$), 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 ($O=CNR_2$), 917 ($C=CH_2$). Specific rotation: $[\alpha]_D^{20}$ = -20 (c = 0.29; CH_2Cl_2). HPLC (method 1): t_R = 19.17 min, purity 91.9 %.

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

As described for the synthesis of (3*S*)-**12**/(3*R*)-**12**, *ent-cis*-**10** (0.30 g, 1.07 mmol) was treated with Me_3Siallyl (2.9 mL, 2.08 g, 18.2 mmol) and $TiCl_4$ (1M in CH_2Cl_2, 6.4 mL, 6.4 mmol) in CH_2Cl_2 (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: $[\alpha]_D^{20}$ = -7.2 (c = 1.04; CH_2Cl_2). 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*-(3*R*)-**12** was not isolated.

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

A solution of nitrile (3*S*)-**11** (0.10 g, 0.326 mmol) in THF (2.6 mL) was added dropwise to a freshly prepared and cooled (0 °C) AlH_3 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 H_2 had ceased. The formed solid was separated, washed with Et_2O, dissolved in NaOH (43 %) and the aqueous solution was extracted with Et_2O. Filtrate and organic extracts were combined, dried (K_2CO_3) and concentrated under reduced pressure. Without further purification the product was used for the synthesis of pyrrolidine **15**. Orange colored liquid. $C_{19}H_{24}N_2O$, M_r = 296.4. MS (EI): *m/z* [%] = 266 (M - CH_2NH_2, 63), 146 (2-benzazepine core, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.79 – 1.84 (m, 1H, $ArCH_2CH_2CH$), 1.98 – 2.08 (m, 1H, $ArCH_2CH_2CH$), 2.76 (dd, J = 16.0/10.0 Hz, 1H, $ArCH_2CH_2CH$), 2.88 (dd, J = 12.8/3.7 Hz, 1H, $CHCH_2NH_2$), 2.97 – 3.05 (m, 1H, $ArCH_2CH_2CH$), 3.14 (t, J = 11.5 Hz, 1H, $CHCH_2NH_2$), 3.4 (d, J = 16.2 Hz, 1H, $ArCH_2N$), 3.61 – 3.65 (m, 2H, $PhCHCH_2OH$ and $ArCH_2CH_2CH$), 3.72 (t, J = 7.0 Hz, 2H, $PhCHCH_2OH$), 4.15 (d, J = 16.0 Hz, 1H, $ArCH_2N$), 6.40 (d, J = 7.4 Hz, 1H 6-H_{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 ($CDCl_3$): δ (ppm) = 29.0 (C-5), 32.0 (C-4), 42.7 (C-3), 48.1 (CH_2NH_2), 57.9 (PhCHN), 63.6 (CH_2OH), 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).

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

As described for the synthesis of **14** a solution of nitrile *ent*-(3*S*)-**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**.

(2*R*)-2-[(3*S*)-3-(Pyrrolidinomethyl)-2,3,4,5-tetrahydro-1*H*-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 $NaHCO_3$ (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 Et_2O. Treatment of the aqueous layer with 2 M NaOH led to a precipitate, which was extracted several times with Et_2O. The organic layer was dried (Na_2SO_4), 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, R_f = 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 (3*S*)-**11**). $C_{23}H_{30}N_2O$, M_r = 350.5. MS (EI): *m/z* [%] = 266 (M – pyrrolidinomethyl), 146 (2-benzazepine core, 100). MS (ESI): *m/z* [%] = 351 (M + H, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.77 (ddd, J = 14.4/9.1/2.2 Hz, 1H, $ArCH_2CH_2CH$), 1.82 – 1.86 (m, 4H, $N(CH_2CH_2)_2$), 1.98 (dddd, J = 12.6/7.4/5.3/2.1 Hz, 1H, $ArCH_2CH_2CH$), 2.33 (dd, J = 12.8/2.6 Hz, 1H, $CHCH_2N$), 2.65 – 2.71 (m, 2H, $N(CH_2CH_2)_2$), 2.75 – 2.78 (m, 2H, $N(CH_2CH_2)_2$), 2.83 – 2.92 (m, 3H, $ArCH_2CH_2CH$ and $CHCH_2N$), 3.43 – 3.49 (m, 1H, $ArCH_2CH_2CH$), 3.57 (d, J = 16.8 Hz, 1H, $ArCH_2N$), 3.68 (dd, J = 11.8/5.0 Hz, 1H, $CHCH_2OH$), 3.75 – 3.77 (m, 1H, $CHCH_2OH$), 4.07 (dd, J = 11.8/3.5 Hz, 1H, $CHCH_2OH$), 4.18 (d, J = 16.8 Hz, 1H, $ArCH_2N$), 6.40 (d, J = 7.5 Hz, 1H, 9-H_{arom}), 6.86 (td, J = 7.3/1.5 Hz, 1H, 8-H_{arom}), 6.94 – 7.01 (m, 2H, 6-H_{arom} and 7-H_{arom}), 7.06 – 7.11 (m, 5H, Ar-H). A signal for the OH proton is not seen in the spectrum. ^{13}C NMR ($CDCl_3$): δ (ppm) = 23.9 (C-3_{py}, C-4_{py}), 31.8 (C-5), 32.9 (C-4), 47.4 (C-3), 55.5 (C-2_{py}, C-5_{py}), 59.8 (PhCHN), 60.2 (CH_2N_{py}), 63.6 (CH_2OH), 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-Ar_q), 140.4 (C-Ar_q), 141.8 (C-Ar_q). IR (neat): ν [cm^{-1}] = 744 (1,2-disubst. benzene). Specific rotation: $[\alpha]_D^{20}$ = -5.7 (c = 1.11; CH_2Cl_2). HPLC (method 2): t_R =

15.70 min, purity 99.5 %.

(2*S*)-2-[(3*R*)-3-(Pyrrolidinomethyl)-2,3,4,5-tetrahydro-1*H*-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 $NaHCO_3$ (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, R_f = 0.50). Pale yellow liquid, which solidified on cooling in the refrigerator, pale yellow solid, yield 0.127 g (45 %, two steps from *ent*-(3*S*)-**11**). Specific rotation: $[\alpha]_D^{20}$ = +5.8 (c = 1.11; CH_2Cl_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 H_2 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 H_2. The catalyst was filtered off. The mixture was alkalized with NaOH and extracted several times with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, the solvent was removed under reduced pressure and the residue (**16**, 33 mg) was dissolved in CH_2Cl_2. After cooling to 0 °C in an ice-bath, 3,4-dichlorophenylacetyl chloride (0.1 mL) and NEt_3 (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 CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), 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, R_f = 0.30). Colorless oil, yield 18 mg (31 %). $C_{23}H_{28}Cl_2N_2O$, M_r = 419.4. MS (EI): *m/z* [%] = 418

(M, 6), 84 (pyrrolidinomethyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66 – 1.75 (m, 5H, $ArCH_2CH_2CH$, $CH_2N(CH_2CH_2)_2$), 1.77 – 1.86 (m, 1H, $ArCH_2CH_2CH$), 2.24 (s, 3H, $ArCH_3$), 2.40 – 2.50 (m, 5H, $CH_2N(CH_2CH_2)_2$, $ArCH_2CH_2CH$), 2.55 – 2.62 (m, 3H, $CH_2N(CH_2CH_2)_2$, 3.50 (s, 2H, $HNC(=O)CH_2Ar$), 3.96 – 4.05 (m, 1H, $ArCH_2CH_2CH$), 5.85 (d, J = 6.7 Hz, 1H, $HNC(=O)CH_2Ar$), 7.06 – 7.15 (m, 5H, ArH), 7.39 – 7.41 (m, 2H, ArH). IR (neat): ν [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 %.

(3*S*)-2-[(1*R*)-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 (3*S*)-**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_2SO_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 %). $C_{19}H_{17}ClN_2O$, M_r = 324.8. MS (EM): *m/z* = 325.1090 (calcd. 325.1102 for $C_{19}H_{17}{}^{35}ClN_2OH^+$ [M+H$^+$]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.22 – 2.31 (m, 1H, $ArCH_2CH_2CH$), 2.53 – 2.60 (m, 1H, $ArCH_2CH_2CH$), 2.87 – 2.92 (m, 1H, $ArCH_2CH_2CH$), 3.13 – 3.21 (m, 1H, $ArCH_2CH_2CH$), 4.16 (d, J = 5.5 Hz, 2H, $NCHCH_2Cl$), 4.32 (dd, J = 7.6/2.7 Hz, 1H, $ArCH_2CH_2CH$), 6.24 – 6.32 (m, broad, 1H, $PhCHCH_2Cl$), 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 ($CDCl_3$): δ (ppm) = 29.3(C-5), 35.9 (C-4), 43.8 (C-3), 53.6 (PhCHN), 59.0 (CH_2Cl), 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): ν [cm^{-1}] = 1646 ($O=CNR_2$), a signal for the CN group is not seen.

(±)-1-Oxo-2-(1-phenylvinyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine-3-carbonitrile (19)

Under N_2, 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, R_f = 0.19). Colorless viscous oil, yield 65 mg (53 %). $C_{19}H_{16}N_2O$, M_r = 288.3. MS (EM): *m/z* = 289.1335 (calcd. 289.1335 for $C_{19}H_{16}N_2OH^+$ [M+H$^+$]); *m/z* = 335.1754 (calcd. 335.1754 for $C_{19}H_{16}N_2OC_2H_5OH_2^+$ [M+2H$^+$]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.33 (dddd, J = 13.8/8.6/7.1/5.1 Hz, 1H, $ArCH_2CH_2CH$), 2.51 (dtd, J = 12.7/7.2/5.2 Hz, 1H, $ArCH_2CH_2CH$), 2.85 – 2.99 (m, 1H, $ArCH_2CH_2CH$), 3.02 – 3.19 (m, 1H, $ArCH_2CH_2CH$), 4.57 (dd, J = 6.7/5.1 Hz, 1H, $ArCH_2CH_2CH$), 5.38 (d, J = 0.9 Hz, 1H, $C=CH_2$), 5.80 (d, J = 0.9 Hz, 1H, $C=CH_2$), 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-$H_{arom.}$). IR (neat): ν [cm^{-1}] = 1643 ($O=CNR_2$), a signal for the CN group is not observed.

(±)-1-Oxo-2,3,4,5-tetrahydro-1*H*-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 $NaHCO_3$, the mixture was extracted with ethyl acetate, the combined organic layers were dried (Na_2SO_4), 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 acetophenone had been eluted, then cyclohexane : ethyl acetate = 1 : 2, V = 14 mL, R_f = 0.25 (cyclohexane : ethyl acetate = 1 : 2). Pale yellow liquid, yield 31 mg (76 %). $C_{11}H_{10}N_2O$, M_r = 186.2. MS (EM): *m/z* = 187.0866 (calcd. 187.0869 for $C_{11}H_{10}N_2OH^+$ [M+H$^+$]);

m/z = 395.1478 (calcd. 395.1478 for $(C_{11}H_{10}N_2O)_2Na^+$ [2M+Na$^+$]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.25 – 2.46 (m, 2H, $ArCH_2CH_2CH$), 2.75 – 3.07 (m, 2H, $ArCH_2CH_2CH$), 4.21 (dt, J = 9.0/6.4 Hz, 1H, $ArCH_2CH_2CH$), 6.47 – 6.60 (s, broad, 1H, CONH), 7.15 – 7.17 (m, 1H, 6-$H_{arom.}$), 7.32 – 7.45 (m, 2H, 7-$H_{arom.}$, 8-$H_{arom.}$) 7.68 (dd, J = 7.5/1.5 Hz, 1H, 9-$H_{arom.}$). 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 N_2, 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 AlH_3 (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 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 combined filtrates were dried (Na_2SO_4), 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 CH_2Cl_2 (75 mL). Under N_2 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 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), 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, R_f = 0.12). Pale yellow oil, yield 48 mg (36 %, two steps from nitrile **20**). $C_{25}H_{26}N_2O$, M_r = 370.5. MS (EM): *m/z* = 371.2196 (calcd. 371.2118 for $C_{25}H_{26}N_2OH^+$ [M+H$^+$]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.57 – 1.63 (m, 1H, $ArCH_2CH_2CH$), 1.83 – 1.52 (m, 1H, $ArCH_2CH_2CH$), 2.40 (dd, J = 13.0/4.4 Hz, 1H, $CHCH_2NR_2$), 2.56 (dd, J = 13.0/10.5 Hz, 1H, $CHCH_2NR_2$), 2.64 (dd, 13.6/6.2 Hz, 1H, $ArCH_2CH_2CH$), 2.93 (td, J = 13.0/7.7 Hz, 1H, $ArCH_2CH_2CH$), 3.23 – 3.31 (m, 3H, $N(CH_2Ph)_2$, $ArCH_2CH_2CH$), 3.70 (d,

J = 13.3 Hz, 2H, N(C*H*$_2$Ph)$_2$), 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).

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

Under N_2, a solution of AlH_3 (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 (3*S*)-**12** (70 mg, 0.218 mmol) in THF (1.8 mL) was slowly transferred into the solution of AlH_3. 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 Et_2O. The layers were separated and the aqueous layer was washed several times with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 1 cm, h = 15 cm, cyclohexane : ethyl acetate = 8 : 2, V = 7 mL, R_f = 0.42). Colorless oil, yield 36 mg (54 %). $C_{21}H_{25}NO$, M_r = 307.4. MS (EM): *m/z* = see enantiomer *ent*-**22**. ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.70 – 1.77 (m, 1H, ArCH$_2$C*H*$_2$CH), 1.98 – 2.06 (m, 1H, ArCH$_2$C*H*$_2$CH), 2.39 (dt, J = 14.1/7.1 Hz, 1H, C*H*$_2$CH=CH$_2$), 2.62 – 2.74 (m, 2H, ArC*H*$_2$CH$_2$CH, C*H*$_2$CH=CH$_2$), 3.10 – 3.17 (m, 1H, ArC*H*$_2$CH$_2$CH), 3.37 – 3.41 (m, 2H, ArC*H*$_2$N, ArCH$_2$CH$_2$C*H*), 3.66 – 3.71 (m, 2H, NC*H*CH$_2$OH, NCHC*H*$_2$OH), 3.82 – 3.88 (m, 1H, NCHC*H*$_2$OH), 4.19 (d, J = 15.7 Hz, 1H, ArC*H*$_2$N), 5.11 – 5.17 (m, 2H, CH$_2$CH=C*H*$_2$), 5.98 (ddt, J = 17.2/10.1/7.1 Hz, 1H, CH$_2$C*H*=CH$_2$), 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. ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.9 (*C*H$_2$CH=CH$_2$), 29.1 (C-5), 36.9 (C-4), 49.3 (C-3), 57.3 (PhCHN), 64.1 (C-1), 64.7 (CH$_2$OH), 116.6 (CH=C*H*$_2$), 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 (C*H*=CH$_2$), 139.4 (C-Ar$_q$),

140.7 (C-Ar_q), 142.7 (C-Ar_q). IR (neat): ν [cm^{-1}] = see enantiomer *ent*-**22**. Specific rotation: $[\alpha]_D^{20}$ = -17 (c = 0.60; CH_2Cl_2).HPLC (method 2): t_R = 13.53 min, purity 97.8 %.

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

As described for the synthesis of **22**, allylbenzazepinone *ent*-(3*S*)-**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_2Cl_2, washed with 2 M NaOH, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 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): ν [cm^{-1}] = 3854 (O-H), 1638 (C-$H_{arom.}$), 1491 (C-$H_{arom.}$). Specific rotation: $[\alpha]_D^{20}$ = +16 (c = 0.72; CH_2Cl_2). HPLC (method 1): t_R = 15.97 min, purity 99.7 %.

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

A mixture of allylbenzazepinone (3*S*)-**12** (0.10 g, 0.31 mmol), CH_3OH (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): δ [ppm] = 0.01 – 0.04 (m, 3H, CH_3), 0.30 – 0.42 (m, 2H, $CH_2CH_2CH_3$), 0.58 – 0.63 (m, 2H, $CH_2CH_2CH_3$), 1.60 – 1.62 (m, 1H, $ArCH_2CH_2CH$), 1.69 (s, 1H,

$CHCH_2OH$), 1.92 – 1.97 (m, 1H, $ArCH_2CH_2CH$), 2.48 – 2.52 (m, 1H, $ArCH_2CH_2CH$), 2.72 – 2.79 (m, 1H, $ArCH_2CH_2CH$), 3.19 – 3.22 (m, 1H, $ArCH_2CH_2CH$), 4.02 – 4.05 (m, 1H, $CHCH_2OH$), 4.12 – 4.18 (m, 1H, $CHCH_2OH$), 5.50 – 5.58 (s, broad, 1H, $CHCH_2OH$), 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_2Cl_2). HPLC (method 1): t_R = 20.11 min, purity 98.4 %.

(3*S*)-2-[(1*S*)-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*-(3*S*)-**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_2Cl_2). HPLC (method 1): t_R = 19.35 min, purity 99.2 %.

(2*R*)-2-Phenyl-2-[(3*R*)-3-propyl-2,3,4,5-tetrahydro-1*H*-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_2O, the solution was washed with 2 M NaOH, dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by fc (Ø = 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^+]). ^1H NMR ($CDCl_3$): δ [ppm] = 1.01 (t, J = 7.1 Hz, 3H, $CH_2CH_2CH_3$), 1.45 – 1.69 (m, 4H, $CH_2CH_2CH_3$, $ArCH_2CH_2CH$), 1.95 – 2.04 (m,

2H, C*H*$_2$CH$_2$CH$_3$, ArCH$_2$C*H*$_2$CH), 2.61 (m, 1H, ArC*H*$_2$CH$_2$CH), 3.16 (m, 1H, ArC*H*$_2$CH$_2$CH), 3.28 – 3.32 (m, 2H, ArCH$_2$CH$_2$C*H*, ArC*H*$_2$N), 3.66 – 3.70 (m, 2H, NCHC*H*$_2$OH), NC*H*CH$_2$OH), 3.79 – 3.85 (m, 1H, NCHC*H*$_2$OH), 4.17 (d, J = 15.6 Hz, 1H, ArC*H*$_2$N), 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 ($CDCl_3$): δ (ppm) = 14.6 (CH$_2$CH$_2$*C*H$_3$), 20.1 (CH$_2$*C*H$_2$CH$_3$), 28.8 (C-5), 31.0 (*C*H$_2$CH$_2$CH$_3$), 34.4 (C-4), 49.3 (C-3), 56.3 (PhCHN), 64.3 (CH$_2$OH), 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): ν [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 %.

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

As described for the synthesis of **25**, propylbenzazepinone *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 (Ø = 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 %.

(3*R*)-2-[(1*R*)-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 $C_{21}H_{24}{}^{35}ClNONa^+$ [M+Na$^+$]).

(3*S*)-2-[(1*S*)-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 $SOCl_2$ (0.093 mL, 1.24 mmol) in THF (12 mL). After removal of the solvent and $SOCl_2$, the colorless liquid was immediately used in the next step.

(3*R*)-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 Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), 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, R_f = 0.16 (cyclohexane : ethyl acetate = 4 : 1). Pale yellow oil, yield 16 mg (34 %, two steps from **24**). $C_{21}H_{23}NO$, M_r = 305.4 MS (EM): *m/z* = 306.1852 (calcd. 306.1852 for $C_{21}H_{23}NOH^+$ [M+H$^+$]); *m/z* = 328.1672 (calcd. 328.1617 for $C_{21}H_{23}NONa^+$ [M+Na$^+$]). $_1$H NMR ($CDCl_3$): δ [ppm] = 0.68 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 0.97 – 1.52 (m, 4H, $CH_2CH_2CH_3$), 1.83 – 1.95 (m, 1H, $ArCH_2CH_2CH$), 2.07 (dddd, J = 13.5/11.7/ 6.8/5.0 Hz, 1H, $ArCH_2CH_2CH$), 2.82 (ddd, J = 13.7/6.9/2.4 Hz, 1H, $ArCH_2CH_2CH$), 3.07 (ddd, J = 13.6/11.1/7.6 Hz, 1H, $ArCH_2CH_2CH$), 3.58 – 3.69 (m, 1H, $ArCH_2CH_2CH$), 5.28 (s, 1H, $C=CH_2$), 5.87 (s, 1H, $C=CH_2$), 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-$H_{arom.}$). IR (neat): ν [cm^{-1}] = 2957 (C-H), 1646 ($CONR_2$). HPLC (method 1): t_R = 21.76 min, purity 99.3 %.

(3*S*)-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, R_f = 0.40 (cyclohexane : ethyl acetate = 7 : 3). Colorless oil, yield 0.148 g (78 %. two steps from *ent*-**24**).

(3*R*)-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 Et_2O (0.75 mL). The mixture was heated to reflux for 4.5 h and then poured into a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4), 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, R_f = 0.13). Colorless solid, yield 10 mg (95 %). $C_{13}H_{17}NO$, M_r = 203.3. MS (EM): *m/z* = 226.1202 (calcd. 226.1202 for $C_{13}H_{17}NONa^+$ [M+Na^+]); *m/z* = 429.2512 (calcd. 429.2513 for $(C_{13}H_{17}NO)_2Na^+$ [2M+Na^+]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.88 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.29 – 1.55 (m, 4H, $CH_2CH_2CH_3$), 1.79 – 1.87 (m, 1H, $ArCH_2CH_2CH$), 1.97 (tdd, J = 12.2/6.6/5.4 Hz, 1H, $ArCH_2CH_2CH$), 2.70 (dd, 13.6/6.6 Hz, 1H, $ArCH_2CH_2CH$), 3.00 (td, J = 13.0/8.0 Hz, 1H, $ArCH_2CH_2CH$), 3.09 – 3.19 (m, 1H, $ArCH_2CH_2CH$), 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). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.0 ($CH_2CH_2CH_3$), 19.6 ($CH_2CH_2CH_3$), 30.8 (C-5), 36.9 (C-4), 37.3 ($CH_2CH_2CH_3$)), 51.1 (C-3), 127.1 (C-Ar), 128.7 (C-Ar), 128.8 (C-Ar), 131.3 (C-Ar), 135.3 ($C\text{-}Ar_q$), 138.9 ($C\text{-}Ar_q$), 172.7 (C=O). IR (neat): ν [cm^{-1}] = 3192 (N-H), 1652 (O=CNHR). Specific rotation: $[\alpha]_D^{20}$ = -180 (c = 1.01; CH_2Cl_2). HPLC (method 1): t_R = 17.93 min, purity 84.1 %.

(3*S*)-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 Et_2O (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, R_f = 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: $[\alpha]_D^{20}$ = +200 (c = 1.00; CH_2Cl_2). HPLC (method 1): t_R = 17.45 min, purity 99.3 %.

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

Under N_2, a freshly prepared AlH_3 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 for1 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 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 combined filtrates were evaporated with gentle heating. The residue was dissolved in CH_2Cl_2, washed with 2 M NaOH dried (Na_2SO_4), filtered and the solvent was removed under vacuum with gentle heating. (Cave! The product **29** is volatile). Colorless oil, yield 31 mg (100 %) $C_{13}H_{19}N$, M_r = 189.3. MS (ESI): *m/z* [%] = 190 (M + H, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.92 (t, J = 6.9 Hz, 3H, $CH_2CH_2CH_3$), 1.24 (qd, J = 12.2/1.6 Hz, 1H, $ArCH_2CH_2CH$), 1.34 – 1.44 (m, 4H, $CH_2CH_2CH_3$), 1.96 (ddt, J = 13.7/7.0/2.1 Hz, 1H, $ArCH_2CH_2CH$), 2.82 (ddd, J = 14.6/6.9/1.6 Hz, 1H, $ArCH_2CH_2CH$), 2.86 – 2.92 (m, 1H, $ArCH_2CH_2CH$), 3.01 (ddd, J = 14.1/12.2/1.6 Hz, 1H, $ArCH_2CH_2CH$), 3.83 (d, J = 14.6 Hz, 1H, $ArCH_2N$), 3.91 (d, J = 14.5 Hz, 1H, $ArCH_2N$), 7.03 – 7.08 (m, 4H, ArH). IR (neat): ν [cm^{-1}] = 2923 (C-H), 1492 (C-$H_{arom.}$), 747 (*1,2*-disubst. benzene).

(3*S*)-3-Propyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (*ent*-29)

As described for the synthesis of **29**, *ent*-**28** (30 mg, 0.148 mmol) was treated with a freshly prepared AlH_3 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.

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

Under N_2, 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 CH_2Cl_2 (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 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was prufified by fc (Ø = 2 cm, h = 18 cm, cyclohexane : ethyl acetate = 18 : 1, V = 14 mL, R_f = 0.4). Colorless oil, yield 16 mg (31 %). $C_{20}H_{25}N$, M_r = 279.4. MS (ESI): *m/z* [%] = 280 (M + H, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.88 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.31 – 1.43(m, 2H, $CH_2CH_2CH_3$), 1.44 – 1.56 (m, 2H, $ArCH_2CH_2CH$, $CH_2CH_2CH_3$), 1.66 – 1.77 (m, 2H, $ArCH_2CH_2CH$, $CH_2CH_2CH_3$), 2.73 – 2.79 (m. 1H, $ArCH_2CH_2CH$), 2.87 – 2.95 (m, 1H, $ArCH_2CH_2CH$), 2.97 – 3.03 (m, 1H, $ArCH_2CH_2CH$), 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, NCH_2Ph), 3.90 (d, J = 15.1 Hz, 1H, NCH_2Ph), 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). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.43 ($CH_2CH_2CH_3$)), 20.2 ($CH_2CH_2CH_3$)), 28.4 (C-5), 34.5 (C-4), 36.7 ($CH_2CH_2CH_3$), 51.1 (C-3), 55.1 ($PhCH_2$), 65.2 (C-1), 125.6 (C-Ar), 126.7 (C-Ar), 127.1 (C-Ar), 128.2 (C-Ar), 128.9 (C-Ar), 128.9 (C-Ar), 130.5 (C-Ar), 139.5 ($C\text{-}Ar_q$), 140.2 ($C\text{-}Ar_q$), 143.1 ($C\text{-}Ar_q$). IR (neat): ν [cm^{-1}] = 2922 (C-H), 1602 ($C\text{-}H_{arom.}$), 1493 ($C\text{-}H_{arom.}$). Specific rotation: $[\alpha]_D^{20}$ = +30 (c = 0.63; CH_2Cl_2). HPLC (method 1): t_R = 18.25 min, purity 98.2 %. HPLC (method

6): t_R = 7.78 min, ratio of enantiomers 86.8 : 13.2.

(3*S*)-2-Benzyl-3-propyl-2,3,4,5-tetrahydro-1*H*-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 (46mg, 0.436 mmol), $NaBH(OAc)_3$ (0.109 g, 0.515 mmol) in CH_2Cl_2 (2.5 mL). After 3 h, a further amount of $NaBH(OAc)_3$ (40 mg) was added. The mixture was stirred for 6.5 h. After work-up, the residue was purified by fc (Ø = 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; CH_2Cl_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.

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

Under N_2, a solution of the unpurified secondary amine **29** (31 mg, 0.164 mmol) cyclohexanecarbaldehyde (61 mg, 0.54 mmol) and $NaBH(OAc)_3$ (0.136 g, 0.64 mmol) in CH_2Cl_2 (3 mL) was stirred The mixture was stirred at rt for 8 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 CH_2Cl_2. The combined organic layers were dried (Na_2SO_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 %). $C_{20}H_{31}N$, M_r = 285.5. MS (EM): *m/z* = 286.2521 (calcd. 286.2529 for $C_{20}H_{31}NH^+$ [M+H$^+$]). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.62 – 0.73 (m, 2H, Cy), 0.87 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.01 – 1.68 (m, 14H, Cy, $CH_2CH_2CH_3$, $ArCH_2CH_2CH$), 1.71 – 1.89 (m, 2H, NCH_2Cy, CH_2), 1.93 – 2.06 (m, 1H, NCH_2Cy), 2.62 – 2.77 (m, 1H, $ArCH_2CH_2CH$), 2.80 – 2.93 (m, 2H, $ArCH_2CH_2CH$), 3.71 (d, J = 15.4 Hz, 1H, $ArCH_2N$), 4.03 (d, J = 15.2 Hz, 1H, $ArCH_2N$), 7.01 – 7.06 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.5($CH_2CH_2CH_3$), 20.4 ($CH_2CH_2CH_3$)), 26.5 ($C_{cyclohex.}$), 26.6 ($C_{cyclohex.}$), 27.2 ($C_{cyclohex.}$), 28.1 (C-5), 31.9 ($C_{cyclohex.}$), 32.1

($C_{cyclohex.}$), 34.5 ($C_{cyclohex.}$), 35.5 (C-4), 36.8 ($CH_2CH_2CH_3$), 54.0 (CH_2Cyclohex.), 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 ($C\text{-}Ar_q$),143.1 ($C\text{-}Ar_q$). IR (neat): ν [cm^{-1}] = 2918 (C-H), 1491 ($C\text{-}H_{arom.}$), 752 (1,2 disubst. benzene). Specific rotation: $[\alpha]_D^{20}$ = +21 (c = 0.64; CH_2Cl_2). HPLC (method 1): t_R = 20.06 min, purity 99.8 %. HPLC (method 6): t_R = 6.95 min, ratio of enantiomeres 96.4 : 3.6.

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

As described for the synthesis of **30b,** unpurified secondary amine *ent*-**29** (17 mg, 0.09 mmol) was treated with cyclohexanecarbaldehyde (33 mg, 0.30 mmol) and $NaBH(OAc)_3$ (78 mg, 0.35 mmol) in CH_2Cl_2 (2 mL). After 2.5 h, an additional amount of $NaBH(OAc)_3$ (31 mg) was added. The mixture was stirred at rt for 6 h. After work-up, the residue was purified by preparative HPLC (method 4): t_R = 54.1 min to 67.6 min. Colorless oil, yield 16 mg (62 %). Specific rotation: $[\alpha]_D^{20}$ = -22 (c = 0.53; CH_2Cl_2). HPLC (method 1): t_R = 19.57 min, purity 99.7 %. HPLC (method 6): t_R = 7.13 min, ratio of enantiomers 97.5 : 2.5.

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 (BrukerAXS, 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 (3*S*)-11

Formula $C_{19}H_{18}N_2O_2$, 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) Å, V = 1653.9(2) $Å^3$, ρ_{calc} = 1.230 gcm^{-3}, μ = 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), λ = 1.54178 Å, T = 223(2) K, ω and φ scans, 6802 reflections collected ($\pm h, \pm k, \pm l$), [(sinθ)/λ] = 0.60 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 (3*R*)-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) Å, β = 103.139(5)°, V = 806.3(1) Å^3, ρ_{calc} = 1.262 gcm^{-3}, μ = 0.663 mm^{-1}, empirical absorption correction ($0.745 \leq T \leq 0.986$), Z = 2, monoclinic, space group $P2_1$ (No. 4), λ = 1.54178 Å, T = 223(2) K, ω and φ scans, 4431 reflections collected ($\pm h, \pm k, \pm l$), [(sinθ)/λ] = 0.59 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 σ_1 receptor

The affinity towards the σ_1 receptor was recorded as described in reference[48,49].

5.6.2. Affinity towards the σ_2 receptor

The affinity towards the σ_2 receptor was recorded as described in reference[48,49].

5.6.3. Affinity towards the κ-opioid receptor

The affinity towards the κ-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[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[53,54].

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Graphical Abstact

Asymmetric synthesis of 3-substitued tetrahydro-2-benzazepines

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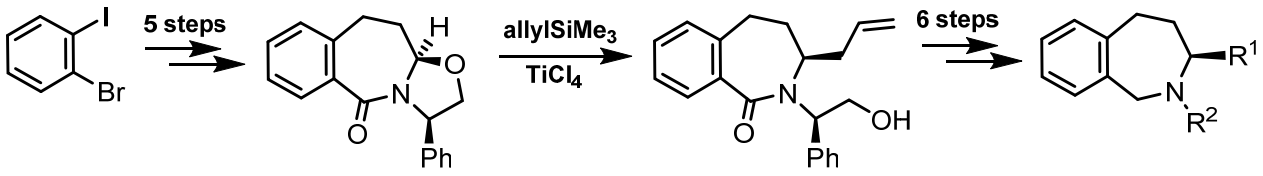

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