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Asymmetric Synthesis of Potent and Selective σ_1 Receptor Ligands with Tetrahydro-3-benzazepine Scaffold

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A new strategy for the synthesis of tetrahydro-3-benzazepinones **6** by reductive amination of keto acid **3** and subsequent carbonyl diimidazole (CDI) mediated cyclization was developed. Use of enantiomerically pure (*R*)-1-phenylethylamine led to the formation of diastereomeric lactams (R_α-*R*)-**6d** and (R_α-*S*)-**6e** in a 80:20 ratio. Diastereoselective alkylation of (R_α-*R*)-**6d**, BH_3-mediated reduction and exchange of the *N*-phenylethyl substituent provided enantiomerically pure tetrahydro-3-benzazepines with various substituents in the 1-, 3-, and 4-positions. High σ_1 affinity was achieved with a benzyl, cyclohexylmethyl, or 1-phenylethyl moiety at the N-atom. Whereas (*R*)-configuration of the N-substituent is crucial for high σ_1 affinity, the configuration of the 3-benzazepine ring system does not influence the σ_1 affinity considerably. Introduction of additional substituents in the 1-position led to almost complete loss of σ_1 affinity. Potent σ_1 ligands show high selectivity against the σ_2 subtype and the NMDA receptor.

Introduction

In 1976 Martin and co-workers postulated the σ receptor as an opioid receptor subtype because the psychotomimetic effects of (±)-*N*-allylnormetazocine (SKF-10,047) could not be explained by activation of μ-opioid or κ-opioid receptors.[1] However, the selectivity of the σ receptor for dextrorotatory benzomorphan enantiomers[2] and the fact that most of the effects of σ ligands neither in vivo nor in vitro were blocked by the classical opioid antagonists naloxone and naltrexone, led to reclassification of the σ receptor.[3,4]

In 1984 the σ receptor was considered to be identical to the phencyclidine (PCP) binding site at the NMDA receptor.[5,6] However, this classification had to be corrected as well because some ligands exist (e.g., haloperidol) that exhibit high affinity towards the σ receptor but no affinity towards the PCP binding site of the NMDA receptor.[7] Further research showed conclusively that σ receptors are a unique nonopioid and non-PCP but haloperidol-sensitive class of receptors containing two subtypes, which are termed σ_1 and σ_2 receptors.[8]

The σ_1 receptor has a specific drug selectivity pattern and a characteristic distribution within the central nervous system as well as in some organs of the periphery. Cloning of the σ_1 receptor subtype from rat brain led to the identification of a protein containing 223 amino acids with a molecular weight of 25.3 kDa.[9] According to a postulated model, the σ_1 receptor contains two transmembrane domains with both the amino and carboxy termini located on the intracellular side of the membrane.[10] In contrast to the σ_1 receptor, the σ_2 receptor has not yet been cloned and only little is known about its structural features. Photoaffinity labeling experiments led to the identification of a protein with a molecular weight of 18–21 kDa.[11]

The σ_1 receptor is considered to play a crucial role in controlling the activity of a variety of ion channels (e.g., K^+, Na^+, Ca^{2+} channels) and neurotransmitter systems (e.g., glutamate, dopamine, acetylcholine systems). Therefore, ligands interacting with σ_1 receptors possess a potential for the treatment of neuropsychiatric disorders including schizophrenia, depression, Alzheimer's disease, and pain, as well as alcohol and cocaine abuse.[12–15] The high density of σ_1 receptors in some human tumor cell lines (e.g., breast, lung, prostate cancer cell lines) could be exploited for tumor diagnosis and therapy.[16,17]

Recently, we have reported on the synthesis of racemic 2,3-disubstituted tetrahydro-3-benzazepines **1** by microwave-assisted condensation of keto acids with various primary amines as a key step. In particular, 3-benzazepines **1** with a small substituent at the 2-position and a lipophilic substituent at the N-atom showed σ_1 affinities in the low nanomolar range. Moreover, high selectivity against the σ_2 subtype was observed. As an example, 3-benzazepine **1a**, bearing a benzyl moiety at the N-atom and a small methyl group in the 2-position (**1a**; R^1 = Bn, R^3 = CH_3), represents a very potent σ_1 ligand (K_i = 12 nM) with more than 20-fold selectivity over the σ_2 subtype[18] (Figure 1).

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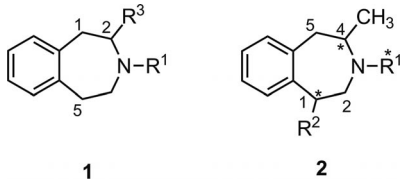


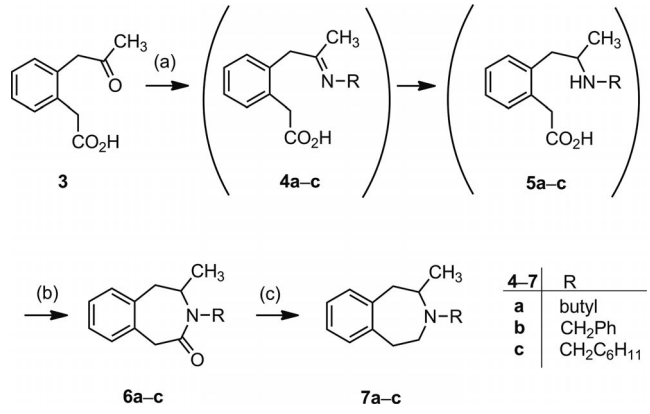
Figure 1. Design of σ_1 ligands based on the tetrahydro-3-benzazepine scaffold.

To investigate the influence of the N-substituent and the stereochemistry on the σ_1 and σ_2 receptor affinity, we planned to synthesize enantiomerically pure 3-benzazepines of type **2** with and without an additional substituent R^2 in the 3-benzazepine scaffold. Herein, we wish to report a new and efficient method for the synthesis of enantiopure 3-benzazepines **2** with high enantiomeric excess. Since we have shown that the corresponding butyl (**1b**; R^1 = Bn, R^3 = Bu) and phenyl derivatives (**1c**; R^1 = Bn, R^3 = Ph) resulted in rather low σ_1 affinities (K_i > 400 and 1500 nM, respectively)[18] compared with the methyl derivative **1a**, we focused herein on 3-benzazepines **2** with a methyl moiety in the 4-postion. Furthermore, the σ_1 and σ_2 receptor affinities of the synthesized ligands were determined in competitive receptor binding assays leading to the identification of novel structure-affinity relationships.

Synthesis

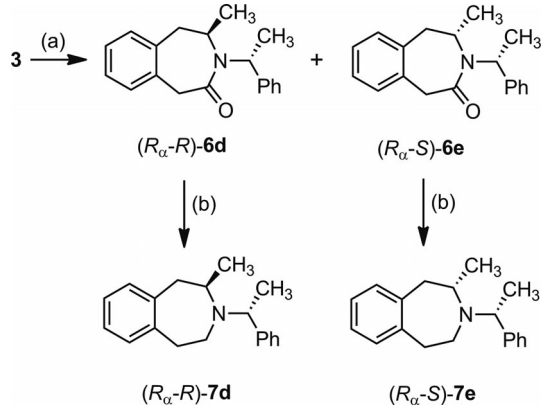
The synthesis of 2,3-disubstituted 3-benzazepines **7** started from methyl keto acid **3**, which was obtained by reaction of *o*-phenylenediacetic acid with an excess of MeLi[19] (Scheme 1). The keto acid **3** was converted into 3-benzazepinones **6a**–**c** by a three-step, consecutive procedure. First, keto acid **3** was condensed with primary amines to give imines **4**, which were reduced by $NaBH(OAc)_3$. The resulting amino acid intermediates **5a**–**c** were cyclized upon heating with two equivalents of carbonyl diimidazole (CDI) to yield 3-benzazepinones **6a**–**c** with various N-substituents. Finally, reduction of **6a**–**c** with BH_3·THF provided tetrahydro-3-benzazepines **7a**–**c**.

In the receptor binding studies the racemic tetrahydro-3-benzazepine **7b** with a benzyl moiety at the N-atom revealed high σ_1 receptor affinity. Therefore, the enantiomers of **7b** should be prepared and pharmacologically evaluated. Additionally, the enantiomers of **7c** were envisaged due to the similarity in space and electronic differences of the cyclohexylmethyl moiety compared to the benzyl group. For this purpose, the keto acid **3** was reductively aminated with enantiomerically pure (*R*)-configured 1-phenylethylamine and $NaBH(OAc)_3$ to afford the amino acid intermediate that was cyclized with CDI to yield the diastereomeric lactams (R_α-*R*)-**6d** and (R_α-*S*)-**6e** (Scheme 2) The ratio of diastereomers was dependent on the reductive amination of keto acid **3**. Therefore, various solvents (e.g., THF, CH_2Cl_2) and temperatures (–20 to +20 °C) were investigated to attain an optimal diastereoselectivity during this key transformation. Performing the reductive amination in THF led to



Scheme 1. Reagents and conditions: (a) R-NH_2, $NaBH(OAc)_3$, CH_2Cl_2, room temp., 20 h. (b) CDI, THF, reflux, 5 h, 30% (**6a**), 40% (**6b**), 50% (**6c**). (c) BH_3·THF, THF, room temp., 16 h, 45% (**7a**), 40% (**7b**), 35% (**7c**).

a ratio (R_α-*R*)-**6d**/(R_α-*S*)-**6e** of 78:22. In CH_2Cl_2 the ratio was slightly increased to 80:20 (20 °C) and 82:18 (0 °C), however, reduction of the temperature also decreased the total yield from 45% (20 °C) to 32% (0 °C). In subsequent experiments the crucial reductive amination step was performed at ambient temperature to obtain good yields of the products in high diastereoselectivity.



Scheme 2. Reagents and conditions: (a) 1. (*R*)-1-phenylethylamine, $NaBH(OAc)_3$, CH_2Cl_2, room temp., 20 h; 2. CDI, THF, reflux, 5 h, ratio (R_α-*R*)-**6d**/(R_α-*S*)-**6e** 80:20, isolated yields 40% [(R_α-*R*)-**6d**], 5% [(R_α-*S*)-**6e**]. (b) BH_3·THF, THF, room temp., 16 h, 60% [(R_α-*R*)-**7d**], 50% [(R_α-*S*)-**7e**]. The corresponding enantiomers were synthesized in the same manner using (*S*)-1-phenylethylamine.

After flash chromatographic separation of the diastereomeric lactams (R_α-*R*)-**6d** and (R_α-*S*)-**6e**, reduction with BH_3·THF provided the enantiomerically pure tetrahydro-3-benzazepines (R_α-*R*)-**7d** and (R_α-*S*)-**7e** in 60 and 50% yield, respectively, based on diastereomerically pure lactams (R_α-*R*)-**6d** and (R_α-*S*)-**6e**. The enantiomers (S_α-*S*)-**7d** and (S_α-*R*)-**7e** were prepared in similar fashion. In conclusion, this reductive amination protocol using enantiomerically pure 1-phenylethylamine to establish the chiral center represents a considerable improvement over the oxazolidine strategy using phenylglycinol, which provided the

diastereomers in 1:1 ratio.[20–22] Moreover, the direct condensation of 1-phenylethylamine with keto acid **3** at 120 °C led to the formation of indanone derivatives.[18]

The absolute configuration of the newly formed center of chirality of (R_α-*R*)-**7d** and (R_α-*S*)-**7e** could not be determined by NMR experiments. Therefore, (R_α-*R*)-**7d** was recrystallized from a mixture of CH_2Cl_2 and *n*-hexane to provide crystals suitable for X-ray crystal structure analysis (Figure 2). The X-ray crystal structure analysis reveals the same configuration for both centers of chirality. Since the configuration of the N-substituent is defined by the starting material to be (*R*), the (*R*)-configuration is assigned to the newly formed center of chirality in the 2-position.

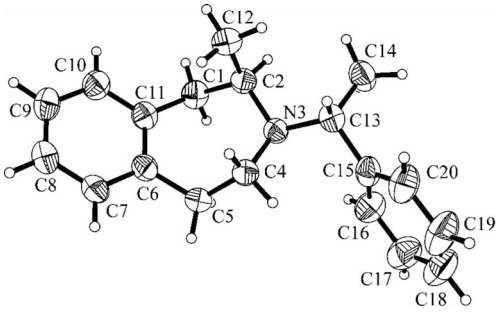


Figure 2. Single X-ray crystal structure analysis of (R_α-*R*)-**7d**.

Since the enantiomerically pure 3-benzazepines (R_α-*R*)-**7d** and (S_α-*S*)-**7d** [prepared in the same manner starting with (*S*)-1-phenylethaylamine] were used for the synthesis of enantiomerically pure 3-benzazepines **7** with various N-substituents, a chiral HPLC method was developed to determine the enantiomeric purity. The separation of the enantiomers was performed with a Daicel Chiralcel OJ-H column and an isocratic elution (isohexane/2-propanol, 90:10). Figure 3 (A) shows the baseline separation of an artificial mixture of (R_α-*R*)-**7d** and (S_α-*S*)-**7d** (25:75). The same analysis performed with the synthetic products (R_α-*R*)-**7d** and (S_α-*S*)-**7d** resulted in a ratio of enantiomers of more than 98:2, respectively (Figure 3, B).

Recently it was shown that oxazolidine annulated 3-benzazepinones can be alkylated in the 1-position with high diastereoselectivity.[21–23] Therefore, the diastereoselective alkylation of (R_α-*R*)-**6d** bearing the chiral 1-phenylethyl substituent at the nitrogen atom was investigated. Thus, (R_α-*R*)-**6d** was deprotonated with LHMDS at –78 °C and subsequently trapped with methyl or ethyl iodide (Scheme 3). According to GC–MS analysis, only one diastereomer was formed, respectively, indicating high diastereoselectivity (*dr* > 99:1) of this transformation. The monoalkylated 3-benzazepines (R_α-*R*,*R*)-**8a** and (R_α-*R*,*R*)-**8b** were isolated as single diastereomers in 51–76% yield. Reduction of the lactams (R_α-*R*,*R*)-**8a** and (R_α-*R*,*R*)-**8b** with BH_3·THF yielded the enantiomerically pure trisubstituted 3-benzazepines (R_α-*R*,*R*)-**9a** and (R_α-*R*,*R*)-**9b**. The enantiomers (S_α-*S*,*S*)-**9a** and (S_α-*S*,*S*)-**9b** were prepared in the same manner.

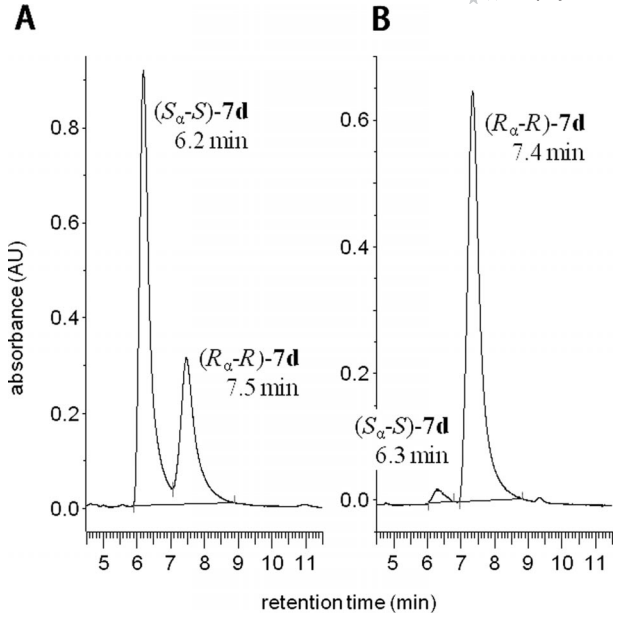
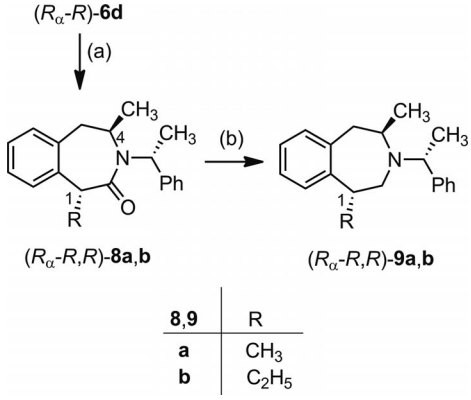


Figure 3. HPLC analysis of (R_α-*R*)-**7d** and (S_α-*S*)-**7d**. (A) Artificial mixture of (R_α-*R*)-**7d** and (S_α-*S*)-**7d** in the ratio 25:75; (B) Analysis of (R_α-*R*)-**7d** after reduction of (R_α-*R*)-**6d** with BH_3·THF leading to an *er* of more than 98:2. HPLC: Daicel Chiralcel OJ-H (5 μM); injection volume 5.0 μL; flow rate: 1.00 mL/min; detection at λ = 206 nm; eluent isohexane/2-propanol, 90:10.

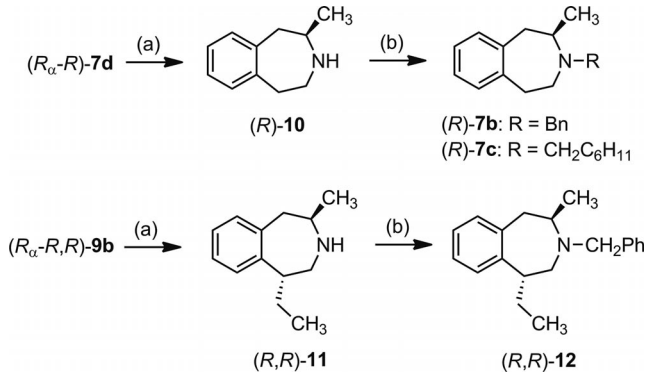


Scheme 3. Reagents and conditions: (a) LHMDS, CH_3I or C_2H_5I, THF, –78 °C, 20 h, 51% [(R_α-*R*,*R*)-**8a**], 60% [(R_α-*R*,*R*)-**8b**]. (b) BH_3·THF, THF, room temp., 16 h, 79% [(R_α-*R*,*R*)-**9a**], 56% [(R_α-*R*,*R*)-**9b**]. The corresponding enantiomers were synthesized in the same manner starting with (S_α-*S*)-**6d**.

The relative configuration of the alkylated products (R_α-*R*,*R*)-**8a** and (R_α-*R*,*R*)-**8b** was determined by NOE experiments. For example, the *cis*-configuration of the proton in the 1-position and the methyl moiety in the 4-position of (R_α-*R*,*R*)-**8b** was shown by a positive NOE interaction, i.e., the signal at δ = 1.41 ppm (CH_3) was increased after irradiation at δ = 3.49 ppm (1-H) and vice versa. This *cis*-configuration directly leads to the absolute (*R*)-configuration of the newly formed chiral center in the 1-position. The (1*R*)-configuration indicates that the methyl moiety in the 4-position of the 3-benzazepinone (R_α-*R*)-**6d** directs the attack of

the electrophile on the enolate to the opposite side (*Re*-face attack).

To introduce further N-substituents, the 1-phenylethyl moiety of (R_α-*R*)-**7d** and (R_α-*R*,*R*)-**9b** was removed hydrogenolytically (H_2, Pd/C) to produce the secondary amines (*R*)-**10** and (*R*,*R*)-**11** (Scheme 4). Subsequent alkylation with benzyl bromide or cyclohexylmethyl bromide led to the enantiomerically pure di- and trisubstituted tetrahydro-3-benzazepines (*R*)-**7b**,**c** and (*R*,*R*)-**12**. The enantiomers (*S*)-**7b**,**c** and (*S*,*S*)-**12** were obtained in the same manner.



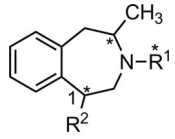
Scheme 4. Reagents and conditions: (a) H_2, Pd/C, CH_3OH, room temp., 4–6 h. (b) Bn-Br or $C_6H_{11}CH_2$-Br, NEt_3, CH_3CN, 42–55%. The corresponding enantiomers were synthesized in the same manner starting with (S_α-*S*)-**7d** and (S_α-*S*,*S*)-**9b**.

The enantiopurity of the enantiomers (*R*)-**7b** and (*S*)-**7b** was determined by chiral HPLC analysis using the same method (Daicel Chiralcel OJ-H column, isocratic elution with isohexane/2-propanol, 90:10) as described for the separation of (R_α-*R*)-**7d** and (S_α-*S*)-**7d**. According to this chiral HPLC analysis, 1.5% of (*S*)-**7b** was present in the enantiomer (*R*)-**7b** (> 97%*ee*). The enantiomer (*S*)-**7b** showed an even higher enantiomeric excess of 99%*ee*. This result led to the conclusion that neither racemization nor epimerization had occurred during the synthesis of the enantiomerically pure products **7b** and its analogues **7c** and **12**.

Receptor Affinity

The affinities of racemic and enantiomerically pure tetrahydro-3-benzazepines **7**, **9** and **12** towards σ_1 and σ_2 receptors were determined in competitive receptor binding studies. [^{3}H]-(+)-Pentazocine and [^{3}H]-(+)-di-*o*-tolylguanidine were the competitors used in the σ_1 and σ_2 assays, respectively. Because di-*o*-tolylguanidine also interacts with σ_1 receptors, an excess of non-tritiated (+)-pentazocine was added to mask σ_1 sites. Guinea pig brain and rat liver preparations served as receptor sources in the σ_1 and σ_2 assays, respectively.[24–28] The K_i values given in Table 1 represent mean values ± SEM (standard error of the mean) of three independent experiments. Competition curves of compounds leading to K_i values greater than 250 nM in the first experiment were not repeated (n = 1). Because some σ ligands also interact with the phencyclidine binding site of the NMDA receptor and vice versa,[29,30] the affinities of the 3-benzazepines towards the PCP binding site of the NMDA receptor were also determined in competition experiments. [^{3}H]-(+)-MK-801 served as radioligand and

Table 1. Affinities of racemic and enantiomerically pure tetrahydro-3-benzazepines towards σ_1 and σ_2 receptors.



	R^1	R^2	K_i ± SEM [nM][a] σ_1	σ_2	σ_1/σ_2 selectivity
7a	Butyl	H	325	79 ± 18	0.25
7b[18]	CH_2Ph	H	12 ± 5.6	257	21
(*R*)-**7b**	CH_2Ph	H	3.2 ± 0.6	57 ± 6.3	18
(*S*)-**7b**	CH_2Ph	H	13 ± 2.0	217 ± 130	17
(*R*)-**7c**	$CH_2C_6H_{11}$	H	31 ± 9.3	48 ± 8.5	1.5
(*S*)-**7c**	$CH_2C_6H_{11}$	H	6.6 ± 0.33	108 ± 13	16
(R_α-*R*)-**7d**	$CH(CH_3)Ph$	H	16 ± 8.4	290	18
(S_α-*S*)-**7d**	$CH(CH_3)Ph$	H	520 ± 123	>1000	>2
(R_α-*S*)-**7e**	$CH(CH_3)Ph$	H	24 ± 9.0	101 ± 22	4
(S_α-*R*)-**7e**	$CH(CH_3)Ph$	H	270 ± 79	19 ± 10	0.07
(R_α-*R*,*R*)-**9a**	$CH(CH_3)Ph$	CH_3	>1000	>1000	–
(S_α-*S*,*S*)-**9a**	$CH(CH_3)Ph$	CH_3	>1000	>1000	–
(R_α-*R*,*R*)-**9b**	$CH(CH_3)Ph$	C_2H_5	>1000	>1000	–
(S_α-*S*,*S*)-**9b**	$CH(CH_3)Ph$	C_2H_5	>1000	>1000	–
(*R*,*R*)-**12**	CH_2Ph	C_2H_5	496	>1000	>2
(*S*,*S*)-**12**	CH_2Ph	C_2H_5	>1000	>1000	–
(+)-Pentazocine			5.7 ± 2.2	n.d.	–
Haloperidol			6.3 ± 1.6	78 ± 2.3	13
Di-*o*-tolylguanidine			89 ± 29	58 ± 18	0.6

[a] Generally, the K_i values were determined in triplicate (n = 3). For compounds showing very low affinity (K_i > 250 nM) in the first experiment, repetitions were not performed (n = 1); n.d. = not determined.

membrane preparations from pig brain cortex as receptor material in this assay.[31]

The data in Table 1 clearly indicate that 3-benzazepine **7a** with an aliphatic butyl substituent at the N-atom shows only low σ_1 affinity. However, replacement of the butyl substituent with the benzyl substituent resulted in the very potent σ_1 ligand **7b** (K_i = 12 nM).[18] The σ_1 receptor protein is able to discriminate between the enantiomers of **7b** and **7c**. Surprisingly, the (*R*)-configured enantiomer of the *N*-benzyl derivative (*R*)-**7b** and the (*S*)-configured enantiomer of the *N*-cyclohexylmethyl derivative (*S*)-**7c** are preferably bound by the σ_1 receptor.

Introduction of an additional methyl moiety in the α-position of the *N*-benzyl substituent provided the four stereoisomeric 1-phenylethyl derivatives **7d** and **7e**. In this series of compounds the configuration of the *N*-(1-phenylethyl) moiety is crucial for high σ_1 affinity. Whereas the 3-benzazepines (R_α-*R*)-**7d** and (R_α-*S*)-**7e** with (*R*)-configuration in the α-position reveal high σ_1 affinities, the corresponding (S_α)-configured stereoisomers (S_α-*S*)-**7d** and (S_α-*R*)-**7e** are 10–30-fold less active. The configuration of the chiral center in the 4-position of the 3-benzazepine scaffold appears to be less important for interaction with the σ_1 receptor.

An additional methyl or ethyl substituent in the 1-position of the 3-benzazepine system (**9** and **12**) eliminated the σ_1 (and σ_2) receptor affinity almost completely, on condition that the configuration in the 1- and 4-position is the same (*like* configuration). Clearly even a small substituent in the 1-position of the 3-benzazepine ring with *like*-configuration is not tolerated by the σ_1 (and σ_2) receptor protein.

Most of the investigated 3-benzazepines show high selectivity for the σ_1 receptor over the σ_2 receptor. The most potent σ_1 ligands of this series [(*R*)-**7b**, (*S*)-**7b**, (*S*)-**7c**, (R_α,*R*)-**7d**] also represent the most selective derivatives. Whereas the racemic *N*-butyl derivative **7a** reveals a slight preference for the σ_2 receptor, the enantiomerically pure phenylethyl derivative (S_α,*R*)-**7e** interacts predominantly with the σ_2 subtype. Moreover, the very low K_i value of 19 nM (σ_2) represents a promising starting point for the development of a novel potent and selective class of σ_2 ligands.

At a test compound concentration of 1 μM, 3-benzazepines **7**, **9** and **12** did not compete significantly with the radioligand [^{3}H]-(+)-MK-801. Therefore, the affinity towards the PCP binding site of the NMDA receptor is rather low (IC_{50} > 1 μM).

Conclusion

Reductive amination of methyl keto acid **3** with (*R*)-1-phenylethylamine and subsequent cyclization of the intermediate amino acid led to the diastereomeric 3-benzazepinones (R_α-*R*)-**6d** and (R_α-*S*)-**6e** in the ratio 80:20. This represents a considerable improvement over the condensation of **3** with phenylglycinol, producing diastereomeric oxazolidines in the ratio 50:50. Alkylation of (R_α-*R*)-**6d** took place with very high diastereoselectivity, indicating that the rigid oxazolidine annulated 3-benzazepine scaffold is not required for high diastereoselectivity. The novel 3-benzazepine building blocks were exploited for the preparation of enantiomerically pure 3-benzazepines. Very potent σ_1 ligands were obtained by introduction of a benzyl, a cyclohexylmethyl, or a methyl-substituted benzyl moiety at the N-atom. Whereas the configuration of the N-substituent is crucial for high σ_1 receptor affinity, the configuration of the 3-benzazepine ring is less important. Introduction of further substituents in the 1-position of the 3-benzazepine ring eliminates the σ_1 affinity almost completely. The enantiomerically pure 3-benzazepine (S_α-*R*)-**7e**, showing high σ_2 affinity and selectivity over the σ_1 subtype, represents a promising starting point for the development of potent and selective σ_2 ligands.

Experimental Section

General: Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin-layer chromatography (TLC) was performed with Silica gel 60 F254 plates (Merck); given R_f values refer to TLC. Flash chromatography was performed with silica gel 60, 40–64 μm (Macherey–Nagel); parentheses include: diameter of the column, length of column, fraction size, eluent, R_f value. Melting points were determined with a melting point apparatus SMP 3 (Stuart Scientific), and are uncorrected. IR spectra were recorded with an IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded with a Mercury plus 400 spectrometer (Varian); δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Where necessary, the assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra was performed by using ^{1}H-^{1}H and ^{1}H-^{13}C COSEY NMR spectra as well as NOE difference spectroscopy. Optical rotation [*α*] was determined with a Polarimeter 341 (Perkin–Elmer); length 1 dm, wavelength 589 nm (sodium D line); the unit of the specific rotation $[\alpha]_l^T$ [deg mL dm^{-1} g^{-1}] is omitted; concentration of the sample *c* [g/100 mL] and the solvents used are given in brackets. MS (EI or ESI) spectra were recorded with a MicroTof (Bruker Daltronics, Bremen), which was calibrated with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment. UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method for the determination of compound purity: column: LiChrospher 60 RP-select B (5 μm), 250–4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm for 30 min; solvents: (A) water plus 0.05% (v/v) trifluoroacetic acid; (B) acetonitrile plus 0.05% (v/v) trifluoroacetic acid: gradient elution: 0–4 min (90% A), 4–29 min (gradient from 90 to 0% A), 29–31 min (0% A), 31–31.5 min (gradient from 0 to 90% A), 31.5–40 min (0% A). Chiral HPLC method for determination of the enantiomeric excess: all except Rheodyne 7125i are Merck–Hitachi equipment; diode array detector: L-7455; pump: L-6200A; degasser: L-7614; injection: Rheodyne 7125i; column: Daicel Chiralcel OJ-H (5 μM) 250–4.6 mm; precolumn: Daicel Chiralcel OJ-H (5 μM) 10–4 mm; injection volume: 5.0 μL; flow rate: 1.00 mL/min; detection at λ = 206 nm; solvents: isohexane/2-propanol, 90:10. Gas liquid chromatography (GLC) was performed with a Shimadzu GC-17A

gas chromatograph equipped with a SE-54 capillary column (30 m × 0.32 mm, 0.25 μm film thickness) by the CS-Chromatography Service using the following program: N_2 carrier gas, injection temperature 250 °C, detector temperature 300 °C; temperature program: start temperature 40 °C, heating rate 10 °C/min, end temperature 280 °C for 5 min.

General Procedures

Synthesis of Lactams 6. General Procedure A: Under N_2, primary amine (1 equiv.) was added to a solution of methyl keto acid **3** (1 equiv.) in CH_2Cl_2 (6 mL). After stirring for 30 min at room temp., $NaBH(OAc)_3$ (2 equiv.) was added and the reaction mixture was stirred for 20 h at room temp. The mixture was extracted with $NaHCO_3$ solution (3 × 10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was dissolved in THF (20 mL). CDI (2 equiv.) was added and the reaction mixture was heated to reflux for 5 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in EtOAc (10 mL) and the solution was washed with water. The aqueous layer was extracted with EtOAc (3 × 15 mL), the organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by flash chromatography.

Monoalkylation of Lactams 6d. General Procedure B: Under N_2, LHMDS (1 M in THF, 1.2 equiv.) was added to a cooled (–78 °C) solution of lactam **6d** (1.0 equiv.) in THF (6 mL). After stirring for 1 h at –78 °C, methyl iodide or ethyl iodide (1.2 equiv.) was added and the solution was further stirred for 3 h at –78 °C. Saturated NaCl solution (10 mL) was added to hydrolyze excess LHMDS and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with NaCl solution (10 mL) and water (10 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography.

Reduction of Lactams 6 and 8. General Procedure C: BH_3·THF complex (1 M in THF, 2 equiv.) was added to lactam **6** or **8** (1 equiv.) dissolved in THF (5 mL) and the mixture was stirred for 16 h at room temp. 1 M NaOH (3 × 5 mL) was added, the aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by flash chromatography.

Synthetic Procedures

Compound 3: Prepared by reaction of *o*-phenylenediacetic acid with an excess of methyllithium.[19]

3-Butyl-4-methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (6a): Following General Procedure A, methyl keto acid **3** (203 mg, 1.10 mmol) was treated with butylamine (108 μL, 1.10 mmol) and $NaBH(OAc)_3$ (466 mg, 2.20 mmol). The crude product was further reacted with CDI (356 mg, 2.20 mol). After complete transformation, the crude product was purified by flash chromatography [*d* = 3 cm, *l* = 20 cm, *V* = 25 mL, cyclohexane/EtOAc, 80:20, R_f = 0.29 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 73 mg (30%). $C_{15}H_{21}NO$ (231.3 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2957 (aliphatic C–H), 1622 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.07–1.22 (m, 5 H, $CH_2CH_2CH_2CH_3$/CH_3), 1.32–1.44 (m, 2 H, $CH_2CH_2CH_2CH_3$), 2.86 (dd, *J* = 15.6, 9.3 Hz, 1 H, 5-H), 2.98 (dt, *J* = 13.5, 7.6 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.14 (dd, *J* = 15.6, 4.0 Hz, 1 H, 5 H), 3.45 (dt, *J* = 13.5, 7.5 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.63 (d, *J* = 15.4 Hz, 1 H, 1-H), 3.80–3.90 (m, 1 H, 4-H), 3.94 (d, *J* = 15.4 Hz, 1 H, 1-H), 6.94–7.18 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (1 C, $CH_2CH_2CH_2CH_3$), 20.2 (1 C, CH_3), 20.4 (1 C, $CH_2CH_2CH_2CH_3$), 30.6 (1 C, $CH_2CH_2CH_2CH_3$), 40.1 (1 C, $CH_2CH_2CH_2CH_3$), 43.7 (1 C, C-5), 45.9 (1 C, C-1), 53.4 (1 C, C-4), 126.9, 127.0, 129.2, 129.3 (4 C, Ph-CH), 134.2, 135.9 (2 C, Ph-C), 169.9 (1 C, C=O) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{21}NONa$ 254.1515; found 254.1514. Purity (HPLC): 98.5% (t_R = 19.1 min).

3-Benzyl-4-methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (6b):[18] Following the General Procedure A, methyl keto acid **4** (113 mg, 0.59 mmol) was treated with benzylamine (64 μL, 0.59 mmol) and $NaBH(OAc)_3$ (250 mg, 1.18 mmol). The crude product was further reacted with CDI (191 mg, 1.18 mmol). After complete transformation, the crude product was purified by flash chromatography [*d* = 3 cm, *l* = 20 cm, *V* = 25 mL, cyclohexane/EtOAc, 80:20, R_f = 0.34 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 90 °C; yield 62 mg (40%). $C_{18}H_{19}NO$ (265.3 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2928 (aliphatic C–H), 1635 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.88 (dd, *J* = 15.6, 9.4 Hz, 1 H, 5-H), 3.13 (dd, *J* = 15.6, 4.4 Hz, 1 H, 5-H), 3.83 (d, *J* = 15.2 Hz, 1 H, 1-H), 3.88–3.96 (m, 1 H, 4-H), 4.09 (d, *J* = 15.2 Hz, 1 H, 1-H), 4.20 (d, *J* = 15.6 Hz, 1 H, NCH_2Ph), 5.07 (d, *J* = 15.5 Hz, 1 H, NCH_2Ph), 6.97–7.28 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (1 C, CH_3), 39.9 (1 C, C-5), 43.5 (1 C, C-1), 48.1 (1 C, C-4), 52.9 (1 C, NCH_2Ph), 126.9, 127.0, 127.1, 127.2, 128.4, 129.2, 129.3 (9 C, Ph-CH), 134.1, 136.0, 138.2 (3 C, Ph-C), 170.8 (1 C, C=O) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{19}NONa$ 288.1359; found 288.1347. Purity (HPLC): 97.6% (t_R = 19.2 min).

3-Cyclohexylmethyl-4-methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (6c): Following the General Procedure A, methyl keto acid **3** (132 mg, 0.69 mmol) was treated with cyclohexylmethylamine (89 μL, 0.69 mmol) and $NaBH(OAc)_3$ (292 mg, 1.38 mmol). The crude product was further reacted with CDI (224 mg, 1.38 mmol). After complete transformation, the crude product was purified by flash chromatography [*d* = 3 cm, *l* = 20 cm, *V* = 25 mL, cyclohexane/EtOAc, 80:20, R_f = 0.33 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 93 mg (50%). $C_{18}H_{25}NO$ (271.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2921 (aliphatic C–H), 1631 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.67–0.85 (m, 2 H, CH_2), 0.95–1.09 (m, 3 H, CH_2), 1.14 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.30–1.59 (m, 6 H, CH_2), 2.63 (dd, *J* = 13.6, 7.9 Hz, 1 H, NCH_2), 2.84 (dd, *J* = 15.5, 9.1 Hz, 1 H, 5-H), 3.17 (dd, *J* = 15.4, 4.5 Hz, 1 H, 5-H), 3.56 (dd, *J* = 13.6, 6.8 Hz, 1 H, NCH_2), 3.66 (d, *J* = 15.2 Hz, 1 H, 1-H), 3.74–3.84 (m, 1 H, 4-H), 3.89 (d, *J* = 15.2 Hz, 1 H, 1-H), 6.97–7.26 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (1 C, CH_3), 25.8, 25.9, 26.5, 30.6, 30.8 (5 C, CH_2), 36.9 (1 C, CH_2), 39.9 (1 C, C-5), 43.9 (1 C, C-1), 52.0 (1 C, CH_2), 53.9 (1 C, C-4), 126.9, 127.0, 129.1 (4 C, Ph-CH), 134.6, 136.0 (2 C, Ph-C), 170.5 (1 C, C=O) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{25}NONa$ 294.1828; found 294.1824. Purity (HPLC): 90.0% (t_R = 20.7 min).

(*R*)-4-Methyl-3-[(*R*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(R_α-*R*)-6d] and (*S*)-4-Methyl-3-[(*R*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(R_α-*S*)-6e]: Following the General Procedure A, methyl keto acid **3** (90 mg, 0.47 mmol) was treated with (*R*)-1-phenylethylamine (60 μL, 0.47 mmol) and $NaBH(OAc)_3$ (199 mg, 0.94 mmol). The crude product was further reacted with CDI (152 mg, 0.94 mmol). After complete transformation, the crude product was purified by flash chromatography (*d* = 3 cm, *l* = 20 cm, *V* = 25 mL, cyclohexane/EtOAc, 80:20).

(R_α-*R*)-6d: Colorless viscous oil; yield 52 mg (40%); R_f = 0.36 (cyclohexane/EtOAc, 60:40); $[\alpha]_{589}^{23}$ = +104.4 (*c* = 0.12, CH_2Cl_2). $C_{19}H_{21}NO$ (279.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2930 (aliphatic

C–H), 1620 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, J = 7.0 Hz, 3 H, CH_3), 1.50 (d, J = 7.1 Hz, 3 H, NCHCH_3Ph), 2.56 (dd, J = 16.0, 6.0 Hz, 1 H, 5-H), 2.65 (dd, J = 16.0, 6.2 Hz, 1 H, 5-H), 3.41–3.52 (m, 1 H, 4-H), 3.71 (d, J = 15.5 Hz, 1 H, 1-H), 3.97 (d, J = 15.5 Hz, 1 H, 1-H), 5.90 (q, J = 7.1 Hz, 1 H, NCHCH$_3$Ph), 6.81–7.19 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (1 C, CH$_3$), 22.4 (1 C, NCHCH$_3$Ph), 40.0 (1 C, C-1), 44.6 (1 C, C-5), 47.1 (1 C, C-4), 52.0 (1 C, NCHCH$_3$Ph), 126.7, 126.8, 127.1, 127.5, 128.2, 129.1, 129.9 (9 C, Ph-CH), 133.4, 135.9, 140.6 (3 C, Ph-C), 171.4 (1 C, C=O) ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{21}NONa$ 302.1515; found 302.1509. Purity (HPLC): 95.0% (t_R = 20.8 min).

(R_α-*S*)-6e: Colorless viscous oil; yield 9 mg (5%); R_f = 0.39 (cyclohexane/EtOAc, 60:40); $[\alpha]_{589}^{23}$ = +60.7 (c = 0.10, CH_2Cl_2). $C_{19}H_{21}NO$ (279.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2971 (aliphatic C–H), 1632 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, J = 7.0 Hz, 3 H, CH_3), 1.39 (d, J = 7.1 Hz, 3 H, NCHCH_3Ph), 2.83 (dd, J = 16.2, 5.9 Hz, 1 H, 5-H), 3.17 (dd, J = 16.2, 5.2 Hz, 1 H, 5-H), 3.57–3.70 (m, 1 H, 4-H), 3.75 (d, J = 16.0 Hz, 1 H, 1-H), 4.00 (d, J = 16.0 Hz, 1 H, 1-H), 5.79 (q, J = 7.0 Hz, 1 H, NCHCH$_3$Ph), 6.91–7.31 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (1 C, CH$_3$), 20.4 (1 C, NCHCH$_3$Ph), 40.6 (1 C, C-1), 44.9 (1 C, C-5), 48.1 (1 C, C-4), 52.8 (1 C, NCHCH$_3$Ph), 126.8, 126.9, 127.3, 127.7, 128.3, 129.7, 130.2 (9 C, Ph-CH), 132.8, 135.5, 140.8 (3 C, Ph-C), 170.8 (1 C, C=O) ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{21}NONa$ 302.1515; found 302.1512. Purity (HPLC): 90.3% (t_R = 20.0 min).

(*S*)-4-Methyl-3-[(*S*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(S_α-*S*)-6d] and (*R*)-4-Methyl-3-[(*S*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(S_α-*R*)-6e]: Following the General Procedure A, methyl keto acid **3** (87 mg, 0.45 mmol) was treated with (*S*)-1-phenylethylamine (58 μL, 0.45 mmol) and NaBH(OAc)$_3$ (190 mg, 0.90 mmol). The crude product was further reacted with CDI (146 mg, 0.90 mmol). After complete transformation, the crude product was purified by flash chromatography (d = 3 cm, l = 20 cm, V = 25 mL, cyclohexane/EtOAc, 80:20).

Compound (S_α-*S*)-6d: Colorless viscous oil; yield 52 mg (40%); R_f = 0.36 (cyclohexane/EtOAc, 60:40); $[\alpha]_{589}^{23}$ = –101.1 (c = 0.11, CH_2Cl_2). HRMS (ESI): m/z calcd. for $C_{19}H_{21}NONa$ 302.1515; found 302.1504. Purity (HPLC): 91.0% (t_R = 20.8 min). The analytical and spectroscopic data of (S_α-*S*)-**6d** are in accordance with those of the enantiomer (R_α-*R*)-**6d**.

Compound (S_α-*R*)-6e: Colorless viscous oil; yield 9 mg (5%); R_f = 0.39 (cyclohexane/EtOAc, 60:40); $[\alpha]_{589}^{23}$ = –59.8 (c = 0.10, CH_2Cl_2). HRMS (ESI): m/z calcd. for $C_{19}H_{21}NONa$ 302.1515; found 302.1511. Purity (HPLC): 92.0% (t_R = 20.1 min). The analytical and spectroscopic data of (S_α-*R*)-**6e** are in accordance with those of the enantiomer (S_α-*R*)-**6e**.

3-Butyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7a): Following the General Procedure C, **6a** (34 mg, 0.15 mmol) was reduced with BH$_3$·THF complex (1 M in THF, 0.30 mL, 0.30 mmol) and the crude product was purified by flash chromatography [d = 2 cm, l = 10 cm, V = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.53 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 14 mg (45%). $C_{15}H_{23}N$ (217.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2960 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.69–0.94 (m, 5 H, CH$_2$CH$_2$CH_2CH_3), 1.13–1.32 (m, 5 H, CH_3/CH$_2$CH_2CH$_2$CH_3), 1.45–1.76 (m, 2 H, CH_2CH$_2$CH$_2$CH_3), 2.46–2.79 (m, 3 H, 1-H/4-H/5-H), 2.85–2.98 (m, 2 H, 4-H/5-H), 3.09–3.24 (m, 1 H, 1-H), 3.37–3.49 (m, 1 H. 2-H), 6.92–7.12 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 20.8, 20.9 (4 C, CH$_2$$CH_2$$CH_2$$CH_3$), 25.1 (1 C, CH$_3$), 29.7 (1 C, C-5), 31.6 (1 C, C-1), 37.4 (1 C, C-4), 56.4 (1 C, C-2), 126.5, 126.7, 128.6, 128.7 (4 C, Ph-CH), 138.2, 140.1 (2 C, Ph-C) ppm. HRMS (ESI): m/z calcd. for $C_{15}H_{23}NH$ 218.1903; found 218.1885. Purity (HPLC): 95.1% (t_R = 15.5 min).

3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7b):[18] Following the General Procedure C, **6b** (35 mg, 0.13 mmol) was reduced with BH$_3$·THF complex (1 M in THF, 0.26 mL, 0.26 mmol) and the crude product was purified by flash chromatography [d = 2 cm, l = 15 cm, V = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.56 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 14 mg (40%). $C_{18}H_{21}N$ (251.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2975 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J = 6.7 Hz, 3 H, CH_3), 2.50–2.62 (m, 2 H, 1-H/5-H), 2.66–2.76 (m, 2 H, 4-H/5-H), 3.10–3.17 (m, 2 H. 2-H/4-H), 3.30 (d, J = 14.2 Hz, 1 H, 1-H), 3.73 (d, J = 13.8 Hz, 1 H, NCH_2Ph), 3.79 (d, J = 13.8 Hz, 1 H, NCH_2Ph), 6.89–7.37 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (1 C, CH$_3$), 35.8 (1 C, C-5), 41.9 (C-1), 47.5 (1 C, C-4), 54.2 (1 C, C-2), 59.1 (1 C, NCH$_2$Ph), 126.1, 126.3, 127.0, 128.5, 128.8, 130.3 (9 C, Ph-CH), 139.6, 140.3, 142.3 (3 C, Ph-C) ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{21}NH$ 252.1747; found 252.1783. Purity (HPLC): 96.6% (t_R = 15.4 min).

(*R*)-3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-7b]: A mixture of 3-benzazepine (R_α-*R*)-**7d** (48 mg, 0.18 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred at room temp. under a H_2 atmosphere (balloon) for 4–6 h. The reaction mixture was filtered using a Celite bed and the solvent was removed under reduced pressure to obtain secondary amine (*R*)-**10**. The residue was dissolved in CH_3CN (6 mL) and Et_3N (124 μL, 0.90 mmol) and benzyl bromide (107 μL, 0.90 mmol) were added. The mixture was stirred at room temp. for 2 h, then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography [d = 2 cm, l = 15 cm, V = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.56 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 21 mg (45%). $C_{18}H_{21}N$ (251.4 g/mol). $[\alpha]_{589}^{23}$ = +15.5 (c = 0.30, CH_2Cl_2). HRMS (ESI): m/z calcd. for $C_{18}H_{21}NH$ 252.1747; found 252.1721. Purity (HPLC): 95.2% (t_R = 16.2 min). Chiral HPLC: Ratio of (*R*)-**7b**/(*S*)-**7b** = 98.5:1.5 (t_R = 11.16 min).

(*S*)-3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-7b]: As described for (*R*)-**7b**, a mixture of 3-benzazepine (S_α-*S*)-**7d** (50, 0.19 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred under H_2, and subsequently benzylated with benzyl bromide (113 μL, 0.95 mmol) and Et_3N (132 μL, 0.95 mmol) in CH_3CN (6 mL). Colorless viscous oil; yield 26 mg (55%); $[\alpha]_{589}^{23}$ = –17.8 (c = 0.30, CH_2Cl_2). HRMS (ESI): m/z calcd. for $C_{18}H_{21}NH$ 252.1747; found 252.1731. Purity (HPLC): 96.0% (t_R = 16.0 min). Chiral HPLC: Ratio of (*R*)-**7b**/(*S*)-**7b** = 0.5:99.5 (t_R = 7.67 min). The analytical and spectroscopic data of (*S*)-**7b** are in accordance with those of the enantiomer (*R*)-**7b**.

3-Cyclohexylmethyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7c): Following the General Procedure C, **6c** (60 mg, 0.22 mmol) was reduced with BH$_3$·THF complex (1 M in THF, 0.44 mL, 0.44 mmol) and the crude product was purified by flash chromatography [d = 2 cm, l = 15 cm, V = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.54 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 20 mg (35%). $C_{18}H_{27}N$ (257.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2918 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.71 (d, J = 6.7 Hz, 3 H, CH_3), 0.75–1.83 (m, 11 H, CH_2), 2.25–2.34 (m, 2 H, NCH_2), 2.50–2.60 (m, 2 H, 1-H/5-H), 2.66–2.76 (m, 2 H, 2-H/5-H), 2.95–3.05 (m, 2 H, 4-H), 3.20 (d, J = 14.3 Hz, 1 H, 1-H), 6.91–7.06 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (1 C, CH$_3$), 26.2, 26.3, 26.9, 31.9, 32.0 (5 C, CH$_2$), 35.3 (1 C, CHCH$_2$), 36.4 (1 C, C-5), 41.4 (C-1), 48.4 (1 C, C-4), 54.8 (1 C, C-

2), 61.2 (1 C, NCH_2), 125.8, 126.0, 128.6, 130.0 (4 C, Ph-*C*H), 134.1, 137.4 (2 C, Ph-*C*) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{27}NH$ 258.2216; found 258.2209. Purity (HPLC): 93.5% (t_R = 17.2 min).

(*R*)-3-Cyclohexylmethyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-7c]: A mixture of 3-benzazepine (R_α-*R*)-**7d** (50 mg, 0.19 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred at room temp. under a H_2 atmosphere (balloon) for 4–6 h. The reaction mixture was filtered using a Celite bed and the solvent was removed under reduced pressure to obtain secondary amine (*R*)-**10**. The residue was dissolved in CH_3CN (6 mL) and Et_3N (132 μL, 0.95 mmol) and cyclohexylmethyl bromide (131 μL, 0.95 mmol) were added. The mixture was heated to reflux for 5 h, then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography [*d* = 2 cm, *l* = 15 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.54 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 24 mg (50%). $C_{18}H_{27}N$ (257.4 g/mol). $[\alpha]_{589}^{23}$ = +1.1 (*c* = 0.20, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{27}NH$ 258.2216; found 258.2201. Purity (HPLC): 95.0% (t_R = 17.3 min).

(*S*)-3-Cyclohexylmethyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*)-7c]: As described for (*R*)-**7c**, a mixture of 3-benzazepine (S_α-*S*)-**7d** (50 mg, 0.19 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred under H_2, and subsequently alkylated with cyclohexylmethyl bromide (131 μL, 0.95 mmol) and Et_3N (132 μL, 0.95 mmol) in CH_3CN (6 mL). Colorless viscous oil; yield 23 mg (48%); $[\alpha]_{589}^{23}$ = –1.9 (*c* = 0.20, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{27}NH$ 258.2216; found 258.2211. Purity (HPLC): 96.6% (t_R = 17.4 min). The analytical and spectroscopic data of (*S*)-**7c** are in accordance with those of the enantiomer (*R*)-**7c**.

(*R*)-2-Methyl-3-[(*R*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(R_α-*R*)-7d]: Following the General Procedure C, (R_α-*R*)-**6d** (32 mg, 0.12 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.24 mL, 0.24 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.58 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 68–70 °C; yield 18 mg (60%); $[\alpha]_{589}^{23}$ = +29.0 (*c* = 0.17, CH_2Cl_2). $C_{19}H_{23}N$ (265.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2968 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.26 (d, *J* = 6.6 Hz, 3 H, NCHCH_3Ph), 2.39 (dd, *J* = 14.6, 6.1 Hz, 1 H, 5-H), 2.47 (dd, *J* = 14.4, 6.1 Hz, 1 H, 1-H), 2.63 (dd, *J* = 13.3, 11.2 Hz, 1 H, 4-H), 2.81 (dd, *J* = 13.5, 6.3 Hz, 1 H, 4-H), 3.00 (dd, *J* = 13.7, 11.5 Hz, 1 H, 5-H), 3.22–3.30 (m, 1 H, 2-H), 3.39 (d, *J* = 14.4 Hz, 1 H, 1-H), 3.83 (q, *J* = 6.6 Hz, 1 H, NC*H*CH_3Ph), 6.90–7.37 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (1 C, CH_3), 21.8 (1 C, NCHCH_3Ph), 35.6 (1 C, C-5), 41.5 (1 C, C-1), 44.5 (1 C, C-4), 50.1 (1 C, C-2), 60.7 (1 C, N*C*HCH_3Ph), 126.0, 126.3, 126.8, 127.4, 128.5, 128.6, 130.3 (9 C, Ph-*C*H), 139.6, 142.6, 147.4 (3 C, Ph-*C*) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{23}NH$ 266.1903; found 266.1897. Purity (HPLC): 99.4% (t_R = 16.5 min). Chiral HPLC: Ratio of (R_α-*R*)-**7d**/(S_α-*S*)-**7d** > 98:2 (t_R = 7.35 min).

For the X-ray crystal structure analysis, (R_α-*R*)-**7d** was recrystallized from CH_2Cl_2/*n*-hexane. Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (Nonius B. V., 1998); data reduction Denzo-SMN;[32] absorption correction, Denzo;[33] structure solution SHELXS-97;[34] structure refinement SHELXL-97[35] and graphics, XP (BrukerAXS, 2000). Thermal ellipsoids are shown with 50% probability, *R*-values are given for observed reflections, and wR^2 values are given for all reflections. The Flack parameter was refined to –0.1(8).

X-ray Crystal Structure Analysis of (R_α-*R*)-7d: Formula $C_{19}H_{23}N$; *M* = 265.38; colorless crystal, 0.20 × 0.10 × 0.05 mm; *a* = 5.3639(2), *b* = 8.4673(4), *c* = 33.8116(18) Å; *V* = 1535.65(12) $Å^3$; ρ_{calc} = 1.148 g cm^{-3}; μ = 4.940 mm^{-1}; empirical absorption correction (0.908 ≤ *T* ≤ 0.976); *Z* = 4; orthorhombic; space group $P2_12_12_1$ (No. 19); λ = 1.54178 Å; *T* = 223(2) K, ω and ϕ scans, 11654 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.60 $Å^{-1}$, 2705 independent (R_{int} = 0.049) and 2410 observed reflections [$I > 2\sigma(I)$], 184 refined parameters, *R* = 0.039, wR^2 = 0.092, max. (min.) residual electron density 0.14 (–0.13) e $Å^{-3}$, hydrogen atoms calculated and refined as riding atoms.

CCDC-869710 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

(*S*)-2-Methyl-3-[(*S*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(S_α-*S*)-7d]: Following the General Procedure C, (S_α-*S*)-**6d** (30 mg, 0.11 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.22 mL, 0.22 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.58 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 68–70 °C; yield 17 mg (60%); $[\alpha]_{589}^{23}$ = –31.0 (*c* = 0.17, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{23}NH$ 266.1903; found 266.1911. Purity (HPLC): 98.7% (t_R = 16.4 min). Ratio of (R_α-*R*)-**7d**/(S_α-*S*)-**7d** < 2:98 (t_R = 6.29 min). The analytical and spectroscopic data of (S_α-*S*)-**7d** are in accordance with those of the enantiomer (R_α-*R*)-**7d**.

(*S*)-2-Methyl-3-[(*R*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(R_α-*S*)-7e]: Following the General Procedure C, (R_α-*S*)-**6e** (30 mg, 0.11 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.22 mL, 0.22 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.60 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 14 mg (50%); $[\alpha]_{589}^{23}$ = +14.0 (*c* = 0.22, CH_2Cl_2). $C_{19}H_{23}N$ (265.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2926 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.38 (d, *J* = 6.6 Hz, 3 H, NCHCH_3Ph), 2.50 (dd, *J* = 14.3, 6.2 Hz, 1 H, 5-H), 2.56 (dd, *J* = 14.7, 6.4 Hz, 1 H, 1-H), 2.65–2.75 (m, 1 H, 4-H), 2.92 (dd, *J* = 12.5, 5.6 Hz, 1 H, 4-H), 3.13–3.23 (m, 1 H, 5-H), 3.27–3.39 (m, 1 H, 2-H), 3.45 (d, *J* = 14.7 Hz, 1 H, 1-H), 3.94 (q, *J* = 6.6 Hz, 1 H, NC*H*CH_3Ph), 6.97–7.43 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (1 C, CH_3), 22.1 (1 C, NCHCH_3Ph), 36.3 (1 C, C-5), 42.2 (1 C, C-1), 42.8 (1 C, C-4), 51.1 (1 C, C-2), 60.6 (1 C, N*C*HCH_3Ph), 126.0, 126.2, 126.8, 127.4, 128.5, 128.7, 130.2 (9 C, Ph-*C*H), 139.7, 142.3, 146.8 (3 C, Ph-*C*) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{23}NH$, 266.1903; found 266.1895. Purity (HPLC): 97.3% (t_R = 16.8 min).

(*R*)-2-Methyl-3-[(*S*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(S_α-*R*)-7e]: Following the General Procedure C, (S_α-*R*)-**6e** (40 mg, 0.14 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.28 mL, 0.28 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.60 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 16 mg (42%); $[\alpha]_{589}^{25}$ = –12.3 (*c* = 0.32, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{23}NH$, 266.1903; found 266.1893. Purity (HPLC): 98.3% (t_R = 16.9 min). The analytical and spectroscopic data of (S_α-*R*)-**7e** are in accordance with those of the enantiomer (R_α-*S*)-**7e**.

(1*R*,4*R*)-1,4-Dimethyl-3-[(*R*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(R_α-*R*,*R*)-8a]: Following the General Procedure

B, (R_α-*R*)-**6d** (68 mg, 0.24 mmol) was alkylated with methyl iodide (18 μL, 0.29 mmol). The crude product was purified by flash chromatography [*d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/EtOAc, 85:15, R_f = 0.46 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 87–89 °C; yield 36 mg (51%); $[\alpha]_{589}^{22}$ = +8.0 (*c* = 0.4, CH_2Cl_2). $C_{20}H_{23}NO$ (293.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2928 (aliphatic C–H), 1635 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 1.45 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.57 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$), 2.63 (dd, *J* = 14.8, 7.4 Hz, 1 H, 5-H), 2.75 (dd, *J* = 14.8, 9.7 Hz, 1 H, 5-H), 3.28–3.41 (m, 1 H, 4-H), 3.78 (q, *J* = 6.8 Hz, 1 H, 1-H), 5.75 [q, *J* = 7.1 Hz, 1 H, NC*H*(CH$_3$)Ph], 6.37–7.30 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (1 C, *C*H$_3$), 17.2 (1 C, *C*H$_3$), 25.3 (1 C, *C*H$_3$), 40.9 (1 C, C-1), 46.9 (1 C, C-5), 48.9 (1 C, C-4), 51.9 [1 C, N*C*H(CH$_3$)Ph], 126.5, 126.7, 127.1, 127.2, 128.0, 128.9 (9 C, Ph-*C*H), 134.8, 137.0, 140.8 (3 C, Ph-*C*), 174.1 (1 C, *C*=O) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}NOH$ 294.1852; found 294.1854. Purity (HPLC): 94.8% (t_R = 21.3 min). GLC: t_R = 10.4 min.

(1*S*,4*S*)-1,4-Dimethyl-3-[(*S*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(S_α-*S*,*S*)-8a]: Following the General Procedure B, (S_α-*S*)-**6d** (88 mg, 0.31 mmol) was alkylated with methyl iodide (23 μL, 0.37 mmol). The crude product was purified by flash chromatography [*d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/EtOAc, 85:15, R_f = 0.46 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 87–89 °C; yield 51 mg (55%); $[\alpha]_{589}^{22}$ = –7.5 (*c* = 1.0, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{23}NOH$ 294.1852; found 294.1855. Purity (HPLC): 97.1% (t_R = 21.2 min). The analytical and spectroscopic data of (S_α-*S*,*S*)-**8a** are in accordance with those of the enantiomer (R_α-*R*,*R*)-**8a**.

(1*R*,4*R*)-1-Ethyl-4-methyl-3-[(*R*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(R_α-*R*,*R*)-8b]: Following the General Procedure B, (R_α-*R*)-**6d** (0.64 mg, 0.23 mmol) was alkylated with ethyl iodide (22 μL, 0.28 mmol). The crude product was purified by flash chromatography [*d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/EtOAc, 85:15, R_f = 0.54 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 42 mg (60%); $[\alpha]_{589}^{22}$ = +16.8 (*c* = 0.30, CH_2Cl_2). $C_{21}H_{25}NO$ (307.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2966 (aliphatic C–H), 1641 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 1.41 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 1.46 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.85–1.96 (m, 1 H, C*H*$_2$CH$_3$), 2.34–2.46 (m, 1 H, C*H*$_2$CH$_3$), 2.63 (dd, *J* = 14.8, 7.2 Hz, 1 H, 5-H), 2.75 (dd, *J* = 14.8, 9.9 Hz, 1 H, 5-H), 3.30–3.40 (m, 1 H, 4-H), 3.49 (dd, *J* = 8.3, 5.9 Hz, 1 H, 1-H), 5.79 [q, *J* = 7.1 Hz, 1 H, NC*H*(CH$_3$)Ph], 6.38–7.23 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (1 C, CH$_2$*C*H$_3$), 17.5 (1 C, *C*H$_3$), 20.3 (1 C, *C*H$_2$CH$_3$), 25.3 (1 C, *C*H$_3$), 41.1 (1 C, C-1), 47.0 (1 C, C-5), 50.0 (1 C, C-4), 51.7 [1 C, N*C*H(CH$_3$)Ph], 123.4, 126.6, 126.9, 127.3, 127.4, 128.2, 129.2 (9 C, Ph-*C*H), 137.4, 140.3, 140.9 (3 C, Ph-*C*), 173.6 (1 C, *C*=O) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{25}NOH$ 308.2009; found 308.2006. Purity (HPLC): 90.4% (t_R = 21.6 min). GLC: t_R = 10.5 min.

(1*S*,4*S*)-1-Ethyl-4-methyl-3-[(*S*)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-one [(S_α-*S*,*S*)-8b]: Following the General Procedure B, (S_α-*S*)-**6d** (92 mg, 0.33 mmol) was alkylated with ethyl iodide (32 μL, 0.40 mmol). The crude product was purified by flash chromatography [*d* = 2 cm, *l* = 20 cm, *V* = 10 mL, cyclohexane/EtOAc, 85:15, R_f = 0.54 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 77 mg (76%); $[\alpha]_{589}^{22}$ = –15.4 (*c* = 0.30, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{25}NOH$ 308.2009; found 308.2008. Purity (HPLC): 96.8% (t_R = 22.0 min). The analytical and spectroscopic data of (S_α-*S*,*S*)-**8b** are in accordance with those of the enantiomer (R_α-*R*,*R*)-**8b**.

(1*R*,4*R*)-1,4-Dimethyl-3-[(*R*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(R_α-*R*,*R*)-9a]: Following the General Procedure C, (R_α-*R*,*R*)-**8a** (40 mg, 0.13 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.26 mL, 0.26 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.59 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 75–76 °C; yield 30 mg (79%); $[\alpha]_{589}^{23}$ = +36.2 (*c* = 0.60, CH_2Cl_2). $C_{20}H_{25}N$ (279.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2970 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$), 1.08 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.20 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 2.36 (dd, *J* = 13.2, 6.9 Hz, 1 H, 5-H), 2.57 (dd, *J* = 14.1, 5.5 Hz, 1 H, 2-H), 2.66 (dd, *J* = 13.2, 4.1 Hz, 1 H, 5-H), 2.70–2.80 (m, 1 H, 1-H), 3.21–3.37 (m, 2 H, 2-H/4-H), 3.69 [q, *J* = 7.0 Hz, 1 H, NC*H*(CH$_3$)Ph], 6.87–7.33 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.0 (1 C, *C*H$_3$), 17.2 (2 C, *C*H$_3$/*C*H$_3$), 40.2 (1 C, C-1), 41.9 (1 C, C-5), 50.0 (2 C, C-2/C-4), 59.3 [1 C, N*C*H(CH$_3$)Ph], 124.6, 125.2, 125.3, 126.4, 126.9, 129.3 (9 C, Ph-*C*H), 136.9, 144.5, 145.9 (3 C, Ph-*C*) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{25}NH$ 280.2060; found 280.2049. Purity (HPLC): 95.2% (t_R = 18.0 min).

(1*S*,4*S*)-1,4-Dimethyl-3-[(*S*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(S_α-*S*,*S*)-9a]: Following the General Procedure C, (S_α-*S*,*S*)-**8a** (50 mg, 0.17 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.34 mL, 0.34 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.59 (cyclohexane/EtOAc, 60:40)]. Colorless solid; m.p. 75–76 °C; yield 38 mg (79%); $[\alpha]_{589}^{23}$ = –38.2 (*c* = 0.60, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{25}NH$ 280.2060; found 280.2050. Purity (HPLC): 98.9% (t_R = 18.2 min). The analytical and spectroscopic data of (S_α-*S*,*S*)-**9a** are in accordance with those of the enantiomer (R_α-*R*,*R*)-**9a**.

(1*R*,4*R*)-1-Ethyl-4-methyl-3-[(*R*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(R_α-*R*,*R*)-9b]: Following the General Procedure C, (R_α-*R*,*R*)-**8b** (34 mg, 0.11 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.22 mL, 0.22 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.64 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 18 mg (56%); $[\alpha]_{589}^{23}$ = +40.4 (*c* = 0.18, CH_2Cl_2). $C_{21}H_{27}N$ (293.5 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2968 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.59 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 0.77 (d, *J* = 5.7 Hz, 3 H, C*H*$_3$), 1.22 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 1.41–1.56 (m, 1 H, C*H*$_2$CH$_3$), 1.62–1.78 (m, 1 H, C*H*$_2$CH$_3$), 2.33–2.57 (m, 3 H, 1-H/2-H/5-H), 2.68 (dd, *J* = 13.1, 3.4 Hz, 1 H, 5-H), 3.24–3.41 (m, 2 H, 2-H/4-H), 3.65 [q, *J* = 7.0 Hz, 1 H, NC*H*(CH$_3$)Ph], 6.83–7.84 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (2 C, CH$_2$C*H*$_3$/*C*H$_3$), 24.4 (2 C, C*H*$_2$CH$_3$/*C*H$_3$), 43.0 (1 C, C-1), 49.4 (2 C, C-2/C-5), 50.6 (1 C, C-4), 61.1 [1 C, N*C*H(CH$_3$)Ph], 124.6, 125.2, 125.3, 126.4, 126.9, 129.3 (9 C, Ph-*C*H), 136.9, 144.5, 145.9 (3 C, Ph-*C*).HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{27}NH$ 294.2216; found 294.2207. Purity (HPLC): 95.0% (t_R = 19.1 min).

(1*S*,4*S*)-1-Ethyl-4-methyl-3-[(*S*)-1-phenylethyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(S_α-*S*,*S*)-9b]: Following the General Procedure C, (S_α-*S*,*S*)-**8b** (65 mg, 0.21 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.42 mL, 0.42 mmol) and the crude product was purified by flash chromatography [*d* = 2 cm, *l* = 10 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.64 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 40 mg (65%); $[\alpha]_{589}^{23}$ = –41.7 (*c* = 0.20, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{21}H_{27}NH$ 294.2216; found 294.2201. Purity (HPLC): 97.2% (t_R = 18.6 min). The analytical and spectroscopic data of (S_α-*S*,*S*)-**9b** are in accordance with those of the enantiomer (R_α-*R*,*R*)-**9b**.

(1*R*,4*R*)-3-Benzyl-1-ethyl-4-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*,*R*)-12]: A mixture of 3-benzazepine (R_a-*R*,*R*)-**9b** (35 mg, 0.12 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred at room temp. under a H_2 atmosphere (balloon) for 4–6 h. The reaction mixture was filtered using a Celite bed and the solvent was removed under reduced pressure to obtain secondary amine (*R*,*R*)-**11**. The residue was dissolved in CH_3CN (6 mL) and Et_3N (83 μL, 0.60 mmol) and benzyl bromide (71 μL, 0.60 mmol) were added. The mixture was stirred at room temp. for 2 h, then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography [*d* = 2 cm, *l* = 15 cm, *V* = 10 mL, cyclohexane/EtOAc, 90:10, R_f = 0.63 (cyclohexane/EtOAc, 60:40)]. Colorless viscous oil; yield 14 mg (42%); $[\alpha]_{589}^{23}$ = +17.3 (*c* = 0.20, CH_2Cl_2). $C_{20}H_{25}N$ (279.4 g/mol). FTIR (ATR, film): $\tilde{\nu}$ = 2957 (aliphatic C–H) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.3 Hz, 3 H, CH_3), 0.79 (d, *J* = 3.7 Hz, 3 H, CH_3), 1.63–1.82 (m, 2 H, CH_2CH_3), 2.42–2.58 (m, 3 H, 2-H/5-H), 2.76–2.86 (m, 1 H, 1-H), 3.03–3.14 (m, 1 H, 4-H), 3.36 (d, *J* = 12.7 Hz, 1 H, 5-H), 3.62 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 3.52 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 6.81–7.40 (m, 9 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (2 C, CH_3), 24.4 (1 C, CH_2CH_3), 43.0 (1 C, C-2/C-5), 51.2 (1 C, C-1), 54.7 (1 C, C-4), 60.9 (1 C, NCH_2Ph), 126.0, 126.2, 126.9, 128.3, 128.9, 131.1 (9 C, Ph-*C*H), 138.3, 140.9, 144.6 (3 C, Ph-C) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{25}NH$ 280.2060; found 280.2061. Purity (HPLC): 95.1% (t_R = 18.5 min).

(1*S*,4*S*)-3-Benzyl-1-ethyl-4-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*S*,*S*)-12]: As described for (*R*,*R*)-**12b**, a mixture of 3-benzazepine (S_α-*S*,*S*)-**9b** (40 mg, 0.14 mmol), Pd/C (10 wt.-%) and methanol (6 mL) was stirred under H_2, and the resulting secondary amine (*S*,*S*)-**11** was benzylated with benzyl bromide (83 μL, 0.70 mmol) and Et_3N (97 μL, 0.70 mmol) in CH_3CN (6 mL). Colorless viscous oil; yield 20 mg (53%); $[\alpha]_{589}^{23}$ = –19.8 (*c* = 0.60, CH_2Cl_2). HRMS (ESI): *m*/*z* calcd. for $C_{20}H_{25}NH$ 280.2060; found 280.2091. Purity (HPLC): 95.7% (t_R = 18.4 min). The analytical and spectroscopic data of (*S*,*S*)-**12** are in accordance with those of the enantiomer (*R*,*R*)-**12**.

Receptor Binding Studies

Materials and General Procedures: Guinea pig brains and rat livers were commercially available (Harlan–Winkelmann, Germany). Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Type A (Perkin–Elmer), presoaked in 0.5% aqueous polyethylenimine for 2 h at room temp. before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin–Elmer). The scintillation analysis was performed using Meltilex (Type A) solid scintillator (Perkin–Elmer). The solid scintillator was melted on the filtermat at a temperature of 95 °C for 5 min. After solidification of the scintillator at room temp., the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin–Elmer). The overall counting efficiency was 20%.

Membrane Preparation for the σ_1 Assay:[24–28] Five guinea pig brains were homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 × *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500 × *g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23500 *g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5–6 volumes of buffer, the protein concentration was determined according to the method of Bradford[36] using bovine serum albumin as standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

The σ_1 Assay:[26–28] The test was performed with the radioligand [^{3}H]-(+)-pentazocine (42.5 Ci/mmol; Perkin–Elmer). The thawed membrane preparation (about 75 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and buffer (50 mM TRIS, pH 7.4) in a total volume of 200 μL for 180 min at 37 °C. The incubation was terminated by rapid filtration through the presoaked filtermats by using the cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was put on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temp. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The nonspecific binding was determined with 10 μM unlabeled (+)-pentazocine. The K_d value of the radioligand [^{3}H]-(+)-pentazocine is 2.9 nM.[37]

Membrane Preparation for the σ_2 Assay:[24–28] Two rat livers were cut into small pieces and homogenized with a potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31000 *g* for 20 min at 4 °C. The pellet was resuspended in buffer (50 mM TRIS, pH 8.0) and incubated at room temp. for 30 min. After the incubation, the suspension was centrifuged again at 31000 *g* for 20 min at 4 °C. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[36] using bovine serum albumin as standard, and subsequently the preparation was frozen (–80 °C) in 1.5 mL portions containing about 2 mg protein/mL.

The σ_2 Assay:[26–28] The test was performed with the radioligand [^{3}H]-di-*o*-tolylguanidine (50 Ci/mmol; ARC). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-di-*o*-tolylguanidine, 500 nM (+)-pentazocine and buffer (50 mM TRIS, pH 8.0) in a total volume of 200 μL for 180 min at room temp. The incubation was terminated by rapid filtration through the presoaked filtermats using a cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was put on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temp. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The nonspecific binding was determined with 10 μM unlabeled ditolylguanidine. The K_d value of the radioligand [^{3}H]-ditolylguanidine is 17.9 nM.[38]

Determination of the Affinity to the Phencyclidine Binding Site of the NMDA Receptor: The preparation of the membranes from pig brain cortex and the performance of the assay with [^{3}H]-MK-801 were done according to the literature.[31]

Data Analysis: Typically, all experiments were carried out in triplicate using standard 96-well-multiplates (Diagonal). The IC_{50} values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism 3.0 (GraphPad Software) by nonlinear regression analysis. The K_i values were calculated according to Cheng and Prusoff.[39] The K_i values are given as mean values ± SEM from three independent experiments.

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C NMR and NOE difference spectra of the newly synthesized compounds.

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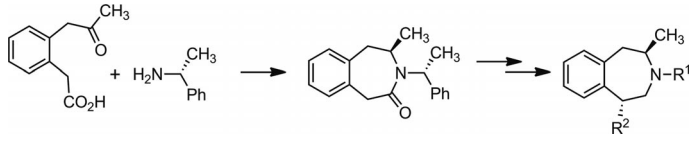
Asymmetric Synthesis



The key step in the synthesis of enantiomerically pure tetrahydro-3-benzazepines is the diastereoselective, consecutive, three-step transformation of keto acids into lactams. Relationships between the structure and the σ_1 affinity are elaborated.

Keywords: Drug discovery / Reduction / Amination / Asymmetric synthesis / Diastereoselectivity / Receptors

