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Synthesis and pharmacological evaluation of *like*- and *unlike*-configured tetrahydro-2-benzazepines with α-substituted benzyl moiety in 5-position

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Abstract

A large set of tetrahydro-2-benzazepines with an α-hydroxy or α-(aryl)alkoxy substituted benzyl moiety in 5-position was prepared according to the recently reported $C_6C_1 + C_3N$ synthetic strategy. *Heck* reaction of 2-iodobenzaldehyde acetal **4** and subsequent *Stetter* reaction led to the ketone **7**, which was reduced diastereoselectively to form the *like*-configured alcohol **8**. The diastereomeric *unlike*-configured alcohol **9** was obtained by a *Mitsunobu* inversion of **8**. Alkylation and reductive cyclization of the diastereomeric alcohols **8** and **9** provided *like*- and *unlike*-configured 2-benzazepines **13** and **23**, which allowed the introduction of various substituents at the *N*-atom. Analysis of the relationships between the structure and the σ_1 affinity revealed that large substituents such as butyl, benzyl or 4-phenylbutyl moiety at the benzazepine *N*-atom resulted in high affinity ligands. A

p-methoxybenzyl ether is less tolerated by the σ_1 receptor than a methyl ether or an alcohol. The *unlike*-configured alcohols **25d** and **27d** show slightly higher σ_1 affinity than their *like*-configured diastereomers **15d** and **17d**. With respect to σ_1 affinity, σ_1/σ_2 selectivity and lipophilic ligand efficiency *like*- and *unlike*-configured alcohols **15d** and **25d** represent the most promising σ_1 ligands of this series. Interactions of the novel 2-benzazepines with various binding sites of the NMDA receptor were not observed.

Keywords: σ_1 receptor ligands; tetrahydro-2-benzazepines; *Heck* reaction; *Stetter* reaction; reductive cyclization; structure - σ_1 affinity relationships; lipophilic ligand efficiency

1. Introduction

In 1976 different pharmacological profiles of various opioids led Martin and coworkers to the hypothesis that at least three opioid receptors exist, which were termed μ (for morphine), κ (for ketocyclazocine) and σ receptor (for SKF-10,047).[1] After it was shown that the σ receptor does not belong to the class of opioid receptors, it was hypothesized that it is identical with the phencyclidine (PCP) binding site of the *N*-methyl-*D*-aspartate (NMDA) receptor.[2] Finally σ receptors were recognized as specific, non-opioid, non-PCP but haloperidol-sensitive binding sites, which are divided into two subtypes termed σ_1 and σ_2 receptors.[3]

Although the signal transduction pathway after activation of the σ_1 receptor is not yet elucidated, the modulation of various ion channels and neurotransmitter systems as well as a chaperone activity[4] have been shown as consequence of σ_1 receptor activation. The σ_1 receptor is in particular able to modulate the activity of Kv 1.4 K^+-channels in nerve terminals,[5,6] Ca^{2+}-channels in cultured cardiac myocytes,[7] and voltage-gated Na^+-channels in

cardiac myocytes.[8] Moreover, NMDA receptors,[9] inositol triphosphate (IP_3) receptors[10] and ankyrin, a cytoskeletal adaptor protein, are modulated by the σ_1 receptor.[11]

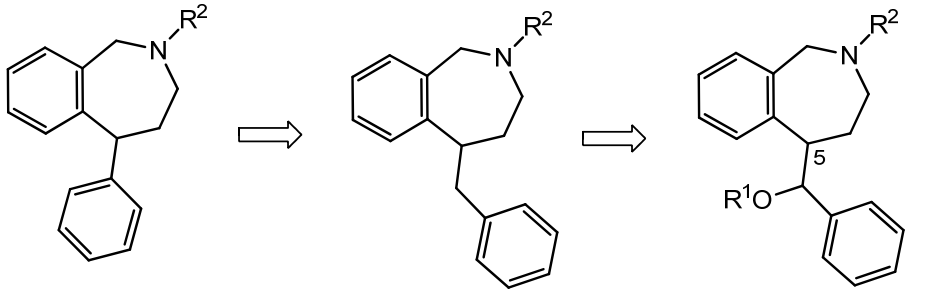
Due to the high expression in the central nervous system (CNS), in particular in brain regions involved in memory, emotion, sensoric and motor functions, the σ_1 receptor represents a promising target for the development of innovative therapeutic regimens for the treatment of depression, schizophrenia, anxiety, cocaine, alcohol and methamphetamine addiction, amnesia, neuropathic pain as well as some neurodegenerative disorders (e.g. Alzheimer's Disease, Parkinson's Disease).[12-15]

Neuropathic pain is characterized by a hypersensitive pain response persisting even when the original pain reason has been removed.[16,17] Due to the diffuse origin of neuropathic pain, its treatment is very difficult. σ_1 Receptor knockout mice were used to show the role of σ_1 receptors in neuropathic pain situation.[18] The indazole derivative S1RA represents a potent and selective σ_1 receptor antagonist. In the capsaicin model of neuropathic pain S1RA showed promising analgesic activity. After successfully finishing phase I clinical trials, S1RA is currently investigated in phase II clinical trials for the treatment of neuropathic pain.[19-23]

Although an X-ray crystal structure of the σ_1 receptor (223 amino acids) has not been recorded, a recently published 3D homology model[24] gives valuable information about the interaction of amino acids in the binding site with the prototypical agonist (+)-pentazocine. In particular, ionic interactions between Asp 126 and Glu 172 with the protonated tertiary amine of (+)-pentazocine are observed. Moreover, Tyr 173 and Ile 128 form lipophilic interactions with the aliphatic part of the ligand. Finally, strong interactions of the lipophilic part of Arg119 with the phenol substructure of (+)-pentazocine were identified.[25]

Following our strategy of evaluating compounds with novel scaffolds as σ_1 receptor antagonists, we have recently shown that tetrahydro-2-benzazepines **1** with a phenyl moiety in 5-position reveal high affinity towards the σ_1 receptor and high selectivity over the σ_2 subtype (e.g. R^2 = *n*-Bu, Figure 1).[26] Replacement of the 5-phenyl moiety by a 5-benzyl moiety led to ligands **2** fitting better to the established pharmacophore models,[27-29] since the distance between the basic amino moiety and the second hydrophobic region (6.03 - 6.45 Å) is within the postulated distance of 6 - 10 Å.[30] Herein we report on the synthesis and pharmacological evaluation of tetrahydro-2-benzazepines **3** with α-hydroxybenzyl and α-(aryl)alkoxybenzyl moieties in 5-position. (Figure 1) The general structures of compounds **2** and **3** are very similar. However the additional hydroxy moiety in α–position of the benzyl moiety (R^1 = H) leads to an increased polarity of the rather lipophilic 5-benzyl substituted 2-benzazepines. Increased polarity should improve the pharmacokinetic properties and the lipophilic ligand efficiency (LLE = pK_i – ClogP, ClogP = calculated logP value),[31] which represent crucial features for the evaluation of the quality of a ligand.

Figure 1



1 **2** **3**

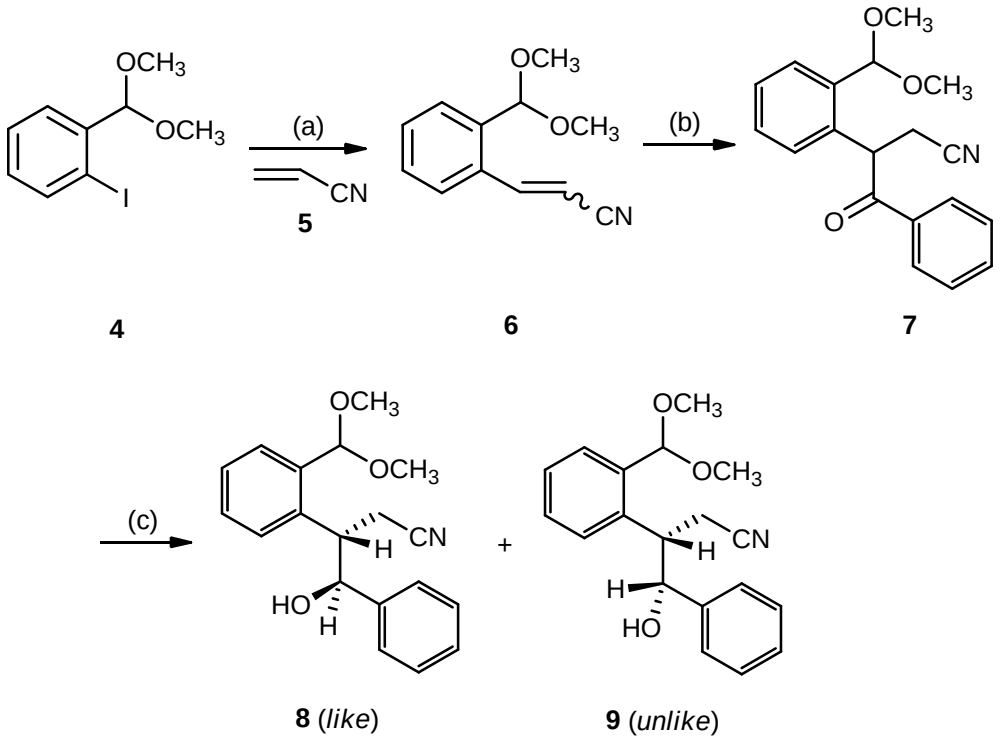
R^1 = H, CH_3, CH_2Ar

2. Synthesis

The synthesis of tetrahydro-2-benzazepines **3** with α-hydroxy- and α-alkoxybenzyl moieties in 5-position followed the recently reported strategy of combining a C_6C_1- with a C_3N-

building block.[26] 2-Iodobenzaldehyde acetal **4** served as C_6C_1-building block. It was reacted with the C_3N building block acrylonitrile (**5**) in a Pd-catalyzed *Heck* reaction.[26] Subsequent *Stetter* reaction[32,33] of the α,β-unsaturated nitrile **6** with benzaldehyde and NaCN provided the ketone **7** in 49 % yield.[30] (Scheme 1)

Scheme 1



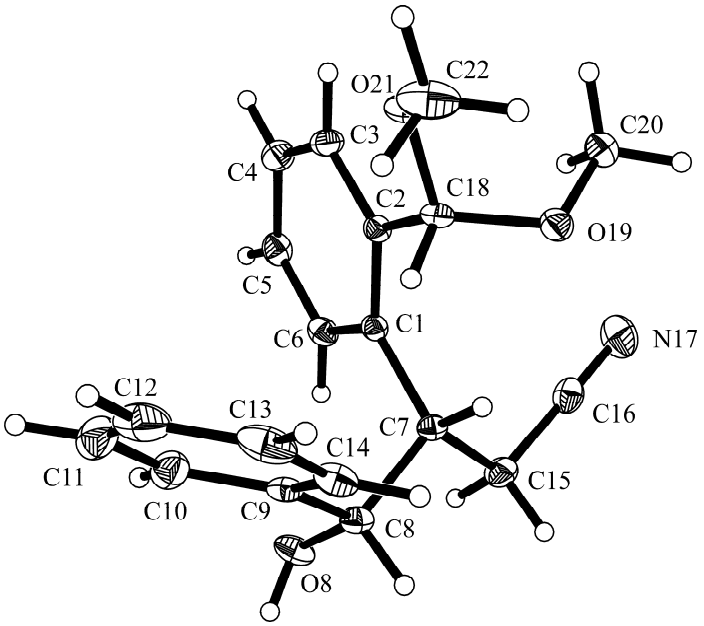
8 (*like*) **9** (*unlike*)

Synthesis of the *like*-configured cyanoacetal **8**. Reagents and reaction conditions: (a) $Pd(OAc)_2$, Bu_4NBr, $NaHCO_3$, DMF, 140 °C, 24 h, 99 %.[26] (b) PhCH=O, NaCN, DMF, 35 °C, 12 h, 49 %.[30] (c) $NaBH_4$, CH_3OH, 0 °C, 16 h, 82 %.
Only one enantiomer of the racemic mixtures **8** and **9** is shown.

Reduction of ketone **7** with $NaBH_4$ at room temperature led to the *like*- and *unlike*-configured alcohols **8** and **9**. (Scheme 1) The ratio of diastereomers (10 : 1) was determined by integration of the signals at 3.43 and 3.39 ppm (OCH_3) in the ^1H NMR spectrum. After decrease of the reaction temperature to 0 °C, only the signal at 3.43 ppm was observed

indicating the selective formation of the *like*-configured alcohol **8**, which was obtained in 82 % yield by recrystallization with petroleum ether/ethyl acetate. The obtained crystals were suitable for an X-ray crystal structure analysis, which is shown in Figure 2. The structure of the racemic mixture displays that both centers of chirality have the same configuration (in Figure 2 (*S*)-configuration). In the following manuscript diastereomers with the same configuration of the centers of chirality are termed *like*-configured, whereas the diastereomers with opposite configuration are termed *unlike*-configured.

Figure 2

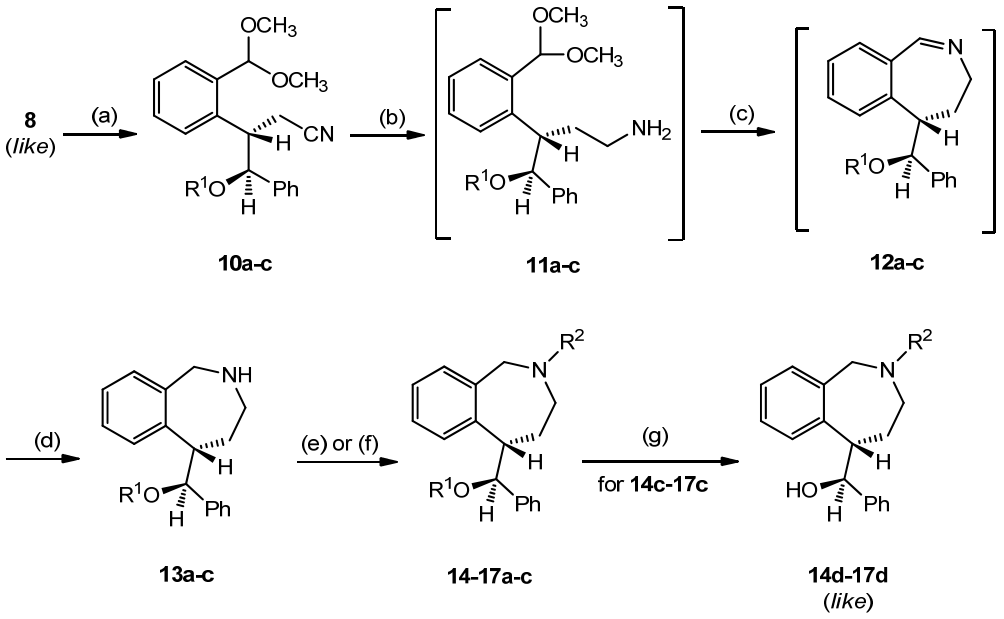


X-ray crystal structure analysis of the *like*-configured alcohol **8**.
Thermals ellipsoids are shown with 30 % probability.

Alkylation of the *like*-configured alcohol **8** with methyl iodide, benzyl bromide and *p*-methoxybenzyl chloride provided the ethers **10a-c** in excellent yields. (Scheme 2) Establishment of the tetrahydro-2-benzazepine framework was performed in a one-pot three-step procedure[26] comprising of reduction of the nitriles **10a-c** into primary amines **11a-c**, hydrolysis of dimethyl acetals into aldehydes with subsequent formation of cyclic imines **12a-c**, and finally reduction of the imines **12a-c** with $NaBH_3CN$ to yield the tetrahydro-2-

benzazepines **13a-c**. According to the concept of late-stage diversification,[34,35] various *N*-substituents were introduced at the end of the synthesis. Alkylation of the secondary amines **13a-c** with butyl bromide and 4-phenylbutyl chloride yielded the tertiary amines **15a-c** and **17a-c**, whereas reductive alkylation of **13a-c** with formaldehyde and benzaldehyde in the presence of $NaBH(OAc)_3$ provided the methyl and benzyl derivatives **14a-c** and **16a-c**, respectively.

Scheme 2



	R^1	R^2
10a-13a	CH_3	-
10b-13b	CH_2Ph	-
10c-13c	PMB	-
14a	CH_3	CH_3
14b	CH_2Ph	CH_3
14c	PMB	CH_3
14d	H	CH_3
15a	CH_3	*n*-Bu
15b	CH_2Ph	*n*-Bu
15c	PMB	*n*-Bu
15d	H	*n*-Bu
16a	CH_3	CH_2Ph
16b	CH_2Ph	CH_2Ph
16c	PMB	CH_2Ph
16d	H	CH_2Ph
17a	CH_3	$(CH_2)_4Ph$
17b	CH_2Ph	$(CH_2)_4Ph$
17c	PMB	$(CH_2)_4Ph$
17d	H	$(CH_2)_4Ph$

Synthesis of *like*-configured α-hydroxy- and α-alkoxybenzyl substituted 2-benzazepines. Reagents and reaction conditions: (a) R-X, NaH, THF or DMF, rt, 16 h. (b) $LiAlH_4$, THF, 4 °C → rt. (c) *p*-TosOH, THF, rt, 2 h. (d) $NaBH_3CN$, rt, 1 h. (e) *n*-BuBr or $Ph(CH_2)_4Cl$, Bu_4NI, CH_3CN, K_2CO_3, 66 °C, 16 h, (f) $H_2C{=}O$ or $PhCH{=}O$, $NaBH(OAc)_3$, CH_2Cl_2, rt, 16 h. (g) **14c-17c**: $(NH_4)_2Ce(NO_3)_6$, CH_3CN:H_2O 9:1, rt, 30 min.
PMB = *p*-methoxybenzyl; only one enantiomer of the racemic mixtures is shown, respectively.

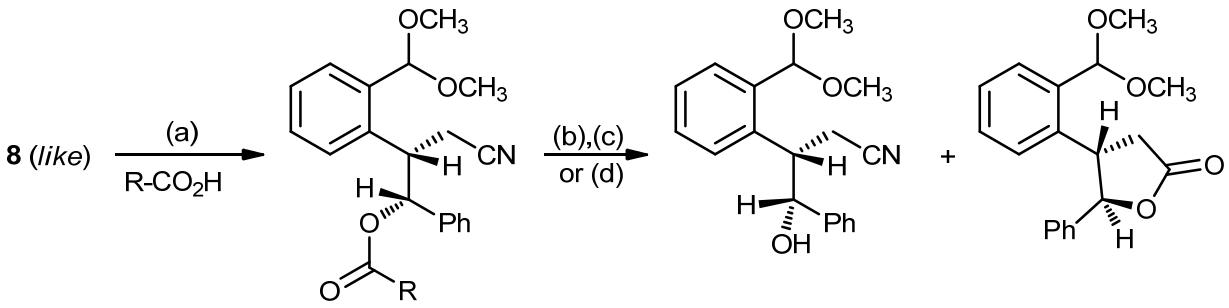
All experiments to cyclize compounds with a benzylic OH moiety such as **8** led to 2-benzopyrans[30] instead of 2-benzazepines. Therefore the alcohols **14d-17d** should be

obtained from the corresponding benzyl (**b**-series) and *p*-methoxybenzyl (PMB) ethers (**c** series). However, hydrogenolytic cleavage of the benzyl ethers **14b** and **15b** using Pd/C as a catalyst failed to give the alcohols **14d** and **15d**. Therefore the PMB ethers **13c**-**17c** were prepared. In general PMB ethers can be cleaved with acid (e.g. trifluoroacetic acid) or oxidatively (DDQ,[36] $(NH_4)_2Ce(NO_3)_6$).[37] Treatment of the PMB ethers **13c**-**15c** with DDQ led to decomposition of the compounds. However, oxidation of the PMB ethers **14c**-**17c** with $(NH_4)_2Ce(NO_3)_6$ resulted in a clean transformation providing the alcohols **14d**-**17d** in 51-86 % yield.

In order to synthesize and evaluate biologically the *unlike*-configured diastereomers of the 2-benzazepines **14**-**17** the configuration at the benzylic position of the alcohol **8** should be inverted. For this purpose a *Mitsunobu* inversion[38] was envisaged. (Scheme 3) Reaction of the *like*-configured alcohol **8** with benzoic acid, diisopropyl diazodicarboxylate (DIAD) and PPh_3 afforded the benzoate **18a** with *unlike*-configuration of the centers of chirality in 69 % yield. Subsequent hydrolysis of the ester **18a** with NaOH and methanol at reflux temperature provided exclusively the lactone **19**, formation of the alcohol **9** was not observed. Decrease of the reaction temperature and the reaction time led to a considerably slower transformation of the benzoate **18a**, but the lactone **19** remained the main product and the alcohol **9** was only formed in traces.

The formation of the lactone **19** is explained by nucleophilic attack of the alcoholate generated under basic conditions from **18a** at the cyano group with subsequent hydrolysis of the resulting imidolactone. (Figure 3) An analogous lactone formation was not observed during the synthesis of the ethers **10** by deprotonation of the *like*-configured alcohol **8** in the first step.

Scheme 3



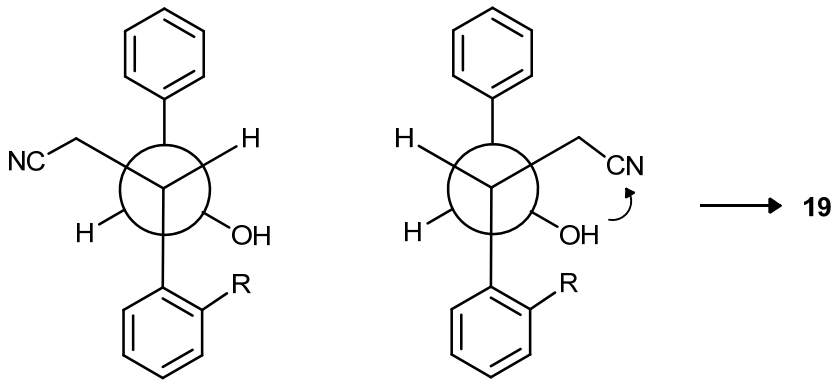
18a: R = Ph
18b: R = *p*-NO_2Ph

9 (*unlike*)

19

Synthesis of *unlike*-configured analogs by inversion of configuration of the benzylic center of chirality: Reagents and reaction conditions: (a) DIAD, PPh_3, THF, 4 °C → rt, 16 h, **18a**: 69 %; **18b**: 90 %. (b) **18a**, CH_3OH, NaOH, reflux, 16 h, product **19**. (c) **18b**, CH_3OH, K_2CO_3, rt, 4 h, product **19**, 86 %. (d) **18b**, CH_3OH, K_2CO_3, 4 °C, 30 min, product **9** (*unlike*), 71 %. Only one enantiomer of the racemic mixture is shown, respectively.

Figure 3



8 (*like*) **9** (*unlike*)

Energetically most favored conformations of the cyanoalcohols **8** and **9** with the large phenyl moieties in an a*nti-periplanar* orientation to each other. The OH and cyanomethyl moieties adopt an *anti-periplanar* and *syn-clinal* orientation to each other, respectively.

We assume that the large phenyl moieties of the diastereomeric cyanoalcohols **8** and **9** prefer an *anti-periplanar* orientation to each other. (Figure 3) Then the OH and cyanomethyl moieties of the resulting energetically favored conformation of the *like*-configured

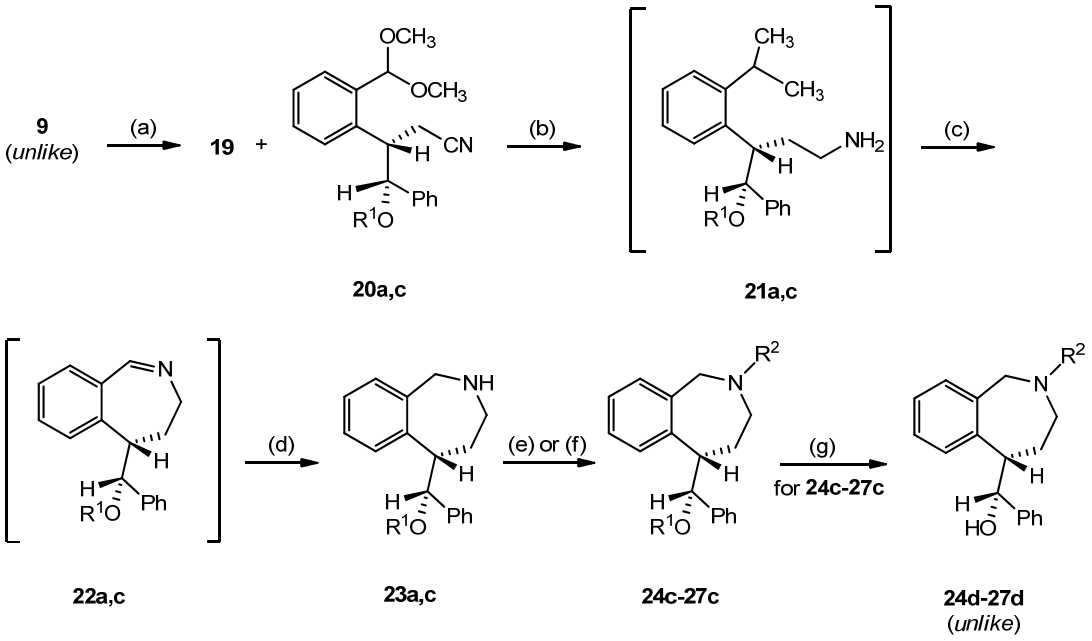
cyanoalcohol **8** are in an *anti-periplanar* orientation allowing for deprotonation and alkylation of the OH moiety without formation of a lactone. The same orientation of the large phenyl rings of the *unlike*-configured cyanoalcohol **9** leads to *syn-clinal* orientation of the OH and cyanomethyl moieties supporting their fast reaction to yield the observed lactone **19**.

In order to inhibit the formation of the lactone **19** mild reaction conditions were required for the hydrolysis of the ester **18**. Therefore *p*-nitrobenzoic acid was used in the *Mitsunobu* inversion to obtain the *p*-nitrobenzoate **18b** in 90 % yield. (Scheme 3) Treatment of the *p*-nitrobenzoate **18b** with methanol and K_2CO_3 for 4 h at rt provided only the lactone **19**, which was isolated in 86 % yield. Decrease of the reaction time to 1 h afforded both the alcohol **9** and the lactone **19** in 17 % and 65 % yield, respectively. Performing the methanolysis for only 30 min at 4 °C gave the highest yield (71 %) of the *unlike*-configured alcohol **9**. Nevertheless the lactone **19** was also formed and isolated in 26 % yield.

It was planned to convert the *unlike*-configured alcohol **9** into the *unlike*-configured 2-benzazepines **23**-**27** using the same reaction sequence, which had been successful for the preparation of the *like*-configured 2-benzazepines **13**-**17**. (Scheme 4) In the first experiments the alcohol **9** was deprotonated with NaH at 4 °C and subsequently methyl iodide and *p*-methoxybenzyl chloride were added. These reaction conditions however led almost exclusively to formation of the lactone **19**, the desired ethers **20a** and **20c** were obtained in less than 25 % yields. Therefore instead of *p*-methoxybenzyl chloride the more reactive *p*-methoxybenzyl bromide was used and the deprotonation of the alcohol **9** was performed in the presence of an excess of the alkyl halide. This procedure led to fast trapping of the intermediate alcoholate inhibiting the attack at the cyano moiety in the neighborhood. Indeed, this procedure provided both ethers **20a** and **20c** in 59 % and 62 % yield, respectively.

Nevertheless the formation of the lactone **19** could not be suppressed completely and the side product was obtained in ca. 30 % yield.

Scheme 4



	R^1	R^2
20a-23a	CH_3	-
20c-23c	PMB	-
24c	PMB	CH_3
24d	H	CH_3
25c	PMB	*n*-Bu
25d	H	*n*-Bu
26c	PMB	CH_2Ph
(26d	H	CH_2Ph)
27c	PMB	$(CH_2)_4Ph$
27d	H	$(CH_2)_4Ph$

Synthesis of *unlike*-configured α-hydroxy- and α-alkoxybenzyl substituted 2-benzazepines. Reagents and reaction conditions: (a) R-X, NaH, DMF, 4 °C, 4 h, then rt, 12 h. (b) $LiAlH_4$, THF, 4 °C → rt. (c) *p*-TosOH, THF, rt, 2 h. (d) $NaBH_3CN$, rt, 1 h. (e) *n*-BuBr or $Ph(CH_2)_4Cl$, Bu_4NI, CH_3CN, K_2CO_3, 66 °C, 16 h, (f) $H_2C{=}O$ or PhCH=O, $NaBH(OAc)_3$, CH_2Cl_2, rt, 16 h. (g) **14c**-**17c**: $(NH_4)_2Ce(NO_3)_6$, CH_3CN:H_2O 9:1, rt, 30 min.
PMB = *p*-methoxybenzyl; only one enantiomer of the racemic mixtures is shown, respectively.

The ethers **20a** and **20c** were transformed into the 2-benzazepines **23a** and **23c** by $LiAlH_4$ reduction (→ **21a**, **21c**), treatment with acid (→ **22a**, **22c**), and reduction with $NaBH_3CN$. For purpose of comparison the same set of substituents as for the *like*-configured compounds was introduced at the 2-benzazepine ring by reductive alkylation ($H_2C{=}O$, PhCH=O and $NaBH(OAc)_3$) and direct alkylation (*n*-BuBr, $Ph(CH_2)_4Cl$) affording the tertiary amines

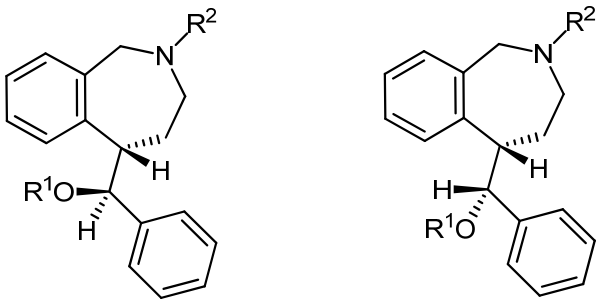
24c-**27c**. Finally, the *p*-methoxybenzyl moiety of the PMB ethers **24c-27c** was oxidatively cleaved off using $(NH_4)_2Ce(NO_3)_6$. In contrast to the *like*-configured alcohols **14d**-**17d**, the addition of 2 M HCl was required during the extraction and isolation procedure. This procedure led to partial decomposition of the alcohols **24d**–**27d**, which resulted in yields of 73 % (**24d**), 20 % (**25d**) and 64 % (**27d**). Unfortunately the benzyl derivative **26d** was decomposed completely during the work-up procedure.

3. Pharmacological evaluation

3.1. Affinity towards σ_1 and σ_2 receptors

The σ_1 and σ_2 receptor affinities of the 2-benzazepines **3** with an α-substituted benzyl moiety in 5-position together with some reference compounds were recorded in radioligand receptor binding studies employing the radioligands [^{3}H]-(+)-pentazocine in the σ_1 assay,[39,40] and [^{3}H]-1,3-di(*o*-tolyl)guanidine in the σ_2 assay.[39,40] Guinea pig brain and rat liver homogenates served as receptor material in the σ_1 and σ_2 assay, respectively. In the σ_2 assay an excess of non-tritiated (+)-pentazocine was added to mask the σ_1 receptors, since the radioligand [^{3}H]-1,3-di(*o*-tolyl)guanidine interacts also with σ_1 receptors, which are present in the rat liver preparation to a considerable amount. In order to prove the assay systems, the σ_1 and σ_2 receptor affinities of the reference compounds (+)-pentazocine, haloperidol and di-*o*-tolylguanidine are recorded periodically. The σ_1 and σ_2 affinity data of the synthesized tetrahydro-2-benzazepines and the reference compounds are summarized in Table 1. In addition to the affinity data, the σ_1/σ_2 selectivity, the calculated ClogP value, and the lipophilic ligand efficiency (LLE) of the compounds are included into Table 1. LLE is the difference between the pK_i value and the calculated ClogP value, representing the activity of a ligand without the contribution of its lipophilicity.

Table 1. σ_1 and σ_2 receptor affinities of *like*- and *unlike*-configured tetrahydro-2-benzazepines with an α-substituted benzyl moiety in 5-position and various residues R^1 and R^2



like racemate *unlike* racemate

compd.	R^1	R^2	*config.*	$K_i \pm$ SEM (nM)[a,b]		σ_1/σ_2 selectivity	ClogP[c]	LLE[d]
				σ_1	σ_2			
13a	CH_3	H	*like*	>10 μM	10 %	-	1.3	-
13b	CH_2Ph	H	*like*	>10 μM	5050	<0.5	2.7	-
13c	PMB	H	*like*	>10 μM	8760	<0.9	2.7	-
14a	CH_3	CH_3	*like*	4180	169	0.04	2.0	-
14b	CH_2Ph	CH_3	*like*	631	5930	9	3.4	2.8
14c	PMB	CH_3	*like*	3250	>10 μM	7	3.3	2.2
14d	H	CH_3	*like*	5440	0 %	-	1.4	3.9
15a	CH_3	*n*-Bu	*like*	16 ± 0.7	128	8	3.6	4.2
15b	CH_2Ph	*n*-Bu	*like*	36 ± 9.2	442	12	5.0	2.4
15c	PMB	*n*-Bu	*like*	121 ± 12	713	6	4.9	2.0
15d	H	*n*-Bu	*like*	52 ± 6.4	6630	127	3.0	4.3
16a	CH_3	CH_2Ph	*like*	48 ± 8.7	3620	75	3.8	3.5
16b	CH_2Ph	CH_2Ph	*like*	9.0 ± 1.6	668	74	5.2	2.8
16c	PMB	CH_2Ph	*like*	704	3180	5	5.1	1.1
16d	H	CH_2Ph	*like*	58 ± 12	0 %	-	3.2	4.0
17a	CH_3	$(CH_2)_4Ph$	*like*	48 ± 8.7	4070	84	5.0	2.3
17b	CH_2Ph	$(CH_2)_4Ph$	*like*	232 ± 42	20 %	-	6.4	0.2
17c	PMB	$(CH_2)_4Ph$	*like*	334 ± 51	850	3	6.3	0.1
17d	H	$(CH_2)_4Ph$	*like*	41 ± 3.1	465	11	4.4	3.0
23a	CH_3	H	*unlike*	>10 μM	>10 μM	-	1.3	-
23c	PMB	H	*unlike*	8490	4720	0.6	2.7	2.4
24c	PMB	CH_3	*unlike*	2820	80 %	-	3.3	2.2

24d	H	CH_3	*unlike*	3680	717	0.2	1.4	4.0
25c	PMB	*n*-Bu	*unlike*	177 ± 15	848	5	4.9	1.9
25d	H	*n*-Bu	*unlike*	40 ± 4.3	2000	50	3.0	4.4
26c	PMB	CH_2Ph	*unlike*	579	1640	3	5.1	1.1
27c	PMB	$(CH_2)_4Ph$	*unlike*	658	1320	2	6.3	-0.1
27d	H	$(CH_2)_4Ph$	*unlike*	13 ± 1.7	142	11	4.4	3.5
(+)-pentazocine				5.7 ± 2.2	-	-		
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 triplicates (n 3). For compounds showing very low affinity in the first experiment repetitions were not performed (n=1).
b) Low affinity is either given with a single K_i value or with the residual binding of the radioligand (in %) at a test compound concentration of 1 μM.
c) ClogP = calculated logP value (ChemDraw).
d) LLE (lipophilic ligand efficiency) = pK_i - ClogP

In general a lipophilic substituent like a *n*-butyl, benzyl or *p*-methoxybenzyl residue should be attached to the basic amino group within the heterocyclic system to achieve high σ_1 affinity; a proton (e.g. compounds **13**, **23**) and a methyl moiety (e.g. compounds **14**, **24**) are too small to produce high σ_1 affinity. With exception of the benzyl ethers **15b** and **16b**, a second large lipophilic ether substituent is less tolerated than a proton or a small methyl moiety at the O-atom (e.g. **15a**, **27d**). The *like*-configured alcohols **15d**, **16d** and **17d** show K_i values in the range of 41-58 nM, indicating moderate to high σ_1 affinity. However, the highest σ_1 affinity within the group of *like*-configured 2-benzazepines was found for the methyl ether **15a** (K_i = 16 nM) and the benzyl ether **16b** (K_i = 9.0 nM).

The same trends, which were observed for the *like*-configured 2-benzazepines, were also observed for the *unlike*-configured diastereomers. The most potent *unlike*-configured alcohols

25d and **27d** show a slightly increased σ_1 affinity compared to their *like*-configured counterparts **15d** and **17d**.

Most of the 5-substituted 2-benzazepins reveal a preference for the σ_1 receptor subtype. Particularly high σ_1/σ_2 selectivity is observed for the *like*- and *unlike*-configured alcohols **15d** and **25d** with a *N*-butyl substituent. The methyl ethers **16a** and **17a** as well as the benzyl ether **16b** also represent σ_1 ligands with high selectivity over the σ_2 subtype (σ_1/σ_2 >74). However the high σ_2 affinity of **15a** (K_i = 128 nM) and **27d** (K_i = 142 nM) should be emphasized, which reduces the σ_1/σ_2 selectivity of these potent σ_1 ligands to 8- and 11-fold, respectively.

On the contrary the *unlike*-configured alcohol **24d** and the *like*-configured methyl ether **14a** can be regarded as σ_2 ligands with moderate (σ_2/σ_1 = 5) and high selectivity (σ_2/σ_1 = 25) over the σ_1 subtype. Due to its high σ_2 affinity (K_i = 169 nM) and σ_2/σ_1 selectivity (25-fold) the methyl ether **14a** with a small methyl substituent at the *N*-atom represents a promising starting point for the development of potent σ_2 ligands.

Introduction of two lipophilic substituents at the α-position of the 5-benzyl moiety and at the 2-benzazepine *N*-atom leads to very potent (e.g. **15b**: $K_i(\sigma_1)$ = 36 nM, **16b**: $K_i(\sigma_1)$ = 9.0 nM), but rather lipophilic σ_1 ligands;. the calculated ClogP values of **15b** and **16b** are 5.0 and 5.2, respectively. The lipophilic ligand efficiency (LLE) modulates the biological activity of a ligand with its lipophilicity by subtracting the ClogP value from the pK_i value. The LLE value of a potential drug should be as high as possible, at least higher than 4.0 in order to become a lead compound. With respect to the LLE value the *like*- and *unlike*-configured alcohols **14d**, **15d**, **16d**, **24d** and **25d** display the best compromise between high σ_1 affinity and low lipophilicity. The highest LLE value was found for the *unlike*-configured alcohol **25d** (LLE = 4.4, $K_i(\sigma_1)$ = 40 nM, ClogP = 3.0) with a butyl substituent at the benzazepine *N*-atom, which

also possesses a high σ_1/σ_2 selectivity. This observation supports our initial idea of introducing a polar OH group at the benzylic α-position.

3.2. Affinity towards various binding sites of the NMDA receptor

It has been shown that the substituent at the basic *N*-atom of a ligand determines the selectivity towards σ_1 receptors or the phencyclidine (PCP) binding site of the NMDA receptor. Ligands with a small substituent like a proton (secondary amine) or a methyl group interact preferably with the PCP binding site of the NMDA receptor, whereas analogs with larger N-substituents (e.g. benzyl, dimethylallyl) show remarkable selectivity for σ_1 receptors.[41-44] Moreover, compounds with the tetrahydro-3-benzazepine scaffold reveal high affinity to the PCP binding site of the NMDA receptor when the polar *N*-phenylacetamido substituent has been attached to the 1-position.[45] Therefore the NMDA receptor affinity of the α-substituted benzyl derivatives **13**-**17** and **23**-**27** was recorded in receptor binding studies using pig brain cortex membrane preparations as receptor material and tritium labeled [^{3}H]-(+)-MK-801 as radioligand.[44,46] At a test compound concentration of 10 μM the tetrahydro-2-benzazepines did not compete significantly with the radioligand indicating very low affinity towards the PCP binding site of the NMDA receptor.

Additionally the affinity of some selected compounds (**13b**, **13c**, **15c**, **15d**, **16c**, **16d**, **17c**, **17d**, **23a**, **23c**, **25d**) towards further binding sites of the NMDA receptor were investigated. At a concentration of 10 μM these tetrahydro-2-benzazepines did not compete considerably with the radioligands [^{3}H]-CGP-39653 (glutamate binding site), [^{3}H]-MDL-105519 (glycine binding site), [^{3}H]-ifenprodil (ifenprodil binding site), and [^{3}H]-TCP (phencyclidine binding site). It can be concluded that the prepared tetrahydro-2-benzazepines represent potent and selective σ_1 ligands. In particular the most promising σ_1 ligands **15d**, **16d** and **25d** with

medium to high σ_1 affinity and high lipophilic ligand efficiency LLE are very selective with respect to different binding sites at the NMDA receptor.

4. Conclusion

A series of tetrahydro-2-benzazepines with various substituents in α-position of the benzyl moiety in 5-position and at the 2-benzazepine *N*-atom was synthesized and pharmacologically evaluated. Compounds with large substituents at the 2-benzazepine *N*-atom (*n*-Bu, CH_2Ph, $(CH_2)_4Ph$) display high σ_1 affinity. The relative configuration has only a minor impact on σ_1 affinity with the *unlike*-configured alcohols **25d** and **27d** having slightly higher σ_1 affinity than their *like*-configured diastereomers **15d** and **17d**. With respect to σ_1 affinity, σ_1/σ_2 selectivity, lipophilicity and lipophilic ligand efficiency LLE the diastereomeric alcohols **15d** and **25d** with a *N*-butyl moiety represent the most promising ligands of this series of compounds.

5. Experimental

5.1. Experimental, Chemistry

5.1.1. General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was distilled freshly 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 the column, eluent, fraction size, Rf value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Elemental analysis: CHN-Rapid Analysator (Fons-Heraeus). MS: MAT GCQ (Thermo-Finnigan); EI = electron impact; Thermo Finnigan LCQ® ion trap mass spectrometer with an ESI = electrospray ionization interface. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB

spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method I: column: LiChrospher® 60 RP-select B (5 µm), 250-4 mm; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at 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 %; Method II: column: phenomenex® Gemini C6-Phenyl 110A (5 µm), 250-4.6 mm; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at λ = 220 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0-3 min: 90 % , 3-28 min: gradient from 90 % to 0 %, 28-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %. According to two different HPLC methods the purity of all test compounds was greater than 95 %.

(±)-3-[2-(Dimethoxymethyl)phenyl]-4-oxo-4-phenylbutyronitrile (7)[30]

Under N_2, a solution of benzaldehyde (1.33 mL, 13.2 mmol) in DMF (6.6 mL) was added slowly (1 h) to a suspension of NaCN (323 mg, 6.58 mmol) in DMF (6.6 mL) at 35 °C. The mixture was stirred at 35 °C for 2 h. Then a solution of **5** (2.00 g, 9.86 mmol) in DMF (13.2 mL) was added within 4 h and the suspension was stirred for 12 h at 35 °C. H_2O (600 mL) was added and the mixture was extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with H_2O (3 x 100 mL), dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (6 cm, 18 cm, petroleum ether/EtOAc = 9:1, 65 mL, Rf = 0.17). The product was recrystallized with petroleum ether/EtOAc = 8:2. Colorless crystals, mp 100 ° C, yield 1.48 g (49%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.86 (dd, J = 16.4/4.5 Hz, 1H, C*H*$_2$CN), 3.07 (dd, J = 16.4/8.5 Hz, 1H, C*H*$_2$CN), 3.48 (s, 3H, OC*H*$_3$), 3.51 (s, 3H, OC*H*$_3$), 5.41 (s, 1H, C*H*(OCH$_3$)$_2$), 5.54 (dd, J = 8.5/4.4 Hz, 1H, C*H*CH$_2$CN), 7.02 - 7.06 (m, 1H,

H_{arom}), 7.19 - 7.28 (m, 2H, H_{arom}), 7.31 - 7.37 (m, 2H, H_{arom}), 7.41 - 7.49 (m, 2H, H_{arom}), 8.02 - 8.05 (m, 2H, H_{arom}).

(±)-(3RS,4RS)-3-[2-(Dimethoxymethyl)phenyl]-4-hydroxy-4-phenyl butyronitrile (8)[30]

Under N_2, a solution of ketone **7** (1.41 g, 4.56 mmol) in CH_3OH (40 mL) was cooled to 0 °C. Then $NaBH_4$ (1.73 g, 45.6 mmol) was added and the solution was stirred for 16 h at 0 °C. A saturated solution of NaCl (30 mL) was added, the mixture was extracted with Et_2O (3 x 30 mL), the combined organic layers were dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (6 cm, 17 cm, petroleum ether/EtOAc = 8:2, 65 mL, Rf = 0.32). The product was recrystallized with petroleum ether/EtOAc = 8:2. Colorless crystals, mp 110 °C, yield 1.16 g (82 %). $C_{19}H_{21}NO_3$ (311.2). Anal. calcd. C 73.3 H 6.80 N 4.50 found C 73.3 H 6.75 N 4.31. MS (ESI): *m/z* (%) = 645 [2·M + Na^+, 100]. IR (ATR): v (cm^{-1}) = 3448, (OH), 3035 (C-H_{arom}), 2960, 2867 (CH_2), 2823 (OCH_3), 2243 (C≡N), 1213, 1049 (C-O), 774, 704 (monosubst. arom.), 766 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.46 (d, J = 7.1 Hz, 2H, CHC*H*$_2$CN), 3.13 (d, J = 5.0 Hz, 1H, *H*OCHPh), 3.32 (s, 3H, OC*H*$_3$), 3.43 (s, 3H, OC*H*$_3$), 4.09 (dt, J = 8.6/7.2 Hz, 1H, C*H*CH_2CN), 4.80 (dd, J = 8.8/5.0 Hz, 1H, HOC*H*Ph), 5.21 (s, 1H, C*H*$(OCH_3)_2$), 7.29 - 7.40 (m, 6H, H_{arom}), 7.42 - 7.48 (m, 2H, H_{arom}), 7.58 - 7.61 (m, 1H, H_{arom}).

For the X-ray crystal structure analysis, **8** was recrystallized from CH_2Cl_2/*n*-hexane. 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;[477] absorption correction, Denzo;[48] structure solution SHELXS-97;[49] structure refinement SHELXL-97[50] and graphics, XP (BrukerAXS, 2000). Thermals ellipsoids are shown with 30% probability, *R*-values are given for observed reflections, and *w*R^2 values are given for all reflections.

X-ray Crystal Structure Analysis of 8: Formula $C_{19}H_{21}NO_3$; M = 311.37; colorless crystal, 0.30 x 0.30 x 0.20 mm; a = 12.552(1), b = 8.490(1), c = 15.725(1) Å; β = 104.140(1)°, V = 1625.0(3) Å^3; ρ_{calc} = 1.273 Mg m^{-3}; μ = 0.086 mm^{-1}; empirical absorption correction (0.974 < T < 0.983); Z = 4; monoclinic, $P2_1/c$ (No.14); λ = 0.71073 Å; T = 198(2) K, ω and φ scans, 10313 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.66 Å^{-1}, 3858 unique (R_{int} = 0.029) and 2852 observed reflections [$I > 2\sigma(I)$], 211 refined parameters, R = 0.045, wR^2 = 0.110, max. (min.) residual electron density 0.23 (–0.20) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. CCDC: 987538 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(±)-(3RS,4RS)-3-[2-(Dimethoxymethyl)phenyl]-4-methoxy-4-phenylbutyronitrile (10a)

Under N_2, the alcohol **8** (540 mg, 1.74 mmol) and CH_3I (540 µL, 8.68 mmol) were dissolved in THF (25 mL). NaH (60 %, 87 mg, 2.17 mmol) was added and the mixture was stirred at rt for 16 h. A saturated NaCl solution (15 mL) was added to the suspension. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), the organic layer was dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (3 cm, 18 cm, petroleum ether/EtOAc = 9:1, 20 mL, Rf = 0.24). Colorless solid, mp 59 °C, yield 561 mg (99 %). $C_{20}H_{23}NO_3$ (325.2). Anal. calcd. C 73.8 H 7.12 N 4.30 found C 73.8 H 6.94 N 4.27. MS (ESI): *m/z* (%) = 673 [2·M + Na$^+$, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3063 (C-H$_{arom}$), 2934, 2901 (CH_2), 2827 (OCH_3), 2245 (C≡N), 1190, 1101 (C-O), 769, 702 (monosubst. arom.), 761 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.52 (dd, J = 16.8/7.3 Hz, 1H, C*H*$_2$CN), 2.80 (dd, J = 16.8/6.9 Hz, 1H, C*H*$_2$CN), 3.11 (s, 3H, OC*H*$_3$), 3.18 (s, 3H, OC*H*$_3$), 3.19 (s, 3H, OC*H*$_3$), 3.89 - 3.95 (m, 1 H, C*H*CH$_2$CN), 4.58 (d, J = 6.0 Hz, 1H, H$_3$CO-C*H*Ph), 4.99 (s, 1H, C*H*(OCH$_3$)$_2$), 7.09 - 7.13 (m, 2H, *H*$_{arom}$), 7.23 - 7.29 (m, 4H, *H*$_{arom}$), 7.34 (td, J = 7.6/1.6 Hz, 1H, *H*$_{arom}$), 7.44 (dd, J = 7.7/1.6 Hz, 1H, *H*$_{arom}$), 7.48 (dd, J = 7.8/1.1 Hz, 1H, *H*$_{arom}$).

(±)-(3RS,4RS)-4-Benzyloxy-3-[2-(dimethoxymethyl)phenyl]-4-phenylbutyronitrile (10b)

Under N_2, the alcohol **8** (364 mg, 1.17 mmol), benzyl bromide (556 µL, 4.68 mmol) and Bu_4NI (85 mg, 0.23 mmol) were solved in THF (25 mL). NaH (60 %, 54 mg, 1.29 mmol) was added and the mixture was stirred at rt for 16 h. Then a saturated NaCl solution (10 mL) was added to and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (4 cm, 20 cm, *n*-hexane/EtOAc = 8:2, 10 mL, Rf = 0.37). Colorless solid, mp 59 °C, yield 465 mg (99 %). $C_{26}H_{27}NO_3$ (401.2). Anal. calcd. C 77.8 H 6.78 N 3.49 found C 77.7 H 6.44 N 3.36. MS (ESI): *m/z* (%) = 825 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3031 (C-H_{arom}), 2934, 2902 (CH_2), 2249 (C≡N), 1092, 1069 (C-O), 756, 699 (monosubst. arom.), 738 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.52 (dd, J = 16.8/7.9 Hz, 1H, C*H*$_2$CN), 2.75 (dd, J = 16.8/6.5 Hz, 1H, C*H*$_2$CN), 3.10 (s, 3H, OC*H*$_3$), 3.18 (s, 3H, OC*H*$_3$), 3.96 - 4.02 (m, 1H, C*H*CH_2CN), 4.19 (d, J = 11.8 Hz, 1H, PhC*H*$_2$O), 4.45 (d, J = 11.8 Hz, 1H, PhC*H*$_2$O), 4.68 (d, J = 6.4 Hz, 1H, BnO-C*H*Ph), 5.09 (s, 1H, C*H*$(OCH_3)_2$), 7.09 - 7.13 (m, 2H, *H*$_{arom}$), 7.16 - 7.19 (m, 2H, *H*$_{arom}$), 7.24 - 7.34 (m, 8H, *H*$_{arom}$), 7.39 - 7.43 (m, 1H, *H*$_{arom}$), 7.46 - 7.49 (m, 1H, *H*$_{arom}$).

(±)-(3RS,4RS)-3-[2-(Dimethoxymethyl)phenyl]-4-(4-methoxybenzyloxy)-4-phenylbutyronitrile (10c)

Under N_2, the alcohol **8** (1.20 g, 3.87 mmol), *p*-methoxybenzyl chloride (788 µL, 5.81 mmol) and Bu_4NI (284 mg, 0.77 mmol) were dissolved in DMF (80 mL). NaH (60 %, 180 mg, 4.50 mmol) was added and the mixture was stirred at rt for 16 h. H_2O (500 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The organic layer was dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (8 cm, 15 cm, *n*-hexane/EtOAc = 8:2, 100 mL, Rf = 0.37). Colorless oil, yield 1.68 g (99 %). $C_{27}H_{29}NO_4$ (431.2). Anal. calcd.

C 75.2 H 6.77 N 3.25 found C 74.8 H 6.86 N 3.10. MS (ESI): *m/z* (%) = 885 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3031 (C-H_{arom}), 2934 (CH_2), 2833 (OCH_3), 2246 (C≡N), 1091, 1071 (C-O), 820 (1,4-disubst. arom.), 756 (1,2-disubst. arom), 702 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.50 (dd, J = 16.8/7.9 Hz, 1H, CHC*H*$_2$CN), 2.72 (dd, J = 16.8/6.4 Hz, 1H, CHC*H*$_2$CN), 3.09 (s, 3H, OC*H*$_3$), 3.17 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, PhOC*H*$_3$), 3.97 - 3.99 (m, 1H, C*H*CH_2CN), 4.12 (d, J = 11.5 Hz, 1H, PhC*H*$_2$O), 4.38 (d, J = 11.5 Hz, 1H, PhC*H*$_2$O), 4.68 (d, J = 6.4 Hz, 1H, ArCH_2O-C*H*Ph), 5.09 (s, 1H, C*H*$(OCH_3)_2$), 6.79 - 6.84 (m, 2H, *H*$_{arom}$), 7.00 - 7.05 (m, 2H, *H*$_{arom}$), 7.15 - 7.19 (m, 2H, *H*$_{arom}$), 7.25 - 7.33 (m, 5H, *H*$_{arom}$), 7.36 - 7.40 (m, 1H, *H*$_{arom}$), 7.45 - 7.49 (m, 1H, *H*$_{arom}$).

(±)-(5RS)-5-[(RS)-α-Methoxybenzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (13a)

Under N_2, the nitrile **10a** (200 mg, 0.62 mmol) was dissolved in THF (15 mL) and the solution was cooled to 4 °C in an ice-bath. $LiAlH_4$ (24 mg, 0.62 mmol) was added and the mixture was stirred for 4 h at 4 °C and at rt for 12 h. The suspension was diluted with THF (25 mL) before it was hydrolyzed by dropwise addition of water. The resulting precipitate was removed by filtration and the solvent was evaporated in vacuo. The crude product (**11a**) was dissolved in THF (300 mL), *p*-toluenesulfonic acid hydrate (175 mg, 0.92 mmol) was added and the mixture was stirred at rt for 2 h (**12a**). Then $NaBH_3CN$ (47 mg, 1.23 mmol) was added and the mixture was stirred at rt for 1 h. A saturated $NaHCO_3$ solution (100 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 100 mL). The organic layer was dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (3.5 cm, 25 cm, EtOAc/CH_3OH/dimethylethanamine = 9:1:0.01, 20 mL, Rf = 0.25). Colorless oil, yield 105 mg (65 %). $C_{18}H_{21}NO$ (267.2). Anal. calcd. C 80.9 H 7.92 N 5.24 found C 80.4 H 7.77 N 5.12. MS (EI): *m/z* (%) = 267 [M^+, 2], 252 [M^+ - CH_3, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3317 (NH), 3025 (C-H_{arom}), 2978, 2926 (CH_2), 2817 (OCH_3), 1094 (C-O), 767, 700 (monosubst. arom.), 755 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.32 - 1.42 (m, 1H, 4-C*H*$_2$),

1.47 - 1.57 (m, 1H, 4-C*H*$_2$), 1.65 (s broad, 1H, 2-N*H*), 2.84 - 2.93 (m, 1H, 3-C*H*$_2$), 3.07 (s, 3H, OC*H*$_3$), 3.05 - 3.15 (m, 1H, 3-C*H*$_2$), 3.34 - 3.42 (m, 1H, 5-C*H*), 4.01 (d, J = 14.7 Hz, 1H, 1-C*H*$_2$), 4.11 (d, J = 14.6 Hz, 1H, 1-C*H*$_2$), 4.58 (d, J = 9.9 Hz, 1H, H_3CO-C*H*Ph), 7.11 - 7.18 (m, 2H, *H*$_{arom}$), 7.19 - 7.26 (m, 2H, *H*$_{arom}$), 7.31 - 7.39 (m, 2H, *H*$_{arom}$), 7.39 - 7.41 (m, 3H, *H*$_{arom}$).

(±)-(5RS)-5-[(RS)-α-Benzyloxybenzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (13b)

Under N_2, the nitrile **10b** (356 mg, 0.88 mmol) was dissolved in THF (50 mL) and cooled to 4 °C in an ice-bath. $LiAlH_4$ (34 mg, 0.90 mmol) was added and the mixture was stirred for 4 h at 4 °C and at rt for 12 h. The suspension was diluted with THF (50 mL) before water was added dropwise. The resulting precipitate was removed by filtration and the solvent was evaporated in vacuo. The crude product (**11b**) was dissolved in THF (500 mL) and *p*-toluenesulfonic acid hydrate (253 mg, 1.33 mmol) was added. The mixture was stirred at rt for 2 h (**12b**). Then $NaBH_3CN$ (113 mg, 1.80 mmol) was added and the mixture was stirred at rt for 1 h. A saturated $NaHCO_3$ solution (100 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 100 mL). The organic layer was dried (K_2CO_3), concentrated in vacuo and the residue was purified by fc (4 cm, 20 cm, EtOAc/CH_3OH/dimethylethanamine = 9:1:0.01, 10 mL, Rf = 0.23). Colorless oil, yield 147 mg (49 %). $C_{24}H_{25}NO$ (343.2). MS (EI): *m/z* (%) = 343 [M^+, 2], 252 [M^+ - benzyl, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3299 (NH), 3027 (C-H$_{arom}$), 2924, 2860 (CH_2), 1086, 1067 (C-O), 754, 698 (monosubst. arom.), 735 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.33 - 1.42 (m, 1H, 4-C*H*$_2$), 1.47 - 1.64 (m, 1H, 4-C*H*$_2$), 2.85 - 2.94 (m, 1H, 3-C*H*$_2$), 2.98 - 3.07 (m, 1H, 3-C*H*$_2$), 3.36 - 3.45 (m,1H, 5-C*H*), 3.84 (s, 2H, PhC*H*$_2$O), 4.07 (d, J = 12.1 Hz, 1H, 1-C*H*$_2$), 4.33 (d, J = 12.3 Hz, 1H, 1-C*H*$_2$), 4.76 (d, J = 10.4 Hz, 1H, BnO-C*H*Ph), 6.84 (s broad, 2H, *H*$_{arom}$), 7.07 - 7.24 (m, 6H, *H*$_{arom}$), 7.27 - 7.46 (m, 6H, *H*$_{arom}$). A signal for the proton of the NH group is not visible in the ^{1}H NMR spectrum.

(±)-(5RS)-5-[(RS)-α-(Benzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepinium chloride (13b·HCl)

A solution of HCl in Et_2O was added to a solution of the secondary amine **13b** (202 mg, 0.58 mmol) in Et_2O (10 mL). The resulting precipitate was collected by filtration and the solvent was evaporated in vacuo. The residue was purified by recrystallization from petroleum ether/EtOAc = 1:1. Colorless solid, mp 124 °C, yield 178 mg (81 %). $C_{24}H_{26}ClNO$ (379.7). Anal. calcd. C 75.9 H 6.90 N 3.69 found C 75.5 H 6.80 N 3.55. MS (ESI): *m/z* (%) = 344 [M - Cl^-, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3029 (C-H_{arom}), 2925, 2844 (CH_2), 2629 (NH_2^+), 1082, 1066 (C-O), 757, 700 (monosubst. arom.), 738 (1,2-disubst. arom.). ^{1}H NMR (DMSO): δ (ppm) = 1.42 - 1.53 (m, 1H, 4-C*H*$_2$), 1.66 - 1.76 (m, 1H, 4-C*H*$_2$), 2.94 - 3.07 (m, 1H, 3-C*H*$_2$), 3.07 - 3.19 (m, 1H, 3-C*H*$_2$), 3.46 - 3.58 (m, 1H, 5-C*H*), 4.16 (s, 2H, PhC*H*$_2$O), 4.26 (d, J = 14.1 Hz, 1H, 1-C*H*$_2$), 4.34 (d, J = 14.4 Hz, 1H, 1-C*H*$_2$), 4.88 (d, J = 9.3 Hz, 1H, BnO-C*H*Ph), 6.81 - 6.99 (m, 2H, *H*$_{arom}$), 7.14 - 7.53 (m, 12H, *H*$_{arom}$). A signal for the protons of the NH_2^+ group is not visible in the ^{1}H NMR spectrum.

(±)-(5RS)-5-[(RS)-α-(4-Methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (13c)

Under N_2, the nitrile **10c** (861 mg, 1.99 mmol) was dissolved in THF (100 mL) and cooled to 4 °C in an ice-bath. $LiAlH_4$ (113 mg, 2.99 mmol) was added and the mixture was stirred for 4 h at 4 °C and at rt for 12 h. The suspension was diluted with THF (50 mL) and water was added dropwise. The resulting precipitate was removed by filtration and the solvent was evaporated in vacuo. The crude product (**11c**) was dissolved in THF (450 mL), *p*-toluenesulfonic acid hydrate (568 mg, 2.99 mmol) was added and the mixture was stirred for at rt 2 h. Then $NaBH_3CN$ (250 mg, 3.98 mmol) was added and the mixture was stirred at rt for 1 h (**12c**). A saturated $NaHCO_3$ solution (100 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 100 mL). The organic layer was dried (K_2CO_3), concentrated in

vacuo and the residue was purified by fc (4 cm, 25 cm, EtOAc/CH_3OH/dimethylethanamine = 8:2:0.01, 30 mL, Rf = 0.29). Colorless oil, yield 371 mg (50 %). $C_{25}H_{27}NO_2$ (373.2). MS (ESI): *m/z* (%) = 374 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3331 (NH), 3026 (C-H_{arom}), 2923 (CH_2), 2837 (OCH_3), 1115, 1080 (C-O), 819 (1,4-disubst. arom.), 755 (1,2-disubst. arom), 701 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.33 - 1.53 (m, 1H, 4-C*H*$_2$), 1.49 - 1.64 (m, 1H, 4-C*H*$_2$), 2.13 (s broad, 1H, N*H*), 2.83 - 2.94 (m, 1H, 3-C*H*$_2$), 2.98 - 3.08 (m, 1H, 3-C*H*$_2$), 3.34 - 3.42 (m, 1H, 5-C*H*), 3.77 (s, 3H, OC*H*$_3$), 3.86 (s, 2H, PhC*H*$_2$O), 4.01 (d, J = 11.9 Hz, 1H, 1-C*H*$_2$), 4.29 (d, J = 11.9 Hz, 1H, 1-C*H*$_2$), 4.73 (d, J = 10.2 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.70 (d, J = 8.6 Hz, 2H, *H*$_{arom}$), 6.78 (d, J = 8.6 Hz, 2H, *H*$_{arom}$), 7.06 - 7.28 (m, 4H, *H*$_{arom}$), 7.31 - 7.44 (m, 5H, *H*$_{arom}$).

(±)-(5RS)-5-[(RS)-α-(4-Methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepinium chloride (13c·HCl)

A solution of HCl in Et_2O was added to a solution of the secondary amine **13c** (200 mg, 0.53 mmol) in Et_2O (10 mL). The resulting precipitate was collected by filtration and the solvent was evaporated in vacuo. The residue was purified by recrystallization from petroleum ether/EtOAc = 1:1. Colorless solid, mp 122 °C, yield 165 mg (76 %). $C_{25}H_{28}ClNO_2$ (409.9). Anal. calcd. C 73.3 H 6.88 N 3.42 found C 72.5 H 6.77 N 3.26. MS (ESI): *m/z* (%) = 374 [M - Cl^-, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3029 (C-H_{arom}), 2925, 2844 (CH_2), 2629 (NH_2^+), 1082, 1066 (C-O), 757, 700 (monosubst. arom.), 738 (1,2-disubst. arom.). ^{1}H NMR (DMSO): δ (ppm) = 1.42 - 1.55 (m, 1H, 4-C*H*$_2$), 1.62 - 1.77 (m, 1H, 4-C*H*$_2$), 2.94 - 3.05 (m, 1H, 3-C*H*$_2$), 3.05 - 3.18 (m, 1H, 3-C*H*$_2$), 3.45 - 3.53 (m, 1H, 5-C*H*), 3.67 (s, 3H, OC*H*$_3$), 4.09 (s, 2H, PhC*H*$_2$O), 4.23 - 4.35 (m, 2H, 1-C*H*$_2$), 4.83 (d, J = 9.2 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.73 (d, J = 8.5 Hz, 2H, *H*$_{arom}$), 6.85 (d, J = 8.4 Hz, 2H, *H*$_{arom}$), 7.20 - 7.49 (m, 9H, *H*$_{arom}$). A signal for the protons of the NH_2^+ group is not visible in the ^{1}H NMR spectrum.

(±)-(5RS)-5-[(RS)-α-Methoxybenzyl]-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (14a)

Under N_2, the secondary amine **13a** (105 mg, 0.39 mmol) and formalin (37 %, 38 µL, 0.51 mmol) were dissolved in CH_2Cl_2 (5 mL). $NaBH(OAc)_3$ (1.23 g, 5.85 mmol) was added and the solution was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added, the mixture was extracted with CH_2Cl_2 (4 x 10 mL), the organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 22 cm, EtOAc/CH_3OH/dimethylethanamine = 8:2:0.01, 10 mL, Rf = 0.19). Pale yellow oil, yield 68 mg (62 %). $C_{19}H_{23}NO$ (281.2). HPLC (method I) Purity 96.7 %. HPLC (method II) Purity 94.0 %. MS (ESI): *m/z* (%) = 282 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H_{arom}), 2925 (CH_2), 2817 (OCH_3), 2790 (N-C-H), 1093, 1050 C-O), 757, 701 (monosubst. arom.), 754 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.19 - 1.36 (m, 1H, 4-C*H*$_2$), 1.41 - 1.62 (m, 1H, 4-C*H*$_2$), 2.07 (s, 3H, NC*H*$_3$), 2.22 - 2.39 (m, 1H, 3-C*H*$_2$), 2.68 - 2.79 (m, 1H, 3-C*H*$_2$), 2.81 (s, 3H, OC*H*$_3$), 3.14 - 3.27 (m, 1H, 5-C*H*), 3.55 (d, J = 14.3 Hz, 1H, 1-C*H*$_2$), 3.79 - 4.03 (m, 1H, 1-C*H*$_2$), 4.37 (d, J = 10.0 Hz, 1H, H_3CO-C*H*Ph), 6.83 - 7.25 (m, 9H, *H*$_{arom}$). ^{13}C NMR (D_8-toluene): δ (ppm) = 27.7 (1C, 4-*C*H_2), 43.9 (1C, 3-*C*H_2), 52.7 (1C, O*C*H_3), 56.9 (1C, N*C*H_3), 62.5 (1C, 1-*C*H_2), 86.0 (1C, H_3CO-*C*HPh), 125.5, 125.8, 126.1, 126.8, 127.5, 128.3, 128.6, 129.8, 131.1, 138.1, 142.0, 143.3 (12C, *C*$_{arom}$). A signal for the carbon atom C-3 is not seen in the ^{13}C NMR spectrum.

(±)-(RS)-5-[(RS)-α-Benzyloxybenzyl]-2-methyl-2,3,4,5-tetrahydro-1*H*-benzazepine (14b)

Under N_2, the secondary amine **13b** (90 mg, 0.26 mmol) and formalin (37 %, 25 µL, 0.34 mmol) were dissolved in CH_2Cl_2 (4 mL). $NaBH(OAc)_3$ (823 mg, 3.90 mmol) was added and the solution was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 30 cm, EtOAc/dimethylethanamine =

1:0.01, 10 mL, Rf = 0.21). Pale yellow oil, yield 63 mg (68 %). $C_{25}H_{27}NO$ (357.2). HPLC (method I) Purity 99.1 %. HPLC (method II) Purity 97.7 %. MS (ESI): *m/z* (%) = 358 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H_{arom}), 2922, 2861 (CH_2), 2790 (NCH_3), 1067, 1028 (C-O), 753, 698 (monosubst. arom.), 739 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.08 - 1.31 (m, 1H, 4-C*H*$_2$), 1.48 - 1.75 (m, 1H, 4-C*H*$_2$), 2.04 (s, 3H, NC*H*$_3$), 2.22 - 2.39 (m, 1H, 3-C*H*$_2$), 2.66 - 2.85 (m, 1H, 3-C*H*$_2$), 3.17 - 3.29 (m, 1H, 5-C*H*), 3.42 (d, J = 14.9 Hz, 1H, 1-C*H*$_2$), 3.79 (d, J = 12.4 Hz, 1H, PhC*H*$_2$O), 3.87 (d, J = 14.8 Hz, 1H, 1-C*H*$_2$), 4.14 (d, J = 12.4 Hz, 1H, PhC*H*$_2$O), 4.61 (d, J = 9.4 Hz, 1H, BnO-C*H*Ph), 6.62 - 6.78 (m, 2H, *H*$_{arom}$), 6.83 - 7.16 (m, 8H, *H*$_{arom}$), 7.17 - 7.31 (m, 4H, *H*$_{arom}$). ^{13}C NMR (D_8-toluene): δ (ppm) = 25.6 (1C, 4-*C*H_2), 42.1 (1C, 3-*C*H_2), 51.4 (1C, 5-*C*H), 54.9 (1C, N*C*H_3), 60.8 (1C, 1-*C*H_2), 69.3 (1C, Ph*C*H_2O), 80.8 (1C, BnO-*C*HPh), 124.2, 124.6, 125.4, 125.8, 126.4, 126.8, 126.9, 127.1, 127.3, 127.9, 128.3, 136.6, 138.2, 140.5 (18C, *C*$_{arom}$).

(±)-(5RS)-5-[(RS)-α-(4-Methoxybenzyloxy)benzyl]-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (14c)

Under N_2, the secondary amine **13c** (440 mg, 1.18 mmol) and formalin (37 %, 114 µL, 1.53 mmol) were dissolved in CH_2Cl_2 (10 mL). $NaBH(OAc)_3$ (3.25 g, 15.3 mmol) was added and the solution was stirred at rt for 16 h. A saturated NaCl solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (3.5 cm, 24 cm, EtOAc/dimethylethanamine = 1:0.01, 20 mL, Rf = 0.21). Pale yellow oil, yield 288 mg (63 %). $C_{26}H_{29}NO_2$ (387.2). HPLC (method I) Purity 99.9 %. HPLC (method II) Purity 99.8 %. MS (ESI): *m/z* (%) = 388 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H_{Aromat}), 2922 (CH_2), 2790 (NCH_3), 1074, 1034 (C-O), 819 (1,4-disubst. arom.), 755 (1,2-disubst. arom.), 727, 701 (monosubst. arom.). ^{1}H NMR (D_8-toluene, 100 °C): δ (ppm) = 1.22 - 1.32 (m, 1H, 4-C*H*$_2$), 1.56 - 1.67 (m, 1H, 4-C*H*$_2$), 2.04 (s, 3H, NC*H*$_3$), 2.24 - 2.33 (m, 1H, 3-C*H*$_2$),

2.68 - 1.78 (m, 1H, 3-CH_2), 3.16 - 3.24 (m, 1H, 5-C*H*), 3.28 (s, 3H, OCH_3), 3.39 (d, J = 14.7 Hz, 1H, 1-CH_2), 3.81 (d, J = 14.6 Hz, 1H, 1-CH_2), 3.88 (d, J = 11.5 Hz, 1H, PhCH_2O), 4.11 (d, J = 11.6 Hz, 1H, PhCH_2O), 4.63 (d, J = 9.3 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.48 - 6.54 (m, 2H, H_{arom}), 6.64 - 6.71 (m, 2H, H_{arom}), 6.78 - 7.25 (m, 9H, H_{arom}). ^{13}C NMR (D$_8$-toluene): δ (ppm) = 26.6 (1C, 4-*C*H$_2$), 42.9 (1C, N*C*H$_3$), 54.5 (1C, O*C*H$_3$), 55.9 (1C, 1-*C*H$_2$), 61.8 (1C, Ph*C*H$_2$O), 69.8 (1C, ArCH$_2$O-*C*HPh), 124.8, 125.1, 125.3, 126.2, 126.6, 127.7, 127.9, 128.1, 128.2, 128.6, 129.1, 129.2, 130.4, 130.9 (18C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(RS)-1-[(5RS)-2-Methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]-1-phenylmethanol (14d)

$(NH_4)_2Ce(NO_3)_6$ (717 mg, 1.31 mmol) was added to a solution of the *p*-methoxybenzyl ether **14c** (253 mg, 0.65 mmol) in CH_3CN-H_2O (11 mL, 9:1), and the mixture was stirred at rt for 30 min. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2.5 cm, 30 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.11). Pale yellow oil, yield 111 mg (64 %). $C_{18}H_{21}NO$ (267.2). HPLC (method I) Purity 98.1 %. HPLC (method II) Purity 97.8 %. MS (ESI): *m/z* (%) = 268 [M + H$^+$, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3346 (OH), 3059 (C-H$_{arom}$), 2929 (CH$_2$), 2799 (NCH$_3$), 1276 (C-O), 755, 700 (monosubst. arom.), 736 (1,2-disubst. arom.). ^{1}H NMR (D$_8$-toluene, 100 °C): δ (ppm) = 1.60 - 1.68 (m, 1H, 4-CH_2), 1.69 - 1.77 (m, 1H, 4-CH_2), 2.03 (s, 3H, NCH_3), 2.09 - 2.17 (m, 1H, 3-CH_2), 2.74 - 2.86 (m, 1H, 3-CH_2), 3.09 - 3.17 (m, 1H, 5-C*H*), 3.40 (d, J = 15.4 Hz, 1H, 1-CH_2), 3.51 (d, J = 15.6 Hz, 1H, 1-CH_2), 4.89 (d, J = 3.7 Hz, 1H, HOC*H*Ph), 9.39 (d, J = 7.0 Hz, 1H, H_{arom}), 6.68 - 6.76 (m, 2H, H_{arom}), 6.79 - 6.86 (m, 1H, H_{arom}), 6.97 - 7.02 (m, 1H, H_{arom}), 7.07 (t, J = 7.4 Hz, 2H, H_{arom}), 7.19 (d, 7.5 Hz, 2H, H_{arom}). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum.

(±)-(5RS)-2-Butyl-(RS)-5-[(RS)-α-methoxybenzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (15a)

Under N_2, a mixture of the secondary amine **13a** (100 mg, 0.37 mmol), K_2CO_3 (414 mg, 2.99 mmol) and 1-bromobutane (48 µL, 0.45 mmol) and CH_3CN (10 mL) was heated to reflux for 16 h. Then a saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 22 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.42). Pale yellow oil, yield 64 mg (53 %). $C_{22}H_{29}NO$ (323.2). HPLC (method I) Purity 99.3 %. HPLC (method II) Purity 98.6 %. MS (ESI): *m/z* (%) = 324 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H_{Aromat}), 2928 (CH_2), 2815 (OCH_3), 1094, 1053 (C-O), 768, 701 (monosubst. arom.), 754 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 0.83 - 0.95 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.18 - 1.33 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.31 - 1.42 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.39 - 1.49 (m, 1H, 4-CH_2), 1.49 - 1.74 (m, 1H, 4-CH_2), 2.15 - 2.36 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.40 - 2.57 (m, 1H, 3-CH_2), 2.87 (s, 3H, OCH_3), 2.89 - 3.06 (m, 1H, 3-CH_2), 3.23 - 3.38 (m, 1H, 5-CH), 3.71 (d, J = 14.7 Hz, 1H, 1-CH_2), 3.98 - 4.18 (m, 1H, 1-CH_2), 4.46 (d, J = 10.6 Hz, 1H, H_3CO-CHPh), 6.95 - 7.33 (m, 9H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 14.8 (1C, $CH_2CH_2CH_2CH_3$), 20.7 (1C, $CH_2CH_2CH_2CH_3$), 26.8 (1C, 4-CH_2), 30.3 (1C, $CH_2CH_2CH_2CH_3$), 54.2 (1C, OCH_3), 56.3 (1C, $CH_2CH_2CH_2CH_3$), 59.1 (1C, 1-CH_2), 85.5 (1C, H_3CO-CHPh), 124.8, 125.1, 125.5, 126.1, 126.7, 127.7, 128.0, 128.3, 137.5, 138.5, 141.5, 142.6 (12C, C_{arom}). Signals for carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(5RS)-5-[(RS)-α-Benzyloxybenzyl]-2-butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (15b)

Under N_2, a mixture of the secondary amine **13b** (78 mg, 0.23 mmol), K_2CO_3 (252 mg, 1.82 mmol), 1-bromobutane (29 µL, 0.27 mmol) and CH_3CN (10 mL) was heated to reflux for 16 h. Then a saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 25 cm, cyclohexane/EtOAc/dimethylethanamine = 3:7:0.01, 10 mL, Rf = 0.41). Pale yellow oil, yield 54 mg (59 %). $C_{28}H_{33}NO$ (399.3). HPLC (method I) Purity 98.9 %. HPLC (method II) Purity 99.3 %. MS (ESI): *m/z* (%) = 400 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3027 (C-Ha_{rom}), 2927, 2859 (CH_2), 1085, 1027 (C-O), 763, 698 (monosubst. arom.), 753 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 0.89 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.10 - 1.25 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.25 - 1.34 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.31 - 1.38 (m, 1H, 4-CH_2), 1.58 - 1.77 (m, 1H, 4-CH_2), 2.09 - 2.31 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.36 - 2.52 (m, 1H, 3-CH_2), 2.79 - 2.96 (m, 1H, 3-CH_2), 3.23 - 3.35 (m, 1H, 5-CH), 3.58 (d, J = 14.8 Hz, 1H, 1-CH_2), 3.88 (d, J = 14.7 Hz, 1H, 1-CH_2), 3.91 (d, J = 12.2 Hz, 1H, PhCH_2O), 4.21 (d, J = 12.4 Hz, 1H, PhCH_2O), 4.67 (d, J = 10.0 Hz, 1H, BnO-CHPh), 6.67 - 6.82 (m, 2H, H_{arom}), 6.92 - 7.21 (m, 9H, H_{arom}), 7.22 - 7.30 (m, 2H, H_{arom}), 7.31 - 7.37 (m, 1H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 15.2 (1C, $CH_2CH_2CH_2CH_3$), 21.1 (1C, $CH_2CH_2CH_2CH_3$), 27.0 (1C, 4-CH_2), 31.1 (1C, $CH_2CH_2CH_2CH_3$), 54.5 (1C, $CH_2CH_2CH_2CH_3$), 60.1 (1C, 1-CH_2), 71.0 (1C, PhCH_2O), 82.2 (1C, BnO-CHPh), 125.7, 126.0, 126.3, 127.5, 128.2, 128.5, 128.6, 128.8, 129.0, 129.1, 129.3, 129.4, 129.6, 129.7, 130.1, 131.3, 138.3, 142.3 (18C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(5RS)-2-Butyl-5-[(RS)-α-(4-methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (15c)

Under N_2, a mixture of the secondary amine **13c** (189 mg, 0.51 mmol), K_2CO_3 (586 mg, 4.24 mmol), 1-bromobutane (69 µL, 0.64 mmol) and CH_3CN (12 mL) was heated to reflux for 16 h. Then a saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2.5 cm, 28 cm, cyclohexane/EtOAc = 1:1, 10 mL, Rf = 0.14). Pale yellow oil, yield 156 mg (72 %). $C_{29}H_{35}NO_2$ (429.3). HPLC (method I) Purity 99.6 %. HPLC (method II) Purity 99.1 %. MS (ESI): *m/z* (%) = 430 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3026 (C-H_{arom}), 2928, 2860 (CH_2), 2837 (OCH_3), 1069, 1036 (C-O), 819 (1,4-disubst. arom.), 754 (1,2-disubst. arom.), 704 (monosubst. arom.). ^{1}H NMR (D_8-toluene, 100 °C): δ (ppm) = 0.83 (m,3H, $CH_2CH_2CH_2CH_3$), 1.15 - 1.25 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.27 - 1.35 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.28 - 1.34 (m, 1H, 4-CH_2), 1.61 - 1.73 (m, 1H, 4-CH_2), 2.13 - 2.30 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.37 - 2.48 (m, 1H, 3-CH_2), 2.80 - 2.92 (m, 1H, 3-CH_2), 3.25 - 3.31 (m, 1H, 5-C*H*), 3.33 (s, 3H, OCH_3), 3.56 (d, J = 14.2 Hz, 1H, 1-CH_2), 3.89 (d, J = 11.9 Hz, 1H, PhCH_2O), 3.89 (d, J = 14.2 Hz, 1H, 1-CH_2), 4.21 (d, J = 11.8 Hz, 1H, PhCH_2O), 4.69 (d, J = 9.4 Hz, 1H, ArCH_2O-C*H*Ph), 6.52 - 6.58 (m, 2H, H_{arom}), 6.68 - 7.25 (m, 2H, H_{arom}), 6.86 - 7.18 (m, 7H, H_{arom}), 7.20 - 7.31 (m, 2H, H_{arom}).

(±)-(RS)-1-[(5RS)-2-Butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]-1-phenylmethanol (15d)

$(NH_4)_2Ce(NO_3)_6$ (208 mg, 0.38 mmol) was added to a solution of the PMB-ether **15c** (84 mg, 0.19 mmol) in CH_3CN/H_2O (5 mL, 9:1), and the mixture was stirred at rt for 30 min. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 25 cm, cyclohexane/EtOAc = 3:7, 10 mL, Rf = 0.11). Pale yellow oil,

yield 51 mg (86 %). $C_{21}H_{27}NO$ (309.2). HPLC (method I) Purity 95.7 %. HPLC (method II) Purity 96.1 %. MS (ESI): *m/z* (%) = 310 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3342 (OH), 3060 (C-H_{arom}), 2929 (CH_2), 1276 (C-O), 750, 700 (monosubst. arom.), 735 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene, 100 °C): δ (ppm) = 0.78 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.14 - 1.24 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.32 - 1.42 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.66 - 1.77 (m, 1H, 4-CH_2), 1.77 - 1.88 (m, 1H, 4-CH_2), 2.20 - 2.27 (m, 1H, 3-CH_2), 2.20 - 2.34 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.90 - 3.00 (m, 1H, 3-CH_2), 3.15 - 3.23 (m, 1H, 5-CH), 3.48 (d, J = 15.7 Hz, 1H, 1-CH_2), 3.63 (d, J = 15.5 Hz, 1H, 1-CH_2), 4.92 (d, J = 3.5 Hz, 1H, HOCHPh), 6.40 (d, J = 7.3, 1H, H_{arom}), 6.70 - 7.14 (m, 6H, H_{arom}), 7.19 - 7.27 (m, 2H, H_{arom}). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene): δ (ppm) = 14.2 (1C, $CH_2CH_2CH_2CH_3$), 19.8 (1C, $CH_2CH_2CH_2CH_3$), 20.9 (1C, $CH_2CH_2CH_2CH_3$), 29.7 (1C, 4-CH_2), 53.1 (1C, 3-CH_2), 58.1 (1C, 1-CH_2), 61.9 (1C, $CH_2CH_2CH_2CH_3$), 74.8 (1C, HOCHPh), 124.8, 125.1, 125.3, 127.7, 127.9, 128.2, 128.6, 128.8, 129.1, 137.5 (12C, C_{arom}). A signal for the carbon atom C-5 is not seen in the ^{13}C NMR spectrum.

(±)-(5RS)-2-Benzyl-5-[(RS)-α-methoxybenzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16a)

Under N_2, the secondary amine **13a** (100 mg, 0.37 mmol) and benzaldehyde (49 µL, 0.49 mmol) were dissolved in CH_2Cl_2 (1.5 mL). After addition of $NaBH(OAc)_3$ (237 mg, 1.13 mmol), the solution was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 30 cm, cyclohexane/EtOAc = 8:2, 10 mL, Rf = 0.23). Pale yellow oil, yield 93 mg (70 %). $C_{25}H_{27}NO$ (357.2). HPLC (method I) Purity 98.3 %. HPLC (method II) Purity 97.0 %. MS (ESI): *m/z* (%) = 358 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H_{arom}), 2925 (CH_2), 2817 (OCH_3),

1094, 1045 (C-O), 768, 698 (monosubst. arom.), 753 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.14 - 1.39 (m, 1H, 4-CH_2), 1.47 - 1.71 (m, 1H, 4-CH_2), 2.35 - 2.52 (m, 1H, 3-CH_2), 2.83 (s, 3H, OCH_3) 2.85 - 2.98 (m, 1H, 3-CH_2), 3.19 - 3.32 (m, 1H, 5-C*H*), 3.34 (s, 2H, NCH_2Ph), 3.66 (d, J = 14.5 Hz, 1H, 1-CH_2), 3.91 - 4.17 (m, 1H, 1-CH_2), 4.40 (d, J = 7.3 Hz, 1H, H_3CO-C*H*Ph), 6.78 - 6.89 (m, 1H, H_{arom}), 6.91 - 7.20 (m, 8H, H_{arom}), 7.19 - 7.33 (m, 5H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 28.0 (1C, 4-*C*H_2), 55.1 (1C, O*C*H_3), 57.3 (1C, N*C*H_2Ph), 59.9 (1C, 1-*C*H_2), 86.4 (1C, H_3CO-*C*HPh), 125.8, 126.1, 126.5, 127.2, 127.8, 128.1, 128.7, 128.9, 129.0, 129.2, 129.3, 129.5, 129.6, 129.9, 130.2, 131.5, 138.5, 141.1 (18C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(5RS)-2-Benzyl-5-[(RS)-α-benzyloxybenyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16b)

Under N_2, the secondary amine **13b** (70 mg, 0.20 mmol) and benzaldehyde (25 µL, 0.25 mmol) were dissolved in CH_2Cl_2 (1.5 mL). $NaBH(OAc)_3$ (127 mg, 0.60 mmol) was added and the solution was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added and the mixture and was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2.5 cm, 25 cm, cyclohexane/EtOAc = 9:1, 10 mL, Rf = 0.25). Pale yellow oil, yield 59 mg (67 %). $C_{31}H_{31}NO$ (433.2). HPLC (method I) Purity 99.4 %. HPLC (method II) Purity 99.2 %. MS (ESI): *m/z* (%) = 434 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (C-H_{arom}), 2917, 2859 (CH_2), 1066, 1027 (C-O), 759, 697 (monosubst. arom.), 736 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.11 - 1.43 (m, 1H, 4-CH_2), 1.62 - 1.89 (m, 1H, 4-CH_2), 2.31 - 2.59 (m, 1H, 3-CH_2), 2.74 - 3.04 (m, 1H, 3-CH_2), 3.22 - 3.33 (m, 1H, 5-C*H*), 3.29 - 3.47 (m, 2H, NCH_2Ph), 3.59 (d, J = 14.1 Hz, 1H, 1-CH_2), 3.81 - 4.02 (m, 2H, 1-CH_2 und PhCH_2O), 4.26 (d, J = 13.1 Hz, 1H, PhCH_2O), 4.63 - 4.76 (m, 1H, BnO-C*H*Ph), 6.63 - 7.43 (m, 19H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 26.1 (1C, 4-*C*H_2), 54.9 (1C, N*C*H_2Ph), 60.3 (1C, 1-*C*H_2), 71.9 (1C,

Ph*C*H_2O),), 81.6 (1C, BnO-*C*HPh), 125.0, 125.4, 125.7, 127.6, 127.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.4, 137.7, 140.3, 141.6 (24C, C_{arom}). The signals for carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(5RS)-2-Benzyl-5-[(RS)-α-(4-methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16c)

Under N_2, the secondary amine **13c** (275 mg, 0.74 mmol) and benzaldehyde (90 µL, 0.89 mmol) were dissolved in CH_2Cl_2 (2 mL). $NaBH(OAc)_3$ (189 mg, 0.89 mmol) was added and the solution was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (3 cm, 24 cm, cyclohexane/EtOAc = 8:2, 30 mL, Rf = 0.18). Pale yellow oil, yield 199 mg (59 %). $C_{32}H_{33}NO_2$ (463.3). HPLC (method I) Purity 98.2 %. HPLC (method II) Purity 98.7 %. MS (ESI): *m/z* (%) = 464 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (C-H_{arom}), 2930, 2859 (CH_2), 2836 (OCH_3), 1066, 1034 (C-O), 819 (1,4-disubst. arom.), 756, 699 (monosubst. arom.), 739 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.21 - 1.36 (m, 1H, 4-C*H*$_2$), 1.69 - 1.87 (m, 1H, 4-C*H*$_2$), 2.55 - 2.69 (m, 1H, 3-C*H*$_2$), 2.91 - 3.07 (m, 1H, 3-C*H*$_2$), 3.32 - 3.41 (m, 1H, 5-C*H*), 3.45 (s, 2H, NC*H*$_2$Ph), 3.64 (d, J = 13.4 Hz, 1H, 1-C*H*$_2$), 3.76 (s, 3H, OC*H*$_3$), 3.88 (d, J = 13.5 Hz, 1H, 1-C*H*$_2$), 3.99 (d, J = 11.8 Hz, 1H, PhC*H*$_2$O), 4.28 (d, J = 11.9 Hz, 1H, PhC*H*$_2$O), 4.73 (d, J = 10.1 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.61 - 6.89 (m, 3H, H_{arom}), 6.89 - 6.97 (m, 1H, H_{arom}), 7.12 - 7.42 (m, 14H, H_{arom}).

(±)-(RS)-1-[(5RS)-2-Benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]-1-phenylmethanol (16d)

$(NH_4)_2Ce(NO_3)_6$ (427 mg, 0.78 mmol) was added to a solution of the PMB-ether **16c** (180 mg, 0.39 mmol) in CH_3CN-H_2O (8 mL, 9:1) and the mixture was stirred at rt for 30 min.

A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2.5 cm, 25 cm, cyclohexane/EtOAc = 7:3, 10 mL, Rf = 0.19). Pale yellow oil, yield 83 mg (62 %). $C_{24}H_{25}NO$ (343.2). HPLC (method I) Purity 98.2 %. HPLC (method II) Purity 98.2 %. MS (ESI): *m/z* (%) = 344 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3353 (OH), 3060 (C-H_{arom}), 2922 (CH_2), 1276 (C-O), 754, 700 (monosubst. arom.), 736 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene, 100 °C): δ (ppm) = 1.55 - 1.65 (m, 1H, 4-C*H*$_2$), 1.73 - 1.81 (m, 1H, 4-C*H*$_2$), 2.30 - 2.36 (m, 1H, 3-C*H*$_2$), 2.91 - 2.97 (m, 1H, 3-C*H*$_2$), 3.15 - 3.19 (m, 1H, 5-C*H*), 3.34 (d, J = 13.7 Hz, 1H, NC*H*$_2$Ph), 3.44 (d, J = 13.6 Hz, 1H, NC*H*$_2$Ph), 3.48 (d, J = 15.6 Hz, 1H, 1-C*H*$_2$), 3.79 (d, J = 15.7 Hz, 1H, 1-C*H*$_2$), 4.89 (d, J = 5.2 Hz, 1H, HOC*H*Ph), 6.58 - 6.62 (m, 1H, *H*$_{arom}$), 6.66 - 6.71 (m, 1H, *H*$_{arom}$), 6.77 - 6.86 (m, 2H, *H*$_{arom}$), 6.89 - 6.94 (m, 1H, *H*$_{arom}$), 6.97 - 7.13 (m, 5H, *H*$_{arom}$), 7.16- 7.25 (m, 4H, *H*$_{arom}$). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene, 100 °C): δ (ppm) = 29.7 (1C, 4-*C*H_2), 53.8 (1C, 5-*C*H), 53.9 (1C, 3-*C*H_2), 58.4 (1C, 1-*C*H_2), 61.8 (1C, N*C*H_2Ph), 75.9 (1C, HO*C*HPh), 125.3, 125.4, 125.7, 125.9, 126.3, 127.1, 127.4, 128.1, 128.2, 128.4, 129.0, 129.3, 132.2, 137.9 (18C, C_{arom}).

(±)-(5RS)-5-[(RS)-α-Methoxybenzyl]-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (17a)

The secondary amine **13a** (140 mg, 0.52 mmol), K_2CO_3 (574 mg, 4.16 mmol), Bu_4NI (192 mg, 0.52 mmol) and 1-chloro-4-phenylbutane (115 µL, 0.68 mmol) were dissolved in CH_3CN (12 mL) and the mixture was heated to reflux for 16 h. Then a saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 25 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.42). Pale yellow oil, yield 131 mg (63 %). $C_{28}H_{33}NO$ (399.3). HPLC (method I) Purity 98.9 %. HPLC (method II) Purity

98.4 %. MS (ESI): *m/z* (%) = 400 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (C-H_{arom}), 2931, 2855 (CH_2), 2816 (OCH_3), 1093, 1055 (C-O), 763, 698 (monosubst. arom.), 751 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.23 - 1.34 (m, 1H, 4-C*H*$_2$), 1.34 - 1.44 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.47 - 1.57 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.55 - 1.69 (m, 1H, 4-C*H*$_2$), 2.14 - 2.34 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.44 (t, J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.47 - 2.57 (m, 1H, 3-C*H*$_2$), 2.85 (s, 3H, OCH_3), 2.88 - 3.03 (m, 1H, 3-C*H*$_2$), 3.22 - 3.37 (m, 1H, 5-C*H*), 3.69 (d, J = 14.5 Hz, 1H, 1-C*H*$_2$), 3.94 - 4.18 (m, 1H, 1-C*H*$_2$), 4.44 (d, J = 9.4 Hz, 1H, H_3CO-C*H*Ph), 6.93 - 7.32 (m, 14H, *H*$_{arom}$). ^{13}C NMR (D_8-toluene): δ (ppm) = 26.3 (1C, 4-*C*H_2), 27.2 (1C, $CH_2CH_2CH_2CH_2Ph$), 29.1 (1C, $CH_2CH_2CH_2CH_2Ph$), 35.8 (1C, $CH_2CH_2CH_2CH_2Ph$), 51.1 (1C, 5-*C*H), 53.8 (1C, O*C*H_3), 55.9 (1C, *C*$H_2CH_2CH_2CH_2Ph$), 58.6 (1C, 1-*C*H_2), 85.0 (1C, H_3CO-*C*HPh), 125.4, 125.7, 126.1, 126.6, 126.8, 127.4, 128.3, 128.6, 128.7, 128.9, 129.1 ,129.2, 129.3, 129.5, 129.8, 130.9, 138.1, 142.0 (18C, *C*$_{arom}$). A signal for the carbon atom C-3 is not seen in the ^{13}C NMR spectrum.

(±)-(RS)-5-[(RS)-α-Benzyloxybenzyl]-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (17b)

The secondary amine **13b** (75 mg, 0.22 mmol), K_2CO_3 (381 mg, 2.76 mmol), Bu_4NI (81 mg, 0.22 mmol) and 1-chloro-4-phenylbutane (56 µL, 0.33 mmol) were dissolved in CH_3CN (8 mL) and the mixture was heated to reflux for 16 h. Then a saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 26 cm, cyclohexane/EtOAc = 1:1, 10 mL, Rf = 0.41). Pale yellow oil, yield 57 mg (55 %). $C_{34}H_{37}NO$ (475.3). HPLC (method I) Purity 98.7 %. HPLC (method II) Purity 97.7 %. MS (ESI): *m/z* (%) = 476 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (C-H_{arom}), 2929, 2857 (CH_2), 1067, 1027 (C-O), 763, 697 (monosubst. arom.), 735 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.06 - 1.25 (m, 1H, 4-C*H*$_2$), 1.26 - 1.39 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.39 - 1.54 (m,

2H, $CH_2CH_2CH_2CH_2Ph$), 1.59 - 1.77 (m, 1H, 4-CH_2), 2.07 - 2.31 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.40 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.41 - 2.52 (m, 1H, 3-CH_2), 2.79 - 2.97 (m, 1H, 3-CH_2), 3.22 - 3.34 (m, 1H, 5-C*H*), 3.55 (d, J = 13.9 Hz, 1H, 1-CH_2), 3.80 - 3.95 (m, 2H, 1-CH_2 und PhCH_2O), 4.20 (d, J = 12.4 Hz, 1H, PhCH_2O), 4.66 (d, J = 10.2 Hz, 1H, BnO-C*H*Ph), 6.65 - 6.82 (m, 2H, H_{arom}), 6.88 - 7.38 (m, 17H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 26.9 (1C, 4-*C*H_2), 28.0 (1C, $CH_2CH_2CH_2CH_2Ph$), 29.4 (1C, $CH_2CH_2CH_2CH_2Ph$), 36.2 (1C, $CH_2CH_2CH_2CH_2Ph$), 53.2 (1C, $CH_2CH_2CH_2CH_2Ph$), 62.9 (1C, 1-*C*H_2), 71.8 (1C, Ph*C*H_2O), 82.6 (1C, BnO-*C*HPh), 124.2, 124.5, 125.3, 125.7, 126.0, 126.7, 127.0, 127.1, 127.3, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1 128.2, 128.5, 129.7, 136.8, 138.4, 140.8, 141.9, 142.3 (24C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(5RS)-5-[(RS)-α-(4-Methoxybenzyloxy)benzyl]-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (17c)

The secondary amine **13c** (278 mg, 0.75 mmol), K_2CO_3 (815 mg, 5.89 mmol), Bu_4NI (137 mg, 0.37 mmol) and 1-chloro-4-phenylbutane (159 µL, 0.97 mmol) were dissolved in CH_3CN (15 mL) and the mixture was heated to reflux for 16 h. Then a saturated NaCl solution (20 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2.5 cm, 24 cm, cyclohexane/EtOAc/dimethylethanamine = 1:1:0.01, 10 mL, Rf = 0.38). Pale yellow oil, yield 266 mg (71 %). $C_{35}H_{39}NO_2$ (505.3). HPLC (method I) Purity 99.4 %. HPLC (method II) Purity 99.4 %. MS (ESI): *m/z* (%) = 506 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3024 (C-H_{aromat}), 2932, 2855 (CH_2), 2837 (OCH_3), 1074, 1036 (C-O), 819 (1,4-disubst. arom.), 752 (1,2-disubst. arom.), 707 (monosubst. arom.). ^{1}H NMR (D_8-toluene, 100 °C): δ (ppm) =1.18 - 1.30 (m, 1H, 4-CH_2), 1.28 - 1.40 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.43 - 1.55 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.57 - 1.72 (m, 1H, 4-CH_2), 2.12 - 2.31 (m, 2H,

C*H*$_2$CH$_2$CH$_2$CH$_2$Ph), 2.38 - 2.44 (m, 2H, CH$_2$CH$_2$CH$_2$C*H*$_2$Ph), 2.41 - 2.47 (m, 1H, 3-C*H*$_2$), 2.78 - 2.91 (m, 1H, 3-C*H*$_2$), 3.19 - 3.28 (m, 1H, 5-C*H*), 3.31 (s, 3H, OC*H*$_3$), 3.49 (d, J = 14.7 Hz, 1H, 1-C*H*$_2$), 3.88 (d, J = 14.7 Hz, 1H, 1-C*H*$_2$), 3.92 (d, J = 11.7 Hz, 1H, PhC*H*$_2$O), 4.13 (d, J = 11.6 Hz, 1H, PhC*H*$_2$O), 4.69 (d, J = 9.5 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.49 - 6.59 (m, 2H, *H*$_{arom}$), 6.65 - 6.75 (m, 2H, *H*$_{arom}$), 6.82 - 7.09 (m, 9H, *H*$_{arom}$), 7.10 - 7.18 (m, 2H, *H*$_{arom}$), 7.19 - 7.30 (m, 3H, *H*$_{arom}$). ^{13}C NMR (D$_8$-toluene): δ (ppm) = 20.2 (1C, CH$_2$CH$_2$*C*H$_2$CH$_2$Ph), 26.3 (1C, 4-*C*H$_2$), 27.6 (1C, CH$_2$*C*H$_2$CH$_2$CH$_2$Ph), 29.4 (1C, CH$_2$CH$_2$CH$_2$*C*H$_2$Ph), 38.2 (1C, *C*H$_2$CH$_2$CH$_2$CH$_2$Ph), 53.8 (1C, O*C*H$_3$), 54.6 (1C, 1-*C*H$_2$), 58.2 (1C, Ph*C*H$_2$O), 69.8 (1C, ArCH$_2$O-*C*HPh), 113.7, 124.9, 125.1, 125.3, 125.9, 126.2, 126.6, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 129.2, 130.9, 137.5, 141.6, 142.9, 159.4 (24C, *C*$_{aromat}$). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(RS)-1-Phenyl-1-[(5RS)-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]methanol (17d)

(NH$_4$)$_2$Ce(NO$_3$)$_6$ (237 mg, 0.43 mmol) was added to a solution of the PMB-ether **17c** (290 mg, 0.43 mmol) in CH$_3$CN-H$_2$O (10 mL, 9:1) and the mixture was stirred at rt for 30 min. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (4 x 10 mL). The organic layer was dried (Na$_2$SO$_4$), concentrated in vacuo and the residue was purified by fc (2.5 cm, 25 cm, *n*-hexane/EtOAc = 3:7, 10 mL, Rf = 0.11). Pale yellow oil, yield 84 mg (51 %). C$_{27}$H$_{31}$NO (385.2). HPLC (method I) Purity 96.1 %. HPLC (method II) Purity 92.8 %. MS (ESI): *m/z* (%) = 386 [M + H$^+$, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3335 (OH), 3059 (C-H$_{arom}$), 2930 (CH$_2$), 1276 (C-O), 753, 704 (monosubst. arom.), 735 (1,2-disubst. arom.). ^{1}H NMR (D$_8$-toluene, 100 °C): δ (ppm) = 1.33 - 1.55 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$Ph), 1.62 - 1.72 (m, 1H, 4-C*H*$_2$), 1.74 - 1.86 (m, 1H, 4-C*H*$_2$), 2.18 - 2.24 (m, 1H, 3-C*H*$_2$), 2.23 - 2.32 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_2$Ph), 2.36 - 2.47 (m, 2H, CH$_2$CH$_2$CH$_2$C*H*$_2$Ph), 2.87 - 2.98 (m, 1H, 3-C*H*$_2$), 3.14 - 3.23 (m, 1H, 5-C*H*), 3.43 (d, J = 15.5

Hz, 1H, 1-CH_2), 3.61 (d, J = 15.5 Hz, 1H, 1-CH_2), 4.93 (d, J = 3.7 Hz, 1H, HOC*H*Ph), 6.42 (d, J = 7.3 Hz, 1H, H_{arom}), 6.69 - 6.81 (m, 2H, H_{arom}), 6.82 - 7.15 (m, 9H, H_{arom}), 7.18 - 7.28 (m, 2H, H_{arom}). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene): δ (ppm) = 26.9 (1C, $CH_2CH_2CH_2CH_2Ph$), 29.3 (1C, $CH_2CH_2CH_2CH_2Ph$), 30.3 (1C, 4-CH_2), 35.9 (1C, $CH_2CH_2CH_2CH_2Ph$), 53.1 (1C, $CH_2CH_2CH_2CH_2Ph$), 57.9 (1C, 1-CH_2), 74.9 (1C, HOCHPh), 124.9, 125.1, 125.3, 125.8, 126.0, 126.7, 127.0, 127.7, 128.2, 129.1, 132.5, 137.4, 139.3, 142.6 (18C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not seen in the spectrum.

(±)-{(1RS,2SR)-3-Cyano-2-[2-(dimethoxymethyl)phenyl]-1-phenylpropyl} benzoate (18a)

The alcohol **8** (228 g, 0.73 mmol), PPh_3 (957 mg, 3.65 mmol) and benzoic acid (392 mg, 3.21 mmol) were dissolved in THF (20 mL) and the mixture was cooled to 4 °C in an ice-bath. Diisopropyl diazodicarboxylate (709 µL, 3.65 mmol) was added dropwise within 4 h and the solution was stirred at rt for 12 h. A saturated NaCl solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 30 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (5 cm, 15 cm, *n*-hexane/EtOAc = 8:2, 65 mL, Rf = 0.31). Colorless solid, mp 148 °C, yield 209 mg (69 %). $C_{26}H_{25}NO_4$ (415.2). Anal. calcd. C 75.2 H 6.06 N 3.37 found C 74.5 H 6.30 N 3.19. MS (ESI): *m/z* (%) = 853 [2·M + Na^+, 100], 438 [M + Na^+, 9]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3033 (C-H_{arom}), 2933, 2830 (CH_2), 2245 (C≡N), 1719 (COOR), 1093, 1049 (C-O), 764 (1,2-disubst. arom.), 699 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.85 (dd, J = 16.9/4.9 Hz, 1H, CHCH_2CN), 2.98 (dd, J = 16.9/8.9 Hz, 1H, CHCH_2CN), 3.19 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 4.34 - 4.42 (m, 1H, C*H*CH_2CN), 5.14 (s, 1H, C*H*$(OCH_3)_2$), 6.32 (d, J = 7.2 Hz, 1H, COO-C*H*Ph), 7.19 - 7.36 (m, 9H, H_{arom}), 7.39 - 7.44 (m, 1H, H_{arom}), 7.48 - 7.56 (m, 3H, H_{arom}), 7.59 - 7.65 (m, 1H, H_{arom}).

(±)-{(1RS,2SR)-3-Cyano-2-[2-(dimethoxymethyl)phenyl]-1-phenylpropyl} 4-nitrobenzoate (18b)

The alcohol **8** (1.01 g, 3.25 mmol), PPh_3 (4.28 g, 16.3 mmol) and 4-nitrobenzoic acid (2.39 g, 14.3 mmol) were dissolved in THF (70 mL) and the mixture was cooled to 4 °C in an ice-bath. Diisopropyl diazodicarboxylate (3.29 mL, 16.3 mmol) was added dropwise within 4 h and the mixture was stirred at rt for 12 h. A saturated NaCl solution (50 mL) was added and the mixture and was extracted with CH_2Cl_2 (4 x 60 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (8 cm, 20 cm, petroleum ether/EtOAc = 9:1, 100 mL, Rf = 0.27). Colorless solid, mp 66 °C, yield 1.39 g (90 %). $C_{26}H_{24}N_2O_6$ (460.2). MS (ESI): *m/z* (%) = 483 [M + Na^+, 16], 943 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3034 (C-H_{arom}), 2935, 2831 (CH_2), 2246 (C≡N), 1727 (COOR), 1347 (NO_2), 1098, 1047 (C-O), 844 (1,4-disubst. arom.), 765 (1,2-disubst. arom.), 700 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.74 (dd, J = 17.0/5.5 Hz, 1H, CHC*H*$_2$CN), 2.86 (dd, J = 17.0/7.7 Hz, 1H, CHC*H*$_2$CN), 3.15 (s, 3H, OC*H*$_3$), 3.19 (s, 3H, OCH_3), 4.36 - 4.42 (m, 1H, C*H*CH_2CN), 5.04 (s, 1H, C*H*$(OCH_3)_2$), 6.33 (d, J = 7.7 Hz, 1H, COO-C*H*Ph), 7.16 - 7.33 (m, 8H, *H*$_{arom}$), 7.46 (dd, J = 7.8/1.2 Hz, 1H, *H*$_{arom}$), 8.29 - 8.23 (m, 4H, *H*$_{arom}$).

(±)-(4RS,5SR)-4-[2-(Dimethoxymethyl)phenyl]-5-phenyl-4,5-dihydrofuran-2(3*H*)-one (19)

Under N_2, a mixture of the ester **18a** (402 mg, 0.85 mmol), K_2CO_3 (233 mg, 1.69 mmol) and CH_3OH (30 mL) was stirred at rt for 4 h. A saturated NaCl solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 30 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (4 cm, 20 cm, petroleum/EtOAc = 8:2, 20 mL, Rf = 0.34). Colorless oil, yield 228 mg (86 %). ($C_{19}H_{20}O_4$) (312.1). MS (ESI): *m/z* (%) = 647 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058 (C-H_{arom}), 2979, 2938 (CH_2), 2823 (OCH_3), 1779 (COOR), 1199, 1065 (C-O), 764 (1,2-disubst. arom.), 700 (monosubst.

arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.75 (dd, J = 17.6/10.1 Hz, 1H, CHC*H*$_2$CO), 3.01 - 3.12 (m, 1H, CHC*H*$_2$CO), 3.05 (s, 3H, OC*H*$_3$), 3.07 (s, 3H, OC*H*$_3$), 4.92 (s, 1H, C*H*$(OCH_3)_2$), 4.21 - 4.31 (m, 1H, C*H*CH_2CO), 5.56 (d, J = 8.2 Hz, 1H, COO-C*H*Ph), 7.20 - 7.24 (m, 2H, *H*$_{arom}$), 7.29 - 7.33 (m, 4H, *H*$_{arom}$), 7.42 - 7.47 (m, 2H, *H*$_{arom}$), 7.52 - 7.56 (m, 1H, *H*$_{arom}$).

(±)-(3RS,4SR)-3-[2-(Dimethoxymethyl)phenyl]-4-hydroxy-4-phenylbutyronitrile (9)

Under N_2, the ester **18b** (1.82 g, 3.96 mmol) was dissolved in CH_3OH (160 mL) and the mixture was cooled to 4 °C in an ice-bath. Then K_2CO_3 (0.54 g, 3.91 mmol) was added and the mixture was stirred under cooling for 30 min. A saturated NaCl solution (50 mL) was added and the mixture and was extracted with CH_2Cl_2 (4 x 40 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (5.5 cm, 22 cm, cyclohexane/EtOAc = 7:3, 65 mL, Rf = 0.21). Colorless oil, yield 0.87 g (71 %). $C_{19}H_{21}NO_3$ (311.2). MS (ESI): *m/z* (%) = 645 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3439(OH), 2935, 2917 (CH_2), 2823 (OCH_3), 2246 (C≡N), 1216, 1047 (C-O), 765 (1,2-disubst. arom.), 701 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.34 (d, J = 3.3 Hz, 1H, *H*OCHPh), 2.59 (dd, J = 16.9/4.5 Hz, 1H CHC*H*$_2$CN), 2.88 (dd, J = 16.9/9.5 Hz, 1H, CHC*H*$_2$CN), 3.09 (s, 3H, OC*H*$_3$), 3.22 (s, 3H, OC*H*$_3$), 3.94 - 4.00 (m, 1H, C*H*CH_2CN), 4.92 (dd, J = 6.3/3.3 Hz, 1H, HOC*H*Ph), 5.08 (s, 1H, C*H*$(OCH_3)_2$), 7.13 - 7.22 (m, 6H, *H*$_{arom}$), 7.26 - 7.39 (m, 3H, *H*$_{arom}$).

(±)-(3RS,4SR)-3-[2-(Dimethoxymethyl)phenyl]-4-methoxy-4-phenylbutyronitrile (20a)

Under N_2, the alcohol **9** (125 mg, 0.40 mmol) and CH_3I (249 µl, 4.00 mmol) were dissolved in DMF (20 mL) and the mixture was cooled to 4 °C in an ice-bath. Then, NaH (18 mg, 0.44 mmol) was added and the mixture was stirred under cooling for 4 h and at rt for 12 h. H_2O (100 ml) was added and the solution and was extracted with Et_2O (3 x 30 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was

purified by fc (3 cm, 20 cm, cyclohexane/EtOAc = 8:2, 20 mL, Rf = 0.19). Colorless solid, mp 50 °C, yield 77 mg (59 %). $C_{20}H_{23}NO_3$ (325.2). Anal. calcd. C 73.8 H 7.12 N 4.30 found C 73.6 H 7.10 N 4.07. MS (ESI): *m/z* (%) = 673 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061 (C-H_{arom}), 2983, 2932 (CH_2), 2826 (OCH_3), 2245 (C≡N), 1192, 1101 (C-O), 762 (1,2-disubst. arom.), 703 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.73 (dd, J = 16.8/3.9 Hz, 1H, CHC*H*$_2$CN), 3.02 (dd, J = 16.8/8.8 Hz, 1H, CHC*H*$_2$CN), 3.11 (s, 3H, OC*H*$_3$), 3.19 (s, 3H, OC*H*$_3$), 3.25 (s, 3H, OC*H*$_3$), 3.85 - 3.91 (m, 1H, C*H*CH_2CN), 4.44 (d, J = 7.7 Hz, 1H, H_3CO-C*H*Ph), 5.01 (s, 1H, C*H*(OCH_3)$_2$), 7.14 - 7.27 (m, 6H, *H*$_{arom}$), 7.33 - 7.39 (m, 2H, *H*$_{arom}$), 7.58 - 7.63 (m, 1H, *H*$_{arom}$).

(±)-(3RS,4SR)-3-[2-(Dimethoxymethyl)phenyl]-4-(4-methoxybenzyloxy)-4-phenylbutyronitrile (20c)

Under N_2, the alcohol **9** (870 g, 2.79 mmol) and *p*-methoxybenzyl bromide (423 µl, 3.00 mmol) were dissolved in DMF (40 mL) and the solution was cooled to 4 °C in an ice-bath. NaH (134 mg, 3.35 mmol) was added and the mixture was stirred under cooling for 4 h and at rt for 12 h. H_2O (400 ml) was added and the solution was extracted with Et_2O (3 x 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (4 cm, 24 cm, *n*-hexane'/EtOAc = 7:3, 30 mL, Rf = 0.36). Colorless oil, yield 1.04 g (62 %). $C_{27}H_{29}NO_4$ (431.2). MS (ESI): *m/z* (%) = 885 [2·M + Na^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3030 (C-H_{arom}), 2934 (CH_2), 2835 (OCH_3), 2244 (C≡N), 1093, 1049 (C-O), 821 (1,4-disubst. arom.), 758 (1,2-disubst. arom.), 700 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.68 (dd, J = 16.8/3.9 Hz, 1H, CHC*H*$_2$CN), 2.95 (dd, J = 16.8/8.9 Hz, 1H, CHC*H*$_2$CN), 3.00 (s, 3H, OC*H*$_3$), 3.09 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, ArOC*H*$_3$), 3.83 - 3.90 (m, 1H, C*H*CH_2CN), 4.13 (d, J = 10.8 Hz, 1H, PhC*H*$_2$O), 4.32 (d, J = 10.8 Hz, 1H, PhC*H*$_2$O), 4.59 (d, J = 7.6 Hz, 1H, ArCH_2O-C*H*Ph), 4.94 (s, 1H, C*H*(OCH_3)$_2$), 6.80 - 6.82 (m, 2H, $_{arom}$), 7.12 - 7.20 (m, 8H, *H*$_{arom}$), 7.29 - 7.31 (m, 2H, *H*$_{arom}$), 7.50 - 7.52 (m, 1H, *H*$_{aromat}$).

((±)-(5RS)-5-[(SR)-α-Methoxybenzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (23a)

Under N_2, $LiAlH_4$ (46 mg, 1.20 mmol) was added to a cooled (4 °C, ice-bath) solution of the nitrile **20a** (389 mg, 1.20 mmol) in THF (25 mL) and the mixture was stirred under cooling for 4 h and at rt for 12 h. The suspension was diluted with THF (25 mL) and hydrolyzed by dropwise addition of water. The resulting precipitate was removed by filtration and the solvent was evaporated in vacuo. Under N_2, the crude product (**21a**) was dissolved in THF (450 mL), *p*-toluenesulfonic acid hydrate (342 mg, 1.80 mmol) was added and the mixture was stirred at rt for 2 h (**22a**). Afterwards $NaBH_3CN$ (151 mg, 2.40 mmol) was added and the mixture was stirred at rt for 1 h. A saturated $NaHCO_3$ solution (150 mL) was added and the suspension was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layer was dried (K_2CO_3), the solvent was evaporated in vacuo and the residue was purified by fc (3 cm, 24 cm, EtOAc/CH_3OH/dimethylethanamine = 9:1:0.02, 20 mL, Rf = 0.28). Pale yellow oil, yield 103 mg (32 %). $C_{18}H_{21}NO$ (267.2). Anal. calcd. C 80.9 H 7.92 N 5.24 found C 80.2 H 7.97 N 5.15. MS (ESI): m/z (%) = 268 [M + H^+,100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3318 (NH), 3025 (C-H_{arom}), 2979, 2927 (CH_2), 2827 (OCH_3), 1089 (C-O), 768, 699 (monosubst. arom.), 759 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.49 - 1.68 (m, 1H, 4-C*H*$_2$), 1.79 - 1.94 (m, 1H, 4-C*H*$_2$), 2.12 - 2.34 (m, 1H, 3-C*H*$_2$), 3.04 - 3.14 (m, 1H, 3-C*H*$_2$), 3.12 - 3.22 (m, 1H, 5-C*H*), 3.29 (s, 3H, OC*H*$_3$), 3.96 (d, J = 15.2 Hz, 1H, 1-C*H*$_2$), 4.22 (d, J = 15.2 Hz, 1H, 1-C*H*$_2$), 4.73 (d, J = 8.5 Hz, 1H, H_3CO-C*H*Ph), 6.54 - 6.72 (m, 1H, *H*$_{arom}$), 6.82 - 6.93 (m, 1H, *H*$_{arom}$), 6.96 - 7.11 (m, 4H, *H*$_{arom}$), 7.12 - 7.25 (m, 3H, *H*$_{arom}$). A signal for the proton of the NH group is not visible in the 1H NMR spectrum.

(±)-(5RS)-5-[(SR)-α-(4-Methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (23c)

Under N_2, $LiAlH_4$ (87 mg, 2.30 mmol) was added to a cooled (4 °C, ice-bath) solution of the nitrile **20c** (904 mg, 2.09 mmol) in THF (50 mL) and the mixture was stirred under cooling for 4 h and at rt for 12 h. The suspension was diluted with THF (40 mL) and hydrolyzed by dropwise addition of water. The resulting precipitate was removed by filtration and the solvent was evaporated in vacuo. Under N_2, the crude product (**21c**) was solved in THF (450 mL), *p*-toluenesulfonic acid hydrate (798 mg, 2.41 mmol) was added and the solution was stirred at rt for 2 h (**22c**). $NaBH_3CN$ (264 mg, 4.19 mmol) was added and the mixture was stirred at rt for q h. A saturated $NaHCO_3$ solution (100 mL) was added and the suspension was extracted with CH_2Cl_2 (4 x 100 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (5.5 cm, 20 cm, EtOAc/CH_3OH/dimethylethanamine = 8/2/0.01, 40 mL, Rf = 0.28). Colorless oil, yield 335 mg (43 %). $C_{25}H_{27}NO_2$ (373.2). HPLC (method I) Purity 97.4 %. HPLC (method II) Purity 94.8 %. MS (ESI): *m/z* (%) = 374 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3334 (NH), 3026 (C-H_{arom}), 2923 (CH_2), 2838 (OCH_3), 1060, 1033 (C-O), 819 (1,4-disubst. arom.), 755 (1,2-disubst. arom.), 700 (monosubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.49 - 1.60 (m, 1H, N*H*), 1.58 - 1.66 (m, 1H, 4-CH_2), 1.73 - 1.87 (m, 1H, 4-CH_2), 2.24 - 242 (m, 1H, 3-CH_2), 3.06 - 3.18 (m, 1H, 3-CH_2), 3.17 - 3.25 (m, 1H, 5-C*H*), 3.81 (s, 3 H, OCH_3), 3.89 (d, J = 15.1 Hz, 1H, 1-CH_2), 4.13 (d, J = 15.2 Hz, 1H, 1-CH_2), 4.23 (d, J = 11.4 Hz, 1H, PhCH_2O), 4.45 (d, J = 11.2 Hz, 1H, PhCH_2O), 4.89 (d, J = 9.0 Hz, 1H, ArCH_2O-C*H*Ph), 6.79 - 6.89 (m, 4H, H_{arom}), 6.95 - 7.14 (m, 4H, H_{arom}), 7.16 - 7.24 (m, 5H, H_{arom}).

(±)-(5RS)-5-[(SR)-α-(4-Methoxybenzyloxy)benzyl]-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (24c)

Under N_2, a solution of the secondary amine **23c** (313 mg, 0.84 mmol), formalin (37%, 82 µL, 1.09 mmol) and $NaBH(OAc)_3$ (2.66 g, 12.6 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 16 h. A saturated NaCl solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (2 cm, 24 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.19). Pale yellow oil, yield 220 mg (68 %). $C_{26}H_{29}NO_2$ (387.2). HPLC (method I) Purity 97.7 %. HPLC (method II) Purity 99.6 %. MS (ESI): *m/z* (%) = 388 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060 (C-H_{arom}), 2925 (CH_2), 2789 (N-C-H), 1075, 1033 (C-O), 821 (1,4-disubst. arom.), 753 (1,2-disubst. arom.), 701 (monosubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.94 - 2.03 (m, 1H, 4-CH_2), 2.15 (s, 3H, NCH_3), 2.25 - 2.37 (m, 1H, 4-CH_2), 2,58 - 2.72 (m, 1H, 3-CH_2), 2.99 - 3.09 (m, 1H, 3-CH_2), 3.09 - 3.17 (m, 1H, 5-C*H*), 3.29 (s, 3H, OCH_3), 3.50 (d, J = 14.7 Hz, 1H, 1-CH_2), 4.00 - 4.09 (m, 1H, 1-CH_2), 4.08 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.57 (d, J = 11.3 Hz, 1H, PhCH_2O), 4.88 (d, J = 9.1 Hz, 1H, ArCH_2O-C*H*Ph), 6.67 - 6.76 (m, 2H, H_{arom}), 6.81 - 6.87 (m, 2H, H_{arom}), 6.93 - 7.14 (m, 9H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 25.9 (1C, 4-*C*H_2), 43.5 (1C, N*C*H_3), 54.9 (1C, O*C*H_3), 55.8 (1C, 1-*C*H_2), 62.6 (1C, PhCH_2O), 70.7 (1C, ArCH_2O-*C*HPh), 114.2, 125.0, 125.4, 125.7, 126.4, 126.9, 127.8, 127.9, 129.1, 129.4, 129.9, 131.2, 137.7, 141.3 (18C, C_{arom}). Signals for the carbon atoms C-3-C and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(RS)-1-[(5SR)-2-Methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]-1-phenylmethanol (24d)

$(NH_4)_2Ce(NO_3)_6$ (482 mg, 0.88 mmol) was added to a solution of the *p*-methoxybenzyl ether **24c** (162 mg, 0.42 mmol) in CH_3CN-H_2O (7 mL, 9:1) and the mixture was stirred at rt for 30 min. HCl 2 M (0.44 mL, 0.88 mmol) and a saturated NaCl solution (10 mL) were added

and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (2 cm, 20 cm, EtOAc/CH_3OH/dimethylethanamin = 9:1:0.01, 10 mL, Rf = 0.20). Colorless oil, yield 82 mg (73 %). $C_{18}H_{21}NO$ (267.2). HPLC (method I) Purity 98.2 %. HPLC (method II) Purity 97.6 %. MS (ESI): *m/z* (%) = 268 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3142 (OH), 3058 (C-H_{arom}), 2931 (CH_2), 2799 (NCH_3), 1289 (C-O), 752 (1,2-disubst. arom.), 701 (monosubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) =1.45 - 1.60 (m, 1H, 4-C*H*$_2$), 1.61 - 1.84 (m, 1H, 4-C*H*$_2$), 1.95 - 2.15 (m, 1H, 3-C*H*$_2$), 2.46 (s, 3H, NC*H*$_3$), 2.87 - 3.06 (m, 1H, 3-C*H*$_2$), 3.39 - 3.64 (m, 3H, 1-C*H*$_2$ and 5-C*H*), 5.36 (d, J = 3.8 Hz, 1H, HOC*H*Ph), 7.00 (d, J = 7.7 Hz, 1H, *H*$_{arom}$), 7.16 - 7.39 (m, 5H, *H*$_{arom}$), 7.41 - 7.53 (m, 2H, *H*$_{arom}$), 7.65 (s broad, 1H, *H*$_{arom}$). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene): δ (ppm) = 25.5 (1C, 4-*C*H_2), 45.6 (1C, 3-*C*H_2), 52.1 (1C, NCH_3), 55.7 (1C, 5-*C*H), 60.6 (1C, 1-CH_2), 76.3 (1C, HO*C*HPh), 124.9, 125.2, 125.5, 125.9, 126.1, 130.9, 137.5, 138.9, 142.4, 145.8 (12C, *C*$_{arom}$).

(±)-(5RS)-2-Butyl-5-[(SR)-α-(4-methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (25c)

A mixture of the secondary amine **23c** (199 mg, 0.54 mmol), K_2CO_3 (597 mg, 4.32 mmol), 1-bromobutane (81 µl, 0.75 mmol) and CH_3CN (12 mL) was heated to reflux for 16 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 24 cm, cyclohexane/EtOAc = 4:6, 10 mL, Rf = 0.07). Pale yellow oil, yield 119 mg (52 %). $C_{29}H_{35}NO_2$ (429.3). HPLC (method I) Purity 100.0 %. HPLC (method II) Purity 99.8 %. MS (ESI): *m/z* (%) = 430 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3026 (C-H_{arom}), 2928, 2860 (CH_2), 2832 (OCH_3), 1078, 1037 (C-O), 821 (1,4-disubst. arom.), 755 (1,2-disubst. arom.), 700 (monosubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 0.92 (t, J =

7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.24 - 1.40 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.38 - 1.53 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.45 - 1.55 (m, 1H, 4-CH_2), 1.95 - 2.08 (m, 1H, 4-CH_2), 2.24 - 2.43 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.36 - 2.44 (m, 1H, 3-CH_2), 2.69 - 2.97 (m, 1H, 3-CH_2), 3.15 - 3.29 (m, 1H, 5-C*H*), 3.35 (s, 3H, OCH_3), 3.71 (d, J = 14.9 Hz, 1H, 1-CH_2), 4.15 (d, J = 11.3 Hz, 1H, $PhCH_2O$), 4.16 - 4.29 (m, 1H, 1-CH_2), 4.44 (d, J = 11.3 Hz, 1H, $PhCH_2O$), 4.98 (d, J = 9.1 Hz, 1 H, $ArCH_2O$-C*H*Ph), 6.68 - 6.83 (m, 2H, H_{arom}), 6.83 - 6.98 (m, 2H, H_{arom}), 6.99 - 7.32 (m, 9H, H_{arom}). ^{13}C NMR (D_8-toluene): δ (ppm) = 14.5 (1C, $CH_2CH_2CH_2CH_3$), 20.6 (1C, $CH_2CH_2CH_2CH_3$), 25.1 (1C, 4-CH_2), 30.6 (1C, $CH_2CH_2CH_2CH_3$), 33.9 (1C, $CH_2CH_2CH_2CH_3$), 53.1 (1C, OCH_3), 54.4 (1C, 1-CH_2), 59.6 (1C, $PhCH_2O$), 70.3 (1C, $ArCH_2O$-CHPh), 113.7, 124.6, 124.9, 125.2, 125.9, 126.4, 127.3, 127.4, 128.6, 128.9, 129.5, 130.8, 137.3, 141.9 (18C, C_{arom}). Signals for the carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(RS)-1-[(5SR)-2-Butyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]-1-phenylmethanol (25d)

$(NH_4)_2Ce(NO_3)_6$ (208 mg, 0.38 mmol) was added t o a solution of the *p*-methoxybenzyl ether **25c** (83 mg, 0.19 mmol) in CH_3CN-H_2O (5 mL, 9:1) and the mixture was stirred at rt for 30 min. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 20 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.23). Pale yellow oil, yield 11 mg (20 %). $C_{21}H_{27}NO$ (309.2). HPLC (method I) Purity 98.4 %. HPLC (method II) Purity 97.4 %. MS (ESI): *m/z* (%) = 310 [$M + H^+$, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3342 (OH), 3060 (C-H_{arom}), 2929 (CH_2), 1247 (C-O), 756, 700 (monosubst. arom.), 738 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 0.77 (t, J = 7.3 Hz,3H, $CH_2CH_2CH_2CH_3$), 1.05 - 1.19 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.18 - 1.29 (m, 1H, 4-CH_2), 1.25 - 1.39 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.48 - 1.58 (m, 1H, 4-CH_2), 1.78 - 1.95 (m, 1H, 3-CH_2), 2.14

- 2.29 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.69 - 2.89 (m, 1H, 3-C*H*$_2$), 3.19 - 3.27 (m, 1H, 5-C*H*), 3.27 - 3.49 (m, 2H, 1-C*H*$_2$), 5.08 (d, J = 4.6 Hz, 1H, HOC*H*Ph), 6.76 - 7.29 (m, 9H, *H*$_{arom}$). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene): δ (ppm) = 14.7 (1C, CH$_2$CH$_2$CH$_2$*C*H$_3$), 21.3 (1C, CH$_2$CH$_2$*C*H$_2$CH$_3$), 25.6 (1C, 4-*C*H$_2$), 30.8 (1C, CH$_2$*C*H$_2$CH$_2$CH$_3$), 51.9 (1C, *C*H$_2$CH$_2$CH$_2$CH$_3$), 54.3 (1C, 5-*C*H), 58.8 (1C, 1-*C*H$_2$), 76.9 (1C, HO*C*HPh), 125.3, 125.7, 125.9, 126.5, 126.6, 127.1, 138.0, 139.7, 142.9, 146.2, (12C, C$_{arom}$). A signal for the carbon atom C-3 is not seen in the ^{13}C NMR spectrum.

(±)-(5RS)-2-Benzyl-5-[(SR)-α-(4-methoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine (26c)

Under N_2, a solution of the secondary amine **23c** (138 mg, 0.37 mmol), benzaldehyde (41 µl, 0.41 mmol) and NaBH(OAc)$_3$ (86 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL) was stirred at rt for 16 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (2 cm, 20 cm, cyclohexane/EtOAc = 85:15, 10 mL, Rf = 0.17). Pale yellow oil, yield 53 mg (36 %). $C_{32}H_{33}NO_2$ (463.3). HPLC (method I) Purity 97.8 %. HPLC (method II) Purity 97.3 %. MS (ESI): *m/z* (%) = 464 [M + H$^+$, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059 (C-H$_{arom}$), 2932, 2861 (CH$_2$), 2837 (OCH$_3$), 1067, 1037 (C-O), 821 (1,4-disubst. arom.), 752, 700 (monosubst. arom.), 739 (1,2-disubst. arom.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.99 - 2.13 (m, 1H, 4-C*H*$_2$), 2.17 - 2.29 (m, 1H, 4-C*H*$_2$), 2.75 - 2.96 (m, 1H, 3-C*H*$_2$), 3.08 - 3.17 (m, 1H, 3-C*H*$_2$), 3.15 - 3.25 (m, 1H, 5-C*H*), 3.52 (s, 2H, NC*H*$_2$Ph), 3.69 (d, J = 14.8 Hz, 1H, 1-C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 4.09 - 4.18 (m, 1H, 1-C*H*$_2$), 4.19 (d, J = 11.3 Hz, 1H, PhC*H*$_2$O), 4.42 (d, J = 11.2 Hz, 1H, PhC*H*$_2$O), 4.95 (d, J = 8.9 Hz, 1H, ArCH$_2$O-C*H*Ph), 6.79 - 6.91 (m, 4H, *H*$_{arom}$), 6.94 - 7.02 (m, 1H, *H*$_{arom}$), 7.03 - 7.15 (m, 2H, *H*$_{arom}$), 7.14 - 7.36 (m, 11H, *H*$_{arom}$).

((±)-(5RS)-5-[(SR)-α-(4-Methoxybenzyloxy)benzyl]-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (27c)

A mixture of the secondary amine **23c** (299 mg, 0.80 mmol), K_2CO_3 (884 mg, 6.39 mmol), Bu_4NI (148 mg, 0.40 mmol), 1-chloro-4-phenylbutane (176 µl, 1.04 mmol) and CH_3CN (16 mL) was heated to reflux for 24 h. A saturated NaCl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated in vacuo and the residue was purified by fc (2 cm, 26 cm, cyclohexane/EtOAc = 8:2, 10 mL, Rf = 0.09). Pale yellow oil, yield 220 mg (68 %). $C_{35}H_{39}NO_2$ (505.3). HPLC (method I) Purity 100.0 %. HPLC (method II) Purity 100.0 %. MS (ESI): *m/z* (%) = 506 [M + H^+, 100]. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3025 (C-H_{arom}), 2929, 2856 (CH_2), 2838 (OCH_3), 1079, 1037 (C-O), 821 (1,4-disubst. arom.), 751 (1,2-disubst. arom.), 699 (monosubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.17 - 1.38 (m, 1H, 4-C*H*$_2$), 1.37 - 1.47 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.46 - 1.61 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 1.92 - 2.05 (m, 1H, 4-C*H*$_2$), 2.18 - 2.33 (m, 1H, $CH_2CH_2CH_2CH_2Ph$), 2.31 - 2.40 (m, 1H, 3-C*H*$_2$), 2.41 - 2.49 (m, 1H, $CH_2CH_2CH_2CH_2Ph$), 2.46 (t, J = 7.6 Hz, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.67 - 2.88 (m, 1H, 3-C*H*$_2$), 3.12 - 3.21 (m, 1H, 5-C*H*), 3.30 (s, 3H, OCH_3), 3.64 (d, J = 15.8 Hz, 1H, 1-C*H*$_2$), 4.10 (d, J = 11.2 Hz, 1H, $PhCH_2O$), 4.09 - 4.21 (m, 1H, 1-C*H*$_2$), 4.39 (d, J = 11.2 Hz, 1H, $PhCH_2O$), 4.92 (d, J = 9.1 Hz, 1H, $ArCH_2O$-C*H*Ph), 6.65 - 6.76 (m, 2H, *H*$_{arom}$), 6.79 - 6.90 (m, 2H, *H*$_{arom}$), 6.93 - 6.21 (m, 14H, *H*$_{arom}$). ^{13}C NMR (D_8-toluene): δ (ppm) = 21.0 (1C, $CH_2CH_2CH_2CH_2Ph$), 26.9 (1C, 4-*C*H_2), 29.2 (1C, $CH_2CH_2CH_2CH_2Ph$), 31.0 (1C, $CH_2CH_2CH_2CH_2Ph$), 37.8 (1C, $CH_2CH_2CH_2CH_2Ph$), 55.1 (1C, OCH_3), 56.2 (1C, 1-*C*H_2), 61.2 (1C, $PhCH_2O$), 72.0 (1C, $ArCH_2O$-*C*HPh), 114.5, 125.4, 125.7, 126.0, 126.5, 128.1, 128.2, 128.3, 128.5, 128.8, 129.1, 129.3, 129.4, 129.7, 130.3, 131.5, 138.0, 142.6 (24C, *C*$_{arom}$). Signals for carbon atoms C-3 and C-5 are not visible in the ^{13}C NMR spectrum.

(±)-(RS)-1-Phenyl-1-[(5SR)-2-(4-phenylbutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine-5-yl]methanol (27d)

$(NH_4)_2Ce(NO_3)_6$ (328 mg, 0.59 mmol) was added to a solution of the *p*-methoxybenzyl ether **27c** (137 mg, 0.27 mmol) in CH_3CN-H_2O (6 mL, 9:1) and the mixture was stirred at rt for 30 min. HCl 2 M (0.29 mL, 0.59 mmol) and a saturated NaCl solution (10 mL) were added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, 25 cm, EtOAc/dimethylethanamine = 1:0.01, 10 mL, Rf = 0.30). Pale yellow oil, yield 67 mg (64 %). $C_{27}H_{31}NO$ (385.2). HPLC (method I) Purity 98.9 %. HPLC (method II) Purity 96.6 %. MS (ESI): *m/z* (%) = 386 [M + H^+, 100]. IR (ATR): v (cm^{-1}) = 3344 (OH), 3059 (C-H_{arom}), 2931, 2856 (CH_2), 1285 (C-O), 753, 704 (monosubst. arom.), 735 (1,2-disubst. arom.). ^{1}H NMR (D_8-toluene): δ (ppm) = 1.57 - 1.75 (m, 5H, $CH_2CH_2CH_2CH_2Ph$ and 4-CH_2), 1.74 - 1.87 (m, 1H, 4-CH_2), 2.27 - 2.24 (m, 1H, 3-CH_2), 2.38 - 2.53 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.56 - 2.71 (m, 2H, $CH_2CH_2CH_2CH_2Ph$), 2.99 - 3.16 (m, 1H, 3-CH_2), 3.42 - 3.79 (m, 3H, 1-CH_2 and 5-CH), 5.35 (d, J = 3.9 Hz, 1H, HOCHPh), 7.05 (d, J = 7.6 Hz, 1H, H_{arom}), 7.19 - 7.39 (m, 11H, H_{arom}), 7.43 - 7.52 (m, 2H, H_{arom}). A signal for the proton of the OH group is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (D_8-toluene): δ (ppm) = 25.5 (1C, 4-CH_2), 27.5 (1C, $CH_2CH_2CH_2CH_2Ph$), 29.7 (1C, $CH_2CH_2CH_2CH_2Ph$), 36.4 (1C, $CH_2CH_2CH_2CH_2Ph$), 51.9 (1C, $CH_2CH_2CH_2CH_2Ph$), 54.2 (1C, 5-CH), 58.7 (1C, 1-CH_2), 76.7 (1C, HOCHPh), 124.9, 125.1, 125.3, 125.8, 126.0, 126.7, 127.0, 127.7, 128.2, 129.1, 132.5, 137.4, 139.3, 142.6 (18C, C_{arom}). A signal for the carbon atom C-3 is not seen in the ^{13}C NMR spectrum.

Receptor binding studies

Materials

The guinea pig brains and rat liver for the σ_1 and σ_2 receptor binding assays were commercially available (Harlan-Winkelmann, Borchen, Germany). Pig brains were obtained

from the local slaughter-house. Homogenizer: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany). Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Vortex: Vortex Genie 2 (Thermo Fisher Scientific, Langenselbold, Germany). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat type A and B. Scintillator: Meltilex (type A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany). Chemicals and reagents were purchased from different commercial sources and of analytical grade.

Preparation of membrane homogenates from guinea pig brain[39,40]

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 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500 x *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 23,500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Preparation of membrane homogenates from rat liver[39,40]

Two rat livers were cut into small pieces and 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 1,200 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x *g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS,

pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x *g* for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at -80,°C in 1.5 mL portions containing about 2 mg protein/mL.

Preparation of membrane homogenates from big brain cortex[44,46]

Fresh pig brain cortex was 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 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of TRIS/EDTA buffer (5 mM/1 mM, pH 7.5) and centrifuged again at 31,000 x g (20 min, 4 °C). The final pellet was resuspended in 5-6 volumes of buffer, the protein concentration was determined according to Section 5.3.5. and subsequently the preparation was frozen (−80 °C) in 1.5 mL portions containing about 0.8 mg protein/mL.

Protein determination

The protein concentration was determined by the method of Bradford,[51] modified by Stoscheck.[52] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized H_2O and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg /mL). In a 96-well standard multiplate, 10 µL of the calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

General protocol for the binding assays

The test compound solutions were prepared by dissolving approximately 10 μmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 μL of the respective assay buffer, 50 μL test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 μL of corresponding radioligand solution and 50 μL of the respective receptor preparation into each well of the multiplate (total volume 200 μL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 μL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC_{50}-values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i-values using the equation of Cheng and Prusoff.[53] The K_i-values are given as mean value ± SEM from three independent experiments.

Protocol of the σ_1 receptor binding assay

The assay was performed with the radioligand [^{3}H]-(+)-pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain cortex (about 100 μg of protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-Pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 μM unlabeled (+)-Pentazocine. The K_d-value of (+)-pentazocine is 2.9 nM.[54]

Protocol of the σ_2 receptor binding assay

The assays were performed with the radioligand [^{3}H]DTG (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed membrane preparation of rat liver (about 100 μg of protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]DTG and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in 50 mM TRIS, pH 8.0) at room temperature. The non-specific binding was determined with 10 μM non-labeled DTG. The K_d value of [^{3}H]DTG is 17.9 nM.[55]

Protocol of the assay recording interactions with the PCP binding site of the NMDA receptor

The assay was performed with the radioligand [^{3}H]-(+)-MK 801 (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of pig brain cortex (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-MK 801, and TRIS/EDTA buffer (5 mM/1 mM, pH 7.5) at room temperature. The non-specific binding was determined with 10 μM unlabeled (+) MK 801. The K_d-value of [^{3}H]-(+)-MK 801 is 2.26 nM.[44,46]

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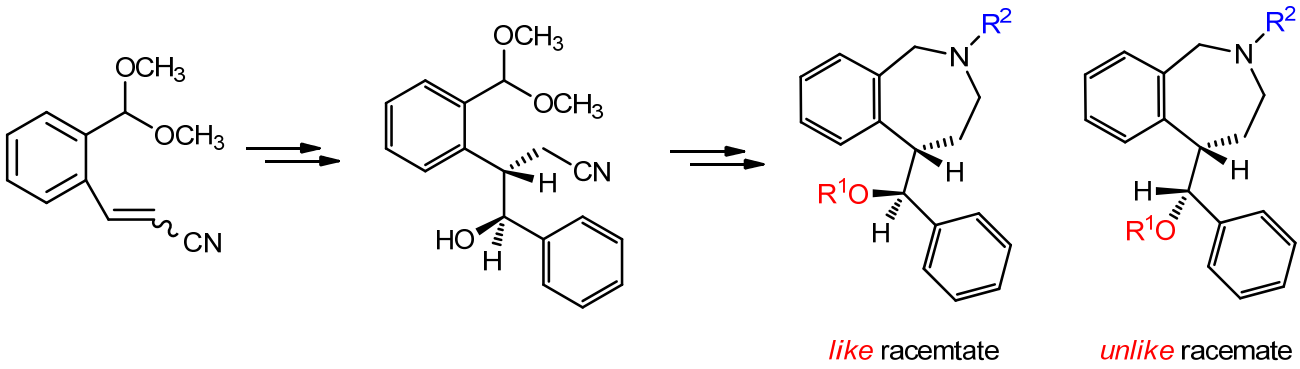
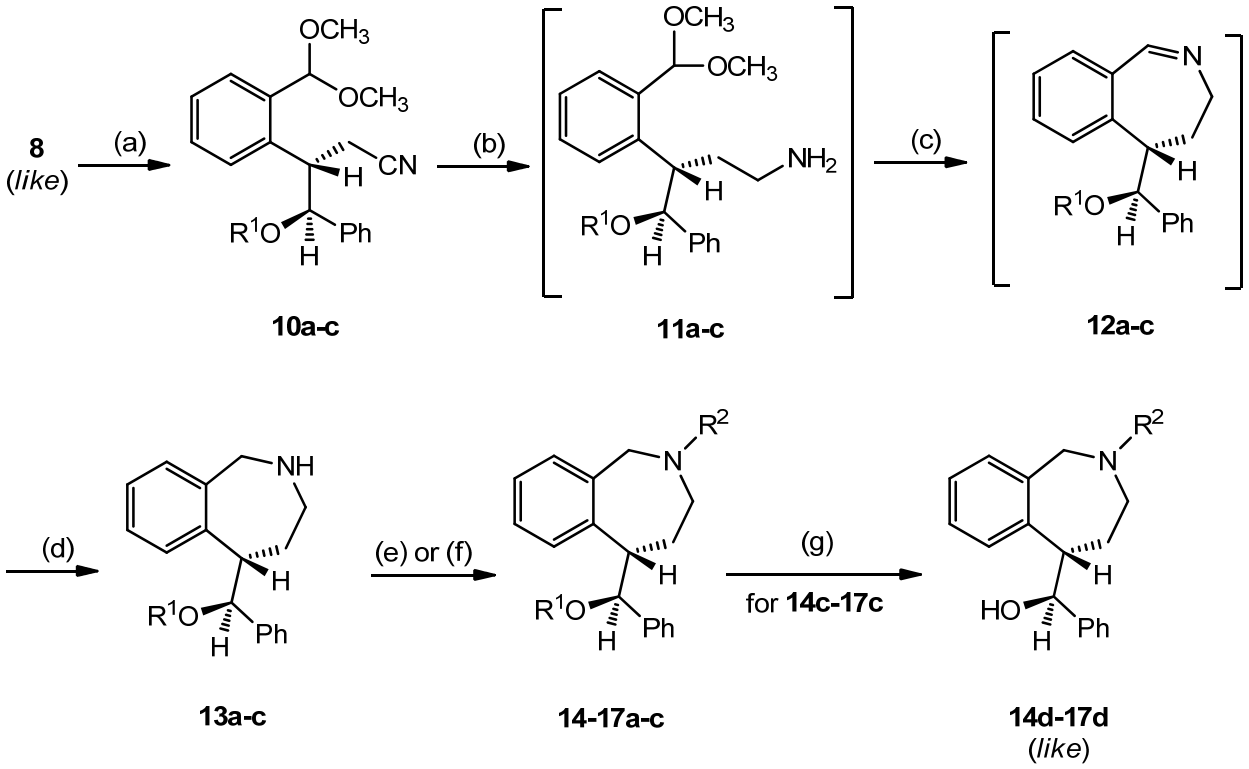
Table of contents entry



5-Substituted tetrahydro-2-benzazepines were prepared and relationships between the structure, in particular the stereochemistry, and the σ_1 affinity were analyzed.

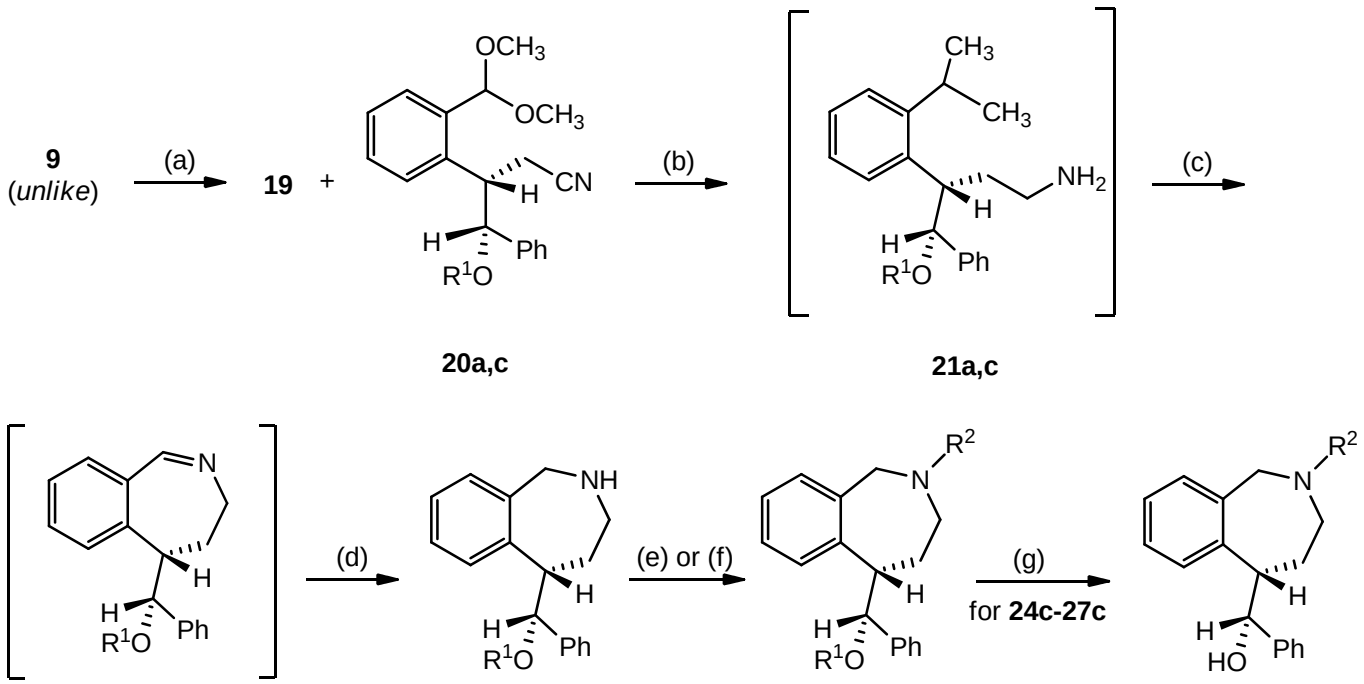
1

Scheme 2



	R^1	R^2
10a-13a	CH_3	-
10b-13b	CH_2Ph	-
10c-13c	PMB	-
14a	CH_3	CH_3
14b	CH_2Ph	CH_3
14c	PMB	CH_3
14d	H	CH_3
15a	CH_3	*n*-Bu
15b	CH_2Ph	*n*-Bu
15c	PMB	*n*-Bu
15d	H	*n*-Bu
16a	CH_3	CH_2Ph
16b	CH_2Ph	CH_2Ph
16c	PMB	CH_2Ph
16d	H	CH_2Ph
17a	CH_3	$(CH_2)_4Ph$
17b	CH_2Ph	$(CH_2)_4Ph$
17c	PMB	$(CH_2)_4Ph$
17d	H	$(CH_2)_4Ph$

Scheme 4



	R^1	R^2
20a-23a	CH_3	-
20c-23c	PMB	-
24c	PMB	CH_3
24d	H	CH_3
25c	PMB	*n*-Bu
25d	H	*n*-Bu
26c	PMB	CH_2Ph
(26d	H	CH_2Ph)
27c	PMB	$(CH_2)_4Ph$
27d	H	$(CH_2)_4Ph$