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Asymmetric Synthesis of Enantiomerically Pure 2-Substituted Tetrahydro-3-benzazepines and Their Affinity to σ_1 Receptors

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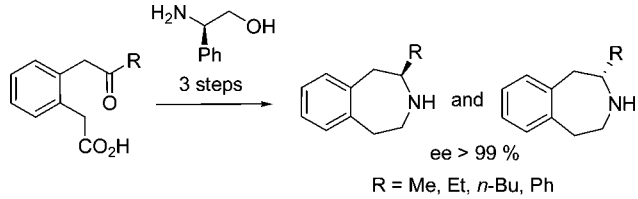

A very short asymmetric synthesis of enantiomerically pure 2-substituted tetrahydro-3-benzazepines is described. First, 3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-ones **3a**−**d** and **4a**−**d** were synthesized by condensation of 2-(2-oxoalkyl)phenylacetic acids **1a**−**d** with (*R*)-phenylglycinol (**2**). With the exception of the 11a-phenyl derivatives **3d/4d** (ratio 91:9), the ratio of the diastereomeric 11a-alkyl derivatives **3a**−**c/ 4a**−**c** was almost 50:50. The configuration of the newly formed chiral center in position 11a was proved by NOE experiments as well as X-ray crystal structure analysis. The reduction of the oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-ones *trans*-**3** and *cis*-**4** with $AlCl_3/LiAlH_4$ (1:3) took place with retention of configuration and yielded 2,3-disubsituted tetrahydro-3-benzazepines **10** and**11**. In the final step, removal of the *N*-(2-hydroxy-1-phenylethyl) residue from **10** and **11** by hydrogenolysis provided four pairs of enantiomerically pure 2-substituted tetrahydro-3-benzazepines **12a**−**d** and *ent*-**12a**−**d**, which were tested for their σ_1, σ_2, and NMDA receptor affinities. The 2-butyl and the 2-phenyl derivatives **12c** and **12d** show very high σ_1 affinity with K_i values of 16 and 50 nM, respectively. The eudismic ratios are greater than 50, reflecting highly stereoselective interaction with the σ_1 receptor. Both σ_1 ligands are very selective against the σ_2 subtype and the PCP binding site of the NMDA receptor.

Introduction

Seven-membered nitrogen heterocycles are constituents of a number of compounds with interesting pharmacological properties.[1−3] The tetrahydro-3-benzazepine ring system is of particular interest from a medicinal chemistry viewpoint because it contains the phenethylamine substructure, which is part of several neurotransmitters (e.g., norepinephrine, dopamine) and corresponding drugs (e.g., salbutamol, pergolide). During the past 30 years, several tetrahydro-3-benzazepines, particularly 1-aryl derivatives, have been developed as dopamine receptor agonists and antagonists, e.g., fenoldopam and SCH-23390[3,4] (Figure 1). Very recently. 1-methyl-2,3,4,5-tetrahydro-1*H*-3-

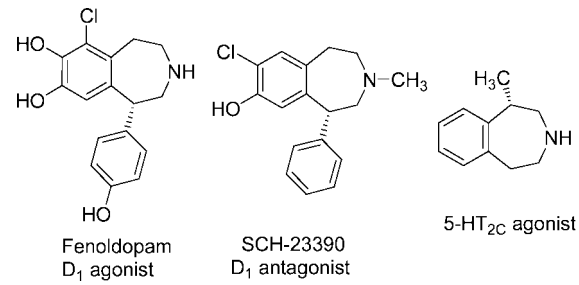

FIGURE 1. Pharmacologically interesting 3-benzazepines.

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benzazepines have been described as selective 5-HT_{2C} receptor agonists, which can be used for the treatment of obesity.[5]

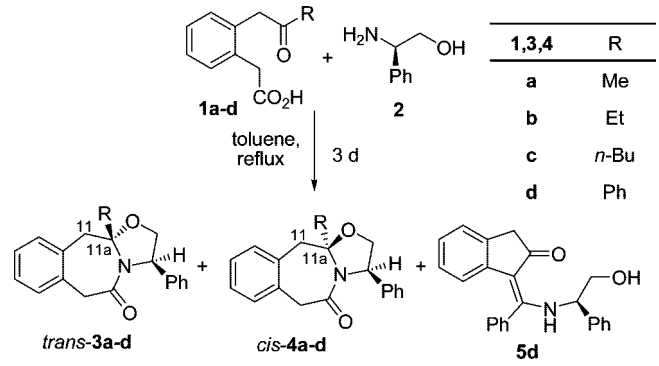
Recently, high σ receptor affinity of enantiopure 1-substituted 3-benzazepines was reported from our group.[6] This prompted us to study binding of enantiopure 2-substituted 3-benzazepines at σ receptors as viable targets. The σ receptors are well established as a nonopioid, nonphencyclidine, and haloperidol-sensitive receptor family with its own binding profile and a characteristic distribution in the central nervous system (CNS) and some peripheral tissues, like kidney, liver, lung, and heart.[7,8] The class of σ receptors comprises two subtypes, termed σ_1 and σ_2 receptors. The σ_1 receptor plays an important role in several physiological and pathophysiological processes. In particular, σ_1 antagonists can be used for the treatment of psychosis, and they represent a new principle for the treatment of neuropathic pain. Furthermore, σ ligands are investigated in clinical studies for the treatment of depression, cocaine abuse, and epilepsy.[9−11] The structures of σ_1 ligands are quite diverse. In order to gain more information about the σ_1 binding site, it is necessary to develop stereochemically defined, conformationally restricted ligands with high σ_1 affinity and high selectivity.

In this work, a new strategy for the asymmetric synthesis of enantiomerically pure 2-substituted 3-benzazepines is described and the σ receptor affinity as well as the affinity to the PCP binding site of the NMDA receptor of the resulting products is detailed.

The asymmetric syntheses of substituted heterocycles by Meyers et al. and Amat et al. make use of enantiomerically pure oxazolidines. The intermediate bicyclic or tricyclic oxazolidines were synthesized by condensation of γ-, δ-, or ε-keto acids with a chiral auxiliary such as (*R*)- or (*S*)-phenylglycinol.[12−15] In particular, Amat et al. have used bicyclic oxazolidines for the synthesis of diversely substituted piperidines and achieved the synthesis of several natural occurring alkaloids.[16−18] However, Meyers et al. make extensive use of chiral nonracemic bicyclic and tricyclic lactams in the asymmetric synthesis of several carbo- and heterocycles such as substituted naphthalenones, azepines, piperidines, and pyrrolidines.[19−21]

In order to show the success of the oxazolidine methodology toward the synthesis of diversely substituted 3-benzazepines, we planned to use different keto acids **1a**−**d**, which have been prepared by reaction of *o*-phenylenediacetic acid with RLi.[22] The condensation of the keto acids **1a**−**d** with (*R*)-phenylglycinol should give *trans*- and *cis*-configured tricyclic oxazolidines, which should be exploited for the synthesis of enantiomerically pure 2-substituted tetrahydro-3-benzazepines.

SCHEME 1. Synthesis of Tricyclic Benzolactams *trans*-3 and *cis*-4[a]



[a] Note: The stereodescriptors *trans* and *cis* define the relative configuration in the oxazolidine ring: In **3** (**4**), the higher ranked substituents (Ph and CH_2aryl) are on opposite sides (the same side) of the oxazolidine ring plane. In order to avoid confusion, the *trans* and *cis* assignment is maintained for the **d**-series (R = phenyl), although the hierarchy of the substituents is changed according to CIP formalism.

Results and Discussion

The *trans*- and *cis*-configured tricyclic benzolactams *trans*-**3** and *cis*-**4** represent the key intermediates in the planned asymmetric synthesis of diversely substituted tetrahydro-3-benzazepines. In order to synthesize the tricyclic benzolactams **3** and **4**, a solution of keto acids **1a**−**d** and (*R*)-phenylglycinol (**2**) in toluene was heated to reflux for 3 days. These reaction conditions produced pairs of *trans*- and *cis*-configured tricyclic benzolactams *trans*-**3a**−**d** and *cis*-**4a**−**d** (Scheme 1).

The *trans*- and *cis*-configured diastereomers *trans*-**3a**−**c** and *cis*-**4a**−**c** were separated and isolated by flash chromatography. The configuration at the newly formed chiral center 11a was determined by NOE experiments.

The ratio of diastereomers, which was formed during the condensation of **1a**−**d** with (*R*)-phenylglycinol, was determined by interpretation of the ^{1}H NMR spectra of the crude reaction mixtures. Generally, 3-H of *trans*-configured benzolactams **3a**−**d** gave characteristic triplets in the range 5.30−5.50 ppm (J = 8.0−8.9 Hz), whereas 3-H of the *cis*-configured benzolactams **4a**−**d** gave characteristic dd's in the range 4.76−5.05 ppm (J = 7.5/2 Hz). The ratio of the diastereomeric tricyclic benzolactams **3a**−**d**:**4a**−**d** was determined by integration of these characteristic 3-H signals. The results are summarized in Table 1, which clearly indicate ratios of about 1:1 when using a keto acid with an aliphatic residue at the keto group (**1a**−**c**).

In contrast to the reaction of alkyl keto acids **1a**−**c**, the phenyl keto acid **1d** reacted with (*R*)-phenylglycinol (**2**) to form the diastereomers *trans*-**3d** and *cis*-**4d** in the ratio 91:9 along with a side product **5d** causing a doublet at 5.60 ppm. The ratio of the three compounds *trans*-**3d**, *cis*-**4d**, and **5d** was 62:6:32, as determined by integration of characteristic signals in the ^{1}H NMR spectrum of the crude reaction mixture.

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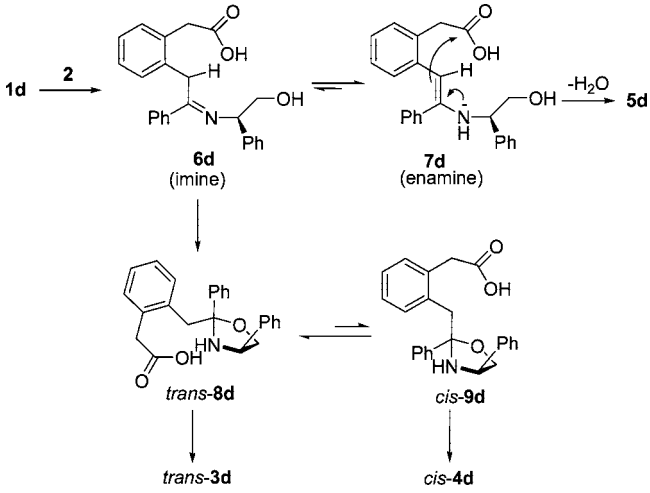
TABLE 1. Ratio of *trans*- and *cis*-Configured Tricyclic Benzolactams Formed by Condensation of 1a−d with 2

trans/cis	ratio	R
3a/4a	52:48	Me
3b/4b	52:48	Et
3c/4c	54:46	*n*-Bu
3d/4d	91:9	Ph
ent-**3d**/*ent*-**4d**	90:10	Ph

SCHEME 2. Formation of the Diastereomeric Oxazolidines 3 and 4 and Indanone 5d



In order to unequivocally assign the configuration an X-ray crystal structure analysis of the main diastereomer *trans*-**3d** was performed. The third product **5d**, which was formed in the reaction of phenyl keto acid **1d** with (*R*)-phenylglycinol, was isolated in 32% yield. The structure of the indanone derivative **5d**, which could not be assigned unequivocally using various NMR spectroscopy techniques, was also identified by an X-ray crystal structure analysis.

The formation of equal amounts of two diastereomers in case of Me, Et, and *n*-Bu derivatives can be explained on the basis of the reaction mechanism proposed by Meyers et al.[14] (Scheme 2). Accordingly, the existence of an equilibrium between *trans*- and *cis*-configured oxazolidines *trans*-**8a−c** and *cis*-**9a−c**, which were formed by the loss of one water molecule, and the equally stable tricyclic products *trans*-**3a−c** and *cis*-**4a−c** resulted in the observed diastereomeric ratios of 1:1. In the case of phenyl derivatives, the 91:9 ratio of *trans*-**3d**/*cis*-**4d** can be explained by stabilizing π/π-interactions of the *cis*-oriented phenyl rings in positions 2 and 4 of the *trans*-configured intermediate *trans*-**8d**. This stabilizing effect shifts the equilibrium to *trans*-**8d** and finally leads to the higher amount of *trans*-**3d**.

The formation of indanone **5d** was explained on the basis of an imine−enamine tautomerism. In the enamine tautomer **7d**, the double bond is stabilized by two phenyl groups, which are shifting the imine (**6d**)−enamine (**7d**) equilibrium on the enamine side. The enamine **7d** is able to attack the carboxy group and provide the indanone **5d**.

The condensation of phenyl keto acid **1d** with (*R*)-phenylglycinol (**2**) provided stereoselectively the *trans*-configured diastereomer *trans*-**3d** with (*R*)-configuration at position 11a in 44% yield. However, the diastereomer *cis*-**4d** with (*S*)-configuration at position 11a was only formed in low amounts. Considering the importance of the (11a*S*)-configured tricyclic benzolactam *cis*-**4d** for the synthesis of the enantiomeric benzazepine *ent*-**12d**, the phenyl keto acid **1d** was also reacted with (*S*)-phenylglycinol (*ent*-**2**). In analogy with the transformation with (*R*)-phenylglycinol (**2**), *trans*- and *cis*-configured diastereomers *ent*-**3d** and *ent*-**4d** were produced in a ratio of 90:10 using (*S*)-phenylglycinol, along with the indanone *ent*-**5d**. The products *ent*-**3d**, *ent*-**4d** and *ent*-**5d** were purified and isolated by flash chromatography in 46%, 2%, and 37% yield, respectively.

The tricyclic benzolactams *trans*-**3a-d**, *ent*-**3d**, and *cis*-**3a−c** were then reduced using alane (AlH_3), which was formed in situ from $AlCl_3/LiAlH_4$ (1:3). The reaction resulted in the formation of two diastereomers **10** and **11**. (Scheme 3) The reduction of both diastereomers *trans*-**3** and *cis*-**4** led predominantly to the products with retention of configuration, respectively. An X-ray crystal structure of the benzylated analogue of **10a** proves that the reduction with AlH_3 had taken place with retention of configuration at the original stereocenter C-11a.[23]

Since HPLC analysis with various achiral stationary phases did not lead to a separation of the diastereomeric pairs **10/11**, the diastereomeric ratios were determined by a chiral HPLC analysis, using CHIRALPAK AD-H column. With this HPLC method it was possible to demonstrate that the flash chromatographic purification led to a considerable improvement of the diastereomeric ratios. Exemplarily, in case of the methyl derivatives the diastereomeric ratios were increased from 93:7 to 98:2 (**10a/11a**) and from 89:11 to 99.5:0.5 (**11a/10a**). The diastereomeric pairs **10b−d/11b−d** were also separated by fc and analyzed using the described chiral HPLC method (Table 2). Since the chromatographic behavior of the diastereomers **10** and **11** was quite similar, the complete separation resulted in reduced yields. However, diastereomerically pure samples were required for the synthesis of enantiomerically pure 2-substituted 3-benzazepines **12**.

In the final step, 2-substituted 3-benzazepines **12** were obtained by hydrogenolysis of compounds **10a−d**, *ent*-**10d**, and **11a-c** (Scheme 4). The removal of the 2-hydroxy-1-phenylethyl moiety was performed with H_2 and Pd/C as catalyst after addition of a small amount of HCl. The compounds **12a−d** and *ent*-**12a−d** were obtained in 60−99% yields. However, the 3-benzazepines **12a** and **12b** with a small methyl or ethyl substituent are rather volatile. So, it was difficult to remove the solvent completely without dramatic loss of products.

The diastereomeric ratios determined for **10** and **11** are identical to the enantiomeric ratios of the produced 2-substituted tetrahydro-3-benzazpines **12**. Thus, with exception of **12a** and **12b** (98:2), the 3-benzazepines **12** were isolated in almost enantiomerically pure form (ee >99%) (Table 3).

Receptor Affinity

The affinity of enantiomerically pure 2-substituted 3-benzazepines **12a−d** and *ent*-**12a−d** to σ_1 and σ_2 receptors as well as the PCP binding site of the NMDA receptor was determined in receptor-binding studies.

In the σ assays, the radioligands [^{3}H]-(+)-pentazocine (σ_1) and [^{3}H]-ditolylguanidine (σ_2) and membrane preparations from guinea pig brains (σ_1) and rat livers (σ_2) were used.[6,24,25] In addition to σ receptor binding, the affinity toward NMDA

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SCHEME 3. Reduction of *trans*- and *cis*-Configured Tricyclic Benzolactams with AlH_3

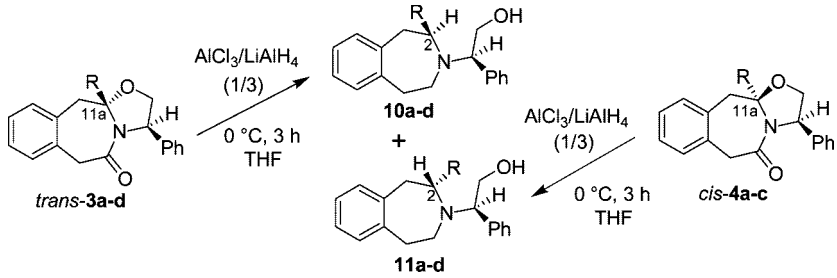


TABLE 2. Diastereomeric Ratios and Yields of the Reduced Products 10a−d, *ent*-10d, and 11a−c after fc Purification

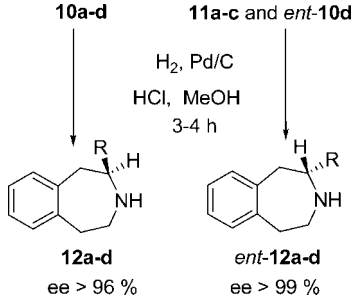
R	diastereomers	ratio	yield of **10** (%)	diastereomers	ratio	yield of **11** (%)
Me	**10a/11a**	98:2	36	**10a/11a**	0.5:99.5	51
Et	**10b/11b**	98:2	41	**10b/11b**	0.2:99.8	32
n-Bu	**10c/11c**	99.7:0.3	45	**10c/11c**	0.3:99.7	47
Ph	**10d/11d**	99.4:0.6	55			
Ph	*ent*-**10d**/*ent*-**11d**	99.7:0.3	45			

TABLE 3. Yields, Enantiomeric Excess, and Specific Optical Rotation of 2-Substituted 3-Benzazepines 12a−d and Their Enantiomers *ent*-12a−d

R	compound	yield (%)	ee[b] (%)	specific rotation	compd	yield (%)	ee[b] (%)	specific rotation
Me[a]	**12a**	88	96	+12.6	*ent*-**12a**	73	99.0	−11.8
Et[a]	**12b**	77	96	+28.9	*ent*-**12b**	83	99.6	−32.8
n-Bu	**12c**	92	99.4	+36.7	*ent*-**12b**	94	99.4	−37.4
Ph	**12d**	60	98.8	+52.7	*ent*-**12d**	80	99.4	−54.9

[a] Volatile compounds! [b] The ee values are derived from the ratio of the diastereomers **10/11**.

SCHEME 4. Hydrogenolysis of the Reduced Products



receptors was also included in this study because some potent σ_1 antagonists also interact with NMDA receptors. The affinity for the PCP binding site of the NMDA receptor was determined in competition experiments using the radioligand [^{3}H]-(+)-MK-801.[6] Fresh pig brain cortex membrane preparations were employed as receptor material.

With exception of *ent*-**12a**, both enantiomers of the 3-benzazepines with small substituents (Me, Et) in position 2 (**12a** and **12b**) show very low σ_1 affinity (K_i > 3000 nM). However, the enantiomers **12c** and **12d** with a butyl or phenyl substituent show high σ_1 receptor affinity with K_i values of 16 and 50 nM, respectively. The corresponding enantiomers *ent*-**12c** and *ent*-**12d** display only low σ_1 affinity indicating high eudismic ratios of greater than 50 for both enantiomeric pairs. The σ_1 receptor shows a clear preference at least for the butyl and phenyl substituted 3-benzazepines with a definite orientation of the 2-substituent ((2*R*) for **12c** and (2*S*) for **12d**).

The high σ_1 affinity of **12c** and **12d** may be due to the presence of the long hydrophobic butyl chain or the large phenyl ring, which fill up the hydrophobic pocket of the σ_1 receptor. In case of the smaller methyl and ethyl groups of **12a** and **12b**, the hydrophobic interactions are too small to produce considerable free energy during binding to the σ_1 receptor protein.

TABLE 4. Affinity of Enantiomerically Pure 2-Substituted 3-Benzazepines toward σ_1, σ_2, and NMDA Receptors

		K_i ± SEM [nM]		
compd	R	σ_1	σ_2	NMDA
12a	Me	3670	3053	40%[a]
ent-**12a**		299 ± 114	9%[a]	48%[a]
12b	Et	36%[a]	1040	15%[a]
ent-**12b**		40%[a]	5%[a]	35%[a]
12c	*n*-Bu	16 ± 1.4	3025 ± 1020	20%[b]
ent-**12c**		879 ± 49	2062	0%[a]
12d	Ph	50 ± 34.8	616	32%[a]
ent-**12d**		0% [a]	427 ± 109	8%[a]
(+)-pentazocine		4.2 ± 1.1		
haloperidol		3.9 ± 1.5	78 ± 2.3	
ditolylguanidine		61 ± 18	42 ± 17	
(*S*)-ketamin				383 ± 41
(+)-MK-801				2.9 ± 0.6

[a] Inhibition of the radioligand binding at a concentration of 1 μM. [b] Inhibition of the radioligand binding at a concentration of 10 μM.

The affinity of the 3-benzazepines **12** toward σ_2 receptors is considerably lower compared with their affinities to σ_1 receptors, indicating high σ_1/σ_2 selectivity. Only the phenyl derivatives **12d** and *ent*-**12d** possess moderate σ_2 affinity. Since both enantiomers have almost the same K_i values, the eudismic ratio is almost one. It should be noted that the receptor selectivity is dramatically influenced by the stereochemistry. Whereas the enantiomer **12d** predominantly interacts with the σ_1 receptor, the enantiomer *ent*-**12d** prefers the σ_2 subtype.

The affinity of all 3-benzazepines **12** and *ent*-**12** toward the PCP binding site of the NMDA receptor is very low. At a concentration of 1 μM, the inhibition of radioligand binding is lower than 50% indicating IC_{50} values greater than 1 μM. In

particular the 2-butyl- and 2-phenyl-3-benzazepines **12c** and **12d** represent potent σ_1 ligands with high selectivity toward the σ_2 receptor and the PCP binding site of the NMDA receptor.

Conclusion

A general procedure for the synthesis of chiral nonracemic tricyclic benzolactams was established, which was used successfully for the synthesis of enantiopure 2-substituted 3-benzazepines in only two reductive steps (AlH_3; H_2, Pd/C). A series of four enantiomeric pairs **12a-d** and *ent*-**12a-d** was synthesized according to the new method. Receptor binding studies revealed that the butyl and the phenyl derivatives **12c** and **12d** bind with high affinity to σ_1 receptors. Compounds **12c** and **12d** show high eudismic ratios (>50) and high selectivity over the σ_2 subtype and the PCP binding site of the NMDA receptor.

Experimental Section

General Methods. The keto acids **1a**−**d** were prepared by reaction of *o*-phenylenediacetic acid with organolithium reagents. The method is being described in literature.[22]

General Procedure A for the Synthesis of Tricyclic Benzolactams (Oxazolo-3-benzazepinones). A solution of keto acid (3.98 mmol, 1 equiv) and (*R*)-phenylglycinol (3.98 mmol, 1 equiv) in toluene (40 mL) was heated to reflux for 3 d. Then the mixture was cooled and concentrated in vacuum, and the residue was dissolved in EtOAc (50 mL). The solution was washed with 1 M NaOH (3 × 15 mL), the aqueous layer was extracted three times with EtOAc, the combined EtOAc layers were washed with 1 M HCl (3 × 15 mL), the HCl layers were extracted three times with EtOAc, and the combined EtOAc layers were washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated in vacuum. The ^{1}H NMR spectrum of the residue was recorded in order to determine the ratio of the two diastereomers. The two diastereomers were separated by flash chromatography and were further purified by recrystallization (CH_2Cl_2/*n*-hexane) if necessary.

General Procedure B for the Reduction of Tricyclic Benzolactams Using Alane (AlH_3). At 0 °C, dry THF (8 mL) was added to anhydrous $AlCl_3$ (1.02 mmol, 1 equiv) under nitrogen atmosphere. The resulting clear colorless solution was allowed to stir at 0 °C for 5 min. Then a solution of $LiAlH_4$ (1.0 M in THF, 3.05 mmol, 3 equiv) was added via syringe. The resulting clear, colorless solution was allowed to warm to room temperature and was stirred for 20 min to give a solution of alane (AlH_3).

A solution of tricyclic benzolactam (1.02 mmol, 1 equiv) in dry THF (8 mL) was added to the stirred, cooled (0 °C) solution of alane in dry THF under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 3 h and then warmed to room temperature over 30 min. The resulting clear solution was recooled to 0 °C and then quenched by careful addition of 1 M HCl (only few drops). The resulting slurry was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with 1 M NaOH (back-extracted with CH_2Cl_2 (15 mL)) and washed with brine (15 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuum to provide the crude product, which was further purified by flash chromatography.

General Procedure C for the Hydrogenolysis. A mixture of phenylethanol derivative and Pd/C (10% by wt) in methanol and 1 M HCl (1.5 mL) was stirred at room temperature under a H_2 atmosphere (balloon) for 4−6 h. The reaction mixture was filtered using a silica bed, and the solvent was removed under reduced pressure to obtain a residue, which was dissolved in CH_2Cl_2 (10 mL) and washed with 1 M NaOH (3 × 4 mL), which was back-extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo (at max 30 °C) to provide an oily liquid which was purified by flash chromatography.

(3*R*,11a*S*)-11a-Methyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one (*trans*-3a) and (3*R*,11a*R*)-11a-Methyl-3-phenyl-2,3,11,11a-tetrahydro[1,3]oxazolo[2,3-*b*][3]benzazepin-5(6*H*)-one (*cis*-4a). Following general procedure A for the synthesis of tricyclic benzolactams, the keto acid **1a** (766 mg, 3.98 mmol) and (*R*)-phenylglycinol (**2**, 546.1 mg, 3.98 mmol) were heated to reflux in toluene (40 mL) for 3 d to obtain 1459 mg of crude product. The ^{1}H NMR spectrum of the residue shows signals for the diastereomers **3a** and **4a** in a ratio 50:50. The diastereomers **3a** and **4a** were separated by flash chromatography (∅ 5 cm, l = 25 cm, V = 30 mL, EtOAc/cyclohexane 10:90 to 40:60) and were further purified by recrystallization (CH_2Cl_2/*n*-hexane). *trans*-**3a**: R_f = 0.48 (petroleum ether/EtOAc 50:50); colorless solid; yield 479 mg (41%); mp 141−143 °C; $[\alpha]^{20}_{589}$ = −56.3 (c = 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H, *CH*$_3$), 3.24 (d, J = 14.7 Hz, 1H, 11-H), 3.51 (d, J = 14.7 Hz, 1H, 11-H), 3.89 (t, J = 8.8 Hz, 1H, 2-H), 3.96 (m, 2H, 6-H), 4.48 (t, J = 8.6 Hz, 1H, 2-H), 5.44 (t, J = 8.0 Hz, 1H, 3-H), 7.15 (d, J = 7.4 Hz, 2H, arom), 7.20−7.32 (m, 7H, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (1C, *CH*$_3$), 43.4 (1C, C-11), 44.2 (1C, C-6), 60.9 (1C, C-2), 69.2 (1C, C-3), 94.5 (1C, C-11a), 125.6, 127.3, 127.9, 128.0, 129.6, 130.3 (9C, Ph-*CH*) 133.9, 134.6, 140.6, (3C, Ph-*C*), 167.1 (1C, *C*=*O*); FT-IR (ATR, film) $\tilde{\nu}$ (cm^{-1}) 3027 (w, arom C−H), 2985, 2883 (w, aliph C−H), 1635 (s, carbonyl C=O); MS (EI) *m*/*z* 293 [M, 6], 251 [M − $COCH_2$, 24], 160 [M − ($COCH_2$, C_7H_7), 72], 120 [$PhCHCH_2O$, 100]; HPLC purity 92.8%, t_R = 20.81 min; HRMS calcd for $C_{19}H_{19}NO_2H$ 294.1489, found 294.1485. *cis*-**4a**: R_f = 0.14 (petroleum ether/EtOAc 50:50); colorless solid; yield 362.4 mg (31%); mp 99−101 °C; $[\alpha]^{20}_{589}$ = +137 (c = 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 3H, *CH*$_3$), 3.31 (d, J = 15.4 Hz, 1H, 11-H), 3.45 (d, J = 14.9 Hz, 1H, 6-H), 3.53 (d, J = 15.4 Hz, 1H, 11-H),3.76 (dd, J = 9.0/ 2.0 Hz, 1H, 2-H), 3.79 (d, J = 14.8 Hz, 1H, 6-H), 4.34 (dd, J = 9.0/ 7.7 Hz, 1H, 2-H), 4.93 (dd, J = 7.4/1.4 Hz, 1H, 3-H), 6.71 (d, J = 7.0 Hz, 2H, arom), 6.97−7.26 (m, 7H, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8 (1C, *CH*$_3$), 43.4 (1C, C-11), 44.8 (1C, C-6), 60.3 (1C, C-2), 70.7 (1C, C-3), 94.0 (1C, C-11a), 125.7, 127.3, 127.6, 127.7, 128.4, 129.3, 130.3 (9C, Ph-*CH*), 134.5, 135.5, 141.9 (3C, Ph-*C*), 167.2 (1C, *C*=*O*). FT-IR (ATR, Film): $\tilde{\nu}$ (cm^{-1}) = 3028 (w, arom. C−H), 2979 (w, aliph C−H), 1652 (s, carbonyl C=O); MS (EI) *m*/*z* 293 [M, 8], 251 [M − $COCH_2$, 24], 160 [M − ($COCH_2$, C_7H_7), 65], 120 [$PhCHCH_2O$, 100]; HPLC purity 99.5%, t_R = 20.07 min; HRMS calcd for $C_{19}H_{19}NO_2H$ 294.1489, found 294.1489.

(*R*)-2-[(*R*)-2-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethanol (10a). Following general procedure B for reduction with AlH_3, *trans*-**3a** (300 mg, 1.02 mmol) was reduced with AlH_3 to give 318 mg of the crude product. The product was purified by column chromatography (EtOAc/cyclohexane 15:85) and analyzed for dr: colorless oil; yield 192.8 mg (66.7%); chiral HPLC (*n*-hex/*i*-pro 98:2) ratio of **10a/11a** = 93: 7, t_R(**10a**) = 14.64, t_R(**11a**) = 16.26. After second column: ∅ = 2 cm, l = 45 cm, V = 100 mL, petroleum ether/EtOAc 95:5. After all columns: yield 104.1 mg (36%); ratio **10a/11a** = 98:2; $[\alpha]^{20}_{589}$ = −48.2 (c = 0.79, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3H, *CH*$_3$), 2.68 (dd, J = 14.6/6.5 Hz, 1H, 1-H), 2.72−2.83 (m, 2H, 4-H/5-H), 2.98−3.09 (m, 2H, 4-H/5-H), 3.20−3.26 (m, 2H, 1-H/ 2-H), 3.78 (dd, J = 10.5/4.8 Hz, 1H, *CH*$_2$OH), 3.95 (dd, J = 10.4/ 7.9 Hz, 1H, *CH*$_2$OH), 4.02 (dd, J = 7.8/4.8 Hz, 1H, N*CH*Ph), 7.00−7.06 (m, 4H, arom), 7.28−7.36 (m, 5H, arom, asignal for OH proton could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (1C, *CH*$_3$), 37.0 (1C, C-5), 43.5 (1C, C-1), 45.6 (1C, C-4), 51.9 (1C, C-2), 61.5 (1C, *CH*$_2$OH), 67.0 (1C, N*CH*Ph), 126.4, 126.6, 128.0, 128.5, 128.7, 128.8, 130.1 (9C, Ph-*CH*), 139.0, 139.2, 141.2 (3C, Ph-*C*). FT-IR (ATR, film): $\tilde{\nu}$ (cm^{-1}) = 3431 (w, O−H), 3062 (w, arom C−H), 3024 (w, arom C−H), 2928 (w, aliph C−H); MS (EI) *m*/*z* 282 [MH$^+$, 2], 251 [MH − (CH_2OH), 100], 91 [C_7H_7, 21]; HPLC purity 97.4%, t_R = 17.20 min; HRMS calcd for $C_{19}H_{23}NOH$: 282.1852, found 282.1861.

(*R*)-2-[(*S*)-2-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl]-2-phenylethanol (11a). Following general procedure B for reduction with AlH_3, *cis*-**4a** (300 mg, 1.02 mmol) was reduced with AlH_3 to give 328 mg of the crude product. The product was purified by flash chromatography (EtOAc/cyclohexane 15:85) and analyzed for dr: colorless oil; yield 228 mg (79%); chiral HPLC (*n*-hex/*i*-pro 98:2): ratio of **11a**/**10a** = 89:11, t_R(**10a**) = 14.64, t_R(**11a**) = 16.26. After the first column (2 cm × 20 cm): cyclohexane/EtOAc 85:15. After the second column (∅ = 2 cm, l = 45 cm, V = 100 mL, petroleum ether/EtOAc 95:5): yield 180.2 mg (62.6%), ratio of **11a**/**10a** = 99.5:0.5; $[\alpha]^{20}_{589}$ = +5.0 (c = 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J = 6.7 Hz, 3H, *CH*$_3$), 2.63 (dd, J = 14.4/6.3 Hz, 1H, 1-H), 2.69−2.76 (m, 2H, 4-H, 5-H), 3.02−3.08 (m, 2H, 4-H, 5-H), 3.34 (dd, J = 14.4/2.6 Hz, 1H, 1-H), 3.39−3.46 (m, 1H, 2-H), 3.66 (dd, J = 10.8/5.3 Hz, 1H, *CH*$_2$OH), 3.84 (dd, J = 10.8/8.3 Hz, 1H, *CH*$_2$OH), 3.98 (dd, J = 8.2/5.3 Hz, 1H, N*CH*Ph), 7.02−7.15 (m, 4H, arom), 7.28−7.34 (m, 5H, arom), a signal for OH proton could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (1C, *CH*$_3$), 37.2 (1C, C-5), 42.2 (1C, C-4), 43.5 (1C, C-1), 54.9 (1C, C-2), 62.2 (1C, *CH*$_2$OH), 70.1 (1C, N*CH*Ph), 126.4, 126.5, 127.9, 128.7, 128.8, 128.9, 130.2 (9C, Ph-*CH*), 139.0, 140.3, 141.4 (3C, Ph-*C*); FT-IR (ATR, film) $\tilde{\nu}$ (cm^{-1}) = 3414 (b, alcoholic OH), 3058, 3020 (w, arom C−H), 2962, 2927 (w, aliph C−H); MS (EI) m/z 282 [MH$^+$, 0.6], 250 [M − CH_2OH, 100], 91 [C_7H_7, 15]; HPLC purity 98%, t_R = 17.20 min; HRMS calcd for $C_{19}H_{23}NOH$ 282.1852, found 282.1862.

(*R*)-2-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12a). Following general procedure C for hydrogenolysis, **10a** (97.7 mg, 0.34 mmol) was stirred under H_2 to yield 80 mg of a crude yellow oil. Flash chromatography (∅ = 1 cm, l = 25 cm, V = 10 mL, EtOAc/petroleum ether/NH_3 79.5:20:0.5) of the crude product gave a colorless liquid, yield 49 mg (88%), R_f = 0.26 (EtOAc/MeOH/NH_3 30:69:1): $[\alpha]^{20}_{589}$ = +12.6 (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.1 Hz, 3H, C*H*$_3$), 2.72−2.91 (m, 5H, 1-H/2-H/4-H/5-H), 3.01 (ddd, J = 14.7/10.6/1.9 Hz, 1H, 4-H), 3.23 (ddd, J = 12.9/6.5/2.90 Hz, 1H, 5-H), 7.06−7.13 (m, 4H, Ph-*CH*), asignal for NH proton could not be detected; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (1C, *C*H$_3$), 39.3 (1C, C-5), 46.7 (1C, C-1), 47.8 (1C, C-4), 53.5 (1C, C-2), 126.4, 126.4, 129.3, 129.8 (4C, Ph-*C*H), 140.8, 142.4 (2C, Ph-*C*); FT-IR (ATR, film) $\tilde{\nu}$ (cm^{-1}) 3305 (w, NH), 3147, 3015 (w, arom C−H), 2965, 2929, 2897, 2821 (w, aliph C−H); MS (EI) m/z 162 [MH$^+$,100], 146 [M − CH_3, 90], 115 [Ph-C_3H_5, 38]; HRMS calcd for $C_{11}H_{15}NH$ 162.1277, found 162.1274; HPLC purity 99.1%, t_R = 11.79 min.

(*S*)-2-Methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*ent*-12a). Following general procedure C for hydrogenolysis, **11a** (36 mg, 0.13 mmol) was stirred under H_2 to afford a colorless liquid: yield 15.5 mg (73%); $[\alpha]^{20}_{289}$ = −11.8 (c = 0.3, CH_2Cl_2); HRMS calcd for $C_{11}H_{15}NH$ 162.1277, found 162.1276; HPLC purity 98.6%, t_R = 11.95 min.

(*R*)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-3-benzoazepine (12b). Following general procedure C for hydrogenolysis, **10b** (126 mg, 0.42 mmol) was stirred under H_2 to give a colorless liquid: yield 58.4 mg (77%); R_f = 0.26 (EtOAc/MeOH/NH_3 30:69:1); $[\alpha]^{20}_{589}$ = +28.9 (c = 0.58, CH_2Cl_2); HRMS calcd for $C_{12}H_{17}NH$ 176.1434, found 176.1446; HPLC purity 99.1%, t_R = 11.79 min.

(*S*)-2-Ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*ent*-12b). Following general procedure C for hydrogenolysis, **11b** (109 mg, 0.36 mmol) was stirred under H_2 to afford a colorless liquid: yield 54 mg (83%); $[\alpha]^{20}_{589}$ = −32.8 (c = 0.76, CH_2Cl_2); HRMS calcd for $C_{12}H_{17}NH$ 176.1434, found 176.1458; HPLC purity 99.1%, t_R = 11.79 min.

(*R*)-2-Butyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12c). Following general procedure C for hydrogenolysis, **10c** (77 mg, 0.24 mmol) was stirred under H_2 to give a pale yellow liquid: yield 44.8 mg (92%), R_f = 0.12 (EtOAc/petroleum ether/NH_3 80:19.5:0.5); $[\alpha]^{20}_{589}$ = +36.7 (c = 0.72, CH_2Cl_2); HRMS calcd for $C_{14}H_{21}NH$ 204.1747, found 204.1756; HPLC purity 97.2%, t_R = 16.51 min.

(*S*)-2-Butyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*ent*-12c). Following general procedure C for hydrogenolysis, **11c** (106 mg, 0.33 mmol) was stirred under H_2 to afford a colorless liquid: yield 63.1 mg (94.7%); $[\alpha]^{20}_{289}$ = −37.4 (c = 0.7, CH_2Cl_2); HRMS calcd for $C_{14}H_{21}NH$ 204.1747, found 204.1760; HPLC purity 98.5%, t_R = 16.46 min.

(*S*)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12d). Following general procedure C for hydrogenolysis, **10d** (79.6 mg, 0.23 mmol) was stirred under H_2 to produce a colorless liquid: yield 44 mg (85%); R_f = 0.39 (EtOAc/petroleum ether/NH_3 40:59.5:0.5); $[\alpha]^{20}_{589}$ = +34.7 (c = 0.89, CH_2Cl_2); HRMS calcd for $C_{16}H_{17}NH$ 224.1434, found 224.1436; HPLC purity 98%, t_R = 16.45 min.

(*R*)-2-Phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*ent*-12d). Following general procedure C for hydrogenolysis, *ent*-**10d** (52 mg, 0.15 mmol) was stirred under H_2 to afford a colorless liquid: yield 27 mg (80%); $[\alpha]^{20}_{589}$ = −54.9 (c = 0.49, CH_2Cl_2); HRMS calcd for $C_{16}H_{17}NH$ 224.1434, found 224.1425; HPLC purity 98.3%, t_R = 16.47 min.

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Supporting Information Available: ^{1}H and ^{13}C spectra and crystallographic data (CIF) are available along with a description of chiral HPLC methods and receptor binding studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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