Enantioselective Synthesis of a 2,2-Disubstituted Tetrahydro-3-benzazepine as Novel NMDA Receptor Antagonist

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The tricyclic oxazolidines *trans*-**4** and *cis*-**4** were interconverted upon treatment with allyltrimethylsilane/$TiCl_4$. The oxazolidine *trans*-**4** was diastereoselectively reacted with PhMgBr to yield the 4,4-disubstituted 3-benzazepinone **6**, along with two side products. An X-ray crystal structure analysis of **6** proved the (*R*)-configuration of the stereogenic center C-4 and thus the retention of configuration. Reduction of **6** with $AlCl_3$/$LiAlH_4$ (1/3) followed by hydrogenolysis with H_2, Pd/C resulted in the formation of enantiomerically pure 2-methyl-2-phenyl-tetrahydro-3-benzazepine **11** which has a moderate affinity (K_i = 496 nM) to the PCP binding site of the NMDA receptor.

Key words: NMDA Antagonists, X-Ray Crystal Structure Analysis, Isomerization, Asymmetric Synthesis, 2,2-Disubstituted Tetrahydro-3-benzazepines

Introduction

The NMDA receptor belongs to the group of ionotropic glutamate receptors and is activated by *N*-methyl-D-aspartate (NMDA). The ionotropic glutamate receptors have in common substantial permeability to both Na^+ and K^+ ions but differ in permeability to Ca^{2+} ions. The NMDA receptor plays a fundamental role in excitatory neurotransmission in the central nervous system (CNS) and affects plasticity, memory and learning, in addition to neuronal development. The target of this project is specifically the phencyclidine (PCP) binding site, which is located within the NMDA receptor-associated ion channel. Ligands interacting with the PCP binding site block the influx of Ca^{2+} ions and therefore function as NMDA receptor antagonists [1, 2].

Modulators of glutamate receptors have been the subject of intense research since they can be used for the treatment of a wide variety of conditions, ranging from acute ischemia and trauma, to chronic neurodegenerative disorders such as Huntington's, Parkinson's and Alzheimer's diseases, epilepsy, and HIV-associated dementia (HAD). Moreover, even psychiatric disorders have been proposed to be amenable to glutamatergic modulation [3, 4].

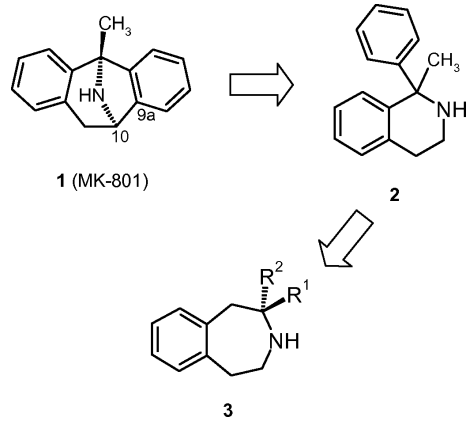


Fig. 1. Lead compound MK-801 (**1**) and tetrahydroisoquinoline **2** along with the desired tetrahydro-3-benzazepines **3**.

The tetracyclic amine MK-801 (**1**) is a very potent non-competitive NMDA receptor antagonist (K_i = 2.6 nM), which acts as an open channel blocker (Fig. 1) [1, 4]. The formal cleavage of the C^{9a}–C^{10} bond of MK-801 results in tetrahydroisoquinolines **2**, which also interact with the PCP binding site. The NMDA receptor affinities of the enantiomeric isoquinolines (*R*)-**2** and (*S*)-**2** differ considerably with (*S*)-**2** showing high (K_i = 35.4 nM) and (*R*)-**2** low affinity (K_i = 3.76 μM) [5].

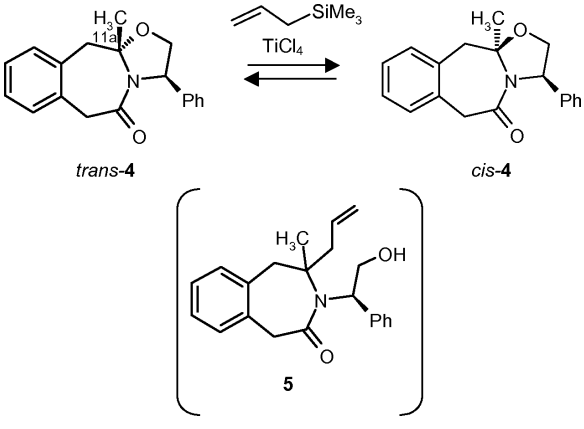
In this work we aimed at synthesizing 2,2-disubstituted tetrahydro-3-benzazepines **3** with an additional methylene moiety in the heterocyclic ring system when compared with the isoquinolines **2**. In particular, tetrahydro-3-benzazepines **3** with the same configuration at the C-2 stereocenter as the more potent enantiomer (*S*)-**2** should be synthesized in order to get novel ligands with high affinity towards the PCP binding site of the NMDA receptor.

The C-2 stereocenter of **3** should be established by stereoselective opening of the oxazolidines *trans*-**4** and *cis*-**4** with carbon nucleophiles. The stereodescriptors *cis* and *trans* define the relative configuration of the higher ordered phenyl and benzyl residues or the lower ordered proton and methyl moiety in the oxazolidine ring [9]. In the literature [6], the opening of an oxazolidine ring in a bicyclic system with two substituents at the N/O-ketalic stereocenter by carbon nucleophiles has not been reported so far.

Results

The key intermediates *trans*-**4** and *cis*-**4** were prepared by heating of 2-[2-(2-oxopropyl)phenyl]acetic acid [7] with (*R*)-phenylglycinol in toluene [8].

At first the stereoselective introduction of an allyl nucleophile at the N/O-ketalic stereocenter in position 11a was investigated (Scheme 1). For this purpose, *trans*-**4** was reacted with allyltrimethylsilane (2 equiv.) and $TiCl_4$ (1 equiv.). Only very low amounts of the desired 4,4-disubstituted tetrahydro-3-benzazepine **5** were detected by ^{1}H-NMR spectroscopy. The reaction resulted in isomerization of *trans*-**4** into *cis*-**4** (*trans*-**4** : *cis*-**4** = 90 : 10). Due to the low yield, the allyl derivative **5** could not be isolated.



Scheme 1. Interconversion of *trans*-**4** and *cis*-**4** upon treatment with allyltrimethylsilane (2 equiv.) and $TiCl_4$ (1 equiv.).

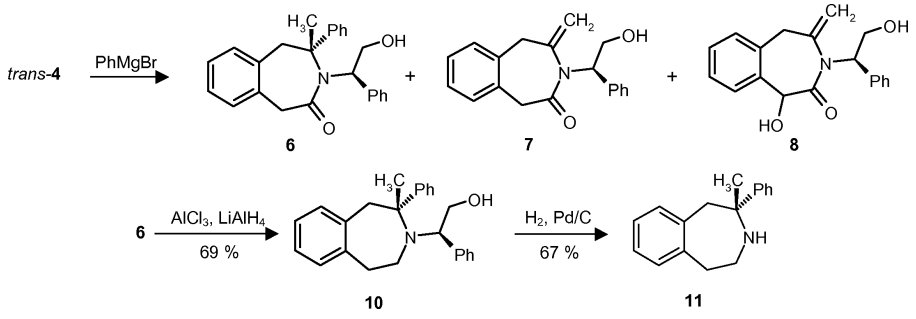
This observation prompted us to study the interconversion reaction in more detail. Very recently we have shown that *p*-toluenesulfonic acid and trifluoroacetic acid are not able to isomerize the diastereomers *trans*-**4** and *cis*-**4** [8, 9]. Treatment of both diastereomers *trans*-**4** and *cis*-**4** with $TiCl_4$, allyltrimethylsilane or triethylsilane alone also did not lead to any interconversion. However, the reaction of the diastereomer *cis*-**4** with allyltrimethylsilane (2 equiv.) and $TiCl_4$ (1 equiv.) led to isomerization, but without formation of any substitution product (*trans*-**4** : *cis*-**4** = 11 : 89). Obviously, both $TiCl_4$ and a silane are required for this isomerization.

Since further products were not formed along with *cis*-**4**, the isomerization reaction was further investigated using *cis*-**4** only. Prolongation of the reaction time from 1 to 3 d led to a ratio of *trans*-**4** : *cis*-**4** of 38 : 62. Work-up of this mixture provided the diastereomer *trans*-**4** in 35 % isolated yield. This isomerization process allows the increase of the yield of the desired stereoisomer and thus represents a considerable improvement of the asymmetric synthesis of tetrahydro-3-benzazepines using tricyclic oxazolidines of type **4**, because the synthesis of **4** always affords 1 : 1 mixtures of *cis* and *trans* diastereomers [8, 9].

In order to introduce carbon nucleophiles into the tetrahydro-3-benzazepine scaffold, Grignard reagents were tried [10]. For this purpose the tricyclic oxazolidine *trans*-**4** was reacted with 3 equivalents of PhMgBr in THF at 0 °C (Scheme 2). This transformation led to the 4,4-disubstituted tetrahydro-3-benzazepine **6** along with two side products, **7** and **8**, which were separated by flash chromatography. The elimination product **7** was isolated in 17 % yield and represented the major product. The yield of the hydroxylated product **8** (only one diastereomer) was 7.5 %, whereas the desired tetrahydro-3-benzazepine derivative **6** was obtained in only 6.5 % yield.

In order to prove the configuration of the 4,4-disubstituted tetrahydro-3-benzazepine derivative **6**, an X-ray crystal structure analysis was performed (Fig. 2). Suitable crystals were obtained by recrystallization from an *n*-hexane/CH_2Cl_2 mixture. The crystal structure of **6** clearly shows the (*R*)-configuration in position 4 indicating that the nucleophilic attack had taken place with retention of configuration.

The formation of products **6** and **7** can be explained by coordination of the magnesium atom of the Grig-



Scheme 2. Reaction of *trans*-**4** with three equivalents of PhMgBr and transformation of **6** into the enantiomerically pure 2,2-disubstituted tetrahydro-3-benzazepine **11**.

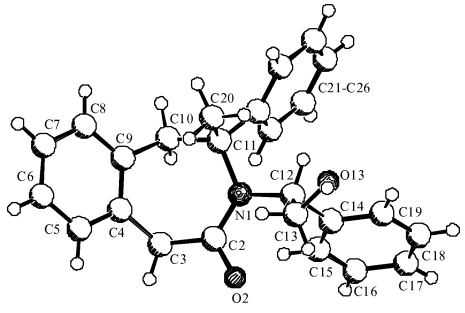
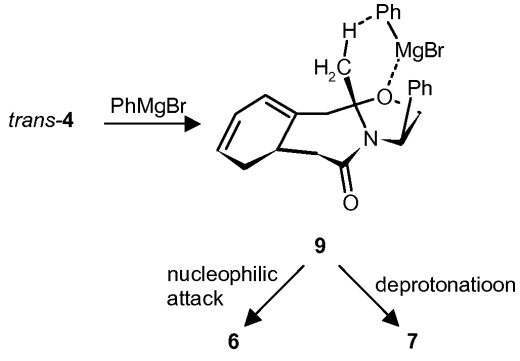


Fig. 2. Molecular structure of the 4,4-disubstituted tetrahydro-3-benzazepine **6** in the crystal.



Scheme 3. Mechanism for the formation of the 4,4-disubstituted tetrahydro-3-benzazepine **6** and the 4-methylene substituted 3-benzazepine **7**.

nard reagent with the oxygen atom of the oxazolidine moiety as shown in intermediate **9** (Scheme 3) [10]. After coordination, the Ph group of PhMgBr can act as a nucleophile as well as a base. The delivery of the phenyl nucleophile from the same face as the C–O bond results in the 4,4-disubstituted tetrahydro-3-benzazepine **6** and accounts for the observed retention of configuration. In addition to the nucleophilic attack, the coordinated phenyl moiety is able to remove a proton from the methyl moiety *via* a six-membered ring transition state. Subsequent oxazolidine ring opening yields the 4-methylene-substituted tetrahydro-3-benzazepine derivative **7**. This side reaction together with the sterically demanding N/O-ketalic substructure is responsible for the low yields of the desired product **6**.

Table 1. Affinity of the 2,2-disubstituted tetrahydro-3-benzazepine **11** towards NMDA, σ_1 and σ_2 receptors.

Receptor	$K_i \pm$ SEM (nM)
NMDA	496 ± 53
σ_1	> 2000
σ_2	134 ± 13

Next, *cis*-**4** was reacted with 3 equivalents of PhMgBr. This reaction did not provide a 4,4-disubstituted or a 4-methylene-substituted tetrahydro-3-benzazepine derivative like **6** or **7**. We assume that in the case of *cis*-configuration both faces of the oxazolidine plane are shielded by the phenyl moiety in position 3 (above the ring plane) and the C-11a methyl moiety (below the ring plane). Therefore, coordination of PhMgBr with the oxazolidine ring O atom is inhibited resulting in fast deprotonation in α-position of the lactame carbonyl moiety [11].

The 4,4-disubstituted tetrahydro-3-benzazepine derivative **6** was used to synthesize the enantiomerically pure 2,2-disubstituted tetrahydro-3-benzazepine **11** (Scheme 2). In the first step, the lactame **6** was reduced with AlH_3, which had been formed *in situ* by mixing $AlCl_3$ and $LiAlH_4$ in the ratio 1 : 3 [12], to obtain the N-substituted tetrahydro-3-benzazepine **10** in 69 % yield. Finally, the *N*-(2-hydroxy-1-phenylethyl) protective group of **10** was removed by hydrogenolysis (H_2, Pd/C) to provide (2*R*)-**11** in 67 % yield.

In competitive receptor binding studies with radioligands [13], the (*R*)-2-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **11** revealed moderate affinity towards the PCP binding site of the NMDA receptor (K_i = 496 nM, Table 1). Compared with the smaller homologous isoquinoline (*S*)-**2** [5], which has the same stereochemistry as **11** [14], the affinity is

about 10-fold reduced. Obviously, increasing of the ring size by one methylene moiety results in lowering of binding at the PCP binding site of the NMDA receptor.

In addition to the NMDA receptor affinity the affinity of the tetrahydro-3-benzazepine **11** towards σ_1 and σ_2 receptors was investigated [15]. The compound did not show any significant affinity to σ_1 receptors ($K_i >$ 2000 nM). However, a surprisingly high σ_2 receptor affinity (K_i = 134 nM) was observed, which even exceeds the NMDA receptor affinity. Nevertheless, **11** represents the starting point for the development of novel potent NMDA receptor antagonists and σ_2 receptor ligands.

In conclusion a method for the interconversion of the diastereomeric tricyclic oxazolidines *trans*-**4** and *cis*-**4** has been developed, which increases the overall yield of the desired diastereomer for subsequent asymmetric syntheses. Whereas the oxazolidine *trans*-**4** reacted with phenylmagnesium bromide to form the 4,4-disubstituted tetrahydro-3-benzazepine **6**, the corresponding *cis*-**4** did not react to form a phenyl addition product. Compound **6** was transformed into the (*R*)-2-methyl-2-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine **11**, which revealed promising affinity to the PCP binding site of the NMDA receptor and the σ_2 receptor.

Experimental Section

General

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, height of silica gel bed, eluent, fraction size, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation: Polarimeter 341 (Perkin Elmer); 1.0 dm tube; concentration c in g/100 mL; T = 20 °C; wavelength 589 nm (D line of Na light); unit of $[\alpha]$ is grad mL dm^{-1} g^{-1}. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electro spray ionization. HRMS: MicroTof (Bruker Daltronics, Bremen), Calibration with sodium formate clusters before measurement. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); δ in ppm relative to tetramethylsilane; coupling constants are given in Hz with 0.5 Hz resolution. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiCroCART® 250-4 mm cartridge; flow rate: 1.000 mL min^{-1}; 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: 90 % to 0 %, 29–31 min: 0 %, 31–31.5 min: 0 % to 90 %, 31.5–40 min: 90 %.

*Conversion of cis-**4** into trans-**4***

Under an atmosphere of N_2 a solution of $TiCl_4$ (4.5 mL of 1.0 M in CH_2Cl_2; 4.5 mmol, 1 equiv.) was added *via* syringe to a stirred solution of allyltrimethylsilane (0.73 mL, 9.0 mmol, 2 equiv.) and oxazolidine *cis*-**4** (1.32 mg, 4.5 mmol) in dry CH_2Cl_2 (24 mL) at r. t. The resulting solution was stirred at r. t. for 3 d. Then it was cooled to 0 °C and carefully quenched with saturated aqueous ammonium chloride (20 mL). The resulting mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.56 g of the crude product. The product was purified by fc (3 cm, 1 = 20 cm, EtOAc/cyclohexane 10/90 to 40/60, 25 mL). *trans*-**4** (R_f = 0.48, EtOAc/petroleum ether 50/50) and *cis*-**4** (R_f = 0.14, EtOAc/petroleum ether 50/50) were isolated as colorless solids [9] in yields of 462 mg (35 %) and 713 mg (54 %), respectively.

*(4R)-3-[(1R)-2-Hydroxy-1-phenylethyl]-4-methyl-4-phenyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**6**), 3-[(1R)-2-hydroxy-1-phenylethyl]-4-methylene-1,3,4,5-tetrahydro-3-benzazepin-2-one (**7**) and 1-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]-4-methylene-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8**)*

A solution of *trans*-**4** (405 mg, 1.38 mmol) in THF (24 mL) was added *via* cannula to a solution of PhMgBr (1.0 M in THF, 4.14 mmol) at 0 °C, and the mixture was stirred at this temperature for 10 h and then at r. t. for 8 h. The reaction was quenched by addition of a saturated NaCl solution, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuum. The residue (520 mg) was purified by fc (2 cm, 1 = 20 cm, EtOAc/cyclohexane 20/80 to 35/65, 15 mL).

6: R_f = 0.14, (EtOAc/cyclohexane 40/60), colorless solid, yield 27 mg (6 %). $[\alpha]_{589}^{20}$ = +7.6 (c = 1.05, CH_2Cl_2). – ^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 3H, CH_3), 3.03 (d, J = 15.0 Hz, 1H, 5-H), 3.61 (d, J = 15.0 Hz, 1H, 5-H), 3.96 (d, J = 15.4 Hz, 1H, 1-H), 3.97–4.05 (m, 3H, CH_2OH, NC*H*Ph), 4.32 (d, J = 15.2 Hz, 1H, 1-H), 6.82–6.84 (m, 2H, arom. CH), 6.93 (d, J = 7.3 Hz, 1H, arom. CH), 7.00–

7.12 (m, 7H, arom. CH), 7.19 – 7.34 (m, 4H, arom. CH). – ^{13}C NMR ($CDCl_3$): δ = 26.8 (1C, CH_3), 45.1 (1C, 1-C), 48.6 (1C, 5-C), 66.9 (1C, N*CH*Ph), 67.8 (1C, *CH*$_2$OH), 67.9 (1C, 4-C), 126.4, 126.6, 127.7, 127.7, 128.0, 128.1, 128.5, 128.5, 129.8 (10C, Ph-*CH*), 134.43, 135.11, 138.4, 143.8 (4C, Ph-*C*), 171.7 (1C, CO). – IR: ν = 3402 (w, OH), 3056, 3033 (w, arom. C-H), 2982, 2930 (m, aliph. C-H), 1617 (s, C=O) cm^{-1}. – HRMS (ESI): *m/z* = 372.1972 (calcd. 372.1958 for $C_{25}H_{25}NO_2H$, $[M+H]^+$). – HPLC: Purity 95.6 %, t_R = 20.19 min.

7: R_f = 0.16, (EtOAc/cyclohexane 40/60), colorless solid, yield 68 mg (17 %). – ^{1}H NMR ($CDCl_3$): δ = 3.03 (d, *J* = 18 Hz, 1H, 5-H), 3.54 (dd, *J* = 15.9/11.7 Hz, 2H, 5-H/1-H), 3.99 (d, *J* = 13.8 Hz, 1H, 1-H), 4.04 (dd, *J* = 9.9/4.9 Hz, 1H, *CH*$_2$OH), 4.16 (t, *J* = 10.4 Hz, 1H, *CH*$_2$OH), 5.00 (d, *J* = 1.0 Hz, 1H, =*CH*$_2$), 5.18 (s, 1H, =*CH*$_2$), 5.54 (dd, *J* = 9.5/5.1 Hz, 1H, N*CH*Ph), 6.78 (d, *J* = 6.6 Hz, 1H, arom. CH), 7.05 – 7.21 (m, 8H, arom. CH). – ^{13}C NMR ($CDCl_3$): δ = 39.3 (1C, 5-C), 41.9 (1C, 1-C), 60.9 (1C, N*CH*Ph), 62.1 (1C, *CH*$_2$OH), 115.6 (1C, =CH_2), 121.8, 125.6, 126.3, 127.1, 127.4, 127.5, 128.6, 129.5 (9C, Ph-CH), 130.9, 133.7, 136.0 (3C, Ph-C), 144.1 (1C, 4-C), 171.4 (1C, CO). – IR: ν = 3390 (w, OH), 2923 (w, arom. C-H), 1632 (s, C=O) cm^{-1}. – $C_{19}H_{19}NO_2$ (293.4). – MS (ESI): *m/z* (%) = 294 (100) $[M+H]^+$. – HPLC: Purity 82.3 %, t_R = 19.67 min.

8: R_f = 0.26, (EtOAc/cyclohexane 40/60), pale-yellow solid, yield 32 mg (7.5 %). – ^{1}H NMR ($CDCl_3$): δ = 3.69 (d, *J* = 18.6 Hz, 1H, 5-H), 3.85 (d, *J* = 18.5 Hz, 1H, 5-H), 4.04 (m, 2H, OH/*CH*$_2$OH), 4.21 (dd, *J* = 11.8/9.4 Hz, 1H, *CH*$_2$OH), 4.76 (d, *J* = 2.4 Hz, 1H, =CH_2), 5.25 (d, *J* = 2.3 Hz, 1H, =CH_2), 5.44 (dd, *J* = 9.3/4.9 Hz, 1H, N*CH*Ph), 5.78 (d, *J* = 4.6 Hz, 1H, 1-H), 6.94 (d, *J* = 7.4 Hz, 1H, arom. CH), 7.15 – 7.26 (m, 7H, arom. CH), 7.78 (1H, *J* = 7.8 Hz, 1H, arom. CH). – ^{13}C NMR ($CDCl_3$): δ = 40.2 (1C, 5-C), 62.8 (1C, *CH*$_2$OH), 65.3 (1C, N*CH*Ph), 68.4 (1C, 1-C), 117.4 (1C, =CH_2), 124.4, 127.1, 127.9, 128.0, 128.4, 128.8, 129.5 (9C, Ph-CH), 132.6, 137.6, 143.8 (3C, Ph-C), 136.8 (1C, 4-C), 173.7 (1C, CO). – IR: ν = 3403 (w, OH), 3054, 3032 (w, arom. C-H), 2984 (m, aliph. C-H), 1619 (s, C=O) cm^{-1}. $C_{19}H_{19}NO_3$ (309.4). – MS (ESI): *m/z* (%) = 310 (100) $[M+H]^+$.

*(2R)-2-[(2R)-2-Methyl-2-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin-3-yl]-2-phenylethanol (**10**)*

Under N_2 at 0 °C dry THF (2mL) was added to anhydrous $AlCl_3$ (7.8 mg, 0.059 mmol, 1 equiv.) and stirred for 5 min. Then a solution of $LiAlH_4$ (0.17 mL, 1.0 M in THF, 0.177 mmol; 3 equiv.) was added *via* syringe. The resulting clear, colorless solution was allowed to warm to r. t. and was stirred for 20 min to give a solution of alane (AlH_3). A solution of **6** (22 mg, 0.059 mmol) in dry THF (2 mL) was added at 0 °C. The resulting solution was stirred at 0 °C for 3 h and then warmed to r. t. over 30 min. The resulting clear solution was cooled 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 × 5 mL). The combined organic layers were washed with 1 M NaOH and brine (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue (20 mg) was purified by fc (1 cm, l = 24 cm, EtOAc/petroleum ether 5/95, 10 mL, R_f = 0.51 (EtOAc/cyclohexane 40/60)). Colorless liquid, yield 14 mg (69 %). – $[\alpha]_{589}^{20}$ = −48.6 (c = 0.5, CH_2Cl_2). – ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 3H, CH_3), 2.68 (d, *J* = 14.2 Hz, 1H, 1-H), 2.92 (ddd, *J* = 14.6/6.9/3.5 Hz, 1H, 5-H), 3.15 (ddd, *J* = 13.6/8.5/3.8 Hz, 1H, 4-H), 3.25 (ddd, *J* = 14.4/8.4/3.6 Hz, 1H, 5-H), 3.43 (ddd, *J* = 13.8/7.0/3.7 Hz, 1H, 5-H), 3.51 (d, *J* = 14.2 Hz, 1H, 1-H), 3.74 – 3.81 (m, 2H, C*H*$_2$OH), 3.92 (dt, *J* = 10.1/6.1 Hz, 1H, NC*H*Ph), 6.14 (d, *J* = 7.3 Hz, 1H, arom. CH), 7.09 – 7.25 (m, 11H, arom. CH), 7.40 (dd, *J* = 7.6/2.0 Hz, 2H, arom. CH). A signal for an OH proton could not be detected. – ^{13}C NMR ($CDCl_3$): δ = 20.7 (1C, CH_3), 37.3 (1C, 5-C), 42.9 (1C, 1-C), 51.6 (1C, 4-C), 63.6 (1C, 2-C), 64.0 (1C, *C*H$_2$OH), 64.2 (1C, N*C*HPh), 126.22, 126.6, 126.7, 126.8, 127.9, 128.2, 128.3, 128.7, 130.6 (14C, Ph*C*H), 138.5, 141.1, 141.6, 148.6 (4C, Ph-*C*). – IR: ν = 3417 (w, OH), 3056, 3026 (w, arom. CH), 2923, 2857 (w, aliph. CH) cm^{-1}. – HRMS (ESI): *m/z* = 358.2166 (calcd. 358.2156 for $C_{25}H_{27}NOH$, $[M+H]^+$). – HPLC: purity 75.96 %, t_R = 18.75 min.

*(2R)-2-Methyl-2-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**11**)*

A mixture of **10** (13 mg, 0.036 mmol) and Pd/C (10 % by wt) in methanol (1.5 mL) and 1 M HCl (0.5 mL) was stirred at r. t. under an H_2 atmosphere (balloon) for 6 h. The reaction mixture was filtered using a silica gel 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). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide an oil (10 mg); fc (1 cm, l = 20 cm, EtOAc/petroleum ether/NH_3 40/59.5/0.5, 10 mL, R_f = 0.33). Colorless liquid, yield 5.8 mg (67 %). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (s, 3H, CH_3), 2.75 – 2.81 (m, 1H, 5-H), 2.88 – 2.98 (m, 3H, 5-H/4-H), 3.01 (d, *J* = 14.2 Hz, 1H, 1-H), 3.40 (d, *J* = 14.1 H, 1H, 1-H), 6.98 – 7.01 (m, 1H, arom. CH), 7.06 (d, *J* = 3.1 Hz, 2H, arom. CH), 7.14 (t, *J* = 7.4 Hz, 1H, arom. CH), 7.27 (t, *J* = 7.7 Hz, 2H, arom. CH), 7.52 (dd, *J* = 8.4/1.0 Hz, 2H, arom. CH). A signal for the NH proton could not be detected. – ^{13}C NMR ($CDCl_3$): δ = 29.9 (1C, CH_3), 38.0 (1C, 5-C), 42.1 (1C, 1-C), 48.9 (1C, 4-C), 57.2 (1C, 2-C), 126.2, 126.3, 126.5, 126.7, 128.5, 130.8 (9C, Ph-*C*H), 138.6, 141.1 (3C, Ph-*C*). – IR: ν = 3063, 3026 (w, arom. CH), 2923 (w, aliph. CH) cm^{-1}. – HRMS (ESI): *m/z* = 283.160 (calcd.

238.1590 for $C_{17}H_{19}NH$, $[M+H]^+$). – HPLC: purity 98.1 %, t_R = 15.49 min.

X-Ray crystal structure analysis of ***6***

Empirical formula $C_{25}H_{25}NO_2$, M = 371.46, colorless crystal 0.25 × 0.15 × 0.05 mm^3, monoclinic, space group $P2_1$ (no. 4), a = 9.1779(3), b = 10.6325(4), c = 11.5696(5) Å, β = 109.838(2)°, V = 1062.01(7) Å^3, Z = 2, ρ_{calc} = 1.16 g cm^{-3}, μ = 0.6 mm^{-1}, empirical absorption correction ($0.870 \leq T \leq 0.972$), CuK_α radiation, λ = 1.54178 Å, T = 293(2) K, ω and ϕ scans, 6934 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda]$ = 0.60 Å^{-1}, 2379 independent (R_{int} = 0.051) and 1999 observed reflections [$I \geq 2\ \sigma(I)$], 255 refined parameters, R = 0.050, $wR2$ = 0.132, max./min. residual electron density 0.16/−0.16 e Å^{-3}, Flack parameter −0.3(4). Hydrogen atoms were calculated and refined as riding atoms. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection: COLLECT [16], data reduction: DENZO-SMN [17], absorption correction: DENZO [18], structure solution: SHELXS-97 [19], structure refinement: SHELXL-97 [20], graphics: SCHAKAL [21].

CCDC 718245 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

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[1] H. B. Bräuner-Osborne, J. Egebjerg, E. Nielsen, U. Madsen, P. Krogsgaard-Larsen, *J. Med. Chem.* **2000**, *43*, 2609 – 2645.
[2] J. C. Watkins, D. E. Jane, *Br. J. Pharmacol.* **2006**, *147*, 100 – 108.
[3] P. K. Syts, S. A. Lipton, *Trends Pharmacol. Sci.* **2007**, *28*, 561 – 566.
[4] D. Lodge, W. Danysz, C. G. Parsons, in *Ionotropic Glutamate Receptors as Therapeutic Targets*, E. P. Graham Publishing Co. Johnson City, Tennessee, **2002**, pp. 1 – 27.
[5] H. J. Sherriffs, K. Shirakawa, J. S. Kelly, H. J. Olverman, A. Kuno, M. Okubo, S. P. Butcher, *Eur. J. Pharmacol.* **1993**, *247*, 319 – 324.
[6] References dealing with oxazolidine chemistry: a) L. Micouin, J. L. Quirion, H. P. Husson, *Synth. Commun.* **1996**, *26*, 1605 – 1611; b) A. I. Meyers, S. V. Downing, M. J. Weiser, *J. Org. Chem.* **2001**, *66*, 1413 – 1419; c) T. Wünsch, A. I. Meyers, *J. Org. Chem.* **1990**, *55*, 4233 – 4235; d) M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919 – 1928; e) M. Amat, M. Pérez, T. Minaglia, J. Bosch, *J. Org. Chem.* **2008**, *73*, 6920 – 6923; f) M. Amat, N. Llor, J. Hidalgo, A. Hernandez, J. Bosch, *Tetrahedron: Asymmetry* **1996**, *7*, 977 – 980; g) D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503 – 9569; h) A. I. Meyers, *J. Org. Chem.* **2005**, *70*, 6137 – 6151; i) M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 7084 – 7085.
[7] S. M. Husain, B. Wünsch, *Synthesis* **2008**, 2729 – 2732.
[8] S. M. Husain, R. Fröhlich, B. Wünsch, *Tetrahedron: Asymmetry* **2008**, *19*, 1613 – 1616.
[9] S. M. Husain, R. Fröhlich, B. Wünsch, *J. Org. Chem.* **2009**, *74*, 2788 – 2793.
[10] M. Amat, C. Escolano, N. Llor, M. Huguet, M. Pérez, J. Bosch, *Tetrahedron: Asymmetry* **2003**, *14*, 1679 – 1683.
[11] S. M. Husain, M. T. Heim, D. Schepmann, B. Wünsch, *Tetrahedron: Asymmetry* **2009**, *20*, 1383 – 1392.
[12] L. E. Burgess, A. I. Meyers, *J. Org. Chem.* **1992**, *57*, 1656 – 1662.
[13] U. Wirt, D. Schepmann, B. Wünsch, *Eur. J. Org. Chem.* **2007**, 562 – 475.
[14] Due to the CIP formalism the stereodescriptors of (*S*)-**2** and (*R*)-**12** are opposite despite the same three-dimensional structure.
[15] a) C. A. Maier, B. Wünsch, *J. Med. Chem.* **2002**, *45*, 438 – 448; b) C. A. Maier, B. Wünsch, *J. Med. Chem.* **2002**, *45*, 4923 – 4930; c) C. Oberdorf, D. Schepmann, J. M. Vela, J. L. Diaz, B. Wünsch, *J. Med. Chem.* **2008**, *51*, 6531 – 6537; d) R. Holl, D. Schepmann, R. Grünert, P. J. Bednarski, B. Wünsch, *Bioorg. Med. Chem.* **2009**, *17*, 777 – 793.
[16] R. Hooft, COLLECT, Nonius KappaCCD Data Collection Software, Nonius BV, Delft (The Netherlands) **1998**.
[17] DENZO-SMN, Z. Otwinowski, W. Minor, in *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, (Eds.: C. W. Carter, Jr., R. M. Sweet), Academic Press, New York, **1997**, p. 307.
[18] DENZO, Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr.* **2003**, *A59*, 228 – 234.
[19] G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**. See also: G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467 – 473.
[20] G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**. See also: G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.
[21] E. Keller, SCHAKAL, A Computer Program for the Graphical Representation of Molecular and Crystallographic Models, University of Freiburg, Freiburg (Germany) **1997**.