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Brief Article

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Enantiomerically Pure 1,3-Dioxanes as Highly Selective NMDA and σ_1 Receptor Ligands

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Supporting Information

ABSTRACT: We synthesized and investigated the NMDA and σ_1 receptor affinity of enantiomerically pure 2-(2-phenyl-1,3-dioxan-4-yl)ethanamines **17**−**26**. The primary amines (*R*,*R*)-**18**−**20** with an axially oriented phenyl moiety in position 2 interacted with high enantioselectivity (eudismic ratios 70−130) and high affinity (K_i((*R*,*R*)-**19**) = 13 nM) with the PCP binding site of the NMDA receptor. Introduction of an *N*-benzyl moiety led to potent σ_1 ligands including compound (*S*,*R*)-**22** (K_i = 6 nM) with an equatorially oriented phenyl moiety in position 2.

INTRODUCTION

The NMDA (*N*-methyl-D-aspartate) receptor is an excitatory ion channel receptor that is activated by (*S*)-glutamate. Simultaneous binding of (*S*)-glutamate and glycine at the NMDA receptor combined with depolarization of the cell membrane leads to an opening of the channel and influx of Ca^{2+} and Na^+ ions.[1] Because of this coagonistic mechanism, the NMDA receptor allows a high synaptic plasticity that is necessary for brain functions such as learning and memory.[2,3] On the other hand, NMDA receptors are also involved in pathophysiological processes caused by an increased concentration of (*S*)-glutamate in the synaptic cleft. The high concentration of (*S*)-glutamate leads to an increased influx of Ca^{2+} ions, resulting in toxic effects (excitotoxicity). These toxic effects can follow acute cerebral ischemia due to brain injury or stroke. They are also involved in chronic processes such as the neurodegenerative disorders Parkinson's or Alzheimer's disease. Therefore, NMDA receptor antagonists blocking the increased Ca^{2+} ion influx possess a potential for the treatment of these disorders.[3−6]

Known NMDA receptor antagonists include the hallucinogenic compound phencyclidine (PCP, **1**), which gave its name to the binding site within the ion channel.[7,8] and (*S*)-ketamine (**2**), which is clinically used as a fast narcotic with analgesic properties.[9] The high affinity of phencyclidine (**1**) for the receptor and the slow release from the binding site in the channel pore lead to strong inhibition of the normal neurotransmission and therefore clinically unacceptable side effects such as hallucinations, drowsiness, and coma. In contrast, memantine (**3**) has a rather low affinity but a short dwell-time and is not known to affect normal brain functions.[5,10]

To develop new drugs combining high affinity with fast off-rate kinetics, the inner structure of the channel pore has to be studied in more detail. Receptor binding studies of enantiomers are of particular value for this purpose because their physicochemical properties are identical whereas their three-dimensional structure differs, thus giving insight into the microstructure of the channel pore at the PCP binding site (Figure 1).

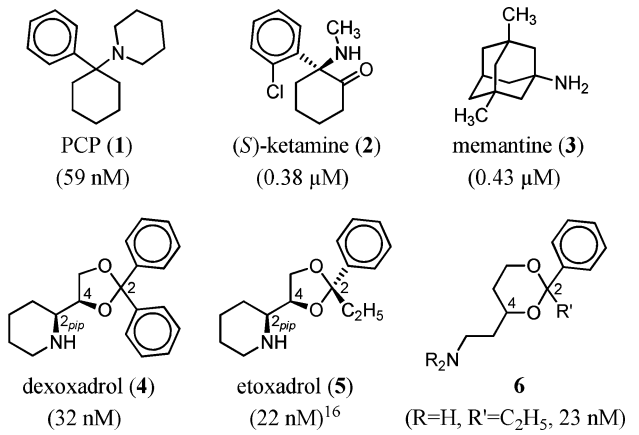

Figure 1. Structures of compounds that bind at the PCP binding site of the NMDA receptor (K_i values).

The piperidyl substituted 1,3-dioxolanes dexoxadrol (**4**) and etoxadrol (**5**) belong to a series of enantiomerically pure NMDA receptor antagonists.[7,11−13] It has been shown that the (2*S*,4*S*,2S_{pip})-configuration of etoxadrol (**5**) is crucial for binding at the PCP binding site.[14,15] Recently, we reported on a series of racemic 1,3-dioxane derivatives with high NMDA and σ_1 receptor affinity.[16,17] The aim of the present study was to investigate the relationship between the structure of enantiomerically pure 4-aminoethyl substituted 1,3-dioxanes **6** and their affinity to the NMDA receptor. We also analyzed the structural differences responsible for high σ_1 receptor affinity.[18]

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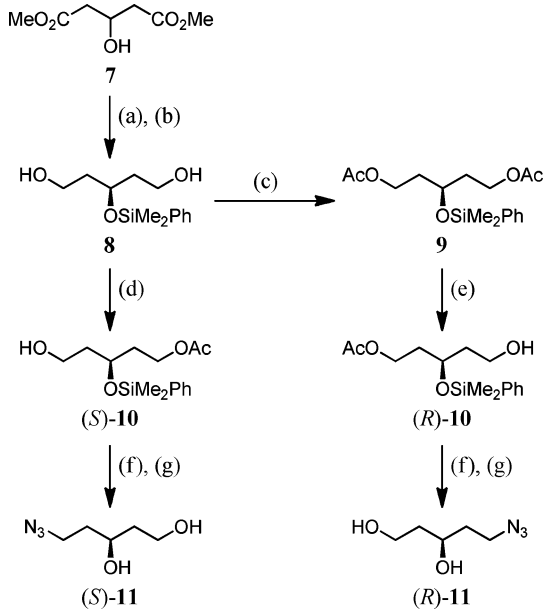
RESULTS

The enantiomeric azidodiols (*S*)-**11** and (*R*)-**11**, which determine the configuration at position 4 of the desired compounds, were synthesized using a lipase as chiral catalyst (Scheme 1). Acetalization of (*S*)-**11** and (*R*)-**11** led to azidodioxanes **12**–**16**, establishing the second center of chirality at position 2 (Scheme 2). Finally, azidodioxanes **12**–**16** were converted into amines **17**–**21** and **22**–**26** (Scheme 3).

Enantioselective Synthesis of Azidodiols (*S*)-11 and (*R*)-11. The diester **7** was silylated with dimethylphenylsilyl chloride and subsequently reduced with $LiBH_4$ to obtain diol **8**, which was acetylated to afford diacetate **9**. To obtain both enantiomers (*S*)-**10** and (*R*)-**10** in high enantiomeric excess (ee), two pathways were followed. At first, monoacetate (*S*)-**10** was produced by acetylation of diol **8** using isopropenyl acetate (IPA) as acylating agent and the lipase from *Burkholderia cepacia* as catalyst in methyl *tert*-butyl ether (MTBE). The enantiomer (*R*)-**10** was synthesized by hydrolysis of diacetate **9** using the same lipase in aqueous $NaHCO_3$ solution. Both monoacetates (*S*)-**10** and (*R*)-**10** were transformed into azidodiols (*S*)-**11** and (*R*)-**11** by a Mitsunobu reaction with $Zn(N_3)_2{\cdot}(pyridine)_2$, diisopropyl azodicarboxylate (DIAD), and PPh_3 followed by removal of the protective groups (Scheme 1).[18,19] The enantiomeric excess (ee) of (*S*)-**11** and (*R*)-**11** was determined by measuring the ee of the synthetic precursors (*S*)-**10** and (*R*)-**10** and in addition after acylation with 4-bromobenzoyl chloride. Both methods led to the same result. The ee of the (*S*)-configured compounds was 99.8%, and the ee of the (*R*)-configured compounds 98.0%. The absolute configuration of the compounds was determined by means of exciton coupled circular dichroism (ECCD) of the corresponding bis-4-bromobenzoates.[18−20]

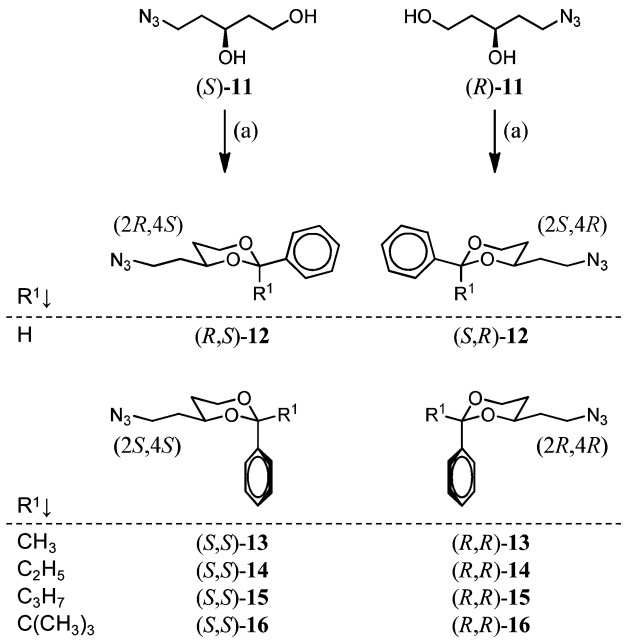
Scheme 1. Synthesis of Enantiomerically Pure Azidodiols (*S*)-11 (99.8% ee) and (*R*)-11 (98.0% ee)[a]



[a]Reagents and conditions: (a) $Me_2PhSiCl$, imidazole, CH_2Cl_2; (b) $LiBH_4$, Et_2O; (c) IPA, lipase *Candida antarctica* B, MTBE; (d) IPA, lipase *Burkholderia cepacia*, MTBE; (e) lipase *B. cepacia*, $NaHCO_3$-solution; (f) $Zn(N_3)_2{\cdot}(pyridine)_2$, PPh_3, DIAD, toluene; (g) 1. K_2CO_3, CH_3OH, 2. HCl 0.1 M.

Stereoselective Acetalization. Azidodiols (*S*)-**11** and (*R*)-**11** were used as chiral building blocks for the synthesis of enantiomerically pure azido-1,3-dioxanes **12**–**16** with a second chiral center at position 2. The acetalization of **11** with benzaldehyde predominantly afforded 1,3-dioxanes **12** bearing the phenyl moiety in equatorial position (Scheme 2, R^1 = H),

Scheme 2. Stereoselective Synthesis of Azido-1,3-dioxanes 12–16[a]



[a]After purification by preparative HPLC, all products were obtained with >99.8% de. Reagents and conditions: (a) benzaldehyde (R^1 = H) or phenyl ketone (R^1 = CH_3, C_2H_5, C_3H_7, $C(CH_3)_3$), pTosOH, toluene, Dean–Stark apparatus.

whereas phenyl ketones gave products **13**–**16** with an axially oriented phenyl moiety (Scheme 2, R^1 = CH_3, C_2H_5, C_3H_7, $C(CH_3)_3$). Generally, the axially oriented phenyl moiety of 2-phenyl-1,3-dioxanes adopts a perpendicular conformation.[21,22] The relative configuration of azidodioxanes **12**–**16** was determined by NOE-NMR experiments. Irradiation of **12** at 5.6 ppm (2 H_{ax}) led to an increased signal at 4.0 ppm (6 H_{ax} and 4 H_{ax}) and vice versa, indicating an equatorial orientation of the phenyl moiety. The axial orientation of the phenyl moiety of **13**–**16** was proven by irradiation at 3.8 ppm (6 H_{ax} and 4 H_{ax}), leading to an increased signal of the aromatic protons in ortho position of the phenyl ring (7.4 ppm) and vice versa.

To quantify the diastereoselectivity of the acetalization reaction, we analyzed the ratio of diastereomers in the crude reaction mixtures resulting from acetalization of (*S*)-**11** with benzaldehyde and phenyl ketones. The respective diastereomers were identified by identical mass spectra using APCI-MS detection and quantified by integration of the UV absorption at 210 nm. Major mass fragments detected with high intensities were $[MH-26]^+$ and $[MH-28]^+$, which are typical fragments of organic azides.[23] It was found that the acetalization of (*S*)-**11** with benzaldehyde led to (*R*,*S*)-**12** with a diastereomeric excess (de) of 89.3%. In contrast to this result, acetalization with propiophenone and butyrophenone gave the (2*S*)-configured 1,3-dioxanes (*S*,*S*)-**14** and (*S*,*S*)-**15** with 95.1%

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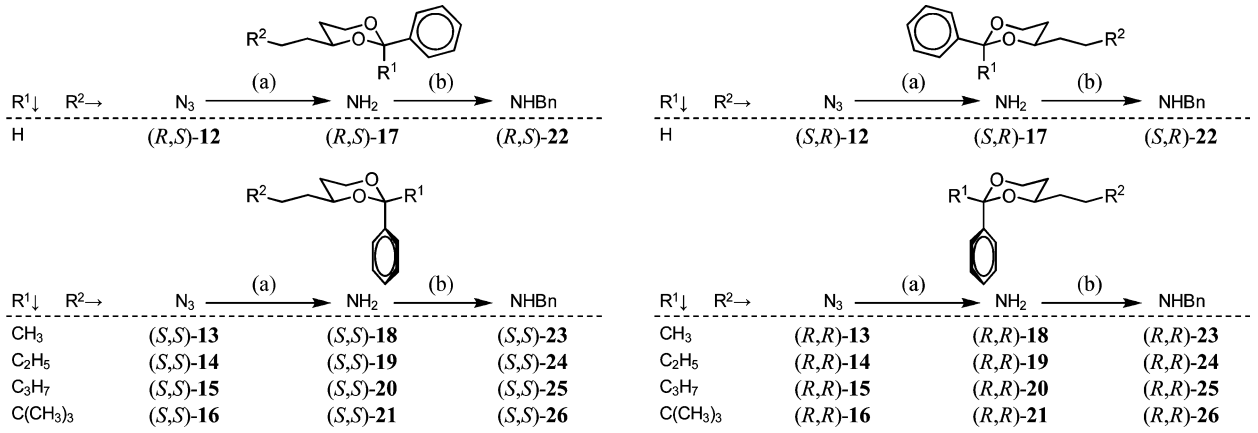
Scheme 3. Conversion of Azido-1,3-dioxanes 12−16 into Primary Amines 17−21 and Benzylamines 22−26[a]



[a]Reagents and conditions: (a) H_2, Pd/C, EtOAc; (b) benzaldehyde, $NaBH(OAc)_3$, CH_2Cl_2.

Table 1. NMDA Receptor (PCP Binding Site) and σ_1 Receptor Affinities of 17−26[a]

compd	R^1	R^2	NMDA K_i ± SEM [nM]	eudismic ratio	σ_1 K_i ± SEM [nM]
(*R*,*S*)-**17**	H	NH_2	>10000		>10000
(*S*,*R*)-**17**	H	NH_2	>10000		>10000
(*S*,*S*)-**18**	CH_3	NH_2	6120 ± 630	130	>10000
(*R*,*R*)-**18**	CH_3	NH_2	46 ± 17		>10000
(*S*,*S*)-**19**	C_2H_5	NH_2	1490 ± 250	115	>10000
(*R*,*R*)-**19**	C_2H_5	NH_2	13 ± 1		>10000
(*S*,*S*)-**20**	C_3H_7	NH_2	1530 ± 670	70	>10000
(*R*,*R*)-**20**	C_3H_7	NH_2	21 ± 3		>10000
(*S*,*S*)-**21**	$C(CH_3)_3$	NH_2	400 ± 47	1.3	>10000
(*R*,*R*)-**21**	$C(CH_3)_3$	NH_2	304 ± 35		>10000
(*R*,*S*)-**22**	H	NHBn	>10000		50 ± 19
(*S*,*R*)-**22**	H	NHBn	>10000		6.0 ± 1
(*S*,*S*)-**23**	CH_3	NHBn	>10000		11 ± 3
(*R*,*R*)-**23**	CH_3	NHBn	>10000		17 ± 2
(*S*,*S*)-**24**	C_2H_5	NHBn	>10000		28 ± 6
(*R*,*R*)-**24**	C_2H_5	NHBn	>10000		20 ± 3
(*S*,*S*)-**25**	C_3H_7	NHBn	>10000		136 ± 23
(*R*,*R*)-**25**	C_3H_7	NHBn	>10000		72 ± 9
(*S*,*S*)-**26**	$C(CH_3)_3$	NHBn	>10000		253 ± 11
(*R*,*R*)-**26**	$C(CH_3)_3$	NHBn	>10000		128 ± 2
phencyclidine (**1**)			59 ± 12		
(*S*)-ketamine (**2**)			383 ± 41		
memantine (**3**)			429 ± 140		
dexoxadrol (**4**)[b]			32 ± 7		
racemic **17**[c]			>10000		>10000
racemic **19**[c]			23 ± 8		>10000
(+)-MK-801			3 ± 2		
(+)-pentazocine					6 ± 2
haloperidol					6 ± 2

[a]R^1 and R^2 refer to the structures shown in Scheme 3. [b]Several studies report that the NMDA receptor affinities of dexoxadrol (**4**) and etoxadrol (**5**) are very similar.[14−17] [c]Resynthesized according to literature.[16]

de and 97.9% de, respectively. The minor diastereomers of (*R*,*S*)-**12**, (*S*,*S*)-**14**, and (*S*,*S*)-**15** turned out to be rather unstable, and those of (*S*,*S*)-**13** and (*S*,*S*)-**16** could not be detected. For the following preparation of amines, the 1,3-dioxanes **12−16** were purified by preparative HPLC, which led to the isolation of the major diastereomers with purities >99.8% de, respectively.

Preparation of Amines 17−26. Azidodioxanes **12−16** were reduced with H_2 in the presence of Pd/C to obtain primary amines **17−21** (Scheme 3). Subsequently, reductive monobenzylation of **17−21** was performed with one equivalent of benzaldehyde and $NaBH(OAc)_3$ affording benzylamines **22−26**.

DISCUSSION

Affinity toward the PCP Binding Site of the NMDA Receptor. The primary amines (*R*,*R*)-**18−21** showed high affinity to the PCP binding site, whereas the introduction of a

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benzyl residue at the amino moiety (**22**–**26**) resulted in a complete loss of NMDA receptor affinity (Table 1). Probably due to the equatorial orientation of the phenyl ring, the benzaldehyde derivatives **17** did not interact with the NMDA receptor, indicating that the affinity of the primary amines **17**–**21** strongly depends on the axial perpendicular orientation of the phenyl moiety.

The eudismic ratios of the primary amines **18**–**21** decreased with increasing size of the second substituent in position 2 (see Table 1): very high eudismic ratios were found for the acetophenone derivatives **18** (R^1 = CH_3, 130: 1) and the propiophenone derivatives **19** (R^1 = C_2H_5, 115: 1). (*R*,*R*)-**19** is the most potent NMDA receptor ligand of this series with a K_i value of 13 nM.

Etoxadrol (**5**) and its homologue (*R*,*R*)-**19** share the axially oriented phenyl moiety and the ethyl moiety at position 2 as common features. Both compounds are highly flexible because the piperidine moiety of etoxadrol (**5**) as well as the 2-aminoethyl moiety of (*R*,*R*)-**19** can rotate freely. However, it is interesting that the (2*R*,4*R*)-configured dioxane (*R*,*R*)-**19** binds to the NMDA receptor with a 115-fold higher affinity than its (2*S*,4*S*)-configured enantiomer (*S*,*S*)-**19** although the absolute configuration of etoxadrol is (2*S*,4*S*,2S_{pip}).

Affinity toward the σ_1 Receptor. The primary amines **17**–**21** did not interact with the σ_1 receptor. In contrast, the corresponding benzylamines **22**–**26** displayed high σ_1 receptor affinity but lacked any NMDA receptor affinity. This observation is in good accordance with different σ_1 pharmacophore models, which defined at least two hydrophobic residues attached to a basic amino moiety as structural requirements.[24] However, the eudismic ratios of the benzylamines **22**–**25** to the σ_1 receptor are considerably lower than the eudismic ratios of the primary amines **18**–**22** to the NMDA receptor. The highest eudismic ratio of 8:1 was found for the enantiomeric benzaldehyde derivatives **22**. (*S*,*R*)-**22** is the compound with the highest σ_1 receptor affinity (K_i = 6.0 nM) of this series.

The σ_2 receptor affinities of compounds **17**–**26** were also investigated. It was found that the primary amines **17**–**21** did not interact with the σ_2 receptor. For benzylamines **22**–**26**, the σ_2 receptor affinities were rather low (>0.2 μM).

CONCLUSION

Ring and side chain homologation of the NMDA receptor antagonist etoxadrol (**5**) provided 2-(2-phenyl-1,3-dioxan-4-yl)ethanamines **17**–**26**. The primary amines (*R*,*R*)-**18**, (*R*,*R*)-**19**, and (*R*,*R*)-**20** interact with high affinity and enantioselectivity with the PCP binding site of the NMDA receptor. It is concluded that the axial orientation of the phenyl moiety in position 2 of these compounds is responsible for the high NMDA receptor affinity. Transformation of the primary amines into benzylamines led to potent σ_1 receptor ligands without any NMDA receptor affinity. In summary, introduction of an *N*-benzyl moiety and changing the configuration at the acetalic position changes the NMDA ligand (*R*,*R*)-**19** (K_i(NMDA) = 13 nM) into the potent σ_1 receptor ligand (*S*,*R*)-**22** ($K_i(\sigma_1)$ = 6 nM).

EXPERIMENTAL SECTION

General. Flash chromatography (fc): silica gel 60, 40–63 μm (diameter, length of the column, fraction size, R_f value). ^{1}H NMR and ^{13}C NMR: Unity Mercury Plus 400 spectrometer (Varian), INOVA 500 spectrometer (Varian). Optical rotation: Polarimeter 341 (Perkin-Elmer), 1.0 dm tube, concentration *c* (g/100 mL), 20 °C, the unit [deg·mL·dm^{-1}·g^{-1}] is omitted.

Compounds 7–11. Dimethyl 3-hydroxyglutarate (**7**) was purchased from Sigma-Aldrich, and compounds **8**, **9**, (*S*)-**10**, (*R*)-**10**, (*S*)-**11**, and (*R*)-**11** were synthesized and characterized as described in the literature.[18,19] A batch of azidodiol (*S*)-**11** with 99.8% ee and azidodiol (*R*)-**11** with 98.0% ee was used for production of all further compounds.

General Procedure A for Acetalization of Azidodiols 11 to Obtain 1,3-Dioxanes 12–16. Azidodiol (*S*)-**11** or (*R*)-**11** (4.2 mmol/0.9 mmol), the respective ketone or aldehyde (2 equiv), and 4-toluenesulfonic acid monohydrate (10 mg/2.5 mg) were heated to reflux in toluene (15 mL/3 mL). The water formed was removed with a Dean–Stark apparatus. After 1 h. the water was removed from the separator, the water separator was filled with molecular sieve (3 Å), and fresh toluene was added. The reaction mixture was heated to reflux for further 3 h and then concentrated (5 mL/1 mL) by removing toluene. The residue was cooled to rt, $CHCl_3$ (80 mL) was added, and the mixture was washed with a saturated solution of $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4) znc concentrated in vacuo, and the remaining crude material was purified by preparative HPLC.

General Procedure B for Reduction of Azides 12–16 to Primary Amines 17–21. In a Schlenk flask, the respective azidodioxane **12**–**16** (3 mmol of (4*S*)-configured compounds/0.6 mmol of (4*R*)-configured compounds) was dissolved in ethyl acetate (40 mL/10 mL), which had been dried over molecular sieve (3 Å). Pd/C (10%, 80 mg/15 mg) was added, and the mixture was stirred under a H_2 atmosphere (balloon, 5 L) for 5 h at rt. Every hour, a part of the gas phase was released (250–500 mL) and replaced by H_2 if necessary. Then the reaction mixture was filtered, concentrated in vacuo, and purified by fc (eluent: homogeneous mixture of CH_2Cl_2/methanol/NH_3 solution (25%) 470/25/4). Compounds **17** and **18** were additionally purified by preparative HPLC.

General Procedure C for Conversion of Primary Amines 17–21 into Benzylamines 22–26. The respective primary amine **17**–**21** (1 mmol of (*S*)-configured compounds/0.25 mmol of (*R*)-configured compounds) was dissolved in CH_2Cl_2 (20 mL/5 mL). Freshly distilled benzaldehyde (1 equiv) was added, and the mixture was stirred at rt. After stirring for 1 h, $NaBH(OAc)_3$ (1.4 equiv) was added, and the mixture was stirred at rt for further 16 h. Then the mixture was diluted with CH_2Cl_2 (40 mL) and carefully washed with a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the combined CH_2Cl_2 layers were dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by fc using the same eluent as for purification of the primary amines **17**–**21**.

(2*R*,4*R*)-2-(2-Ethyl-2-phenyl-1,3-dioxan-4-yl)ethan-1-amine ((*R*,*R*)-19). According to general procedure B, (*R*,*R*)-**14** (172 mg, 0.66 mmol) was treated with H_2. Purification by fc (3 cm, 20 cm, 10 mL, R_f = 0.11). Pale-yellow oil, yield 124 mg (80%). $[\alpha]^{20}_D$ = −16.0 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.79 (t, *J* = 7.5 Hz, 3H, CH_2-CH_3), 1.25 (dtd, *J* = 12.8/2.3/1.6 Hz, 1H, 5-H_{eq}), 1.38 (s, 2H, CH_2-CH_2-NH_2), 1.50–1.81 (m, 5H, CH_2-CH_2-NH_2 and 5-H_{ax} and CH_2-CH_3), 2.82–2.99 (m, 2H, CH_2-CH_2-NH_2), 3.71–3.87 (m, 2H, 6-H_{ax} and 4-H_{ax}), 3.88 (ddd, *J* = 11.4/5.3/1.3 Hz, 1H, 6-H_{eq}), 7.26–7.41 (m, 5H, H_{arom}).

(2*S*,4*R*)-*N*-Benzyl-2-(2-phenyl-1,3-dioxan-4-yl)ethan-1-amine ((*S*,*R*)-22). According to general procedure C, (*S*,*R*)-**17** (63 mg, 0.30 mmol) was reacted with benzaldehyde (33 mg, 0.31 mmol) and $NaBH(OAc)_3$ (92 mg, 0.43 mmol). Purification by fc (2 cm, 22 cm, 5 mL, R_f = 0.27). Pale-yellow oil, yield 58 mg (63%). $[\alpha]^{20}_D$ = +42.4 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.51 (dtd, *J* = 13.3/2.4/1.4 Hz, 1H, 5-H_{eq}), 1.73–1.94 (m, 4H, CH_2-CH_2-NHBn and 5-H_{ax} and CH_2-CH_2-NHBn), 2.83 (t, *J* = 6.8 Hz, 2H, CH_2-CH_2-NHBn), 3.80 (s, 2H, NH-CH_2-Ph), 3.93–4.02 (m, 2H, 6-H_{ax} and 4-H_{ax}), 4.26 (ddd, J = 11.4/5.0/1.3 Hz, 1H, 6-H_{eq}), 5.51 (s, 1H, 2-H_{ax}), 7.22–7.38 (m, 8H, H_{arom}), 7.45–7.48 (m, 2H, H_{arom}).

Purity of Compounds 17–26 (HPLC). Column: LiChrospher 60 RP select B (250 mm, 4 mm) with precolumn (4 mm, 4 mm). Eluent:

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A = water plus 0.05% TFA (v/v), B = acetonitrile plus 0.05% TFA (v/v). Gradient: 0.0−4.0 min 90% A, 4.0−29.0 min from 90% A to 0% A, 29.0−31.0 min 0% A, 31.0−31.5 min from 0% A to 90% A, 31.5−40.0 min 90% A. Flow rate: 1 mL/min. UV detection: 210 nm. The purity of all compounds was ≥98%.

Receptor Binding Studies. The affinities of **17**−**26** toward the PCP binding site of the NMDA receptor were determined in competition experiments using [^{3}H]-(+)-MK-801 as radioligand and membrane preparations from pig brain cortex as receptor material. The σ_1 receptor binding assay was carried out with homogenates of guinea pig brains as receptor material and [^{3}H]-(+)-pentazocine as radioligand. These experiments had been optimized with respect to previously reported binding studies.[16]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Purity data of the primary amines **17**−**21** and the benzyl amines **22**−**26**; synthesis of compounds **12**−**26** and data thereof; materials and procedures for the NMDA, σ_1, and σ_2 receptor binding assays and σ_2 receptor affinities; HPLC methods; ee of (*S*)-**10** and (*R*)-**10**; ee of the bis-4-bromobenzoates of (*S*)-**11** and (*R*)-**11**; CD-/UV-spectra of the bis-4-bromobenzoates of (*S*)-**11** and (*R*)-**11**; de of (*R*,*S*)-**12**, (*S*,*S*)-**14** and (*S*,*S*)-**15**; ^{1}H NMR and NOE spectra of (*R*,*S*)-**12**, (*S*,*S*)-**13**, (*S*,*S*)-**14**, (*S*,*S*)-**15**, and (*S*,*S*)-**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS USED

NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine (= 1-(1-phenylcyclohexyl)piperidine); DIAD, diisopropyl azodicarboxylate; PPh_3, triphenylphosphane; SEM, standard error of the mean; APCI, atmospheric-pressure chemical ionization; ATR, attenuated total reflectance; fc, flash chromatography

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