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(1-Benzylpiperazin-2-yl)methanols: novel EPC synthesis from (*S*)-serine and transformation into ligands for central nervous system receptors

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Abstract—A novel three-step synthesis of 4-substituted-(1-benzylpiperazin-2-yl)methanols **5a**–**5c** is described starting from the methyl ester of the proteinogenic amino acid (*S*)-serine, which involves the diastereomeric oxazolidine derivatives **11a**–**11c** as key intermediates. **5b** and **5c** were transformed into the chiral, non-racemic bicyclic lactams **14b** and **14c** via Swern oxidation followed by Wittig reaction and subsequent hydrogenation. In the screening for central nervous system receptor affinity the butyl derivative **14b** was found to have promising interaction with σ_1-receptors ($K_i = 345$ nM).

1. Introduction

2-Substituted piperazine derivatives display high affinity for various receptors within the central nervous system (CNS). Among these compounds is the (*R*)-configured 1,4-diacylpiperazine **1** with a (pyrrolidin-1-yl)methyl residue in position 2, representing one of the most potent and selective κ-receptor agonists ($IC_{50} = 0.018$ nM).[1] Using (*R*)-2-aminoadipic acid as the lead structure, the potent and selective competitive *N*-methyl-D-aspartate (NMDA) antagonist **2**—a phosphonopropyl substituted piperazine-2-carboxylic acid—has been developed.[2] A further example for a receptor ligand with piperazine structure is the bis-urea derivative **3**, which binds with high affinity at NK_1 receptors (substance P antagonist).[3] In addition to their own pharmacological properties, 2-substituted piperazines are incorporated as substructures into several pharmacologically useful compounds, e.g. HIV-protease inhibitors (Indivavir[4]) or PAF antagonists.[5] Furthermore, 2-substituted piperazines serve as building blocks for the synthesis of pharmacologically active piperazines, including **1**–**3** as well as racemic lactams **4**, which are of interest because of their nootropic activity (Fig. 1).[6]

Herein, we report a novel method for the synthesis of homochiral (piperazin-2-yl)methanols **5**, which are selectively protected in position 1 with a benzyl group and substituted with various residues in position 4. The proteinogenic amino acid (*S*)-serine was used as homochiral starting material in analogy to our strategy with the amino acid (2*S*,3*R*)-threonine.[7] The (piperazin-2-yl)methanols **5** were further transformed into chiral non-racemic bicyclic lactams **14**, which were investigated for their ability to interact with CNS receptors (NMDA-, μ-, κ-, and σ-receptors) (Scheme 1).

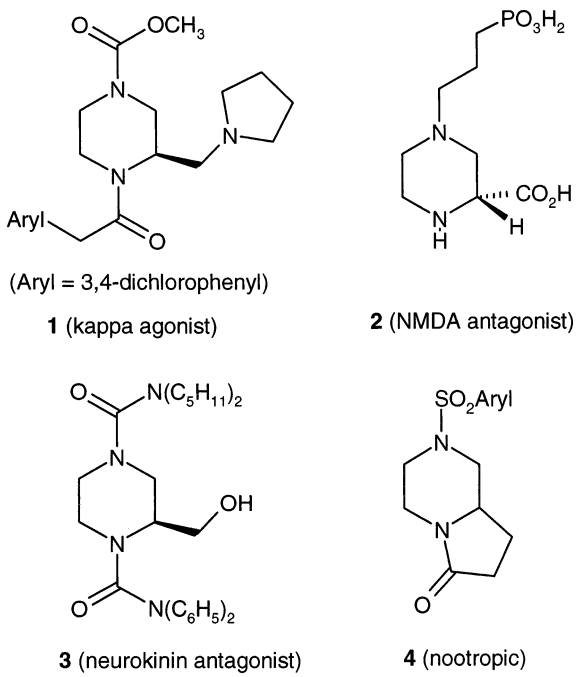

Figure 1.

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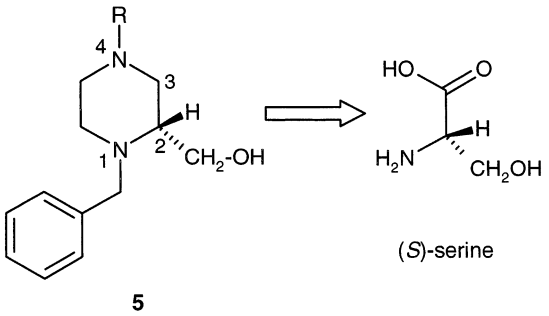


Scheme 1.

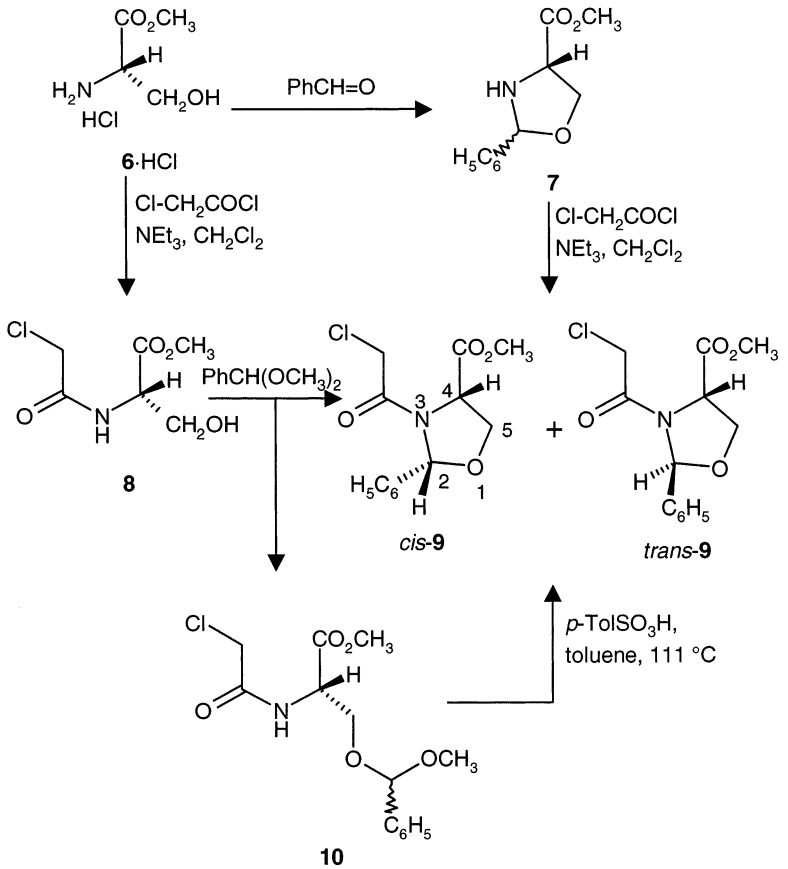
The syntheses of 2-substituted piperazine derivatives starting with (*R*)- or (*S*)-serine is described in the literature.[1,5,8] The unique feature of our strategy is, however, the simultaneous protection of both the amino- and hydroxy-moiety of serine with benzaldehyde to generate a 1,3-oxazolidine ring system. The reductive opening of the N/O-acetalic oxazolidine ring system should generate the benzyl protective group in position 1 and, at the same time, liberate the hydroxy group in the side chain for further transformations (compare Scheme 3).

2. Chemistry

Condensation of methyl esters of serine and threonine with pivalaldehyde and subsequent acylation stereoselectively provided *cis*-configured *N*-acyloxazolidine derivatives.[9] Analogously, threonine methyl ester reacted with benzaldehyde and chloroacetyl chloride to yield the corresponding 3-(chloroacetyl)-2-phenyloxazolidine derivative.[7] However, condensation of the hydrochloride of serine methyl ester, **6**·HCl, with benzaldehyde to give **7** and subsequent acylation with chloroacetyl chloride provided only low 2–5% yields of the stereoisomeric methyl oxazolidine-4-carboxylates **9**.

Therefore, the reaction sequence was reversed and (*S*)-**6**·HCl was acylated with chloroacetyl chloride to give the chloroacetamide **8** (93%), which was condensed with benzaldehyde dimethyl acetal to afford the stereoisomeric oxazolidine derivatives *cis*-**9** and *trans*-**9**. [N.B. The stereodescriptors *cis* and *trans* are used to characterize the relative configuration of the protons in positions 2 and 4 of the oxazolidine ring system.] After reaction of benzaldehyde dimethyl acetal with the chloroacetamide **8**, the mixed acetal **10** (mixture of diastereomers) was obtained as a side product in variable amounts (15–80%). The isolated mixed acetal **10** could be cyclized upon heating with a catalytic amount of *p*-toluenesulfonic acid. However, the yield of the oxazolidine derivatives **9** did not exceed 58% as a result of decomposition of the mixed acetal **10** indicating that the mixed acetal **10** is not the only intermediate during the synthesis of the oxazolidines **9** from the chloroacetamide **8** and benzaldehyde dimethyl acetal (Scheme 2).

The stereoselectivity observed during the formation of 2-phenyloxazolidines **9** is strongly dependent on the



Scheme 2.

reaction conditions. Heating the chloroacetamide **8** with benzaldehyde dimethyl acetal in CH_2Cl_2 (41°C) led to the diastereomeric *cis*- and *trans*-oxazolidines **9** in a ratio of ~9:1. After heating the same components in refluxing toluene *trans*-**9** predominated in a ~3:7 *cis*/*trans* mixture. Obviously, *trans*-**9** is the thermodynamically more stable isomer, whereas the *cis*-isomer *cis*-**9** is formed under kinetic control. With regard to the stereochemistry, the 3-(chloroacetyl)-2-phenyloxazolidines **9** differ significantly from the 2-*tert*-butyl substituted oxazolidines described by Seebach et al.[9]

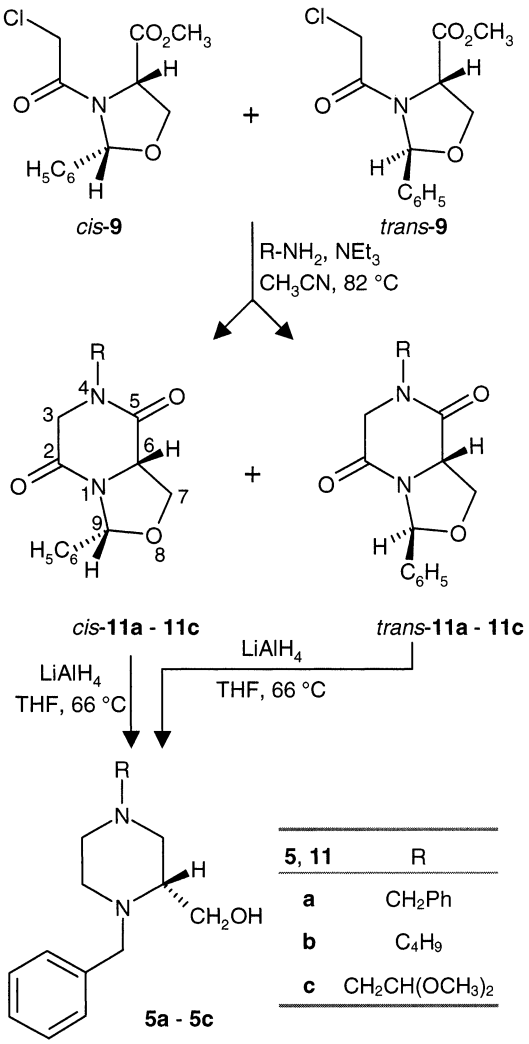
Interpretation of the ^1H NMR spectra of **9** was complicated by the appearance of four sets of broad signals, which are caused by slow rotation around the amidic *N*-*C*=O bond. However, recording the ^1H NMR spectra at elevated temperature (DMSO, 90°C) unequivocally demonstrated the existence of rotamers and facilitated the interpretation of the spectra by the coalescence of corresponding signals.

The chloroacetyl substituted oxazolidines **9** (mixture of *cis*/*trans* diastereomers) reacted with simple primary amines including benzylamine and butylamine as well as further substituted amines like aminoacetaldehyde dimethyl acetal to give the bicyclic piperazinediones **11** in good yields (Scheme 3). During these transformations the diastereomeric ratio of the chloroacetamides **9** is conserved leading to bicyclic piperazinediones **11** in the same *cis*:*trans* diastereomeric ratio. The diastereoisomers of **11** could be easily separated by flash chromatography and the relative configuration of the *cis*-configured benzyl substituted derivative *cis*-**11a** was determined by a NOESY NMR experiment, which confirmed the neighborhood of the protons in positions 6 and 9. The analogous experiment performed with *trans*-**11a** did not lead to enhancement of the C(6)H-signal after irradiation at 6.25 ppm (C(9)H).

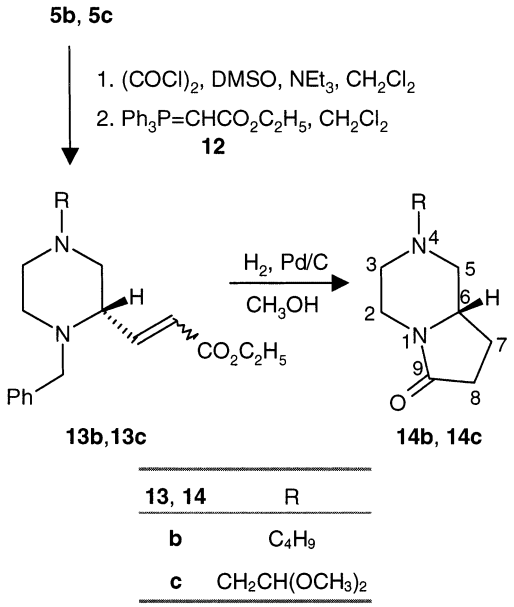
Heating the bicyclic piperazinediones **11** with excess $LiAlH_4$[7,10] afforded the (1-benzylpiperazin-2-yl)methanols **5** with different substituents at position 4. This transformation comprises reduction of both lactam carbonyl moieties and concomitant reductive ring opening of the oxazolidine ring system destroying the initially generated stereogenic center. We demonstrated, that both diastereomeric piperazinediones *cis*-**11** and *trans*-**11** provided the same (1-benzylpiperazin-2-yl)methanol **5** within a comparable time and in the same yield. Therefore, the preparation of **5** was usually performed using a diastereomeric mixture of *cis*-**11** and *trans*-**11**.

Syntheses of (±)-1,4-diazabicyclo[4.3.0]nonan-9-ones with the general formula **4** have been reported.[6,11] However, enantiomerically pure bicyclic lactams **4** have not been described. Herein, we point out, that the (*R*)-configured (1-benzylpiperazin-2-yl)methanols **5** can be used as homochiral building blocks for the preparation of chiral, non-racemic bicyclic lactams **14**, which represent alkyl analogues of the racemic nootropics **4** (Scheme 4).

Thus, the alcohols **5b** and **5c** were oxidized under Swern conditions[12] to afford the corresponding aldehydes, which were trapped without purification with the Wittig reagent **12** to produce the α,β-unsaturated esters



Scheme 3.



Scheme 4.

13b and **13c** as mixtures of *cis*- and *trans*-isomers, respectively. Reaction of the α,β-unsaturated esters **13b** and **13c** with hydrogen in the presence of catalytic Pd/C led to saturation of the double bond, hydrogenolytic cleavage of the benzyl protective group and subsequent intramolecular aminolysis to provide the bicyclic lactams **14b** and **14c**. These transformations correspond to the analogous reactions of (±)-1,4-dibenzylpiperazine-2-carbaldehyde providing (±)-bicyclic lactams **4** with sulfonyl and acyl residues at N(4).[6]

3. Receptor binding studies

To investigate the binding at receptors within the central nervous system, the homochiral bicyclic lactams **14b** and **14c** and the synthetic intermediate **13c** were screened with two concentrations (1 and 10 μM) for their affinities to NMDA-, κ-, μ-, σ_1- and σ_2-receptors. The following tritiated radioligands were employed: (+)-MK-801 (PCP binding site of the NMDA-receptor), U-69593 (κ-receptor), DAMGO (μ-receptor), (+)-pentazocine (σ_1-receptor) and ditolylguanidine in the presence of an excess of unlabelled (+)-pentazocine (σ_2-receptor).[13] In Table 1 the residual binding of the respective radioligand at a test compound concentration of 10 μM is summarized. With exception of the σ_1-receptor affinity of **14b** the residual binding of the radioligands in each experiment exceeds 50%, indicating an IC_{50}-value of greater than 10 μM.

The determination of the exact σ_1-receptor affinity[13] of the butyl substituted bicyclic lactam **14b** by recording the complete competition curves in triplicates led to a K_i value of 345 nM (SEM±23 nM). Compared with the antipsychotic agent BMY-14802,[14] the σ_1-receptor affinity of which has also been determined in our assay [K_i = 265 nM±32 nM (SEM)], **14b** displays similar binding to σ_1-receptors.

4. Conclusion

σ_1-Receptors bind several classes of psychoactive agents including opioid-related compounds, phencyclidine-related compounds and typical neuroleptics.[15] Therefore, the bicyclic lactams **14**, which differ from the nootropics **4** by an alkyl residue at N(4), may have potential in the treatment of psychiatric and neurodegenerative disorders.

5. Experimental

5.1. General procedures

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was distilled from sodium/benzophenone ketyl immediately prior to use. Petroleum ether used refers to the fraction boiling at 40–60°C. Thin-layer chromatography (tlc): silica gel 60 F_{254} plates (Merck). Flash chromatography (fc):[16] silica gel 60, 0.040–0.063 mm (Merck); parentheses include: diameter of the column (cm), eluent, fraction size (mL), R_f. Melting points: melting point apparatus SMP 2 (Stuart Scientific), uncorrected. Optical rotation: polarimeter 241 (Perkin–Elmer); 1.0 dm tube; concentration c (g/100 mL); temperature 20°C. Elemental analyses: Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44 and TSQ 7000 (Finnigan); EI = electron impact, CI = chemical ionization. High resolution MS (HRMS): MAT 8200 (Finnigan). IR: IR spectrophotometer 1605 FT-IR (Perkin–Elmer). (br = broad, m = medium, s = strong.) ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and of ^{1}H NMR signals were supported by 2D NMR techniques.

5.2. (+)-(2*S*)-Methyl 2-(2-chloroacetylamino)-3-hydroxypropanoate 8

A suspension of (*S*)-serine methyl ester hydrochloride[9] **6**·HCl (10.0 g, 64.3 mmol) in CH_2Cl_2 (100 mL) was cooled to −5°C. Triethylamine (17.9 mL, 128.6 mmol) and subsequently a solution of chloroacetyl chloride (4.9 mL, 61.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was stirred for 1 h at −5°C and for 1 h at room temperature. Precipitated Et_3N·HCl was filtered off, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (8 cm, ethyl acetate, 100 mL, R_f = 0.38) to yield **8** as a yellow, viscous oil (11.69 g, 93%). $[\alpha]_{589}$ = +30.8 (c = 0.945, CH_2Cl_2); MS (EI): m/z (%) = 196 (M, 1), 167/165 (M–OCH_3, 16/50), 138/136 (M–CO_2CH_3, 25/75), 118 (M–$ClCH_2CO$, 15), 79/77 ($ClCH_2CO$, 12/33), 59 (138/136–$ClCH_2CO$, 9); IR (film): ν (cm^{-1}) = 3352 (br, OH), 2956 (m, C-H), 1740 (s, C=O ester), 1670 (s, C=O amide), 1536 (s, C-N), 1226 (s, C-O), 775 (m, C-Cl); ^{1}H NMR ($CDCl_3$): δ = 2.48 (s broad, 1H, O*H*), 3.82 (s, 3H, CO_2CH_3), 3.95 (dd, J = 11.3/3.5 Hz,

Table 1. Residual binding (%) of the respective radioligand at a test compound concentration of 10 μM

Compound	NMDA [(+)-MK-801]	κ (U-69593)	μ (DAMGO)	σ_1 [(+)-Pentazocine]	σ_2 Ditolylguanidine
13c	87%	90%	97%	79%	81%
14b	83%	97%	102%	9.3%	58%
14c	82%	96%	100%	84%	89%

1H, 3-H), 4.05 (dd, $J=11.3/3.7$ Hz, 1H, 3-H), 4.10 (s, 2H, CH_2Cl), 4.65–4.70 (m, 1H, 2-H), 7.45 (s broad, 1H, N*H*); calcd for $C_6H_{10}ClNO_4$ (195.6) C, 36.84; H, 5.15; N, 7.16. Found: C, 36.75; H, 5.40; N, 6.93%.

5.3. (2*R*,4*S*)- and (2*S*,4*S*)-Methyl 3-chloroacetyl-2-phenyl-1,3-oxazolidine-4-carboxylate *cis*-9 and *trans*-9

(a) Thermodynamic control: a solution of benzaldehyde dimethyl acetal (2.3 mL, 15.3 mmol), **8** (1.0 g, 5.1 mmol) and *p*-toluenesulfonic acid monohydrate (22 mg, 0.12 mmol) in toluene (20 mL) was heated under reflux for 2 h in a Dean–Stark trap. The reaction mixture was concentrated to a volume of about 5 mL. After adding Et_2O (20 mL) to the cooled solution, the organic layer was washed with a saturated solution of $NaHCO_3$ (2×10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), evaporated in vacuo and the residue was separated by flash chromatography (5 cm, CH_2Cl_2/ethyl acetate 9:1, 15 mL) to provide *cis*-**9**/*trans*-**9** ($R_f=0.47$) and **10** ($R_f=0.29$).

cis-**9**/*trans*-**9**: Pale yellow, viscous oil (1.023 g, 71%). MS (EI): m/z (%) = 248 (M–Cl, 100), 224 (M–CO_2CH_3, 22), 206 (M–$ClCH_2CO$, 58), 148 (2-phenyl-1,3-oxazolidine, 65), 105 (PhCH=O, 55), 91 (benzyl, 30), 65 (benzyl–C_2H_2, 3); MS (CI): m/z (%) = 286/284 (MH^+, 20/70); IR (film): ν (cm^{-1}) = 2954 (m, C-H), 1747 (s, C=O ester), 1673 (s, C=O amide), 1423 (s, C-H), 1362 (m, C-O), 1212 (s, C-O), 759 and 701 (m, aryl-C-H); ^{1}H NMR ($CDCl_3$): $\delta=3.59$ (d, $J=13.3$ Hz, 1H, CH_2Cl), 3.67 (d, $J=13.3$ Hz, 1H, CH_2Cl), 3.82 (s, 3×0.15H, OCH_3, *cis*, rotamer 1), 3.84 (s, 3×0.70H, OCH_3, *trans*), 3.87 (s, 3×0.15H, OCH_3, *cis*, rotamer 2), 4.03 (d broad, $J=6.4$ Hz, 0.15H, 5-H, *cis*, rotamer 2), 4.12 (dd, $J=14.3/7.3$ Hz, 0.70H, 5-H, *trans*), 4.13 (dd, $J=9.5/3.4$ Hz, 0.15H, 5-H, *cis*, rotamer 1), 4.30 (dd, $J=9.2/7.1$ Hz, 2×0.15H, 5-H, *cis*), 4.30 (dd, $J=14.3/12.0$ Hz, 0.70H, 5-H, *trans*), 4.84–4.90 (m, 1H, 4-H), 6.16 (s broad, 0.70H, 2-H, *trans*), 6.37 (s, 0.15H, 2-H, *cis* rotamer 1), 6.49 (s, 0.15H, 2-H, *cis* rotamer 2), 7.38–7.75 (m, 5H, arom.); ^{1}H NMR (DMSO, 27°C): $\delta=3.70$ (s, 3×0.15H, OCH_3, *cis*, rotamer 1), 3.75 (s, 3×0.70H, OCH_3, *trans*), 3.77 (s, 3×0.15H, OCH_3, *cis*, rotamer 2), 4.08–4.30 (m, 3H, 5-H and CH_2Cl(1H)), 4.44 (d broad, $J=8.8$ Hz, 0.70H, CH_2Cl, *trans*), 4.52 (dd, $J=14.2/4.5$ Hz, 0.30H, CH_2Cl, *cis*), 4.71–4.81 (m, 0.35H, 4-H, *trans*, rotamer 2), 4.91 (dd, $J=6.4/2.6$ Hz, 0.15H, 4-H, *cis*, rotamer 2), 5.07 (d, $J=5.8$ Hz, 0.35H, 4-H, *trans*, rotamer 1), 5.19 (d, $J=6.1$ Hz, 0.15H, 4-H, *cis*, rotamer 1), 6.00 (s, 0.35H, 2-H, *trans*, rotamer 1), 6.22 (s, 0.35H, 2-H, *trans*, rotamer 2), 6.25 (s, 0.15H, 2-H, *cis*, rotamer 1), 6.56 (s, 0.15H, 2-H, *cis*, rotamer 2), 7.33–7.72 (m, 5H, arom.); ^{1}H NMR (DMSO, 90°C): $\delta=3.75$ (s, 3H, OCH_3), 4.14–4.31 (m, 4H, 5-H and CH_2Cl_2), 4.94–4.96 (m, 1H, 4-H), 6.16 (s, 0.70H, 2-H, *trans*), 6.37 (s, 0.30H, 2-H, *cis*), 7.37–7.56 (m, 5H, arom.); ratio of *cis*-**9**/*trans*-**9** = 3:7; calcd for $C_{13}H_{14}ClNO_4$ (283.71): C, 55.04; H, 4.97; N, 4.94. Found: C, 54.88; H, 5.13; N, 4.97%.

Compound **10**: Pale yellow, viscous oil (0.105 g, 7%). MS (EI): m/z (%) = 249 (M–Cl–OCH_3, 15), 248 (M–Cl–$HOCH_3$, 100), 206 (M–Cl–CO_2CH_3–CH_3, 71), 121 ($PhCHOCH_3$, 12), 91 (benzyl, 37), 79/77 ($ClCH_2CO$, 9/24), 65 (benzyl–C_2H_2, 3); MS (CI): m/z (%) = 318/316 (MH^+, 0.5/1). IR (film): ν (cm^{-1}) = 2954 (m, C-H), 1744 (s, C=O ester), 1673 (s, C=O amide), 1442 (s, C-H), 1358 (m, C-O), 751 (m, C-Cl); ^{1}H NMR ($CDCl_3$): $\delta=2.95$ (s, 3×0.5H, OCH_3 diastereomer 1), 2.96 (s, 3×0.5H, OCH_3 diastereomer 2), 3.30 (dd, $J=10.1/3.1$ Hz, 0.5H, 3-H diastereomer 1), 3.34 (dd, $J=10.1/3.2$ Hz, 0.5H, 3-H diastereomer 2), 3.38 (s, 3×0.5H CO_2CH_3 diastereomer 1), 3.39 (s, 3×0.5H CO_2CH_3 diastereomer 2), 3.53 (dd, $J=10.1/3.2$ Hz, 0.5H, 3-H diastereomer 1), 3.59 (dd, $J=10.0/3.1$ Hz, 0.5H, 3-H diastereomer 2), 3.64–3.75 (m, 2H, CH_2Cl), 4.26–4.37 (m, 1H, 2-H), 5.09 (s, 0.5H, PhC*H* diastereomer 1), 5.10 (s, 0.5H, PhC*H* diastereomer 2), 7.21–7.38 (m, 5H, arom.). The signal for the proton of the NH group could not be detected; calcd for $C_{14}H_{18}ClNO_5$ (315.75): C, 53.25; H, 5.75; N, 4.44. Found: C, 52.81; H, 5.78; N, 4.47%.

(b) Kinetic control: a solution of benzaldehyde dimethyl acetal (1.53 mL, 10.2 mmol) and **8** (2.0 g, 10.2 mmol) in CH_2Cl_2 (120 mL) was heated under reflux for 60 h. *p*-Toluenesulfonic acid monohydrate (4 mg, 0.02 mmol) was added to the cooled solution, and the mixture was stirred under reflux for an additional 76 h. The solvent was evaporated in vacuo and the residue was separated by flash chromatography (6 cm, CH_2Cl_2/ethyl acetate 9:1, 20 mL) to yield **9** ($R_f=0.47$) as pale yellow, viscous oil (1.122 g, 39%) as a mixture of *cis*-**9**/*trans*-**9** = 9:1 and **10** ($R_f=0.29$) as pale yellow, viscous oil (1.694 g, 56%).

(c) Synthesis of **9** from **10**: a solution of **10** (4.163 g, 13.2 mmol) and *p*-toluenesulfonic acid monohydrate (81 mg, 0.43 mmol) in toluene (100 mL) was heated to reflux for 2 h in a Dean–Stark trap. The reaction mixture was concentrated to a volume of about 5 mL. After addition of Et_2O (30 mL) to the cooled solution, the organic layer was washed with a saturated solution of $NaHCO_3$ (2×15 mL), water (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), evaporated in vacuo and the residue was purified by flash chromatography (6 cm, CH_2Cl_2/ethyl acetate 9:1, 50 mL, $R_f=0.47$). A mixture of *cis*-**9**/*trans*-**9** was obtained as pale yellow, viscous oil (2.18 g, 58%). Ratio *cis*-**9**/*trans*-**9** = 3:7.

5.4. (−)-(6*S*,9*R*)-4-Benzyl-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonane-2,5-dione *cis*-11a and (+)-(6*S*,9*S*)-4-benzyl-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonane-2,5-dione *trans*-11a

A solution of **9** (*cis*-**9**/*trans*-**9** = 3:7, 1.0 g, 3.52 mmol), benzylamine (0.38 mL, 3.52 mmol) and triethylamine (0.49 mL, 3.52 mmol) in acetonitrile (200 mL) was stirred under reflux for 48 h. Removal of the solvent in vacuo followed by flash chromatography (5 cm, ethyl acetate/petroleum ether 1:1, 20 mL) gave *cis*-**11a** ($R_f=0.38$) and *trans*-**11a** ($R_f=0.29$).

cis-**11a**: Colorless solid (0.32 g, 29%; mp 79–80°C; $[\alpha]_{589}=-196.9$ ($c=0.645$, CH_2Cl_2); $C_{19}H_{18}N_2O_3$ (322.36); HRMS: calcd 322.1317, found 322.1317 (±0

ppm); MS (EI): m/z (%) = 322 (M, 36), 231 (M–benzyl, 7), 175 (M–BnNCOCH, 4), 146 (BnNCOCH, 16), 105 (BnN, 34), 91 (benzyl, 100), 65 (benzyl–C_2H_2, 9); IR (KBr): ν (cm^{-1}) = 2891 (w, C-H), 1669 (s, C=O), 1448 (m, C-H), 1224 (m, C-O-C), 740 and 701 (m, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 3.78 (d, J = 16.6 Hz, 1H, 3-H), 4.06 (dd, J = 16.6/1.4 Hz, 1H, 3-H), 4.21 (t, J = 8.4 Hz, 1H, 7-H), 4.45 (td, J = 7.3/1.4 Hz, 1H, 6-H), 4.46 (d, J = 14.6 Hz, 1H, PhCH_2N), 4.58 (dd, J = 8.4/7.2 Hz, 1H, 7-H), 4.76 (d, J = 14.5 Hz, 1H, PhCH_2N), 6.48 (s, 1H, 9-H), 7.23–7.46 (m, 10H, arom.); ^1H NOE: after irradiation at δ = 6.48 ppm (9-H) a NOE was found at δ = 4.21 ppm (7-H) and δ = 4.45 ppm (6-H).

trans-**11a**: Colorless solid (0.75 g, 66%); mp 114–115°C; $[\alpha]_{589}$ = +0.9 (c = 0.505, CH_2Cl_2); calcd for $C_{19}H_{18}N_2O_3$ (322.36): C, 70.79; H, 5.63; N, 8.7. Found: C, 70.26; H, 5.64; N, 8.52%; MS (EI): m/z (%) = 322 (M, 34), 231 (M–benzyl, 6), 175 (M–BnNCOCH, 3), 146 (BnNCOCH, 10), 105 (BnN, 30), 91 (benzyl, 100), 65 (benzyl–C_2H_2, 11); IR (KBr): ν (cm^{-1}) = 2890 (w, C-H), 1674 (s, C=O), 1441 (m, C-H), 1234 (m, C-O), 737 and 700 (m, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 3.80 (d, J = 17.0 Hz, 1H, 3-H), 4.09 (dd, J = 17.0/1.2, 1H, 3-H), 4.32 (t, J = 8.6 Hz, 1H, 7-H), 4.48 (t, J = 8.6 Hz, 1H, 7-H), 4.54 (td, J = 8.6/1.2 Hz, 1H, 6-H), 4.62 (d, J = 14.6 Hz, 1H, PhCH_2N), 4.72 (d, J = 14.5 Hz, 1H, PhCH_2N), 6.25 (s, 1H, 9-H), 7.29–7.38 (m, 10H, arom.); ^1H NOE: after irradiation at δ = 6.25 ppm (9-H) an NOE was found at δ = 4.48 ppm (7-H). An NOE at δ = 4.54 ppm was not detected.

5.5. (–)-(6*S*,9*R*)-4-Butyl-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonane-2,5-dione *cis*-11b and (–)-(6*S*,9*S*)-4-butyl-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonane-2,5-dione *trans*-11b

A solution of **9** (*cis*-**9**/*trans*-**9** = 3:7, 1.33 g, 4.7 mmol), butan-1-amine (0.47 mL, 4.7 mmol) and triethylamine (0.65 mL, 4.7 mmol) in acetonitrile (200 mL) was refluxed for 48 h. Removal of the solvent in vacuo followed by flash chromatography (6 cm, ethyl acetate/ethanol, 5:1, 20 mL) gave *cis*-**11b** (R_f = 0.65) and *trans*-**11b** (R_f = 0.55).

cis-**11b**: Pale yellow, viscous oil (0.39 g, 29%), $[\alpha]_{589}$ = –166.5 (c = 0.895, CH_2Cl_2). $C_{16}H_{20}N_2O_3$ (288.35); HRMS: calcd 288.1474, found 288.1473 (–0.1 ppm); MS (EI): m/z (%) = 288 (M, 100), 259 (M–CH_2CH_3, 10), 245 (M–$CH_2CH_2CH_3$, 8), 231 (M–butyl, 7), 211 (M–Ph, 8), 183 (M–Ph–CH_2CH_3, 23), 147 (2-phenyloxazolidin, 25), 105 (PhCO, 90), 77 (Ph, 26); IR (film): ν (cm^{-1}) = 2958 (m, C-H), 1670 (s, C=O), 1450 (s, C-H), 1224 (m, C-O), 739 and 699 (m, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.34 ('sext', J = 7.4 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.55 ('quint', J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.36 (dt, J = 13.8/7.4 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.52 (dt, J = 13.8/7.5 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.82 (d, J = 16.8 Hz, 1H, 3-H), 4.19 ('t', J = 8.1 Hz, 1H, 7-H), 4.23 (dd, J = 16.5/1.8 Hz, 1H, 3-H), 4.41 (td, J = 7.4/1.5 Hz, 1H, 6-H), 4.54 (dd, J = 8.5/7.3 Hz, 1H, 7-H), 6.49 (s, 1H, 9-H), 7.36–7.49 (m, 5H, arom.).

trans-**11b**: Pale yellow, viscous oil (0.9 g, 66%). $[\alpha]_{589}$ = –54.5 (c = 1.14, CH_2Cl_2); $C_{16}H_{20}N_2O_3$ (288.35); HRMS: calcd 288.1474, found 288.1473 (–0.1 ppm); MS (EI): m/z (%) = 288 (M, 88), 259 (M–CH_2CH_3, 8), 245 (M–$CH_2CH_2CH_3$, 6), 231 (M–butyl, 3), 211 (M–Ph, 16), 183 (211–CH_2CH_3, 23), 147 (2-phenyloxazolidin, 21), 105 (PhCO, 100), 77 (Ph, 62); IR (film): ν (cm^{-1}) = 2958 (m, C-H), 1675 (s, C=O), 1437 (s, C-H), 1234 (m, C-O), 756 and 699 (m, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 0.96 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.36 ('sext', J = 7.4 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.57 ('quint', J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.43 (dt, J = 13.7/7.4 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.53 (dt, J = 13.4/7.4 Hz, 1H, $CH_2CH_2CH_2CH_3$), 3.80 (d, J = 16.7 Hz, 1H, 3-H), 4.20 (dd, J = 16.2/1.0 Hz, 1H, 3-H), 4.26 (t, J = 7.9 Hz, 1H, 7-H), 4.42 (t, J = 7.9 Hz, 1H, 7-H), 4.47 (td, J = 8.2/1.2 Hz, 1H, 6-H), 6.25 (s, 1H, 9-H), 7.35–7.45 (m, 5H, arom.).

5.6. (–)-(6*S*,9*R*)-4-(2,2-Dimethoxyethyl)-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonane-2,5-dione *cis*-11c and (–)-(6*S*,9*S*)-4-(2,2-dimethoxyethyl)-9-phenyl-8-oxa-1,4-diazabicyclo[4.3.0]nonan-2,5-dione *trans*-11c

A solution of **9** (*cis*-**9**/*trans*-**9** = 3:7, 5.0 g, 17.6 mmol), aminoacetaldehyde dimethyl acetal (1.9 mL, 17.6 mmol) and triethylamine (2.45 mL, 17.6 mmol) in acetonitrile (400 mL) was stirred under reflux for 48 h. Removal of the solvent in vacuo followed by flash chromatography (8 cm, ethyl acetate/petroleum ether 9:1, 50 mL) gave *cis*-**11c** (R_f = 0.27) and *trans*-**11c** (R_f = 0.18).

cis-**11c**: Pale yellow oil (1.46 g, 26%); $[\alpha]_{589}$ = –180.5 (c = 1.29, CH_2Cl_2); calcd for $C_{16}H_{20}N_2O_5$ (320.34): C, 59.99; H, 6.29; N, 8.74. Found: C, 59.71; H, 6.87; N, 8.74%; MS (EI): m/z (%) = 289 (M–OCH_3, 2), 105 (PhCH=O, 4), 91 (benzyl, 3), 75 ($CH(OCH_3)_2$, 100); MS (CI): m/z (%) = 321 (MH^+, 4); IR (film): ν (cm^{-1}) = 2942 (w, C-H), 2836 (w, O-CH_3), 1673 (s, C=O), 1449 (m, C-H), 1220 (m, C-O), 1076 (m, O-CH_3), 733 and 699 (s, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 3.33 (dd, J = 13.9/5.3 Hz, 1H, $CH_2CH(OCH_3)_2$), 3.41 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.75 (dd, J = 13.9/5.1 Hz, 1H, $CH_2CH(OCH_3)_2$), 4.00 (d, J = 16.7 Hz, 1H, 3-H), 4.21 (dd, J = 8.3/7.6 Hz, 1H, 7-H), 4.36 (dd, J = 16.5/1.6 Hz, 1H, 3-H), 4.43 (td, J = 7.4/1.6 Hz, 1H, 6-H), 4.50 (t, J = 5.1 Hz, 1H, $CH(OCH_3)_2$), 4.53 (dd, J = 8.3/7.0 Hz, 1H, 7-H), 6.5 (s, 1H, 9-H), 7.35–7.5 (m, 5H, arom.).

trans-**11c**: Pale yellow oil (3.4 g, 60%); $[\alpha]_{589}$ = –48.0 (c = 0.89, CH_2Cl_2); calcd $C_{16}H_{20}N_2O_5$ (320.34): C, 59.99; H, 6.29; N, 8.74. Found: C, 59.85; H, 6.47; N, 8.64%; MS (EI): m/z (%) = 320 (M, 2), 289 (M–OCH_3, 7), 105 (PhCHO, 5), 91 (benzyl, 5), 75 ($CH(OCH_3)_2$, 100); IR (film): ν (cm^{-1}) = 2942 (w, C-H), 2835 (w, O-CH_3), 1681 (s, C=O), 1440 (m, C-H), 1079 (m, O-CH_3), 733 and 699 (s, aryl-C-H); ^1H NMR ($CDCl_3$): δ = 3.42 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.47 (dd, J = 14.0/5.0 Hz, 1H, $CH_2CH(OCH_3)_2$), 3.70 (dd, J = 14.0/5.1 Hz, 1H, $CH_2CH(OCH_3)_2$), 3.99 (d, J = 17.1 Hz, 1H, 3-H), 4.25 (t, J = 8.9 Hz, 1H, 7-H), 4.32 (dd, J = 17.1/1.2 Hz, 1H, 3-H), 4.42 (t, J = 8.8 Hz, 1H, 7-H),

4.47 (td, $J=8.7/1.2$ Hz, 1H, 6-H), 4.52 (t, $J=5.2$ Hz, 1H, C*H*$(OCH_3)_2$), 6.27 (s, 1H, 9-H), 7.31–7.39 (m, 5H, arom.).

5.7. (+)-[(2*R*)-1,4-Dibenzylpiperazin-2-yl]methanol 5a

A solution of **11a** (mixture of *cis*/*trans* isomers, 1.0 g, 3.1 mmol) in THF (80 mL) was added to a stirred suspension of a $LiAlH_4$ pellet (1.12 g, 29.5 mmol) in THF (150 mL). The reaction mixture was heated to reflux for 72 h. Under N_2 atmosphere and cooling (ice bath) water (1 mL), NaOH (3N, 1.0 mL) and again water (1 mL) were successively added. The suspension was refluxed for 30 min. After the mixture was cooled to room temperature, the precipitate was filtered off and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), the solution was washed with NaOH (1N, 2×10 mL) and brine (10 mL), dried with Na_2SO_4 and evaporated in vacuo. Purification of the residue by flash chromatography (3 cm, ethyl acetate, 15 mL, $R_f=0.24$) furnished **5a** as a pale yellow, viscous oil, yield (0.524 g, 57%). $[\alpha]_{589}=+30.0$ ($c=1.165$, CH_2Cl_2); $C_{19}H_{24}N_2O$ (296.41) HRMS: calcd for M–OCH_3 ($C_{18}H_{21}N_2$) 265.1705, found 265.1704 (–0.1 ppm); MS (EI): m/z (%) = 265 (M–CH_2OH, 34), 174 (benzylpiperazine, 4), 146 (BnNCH_2CHN, 19), 106 (BnNH, 13), 91 (benzyl, 100), 65 (benzyl–C_2H_2, 12); MS (CI): m/z (%) = 297 (MH^+, 100); IR (film): ν (cm^{-1}) = 3381 (br, OH), 2937 (m, C-H), 2811 (s, C-O), 1452 (m, C-H), 1147 (m, C-O), 738 and 700 (s, aryl-C-H); ^{1}H NMR ($CDCl_3$): $\delta=2.35$–2.54 (m, 3H, 3-H, 5-H and/or 6-H), 2.57–2.70 (m, 3H, 2-H and 3-H, 5-H and/or 6-H), 2.93–3.00 (m, 1H, 3-H, 5-H or 6-H), 3.47 (d, $J=13.1$ Hz, 1H, PhCH_2N^1), 3.49 (s, 2H, PhCH_2N^4), 3.59 (dd, $J=11.3/2.2$ Hz, 1H, CH_2OH), 3.99 (d, $J=13.3$ Hz, 1H, PhCH_2N^1), 4.05 (dd, $J=11.5/3.2$ Hz, 1H, CH_2OH), 7.22–7.34 (m, 10H, arom.). The signal for the proton of the OH group could not be detected; ^{13}C NMR ($CDCl_3$): $\delta=49.8$ and 52.3 (2C, C-5, C-6), 55.9 (1C, C-3), 57.9 (1C, N^1*C*H$_2$Ph), 58.7 (1C, C-2), 61.9 (1C, *C*H$_2$OH), 63.0 (1C, N^4*C*H$_2$Ph), 126.9 and 127.1 (2C, 2×C-4 arom.), 128.2 and 128.6 (4 C, 2×C-3 and 2×C-5 arom.), 128.8 and 129.0 (4 C, 2×C-2 and 2×C-6 arom.), 137.5 and 138.4 (2C, 2×C-1 arom.).

5.8. (+)-[(2*R*)-1-Benzyl-4-butylpiperazin-2-yl]methanol 5b

A solution of **11b** (mixture of *cis*/*trans* isomers, 1.0 g, 3.47 mmol) in THF (80 mL) was added to a stirred suspension of a $LiAlH_4$ pellet (1.01 g, 26.5 mmol) in THF (150 mL). The mixture was stirred under reflux for 72 h. Under N_2 atmosphere and cooling (ice bath) water (1 mL), NaOH (3N, 1.0 mL) and further water (1 mL) were successively added. The suspension was stirred under reflux for 30 min. After the mixture was cooled to room temperature, the precipitate was filtered off and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), the solution was washed with NaOH (1N, 2×10 mL) and brine (10 mL), dried with Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (4 cm, ethyl acetate/ethanol, 5:1, 20 mL, $R_f=0.26$) furnished **5b** as a pale yellow, viscous oil; (0.909 g, 74%); $[\alpha]_{589}=+19.4$ ($c=0.875$, CH_2Cl_2); $C_{16}H_{26}N_2O$ (262.39); HRMS: calcd for M–CH_2OH ($C_{15}H_{23}N_2$) 231.1861, found 231.1861 (±0 ppm); MS (EI): m/z (%) = 233 (M–CH_2CH_3, 5), 231 (M–CH_2OH, 100), 140 (butylpiperazine, 10), 91 (benzyl, 68), 65 (benzyl–C_2H_2, 6); MS (CI): m/z (%) = 263 (MH^+, 100); IR (film): ν (cm^{-1}) = 3393 (br, OH), 2954 (s, C-H), 2816 (s, C-OH), 1454 (m, C-H), 1153 (m, C-OH), 739 and 699 (s, aryl-C-H); ^{1}H NMR ($CDCl_3$): $\delta=0.91$ (t, $J=7.3$ Hz, 3H, $CH_2CH_2CHCH_3$), 1.32 ('sext', $J=7.3$ Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.47 ('quint', $J=7.4$ Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.31 ('t', $J=7.5$ Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.31–2.39 (m, 1H, 3-H, 5-H or 6-H), 2.43–2.51 (m, 2H, 3-H, 5-H and/or 6-H), 2.58–2.69 (m, 3H, 2-H and 3-H, 5-H and/or 6-H), 2.93–3.01 (m, 1H, 3-H, 5-H or 6-H), 3.46 (d, $J=13.3$ Hz, 1H, PhCH_2N), 3.61 (dd, $J=11.4/1.9$ Hz, 1H, CH_2OH), 3.98 (d, $J=13.3$ Hz, 1H, PhCH_2N), 4.10 (dd, $J=11.5/2.8$ Hz, 1H, CH_2OH), 7.24–7.32 (m, 5H, arom.). The signal for the proton of the OH group could not be detected; ^{13}C NMR ($CDCl_3$): $\delta=13.9$ (1C, $CH_2CH_2CH_2CH_3$), 20.6 (1C, $CH_2CH_2CH_2CH_3$), 28.8 (1C, $CH_2CH_2CH_2CH_3$), 49.9, 52.6 and 56.4 (3C, C-3, C-5, C-6), 58.4 (1C, PhCH_2N), 58.3 (1C, $CH_2CH_2CH_2CH_3$), 58.5 (1C, C-2), 62.2 (1C, CH_2OH), 127.0 (1C, C-4 arom.), 128.3 (2C, C-3 and C-5 arom.), 128.8 (2C, C-2 and C-6 arom.), 138.4 (1C, C-1 arom.).

5.9. (+)-[(2*R*)-1-Benzyl-4-(2,2-dimethoxyethyl)piperazin-2-yl]methanol 5c

A solution of **11c** (mixture of *cis*/*trans* isomers, 1.0 g, 3.1 mmol) in THF (80 mL) was added to a stirred suspension of a $LiAlH_4$ pellet (1.06 g, 27.9 mmol) in THF (150 mL). The reaction mixture was heated under reflux for 72 h. Under N_2 atmosphere and cooling (ice bath) water (1 mL), NaOH (3N, 1.0 mL) and further water (1 mL) were successively added. The suspension was stirred under reflux for 30 min. The mixture was cooled to room temperature, the precipitate was filtered off and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), the solution was washed with NaOH (1N, 2×10 mL) and brine (10 mL), dried with Na_2SO_4 and evaporated in vacuo. Purification of the residue by flash chromatography (3 cm, ethyl acetate/ethanol, 5:1, 10 mL, $R_f=0.26$) furnished **5c** as pale yellow, viscous oil (0.569 g, 62%); $[\alpha]_{589}=+21.9$ ($c=1.12$, CH_2Cl_2); $C_{16}H_{26}N_2O_3$ (294.1); HRMS: calcd for M–OCH_3 ($C_{15}H_{23}N_2O_2$) 263.1759, found 263.1760 (+0.1 ppm); MS (EI): m/z (%) = 294 (M, 1), 263 (M–OCH_3, 100), 219 (M–$CH(OCH_3)_2$, 34), 172 (263–benzyl, 20), 91 (benzyl, 41), 75 ($CH(OCH_3)_2$, 6); MS (CI): m/z (%) = 295 (MH^+, 100); IR (film): ν (cm^{-1}) = 3381 (br, O-H), 2944 (s, C-H), 2825 (s, OCH_3), 1452 (m, C-H), 1128 (s, C-OH), 1070 (s, O-CH_3), 735 and 700 (m, aryl-C-H); ^{1}H NMR ($CDCl_3$): $\delta=2.41$–2.46 (m, 2H, 3-H, 5-H and/or 6-H), 2.48 (dd, $J=13.3/5.3$ Hz, 1H, CH_2CH$(OCH_3)_2$), 2.53 (dd, $J=13.3/5.3$ Hz, 1H, CH_2CH$(OCH_3)_2$), 2.57–2.70 (m, 3H, 2-H and 3-H, 5-H and/or 6-H), 2.74–2.79 (m, 1H, 3-H, 5-H or 6-H), 2.89–2.97 (m, 1H, 3-H, 5-H or 6-H), 3.35 (s, 6H,

2×OCH_3), 3.46 (d, J=13.3 Hz, 1H, PhCH_2N), 3.61 (dd, J=11.5/2.1 Hz, 1H, CH_2OH), 3.98 (d, J=13.3 Hz, 1H, PhCH_2N), 4.05 (dd, J=11.1/3.1 Hz, 1H, CH_2OH), 4.52 (t, J=5.3 Hz, 1H, CH(OCH$_3$)$_2$), 7.25–7.35 (m, 5H, arom.). The signal for the proton of the OH group could not be detected; ^{13}C NMR ($CDCl_3$): δ=49.9, 53.3 and 56.8 (3C, C-3, C-5, C-6), 53.3 (2C, 2×OCH_3), 58.0 (1C, PhCH_2N), 58.6 (1C, C-2), 59,7 (1C, CH_2CH(OCH$_3$)$_2$), 62.1 (1C, CH_2OH), 102.3 (1C, CH(OCH$_3$)$_2$), 127.0 (1C, C-4 arom.), 128.3 (2C, C-3 and C-5 arom.), 128.8 (2C, C-2 and C-6 arom.), 138.5 (1C, C-1 arom.).

5.10. (+)-Ethyl 3-[(2*S*)-1-benzyl-4-butylpiperazin-2-yl]-prop-2-enoate 13b

To a stirred and cooled (−78°C) mixture of CH_2Cl_2 (20 mL) and oxalyl chloride (0.18 mL, 2.1 mmol), was added dropwise a solution of dimethyl sulfoxide (0.3 mL, 4.2 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 min at −78°C a solution of **5b** (0.5 g, 1.9 mmol) in CH_2Cl_2 (30 mL) was added within 5 min. The mixture was stirred for an additional 15 min. Triethylamine (1.32 mL, 9.55 mmol) was added and the reaction mixture was stirred at −78°C for 5 min and then allowed to warm to room temperature. The Wittig reagent **12** (1.33 g, 3.82 mmol) dissolved in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was stirred for 5 h at room temperature. Water (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined, washed with brine (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue (5 cm, petroleum ether/ethyl acetate, 1:3, 20 mL, R_f=0.45) afforded **13b** [(*E*)/(*Z*)=85:15], as a pale yellow oil (0.513 g, 81%); $[\alpha]_{589}$=+36.3 (c=0.420, CH_2Cl_2); $C_{20}H_{30}N_2O_2$ (330.47); HRMS: calcd 330.2307, found 330.2306 (−0.1 ppm); MS (EI): m/z (%)=330 (M, 15), 285 (M−OCH_2CH$_3$, 3), 239 (M−benzyl, 41), 210 (M−benzyl−CH_2CH$_3$, 6), 140 (butylpiperazine, 2), 91 (benzyl, 100), 65 (benzyl−C$_2$H$_2$, 12); MS (CI): m/z (%)=331 (MH$^+$, 100); IR (film): ν (cm^{-1})=2954 (s, C-H), 2808 (s, C-O), 1722 (s, C=O), 1654 (m, C=C), 1453 (m, C-H), 986 (w, H-C=C-H), 738 and 700 (m, aryl-C-H); ^{1}H NMR ($CDCl_3$): δ=0.89 (t, J=7.2 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_3), 1.28 (t, J=7.0 Hz, 3H, OCH$_2$CH_3), 1.29 ('sext', J=7.3 Hz, 2H, CH$_2$CH$_2$CH_2CH$_3$), 1.44 ('quint', J=7.5 Hz, 2H, CH$_2$CH_2CH$_2$CH$_3$), 2.03–2.23 (m, 3H, 3-H, 5-H and/or 6-H), 2.30 (t, J=7.6 Hz, 2H, CH_2CH$_2$CH$_2$CH$_3$), 2.67–2.79 (m, 3H, 3-H, 5-H and/or 6-H), 3.09 (d, J=13.4 Hz, 0.85H, PhCH_2N (*E*)-isomer), 3.11–3.18 (m, 1H, 2-H), 3.20 (d, J=13.4 Hz, 0.15H, PhCH_2N (*Z*)-isomer), 3.84 (d, J=13.4 Hz, 0.15H, PhCH_2N (*Z*)-isomer), 3.91 (d, J=13.4 Hz, 0.85H, PhCH_2N (*E*)-isomer), 4.19 (q, J=7.2 Hz, 2×0.15H, OCH_2CH$_3$ (*Z*)-isomer), 4.20 (q, J=7.2 Hz, 2×0.85H, OCH_2CH$_3$ (*E*)-isomer), 5.90 (d, J=12.0 Hz, 0.15H, CH=CHCO$_2$Et (*Z*)-isomer), 6.06 (d, J=15.9 Hz, 0.85H, CH=CHCO$_2$Et (*E*)-isomer), 6.32 (dd, J=12.4/8.2 Hz, 0.15H, CH=CHCO$_2$Et (*Z*)-isomer), 6.96 (dd, J=15.9/8.6 Hz, 0.85H, CH=CHCO$_2$Et (*E*)-isomer), 7.21–7.29 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$): δ=13.9 (1C, CH$_2$CH$_2$CH$_2$CH_3), 14.2 (1C, OCH$_2$CH_3), 20.6 (1C, CH$_2$CH$_2$CH_2CH$_3$), 28.9 (1C, CH$_2$CH_2CH$_2$CH$_3$), 50.8, 53.0 and 58.2 (3C, C-3, C-5, C-6), 58.5 (1C, CH_2CH$_2$CH$_2$CH$_3$), 59.8 (0.85 C, PhCH_2N (*E*)-isomer), 60.0 (0.15 C, PhCH_2N (*Z*)-isomer), 60.1 (0.15 C, OCH_2CH$_3$ (*Z*)-isomer), 60.4 (0.85 C, OCH_2CH$_3$ (*E*)-isomer), 63.1 (1C, C-2), 121.9 (0.15 C, CH=CHCO$_2$Et (*Z*)-isomer), 123.7 (0.85 C, CH=CHCO$_2$Et (*E*)-isomer), 126.9 (1C, C-4 arom.), 128.1 (2C, C-3 and C-5 arom.), 128.9 (2C, C-2 and C-6 arom.), 138.3 (1C, C-1 arom.), 148.8 (0.85 C, CH=CHCO$_2$OEt (*E*)-isomer), 149.0 (0.15 C, CH=CHCO$_2$Et (*Z*)-isomer), 166.0 (1C, CO_2Et).

5.11. (+)-Ethyl 3-[(2*S*)-1-benzyl-4-(2,2-dimethoxyethyl)-piperazin-2-yl]prop-2-enoate 13c

To a stirred and cooled (−78°C) mixture of CH_2Cl_2 (25 mL) and oxalyl chloride (0.32 mL, 3.7 mmol), was added dropwise a solution of dimethyl sulfoxide (0.53 mL, 7.5 mmol) dissolved in CH_2Cl_2 (10 mL). After stirring for 2 min at −78°C a solution of **5c** (1.0 g, 3.4 mmol) in CH_2Cl_2 (50 mL) was added over 5 min. The mixture was stirred for an additional 15 min and triethylamine (2.4 mL, 17 mmol) was added. The reaction mixture was stirred at −78°C for 5 min. It was allowed to warm to room temperature. The Wittig reagent **12** (2.37 g, 6.8 mmol) dissolved in CH_2Cl_2 (40 mL) was added dropwise. The reaction mixture was stirred for 5 h at room temperature. Water (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined, washed with brine (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue (6 cm, petroleum ether/ethyl acetate 1:3, 20 mL, R_f=0.31) afforded **13c** [(*E*)/(*Z*)=85:15], as a pale yellow oil (0.814 g, 66%); $[\alpha]_{589}$=+29.3 (c=0.915, CH_2Cl_2); calcd for $C_{20}H_{30}N_2O_4$ (362.47): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.09; H, 8.09; N, 7.87%; MS (EI): m/z (%)=362 (M, 15), 331 (M−OCH$_3$, 20), 287 (M−CH(OCH$_3$)$_2$, 100), 196 (287−benzyl, 2), 175 (benzylpiperazine, 10), 91 (benzyl, 90), 75 (CH(OCH$_3$)$_2$, 30); IR (film): ν (cm^{-1})=2942 (s, C-H), 2824 (s, O-CH$_3$), 1719 (s, C=O), 1581 (m, C=C), 1451 (m, C-H), 1368 (m, C-O-Et), 1075 (s, O-CH$_3$), 981 (m, H-C=C-H), 736 and 701 (m, aryl-C-H); ^{1}H NMR ($CDCl_3$): δ=1.30 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 2.18–2.34 (m, 3H, 3-H, 5-H and/or 6-H), 2.52 (d, J=5.3 Hz, 2H, CH_2CH(OCH$_3$)$_2$), 2.70–2.79 (m, 3H, 3-H, 5-H and/or 6-H), 3.12 (d, J=13.7 Hz, 0.85H, PhCH_2N (*E*)-isomer), 3.15 (td, J=8.8/2.9 Hz, 1H, 2-H), 3.34 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.56 (d, J=13.5 Hz, 0.15H, PhCH_2N (*Z*)-isomer), 3.87 (d, J=13.6 Hz, 0.15H, PhCH_2N (*Z*)-isomer), 3.91 (d, J=13.4 Hz, 0.85H, PhCH_2N (*E*)-isomer), 4.19 (q, J=7.1 Hz, 2×0.15H, OCH_2CH$_3$ (*Z*)-isomer), 4.20 (q, J=7.1 Hz, 2×0.85H, OCH_2CH$_3$ (*E*)-isomer), 4.49 (t, J=5.2 Hz, 1H, CH(OCH$_3$)$_2$), 5.91 (d, J=11.9 Hz, 0.15H, CH=CHCO$_2$Et (*Z*)-isomer), 6.07 (d, J=15.9 Hz, 0.85H, CH=CHCO$_2$Et (*E*)-isomer), 6.31 (dd, J=11.6/9.2 Hz, 0.15H, CH=CHCO$_2$Et (*Z*)-isomer), 6.96 (dd, J=15.9/8.5 Hz, 0.85H, CH=CHCO$_2$Et (*E*)-isomer), 7.21–7.33 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$): δ=14.2 (1C, OCH$_2$CH_3), 50.5, 53.3 and 58.8 (3C, C-3, C-5,

C-6), 53.4 and 53.6 (2C, 2×O*C*H$_3$), 59.6 (1C, *C*H$_2$CH(OCH$_3$)$_2$), 59.7 (0.85 C, Ph*C*H$_2$N (*E*)-isomer), 59.9 (0.15 C, Ph*C*H$_2$N (*Z*)-isomer), 60.1 (0.15 C, O*C*H$_2$CH$_3$ (*Z*)-isomer), 60.4 (0.85 C, O*C*H$_2$CH$_3$ (*E*)-isomer), 62.7 (1C, C-2), 102.4 (1C, *C*H(OCH$_3$)$_2$), 122.0 (0.15 C, CH=*C*HCO$_2$Et (*Z*)-isomer), 123.9 (0.85 C, CH=*C*HCO$_2$Et (*E*)-isomer), 126.9 (1C, C-4 arom.), 128.2 (2C, C-3 and C-5 arom.), 128.9 (2C, C-2 and C-6 arom.), 138.2 (1C, C-1 arom.), 148.5 (0.85 C, *C*H=CHCO$_2$Et (*E*)-isomer), 149.0 (0.15 C, *C*H=CHCO$_2$Et (*Z*)-isomer), 166.0 (1C, *C*O$_2$Et).

5.12. (−)-(6*S*)-4-Butyl-1,4-diazabicyclo[4.3.0]nonan-9-one 14b

Pd/C (10%, 88 mg) was added to a solution of **13b** (0.176 g, 0.56 mmol) in CH$_3$OH (15 mL). The suspension was stirred under a H$_2$ atmosphere (5 bar) at room temperature for 12 h. The mixture was filtered through a pad of Celite® AFA and the filtrate was concentrated in vacuo. Flash chromatography (2 cm, ethanol, 2 mL, R_f = 0.29) of the residue yielded **14b** as a pale yellow, viscous oil (42 mg, 40%); $[\alpha]_{589}$ = −32.5 (c = 1.82, CH$_2$Cl$_2$); C$_{11}$H$_{20}$N$_2$O (196.29), HRMS: calcd 196.1576, found 196.1575 (–0.1 ppm); MS (EI): m/z (%) = 196 (M, 9), 153 (M–CH$_2$CH$_2$CH$_3$, 100), 138 (M–CH$_2$CH$_2$-CH$_2$CH$_3$, 8), 112 (ethylpiperazine, 3), 83 (piperazine, 4); IR (film): ν (cm^{-1}) = 2954 (s, C-H), 1678 (s, C=O), 1498 (m, C-H); ^{1}H NMR (CDCl$_3$): δ = 0.90 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH$_2$C*H*$_3$), 1.31 ('sext', J = 7.3 Hz, 2H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.45 ('quint', J = 7.6 Hz, 2H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.52–1.60 (m, 1H, 7-H), 1.67 (t, J = 10.6 Hz, 1H, 5-H), 1.89 (dd, J = 15.4/3.6 Hz, 1H, 3-H), 2.07–2.21 (m, 1H, 7-H), 2.32–2.40 (m, 4H, 8-H and C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.80–2.86 (m, 2H, 2-H and 3-H), 2.98 (ddd, J = 10.9/3.5/1.5 Hz, 1H, 5-H), 3.62 (dtd, J = 10.6/7.1/3.6 Hz, 1H, 6-H), 3.93–3.99 (m, 1H, 2-H); ^{13}C NMR (CDCl$_3$): δ = 13.9 (1C, CH$_2$CH$_2$CH$_2$*C*H$_3$), 20.6 (1C, CH$_2$CH$_2$*C*H$_2$CH$_3$), 22.2 (1C, C-7), 28.8 (1C, CH$_2$*C*H$_2$CH$_2$CH$_3$), 30.2 (1C, C-8), 39.5 (1C, C-2), 51.9 (1C, C-3), 55.5 (1C, C-6), 58.1 (1C, *C*H$_2$CH$_2$CH$_2$CH$_3$), 60.1 (1C, C-5), 173.2 (1C, C-9).

5.13. (−)-(6*S*)-4-(2,2-Dimethoxyethyl)-1,4-diazabicyclo-[4.3.0]nonan-9-one 14c

Pd/C (10%, 25 mg) was added to a solution of **13c** (84 mg, 0.23 mmol) in CH$_3$OH (10 mL). The suspension was stirred under a H$_2$ atmosphere (balloon) at room temperature for 5 h. The mixture was filtered through a pad of Celite® AFA and the filtrate was concentrated in vacuo. Flash chromatography (1 cm, ethanol, 2 mL, R_f = 0.33) of the residue yielded **14c** as pale yellow viscous oil, yield 34 mg (64%); $[\alpha]_{589}$ = −27.9 (c = 1.4, CH$_2$Cl$_2$); C$_{11}$H$_{20}$N$_2$O$_3$ (228.29); HRMS: calcd for M–OCH$_3$ (C$_{10}$H$_{17}$N$_2$O$_2$) 197.1290, found 197.1290 (±0 ppm); MS (EI): m/z (%) = 228 (M, 5), 197 (M–OCH$_3$, 4), 153 (M–CH(OCH$_3$)$_2$, 100), 138 (M–CH$_2$CH-(OCH$_3$)$_2$, 6), 75 (CH(OCH$_3$)$_2$, 7); IR (film): ν (cm^{-1}) = 2945 (m, C-H), 2833 (m, O-CH$_3$), 1675 (s, C=O), 1458 (m, C-H), 1070 (m, O-CH$_3$); ^{1}H NMR (CDCl$_3$): δ = 1.49–1.62 (m, 1H, 7-H), 1.85 (t, J = 10.8 Hz, 1H, 5-H), 2.03–2.19 (m, 2H, 3-H and 7-H), 2.34–2.39 (m, 2H, 8-H), 2.53 (dd, J = 13.4/5.2 Hz, 1H, C*H*$_2$CH(OCH$_3$)$_2$), 2.59 (dd, J = 13.4/5.1 Hz, 1H, C*H*$_2$CH(OCH$_3$)$_2$), 2.85–2.95 (m, 2H, 2-H and 3-H), 3.04 (ddd, J = 10.9/3.5/1.2 Hz, 1H, 5-H), 3.35 (s, 3H, OC*H*$_3$), 3.36 (s, 3H, OC*H*$_3$), 3.64 (dtd, J = 10.7/7.1/3.6 Hz, 1H, 6-H), 3.92–3.98 (m, 1H, 2-H), 4.50 (t, J = 5.2 Hz, 1H, C*H*(OCH$_3$)$_2$); ^{13}C NMR (CDCl$_3$): δ = 22.1 (1C, C-7), 30.2 (1C, C-8), 39.5 (1C, C-2), 50.5 (1C, C-3), 53.5 (1C, O*C*H$_3$), 53.6 (1C, O*C*H$_3$), 55.5 (1C, C-6), 59.7 (1C, *C*H$_2$CH(OCH$_3$)$_2$), 60.7 (1C, C-5), 102.7 (1C, *C*H(OCH$_3$)$_2$), 173.2 (1C, C-9).

5.14. Receptor binding studies, general[13]

Homogenizer: Potter® S (B. Braun Biotech International). Ultraturrax: Euroturrax® T20 (Ika Labortechnik). Centrifuge: high speed cooling centrifuge model J2-HS (Beckman). Filter: Whatman glass fiber filters GF/B, presoaked in the medium described below before use. Filtration was performed with a Brandel 24-well cell harvester. Scintillation cocktail: Rotiscint Eco Plus (Roth). Liquid scintillation analyzer: TriCarb 2100 TR (Canberra Packard), counting efficiency 66%. All experiments were carried out in triplicate. IC_{50} values were determined from competition experiments with at least six concentrations of test compounds and were calculated with the GraphPad Prism® 3.0 program (GraphPad Software) by nonlinear regression analysis. K_i values were calculated according to Cheng and Prusoff.[17] The K_i values are given as mean value ±SEM from three independent experiments.

5.15. Performance of the σ_1-assay

For the σ_1-assay guinea pig brain membranes were prepared as described in Ref. 13. The test was performed with the radioligand [^{3}H]-pentazocine (1036 GBq/mmol; NEN™ Life Science Products). The thawed membrane preparation (about 150 μg of protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]-pentazocine, and buffer (50 mM Tris–HCl, pH 7.4) in a total volume of 500 μL for 120 min at 37°C. The incubation was terminated by rapid filtration through presoaked Whatman GF/B filters (0.5% polyethylenimine in water for 2 h at 4°C) using a cell harvester. After washing four times with 2 mL of cold buffer, 3 mL of scintillation cocktail was added to the filters. After at least 8 h bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Nonspecific binding was determined with 10 μM haloperidol.

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