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European Journal of Medicinal Chemistry 42 (2007) 1247–1262
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
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Original article

Synthesis of bridged piperazines with σ receptor affinity

Manuela Weigl, Bernhard Wünsch*

Institut für Pharmazeutische und Medizinische Chemie, Hittorfstrasse 58-62, 48149 Münster, Germany

Received 28 September 2006; received in revised form 6 February 2007; accepted 12 February 2007
Available online 25 February 2007

Abstract

Bridged piperazines **4** were designed as conformationally restricted piperazine σ receptor ligands. The chiral pool synthesis started from (*S*)-glutamate, which was transformed in five reaction steps into the piperazinediones **5** bearing a propionic acid ester side chain. A two-step Dieckmann analogous cyclization provided the bicyclic ketones **7** as key intermediates. The alcohols **8** were prepared by $LiAlH_4$ reduction of the ketones **7**. $NaBH_4$ reduction, Williamson ether synthesis and $LiAlH_4$ reduction led to the methyl and benzyl ethers **12** and **13**. High σ_1 affinity is attained when one large substituent is introduced either at N-8 or O-2. The most potent σ_1 ligand in this series of compounds is the methyl ether **12b** with the N-butyl substituent ($K_i = 13.2$ nM, selectivity $\sigma_2{:}\sigma_1 = 16$). Moreover, the *N*-methyl derivatives **13a** (σ_2: $K_i = 30.4$ nM) and **12a** (σ_2 preference) represent promising starting points for the development of potent and selective σ_2 ligands.

Keywords: σ Receptor ligands; Structure/affinity relationships; 6,8-Diazabicyclo[3.2.2]nonane; Chiral pool synthesis; Dieckmann cyclization

1. Introduction

The huge group of cell surface receptors is divided into three main families: G-protein coupled receptors, ligand gated ion channels, and receptor protein kinases. However, σ receptors, which are located in the central nervous system and the periphery, do not match this classification. Recently the σ_1 receptor of various tissues and species has been cloned [1]. It was shown that the resulting amino acid sequence is not related to any known mammalian protein. The exact three-dimensional structure of the σ_1 receptor protein as well as the amino acid sequence of the σ_2 receptor still remains to be elucidated [2]. Despite the fact that the exact physiological role of σ receptors is not yet completely understood the involvement of σ receptors in several physiological and pathophysiological events is well documented. Therefore, ligands interacting with σ receptors are of interest for example as atypical antipsychotics [3], antidepressants [4], anti-cocaine agents [5,6], and antitumor agents [7].

Several σ receptor ligands contain the piperazine heterocycle and the 1,4-disubstituted piperazine derivatives **1** [8] and **2** [9] are among the most active σ receptor ligands described so far. Recently, we have shown that piperazine derivatives **3** with an additional hydroxymethyl substituent in position 2 also bind with high affinity at σ receptors [10]. The piperazines **3** can adopt two chair conformations with an equatorially or an axially oriented hydroxymethyl moiety. Moreover, free rotation of the hydroxymethyl group around the indicated bond is possible in both conformers (Fig. 1).

Herein we wish to report on the synthesis and σ receptor affinity of the bridged piperazine derivatives **4**. In the bicyclic compounds **4** the piperazine ring is forced into a boat like conformation leading to a somewhat different orientation of the N substituents. Moreover, the substituent in the former 2-position (of compound **3**) is fixed in an axial orientation and the rotation around the single bond is no longer possible. The conformationally constrained piperazine derivatives **4** are planned in order to learn more about the pharmacologically active conformation, which interacts with the σ receptor protein.

* Corresponding author. Tel.: +49 251 8333311; fax: +49 251 832144.
E-mail address: wuensch@uni-muenster.de (B. Wünsch).

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doi:10.1016/j.ejmech.2007.02.005

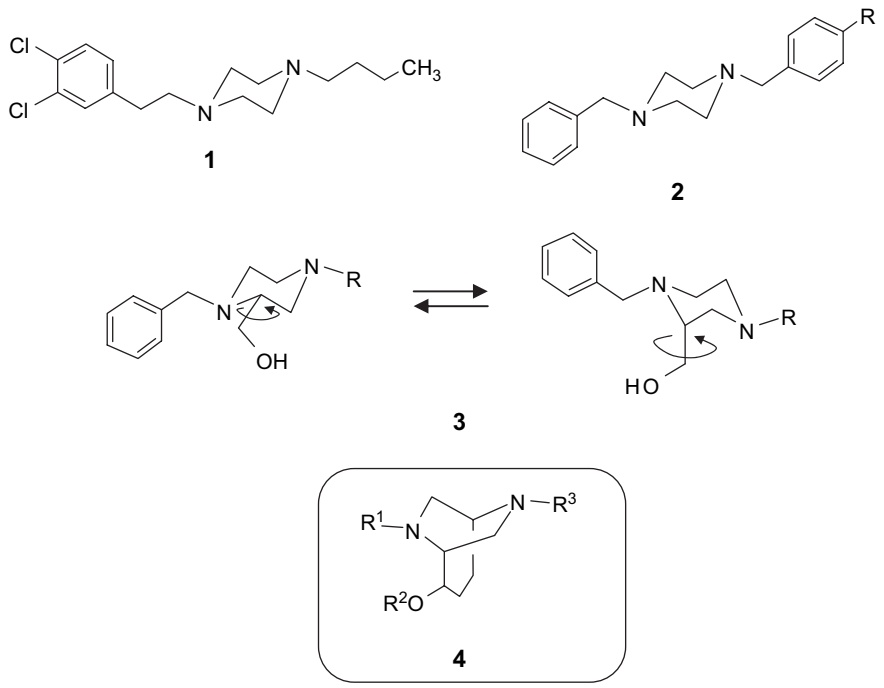


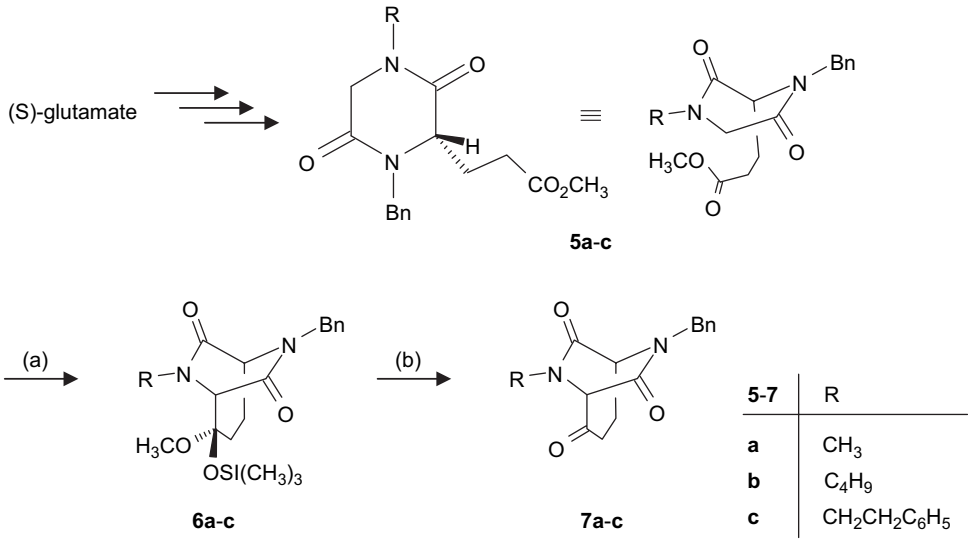
Fig. 1. Comparison of the lead compounds **1**–**3** with the novel σ receptor ligands **4**.

2. Chemistry

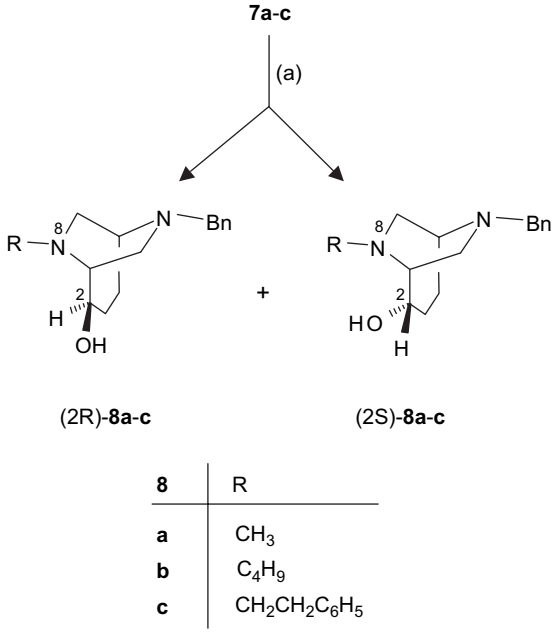
Starting from the proteinogenic amino acid (*S*)-glutamate the monocyclic piperazinedione derivatives **5a**–**c** with a propionic acid ester side chain were synthesized in five steps [11]. The three-carbon bridge of **7a**–**c** was established by the variation of the Dieckmann cyclization recently described by us [12]. This Dieckmann cyclization consists of two steps: at first treatment of **5a**–**c** with lithium hexamethyldisilazane (LHMDS) and subsequent trapping of the intermediate diastereoselectively [13] led to the mixed methyl silyl acetals **6a**–**c**. Careful hydrolysis of **6a**–**c** with acid provided the bicyclic ketones **7a**–**c** in very high yield (Scheme 1).

The bridged piperazinediones **7a**–**c** were reduced with $LiAlH_4$ in refluxing THF and the formed diastereomeric alcohols (2*R*)-**8a**/(2*S*)-**8a** and (2*R*)-**8c**/(2*S*)-**8c** were separated by flash chromatography. The butyl derivative **8b** was obtained by $LiAlH_4$ reduction of a **9b**/**11b** mixture. In this case purification by flash chromatography (fc) led only to a mixture of diastereomers in the ratio (2*S*)-**8b**:(2*R*)-**8b** = 23:77 (Scheme 2).

In order to synthesize 2-alkoxy derivatives of the bicyclic system the ketones **7a**–**c** were reduced with $NaBH_4$ to afford the alcohols **9a**–**c** as mixtures of diastereomers, respectively. The ethers **10a**–**c** and **11a**–**c** were prepared by NaH deprotonation of the corresponding alcohols **9a**–**c** and subsequent alkylation with methyl iodide and benzyl bromide,



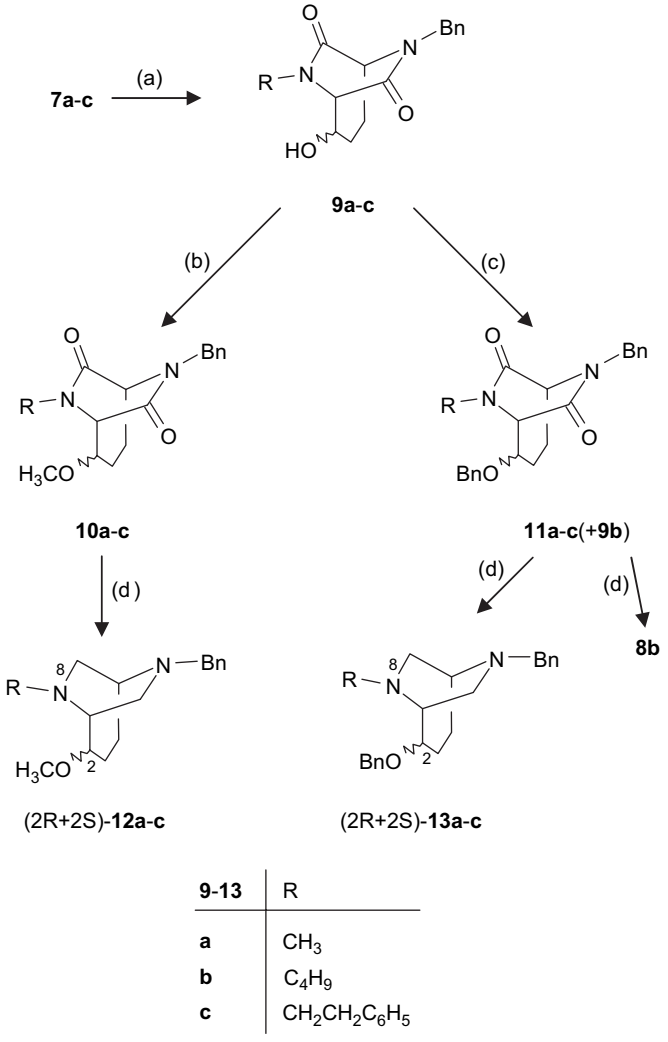
Scheme 1. (a) LHMDS, THF, −78 °C, then TMS-Cl, −78 °C. (b) *p*-TolSO_3H, THF, H_2O, rt.



Scheme 2. (a) $LiAlH_4$, THF, 66 °C.

respectively. At last reduction of the dilactam systems with $LiAlH_4$ produced the diastereomeric methyl ethers (2*R*)-**12**/(2*S*)-**12** and benzyl ethers (2*R*)-**13**/(2*S*)-**13** as inseparable mixtures of diastereomers (Scheme 3).

For the purpose of comparison the dimethoxy derivative **15a** bearing a methyl group at the N-atom was synthesized and pharmacologically evaluated. Transacetalization of the mixed methyl/silyl acetal **6a** with methanol and a catalytic amount of *p*-toluenesulfonic acid afforded the ketone dimethyl acetal **14a**. During this transacetalization small amounts of the ketone **7a** were formed, which was separated after $NaBH_4$ reduction. Finally, $LiAlH_4$ reduction of the lactam carbonyl moieties provided the bridged piperazine **15a** with two methoxy substituents in position 2 (Scheme 4).

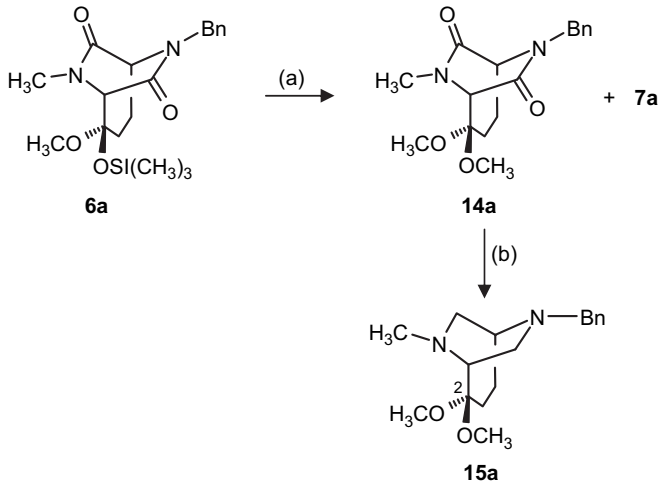


Scheme 3. (a) $NaBH_4$, THF, H_2O, rt. (b) NaH, CH_3I, THF, rt. (c) NaH, $PhCH_2Br$, Bu_4NI, THF, rt. (d) $LiAlH_4$, THF, 66 °C.

3. Receptor binding studies

The σ receptor affinity of the bridged piperazines was evaluated with receptor binding studies. In these assays the test compounds compete with tritium labeled ligands for a limited number of receptors. Homogenates of guinea pig brain and rat liver were used as receptor material in the σ_1 assay and the σ_2 assay, respectively. In the σ_1 assay [^{3}H]-(+)-pentazocine was employed as radioligand, and the non-specific binding was determined in the presence of a large excess of haloperidol. Since a σ_2 selective radioligand is not commercially available, the non-selective radioligand [^{3}H]-ditolylguanidine was employed in the presence of a large excess of non-radiolabeled (+)-pentazocine (100 nM), which selectively occupies σ_1 receptors. Performing of the σ_2 assay in the presence of an excess of non-tritiated 1,3-di(*o*-tolyl)guanidine led to the non-specific binding of the radioligand [14].

Since a structural relationship between σ receptor ligands and NMDA receptor antagonists as well as κ Opioid receptor



Scheme 4. (a) CH_3OH, THF, *p*-$TolSO_3H$, rt. [then $NaBH_4$]. (b) $LiAlH_4$, THF, 66 °C.

agonists exist the affinity of the bridged piperazines towards these receptor systems was investigated as well. In the competition experiments the radioligands [^{3}H]-MK801 (NMDA) [15], [^{3}H]-U69593 (κ Opioid) [16], and [^{3}H]-DAMGO (μ Opioid) [16] were employed.

4. Results and discussion

The receptor affinities of the bridged piperazines are summarized in Table 1.

The σ_1 receptor affinity of the alcohols **8** hardly depends on their stereochemistry: the diastereomeric alcohols with the *N*-methyl group (2*S*)-**8a** and (2*R*)-**8a** as well as the diastereomeric *N*-phenylethyl alcohols (2*S*)-**8c** and (2*R*)-**8c** show very similar K_i-values. Therefore, the receptor affinities of diastereomeric mixtures were investigated when separation by flash chromatography failed to give pure diastereomers (**8b**, **12b**, **12c**, **13b**, **13c**). In contrast the N-8-substituent strongly influences the σ_1 affinity. The bridged piperazines (2*R*)-**8a** and (2*S*)-**8a** with the small methyl group display only low σ_1 receptor affinity ($K_i = 2.4$ μM and 4.97 μM), whereas alcohols bearing larger N-substituents (butyl **8b**, 2-phenylethyl **8c**) interact with σ_1 receptors in the low nanomolar range.

The same tendency is observed for the methyl ether series **12**. The σ_1 affinity of the *N*-methyl derivative **12a** is rather low, whereas the corresponding butyl derivative **12b** ($K_i = 13.2$ nM) and the 2-phenylethyl derivative **12c** ($K_i = 76$ nM) strongly bind at σ_1 receptors. An additional methoxy group in position 2 (**15a**) does not raise the σ_1 affinity of *N*-methyl derivatives.

In the benzyl ether series **13** the σ_1 affinity is reversed and decreases with increasing size of the N-8-substituent. Thus the *N*-methyl derivative **13a** is the most potent compound ($K_i = 16.2$ nM) in the benzyl ether series. Obviously, one large substituent favours the interaction with the σ_1 receptor, but a second large substituent disturbs binding at the σ_1 receptor protein. The position of the large substituent (N-8 or O-2) is of minor importance since **13a** (*N*-methyl, *O*-benzyl, $K_i = 16.2$ nM) and **12b** (*N*-butyl, *O*-methyl, $K_i = 13.2$ nM) are almost equipotent.

The σ_2 receptor affinities of diastereomeric alcohols (2*R*)-**8a** and (2*S*)-**8a** as well as (2*R*)-**8c** and (2*S*)-**8c** do not differ significantly. A large N-substituent leads to little increase of the σ_2 affinity compared to the *N*-methyl derivatives. The σ_2 affinities of the butyl (**8b**) and 2-phenylethyl derivatives (**8c**) are still in the high nanomolar range ($K_i = 340–590$ nM). The corresponding methyl ethers **12a**, **12b** and **12c** reveal very similar σ_2 affinity ($K_i = 327$ nM, 219 nM, 297 nM, respectively). In this series the nitrogen substituent has little influence on the σ_2 affinity. Somewhat different properties are observed in the benzyl ether series **13**. Here the *N*-methyl derivative **13a** binds with extraordinarily high affinity towards σ_2 receptors ($K_i = 30.4$ nM) whereas the corresponding *N*-butyl (**13b**) and *N*-phenylethyl derivatives (**13c**) are less active. The benzyl ether **13a** represents the most potent σ_2 ligand of this series.

Generally most of the bridged piperazines **8**, **12**, **13** and **15** interact selectively with σ_1 receptors. However, four compounds (**12a**, **12b**, **13a**, **13b**) will be discussed with respect of their σ_1/σ_2 receptor selectivity. The most σ_1 selective compounds are the butyl derivatives **12b** and **13b** (σ_2:$\sigma_1 = 16$ and 21, respectively). Exchange of the N-butyl substituent of **12b** against a methyl group (**12a**) reduces the σ_1 affinity 100-fold but retains the σ_2 affinity, which leads to a ligand with a 4-fold preference for the σ_2 receptor over the σ_1 receptor. Compared to the methyl ether **12a** the σ_1 affinity of the benzyl ether **13a** is increased 100-fold and the σ_2 affinity 10-fold. Thus, the benzyl ether **13a** represents the most potent σ_2 ligand in this

Table 1
Receptor affinity of the bridged piperazines

Compound	$K_i \pm$ SEM [*n*M] ($n = 3$)				
	σ_1 ([^{3}H](+)-pentazocine)	σ_2 ([^{3}H]-ditolylguanidine)	κ ([^{3}H]-U69593)	μ ([^{3}H]-DAMGO)	NMDA ([^{3}H]-MK801)
8a (2*S*)	4970 ± 180	2890 ± 750	n.d. 13.2%[a]	n.d. 4.7%[a]	n.d. 13.7%[a]
8a (2*R*)	2400 ± 300	4180 ± 780	n.d. 12.6%[a]	n.d. 8.5%[a]	n.d. 21.0%[a]
8b (2*S*:2*R* = 23:77)	23.4 ± 6.9	447 ± 31	1600 ± 200	n.d. 37.9%[a]	n.d. 52.3%[a]
8c (2*S*)	33.3 ± 6.9	343 ± 58	2460 ± 790	4960 ± 2410	n.d. 21.9%[a]
8c (2*R*)	29.5 ± 8.5	588 ± 81	1290 ± 130	4050 ± 400	n.d. 20.6%[a]
12a (2*R*)	1350 ± 450	327 ± 57	3590 ± 450	n.d. 21.5%[a]	n.d. 8.7%[a]
12b (2*S*:2*R* = 25:75)	13.2 ± 4.1	219 ± 108	157 ± 21	n.d. 37.4%[a]	n.d. 55.5%[a]
12c (2*S*:2*R* = 23:77)	76 ± 17.6	297 ± 107	5020 ± 460	n.d. 68.6%[a]	n.d. 50.5%[a]
13a (2*R*)	16.2 ± 5.6	30.4 ± 3.6	585 ± 160	n.d. 70.4%[a]	n.d. 0%[a]
13b (2*S*:2*R* = 36:64)	39.5 ± 15.3	820 ± 250	1110 ± 450	3320 ± 1680	n.d. 21.5%[a]
13c (2*S*:2*R* = 22:78)	175 ± 37	628 ± 79	2230 ± 200	n.d. 34.8%[a]	n.d. 16.4%[a]
15a	3500 ± 500	1830 ± 320	>10 μM	n.d. 27.6%[a]	n.d. 44.3%[a]
Haloperidol	2.20 ± 0.31	34.2 ± 2.3	–	–	–
(+)-Pentazocine	3.58 ± 0.20	n.d.	–	–	–
Ditolylguanidine	164 ± 47	63.9 ± 10.8	–	–	–
U-50488	–	–	0.49 ± 0.16	–	–
Naoxone	–	–	3.17	0.68 ± 0.04	–
Phencyclidine	–	–	–	–	28 ± 4.6
(*S*)-Ketamine	–	–	–	–	108 ± 12

[a] Inhibition of radioligand binding at a test compound concentration of 10 μM.

series, however due to its strong σ_1 affinity increase it shows little preference for the σ_1 receptor over the σ_2 receptor.

The bridged piperazines binding in the low nanomolar range at σ_1 and/or σ_2 receptors are selective over κ Opioid, μ Opioid, and NMDA receptors. Some of the compounds show moderate κ affinity in the low micromolar range (e.g. **8b**: $K_i = 1600$ nM). However, a surprisingly high κ receptor affinity was found for the methyl ether of the *N*-butyl derivative **12b**. The K_i value of 157 nM is in the range of its σ_2 affinity ($K_i = 219$ nM). Nevertheless, **12b** is still 10-fold selective for the σ_1 receptor over the κ receptor. In Table 1 the μ and NMDA receptor affinities are given as inhibition (in %) of radioligand binding at a test compound concentration of 10 μM. It is shown that the investigated bridged piperazines do not interact significantly with μ Opioid, and NMDA receptors. At a concentration of 10 μM the inhibition is generally lower than 50% indicating an IC_{50} value greater than 10 μM.

5. Conclusion

The bridged piperazines represent a novel class of potent σ receptor ligands. High σ_1 affinity is attained when one large substituent (butyl, benzyl) is attached either to N-8 or the oxygen atom in position 2 (**8b**, **8c**, **12b**, **13a**, **13b**). Two large substituents are not tolerated by the σ_1 receptor protein. The benzyl ether **13a**, the most potent σ_2 ligand of this series, and the σ_2 selective methyl ether **12a** represent promising starting points for the development of potent and selective σ_2 receptor ligands.

6. Experimental

6.1. Chemistry, general

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was distilled from sodium/benzophenone ketyl 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) [17]: 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]. Elemental analyses: CHN-Elementaranalysator Rapid (Heraeus), Elemental Analyzer 240 (Perkin–Elmer) and Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI = electron impact, CI = chemical ionization. High resolution MS (HR-MS): MAT 8200 (Finnigan). IR: IR spectrophotometer 1600 FT-IR and 2000 FT-IR (Perkin–Elmer); s = strong, m = medium, w = weak. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), δ in parts per million 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.

6.1.1. (1*S*,5*S*)-6-Benzyl-2-methoxy-8-methyl-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (**6a**)

Under N_2 a solution of lithium hexamethyldisilazane (LHMDS, 1 M in THF; 3.30 mL, 3.30 mmol) was added dropwise to a solution of **5a** [11] (877 mg, 2.88 mmol) in THF (50 mL) at −78 °C. After a reaction time of 30 min at −78 °C a solution of chlorotrimethylsilane (1.15 mL, 8.97 mmol) in THF (6.0 mL) was added and the reaction mixture was stirred for 30 min at −78 °C, then for 60 min at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (80 mL). The solution was washed with NaOH (0.5 M, 2 × 50 mL), with HCl (0.5 M, 2 × 50 mL) and with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting product **6a** was characterized and directly used for the next reaction without further purification. Colorless solid, yield 1.05 g (97%); tlc: ethyl acetate, $R_f = 0.50$. $C_{19}H_{28}N_2O_4Si$ (376.4). MS (EI): *m/z* (%) = 376 (M, 48), 361 (M − CH_3, 15), 345 (M − OCH_3, 12), 285 (M − CH_2Ph, 4). $[\alpha]_{589}^{25} = +60.4$ ($c = 0.56$, CH_2Cl_2). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3032 (w, $\nu_{CH\ arom.}$), 2959 (m, $\nu_{CH\ aliph.}$), 1682 (s, $\nu_{C=O,\ tert.\ amides}$), 1254, 1017 (m, ν_{COC}), 733, 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 0.21$ (s, 9H, $Si(CH_3)_3$), 1.40–1.51 (m, 1H, 4-H), 1.65–1.89 (m, 3H, 4-H, 3-H), 3.00 (s, 3H, NCH_3), 3.25 (s, 3H, OCH_3), 3.82 (dd, $J = 5.5/2.4$ Hz, 1H, 5-H), 3.93 (s, 1H, 1-H), 4.30 (d, $J = 14.6$ Hz, 1H, NCH_2Ph), 4.72 (d, $J = 14.6$ Hz, 1H, NCH_2Ph), 7.20–7.36 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): $\delta = 1.3$ (3C, $Si(CH_3)_3$), 24.2 (1C, C-4), 32.7 (1C, C-3), 33.1 (1C, NCH_3), 48.6 (1C, NCH_2Ph), 48.8 (1C, OCH_3), 59.0 (1C, C-5), 69.5 (1C, C-1), 98.3 (1C, C-2), 127.7 (1C, arom. CH), 128.3 (2C, arom. CH), 128.6 (2C, arom. CH), 135.8 (1C, arom. C), 166.0 (1C, C=O), 168.4 (1C, C=O).

6.1.2. (1*S*,5*S*)-6-Benzyl-8-butyl-2-methoxy-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (**6b**)

Under N_2 a solution of LHMDS (1 M in THF; 17.5 mL, 17.5 mmol) was added dropwise to a solution of **5b** [11] (5.01 g, 14.5 mmol) in THF (140 mL) at −78 °C. After a reaction time of 60 min at −78 °C a solution of chlorotrimethylsilane (5.6 mL, 43.7 mmol) in THF (4 mL) was added and the reaction mixture was stirred for 15 min at −78 °C, then for 3 h at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (150 mL). The solution was washed with HCl (0.5 M, 100 mL), with NaOH (0.5 M, 100 mL), and with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting product **6b** was characterized and directly used for the next reaction without further purification. Colorless oil, yield 5.33 g (88%). $C_{22}H_{34}N_2O_4Si$ (418.6). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3028 (w, $\nu_{CH\ arom.}$), 2958 (m, $\nu_{CH\ aliph.}$), 1685 (s, $\nu_{C=O,\ tert.\ amides}$), 1253 (m, ν_{COC}), 1106 (m, O–Si), 733, 700 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 0.22$ (s, 9H, $Si(CH_3)_3$), 0.92 (t, $J = 7.2$ Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.30 (sext, $J = 7.3$ Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.40–1.61 (m, 3H, 4-H, $NCH_2CH_2CH_2CH_3$), 1.80–1.88 (m, 3H, 3-H, 4-H), 3.00 (ddd, $J = 13.9/7.9/6.0$ Hz, 1H, $NCH_2CH_2CH_2CH_3$), 3.26 (s, 3H, OCH_3), 3.80 (dt, $J = 14.3/7.7$ Hz, 1H,

NCH_2CH$_2$CH$_2$CH$_3$), 3.81 (dd, J = 6.4/1.5 Hz, 1H, 5-H), 3.98 (s, 1H, 1-H), 4.36 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.71 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.23–7.36 (m, 5H, arom. H).

6.1.3. (1S,5S)-6-Benzyl-2-methoxy-8-(2-phenylethyl)-2-(trimethylsilyloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (**6c**)

Under N_2 a solution of LHMDS (1 M in THF; 3.0 mL, 3.0 mmol) was added dropwise to a solution of **5c** [11] (1.02 g, 2.58 mmol) in THF (50 mL) at −78 °C. After a reaction time of 40 min at −78 °C a solution of chlorotrimethylsilane (1.2 mL, 9.4 mmol) in THF (7 mL) was added and the reaction mixture was stirred for 30 min at −78 °C, then for 30 min at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (70 mL). The solution was washed with NaOH (0.5 M, 2 × 40 mL), with HCl (0.5 M, 2 × 40 mL) and with brine (40 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting product **6c** was characterized and directly used for the next reaction without further purification. Colorless solid, yield 1.19 g (99%), R_f = 0.60 (ethyl acetate), R_f = 0.66 (petroleum ether/ethyl acetate 3:7). $C_{26}H_{34}N_2O_4Si$ (466.6). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3029 (w, $\nu_{CH\ arom.}$), 2958 (w, $\nu_{CH\ aliph.}$), 1682 (s, $\nu_{C=O,\ tert.\ amides}$), 1254, 1208 (m, ν_{COC}), 732, 698 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 0.25 (s, 9H, Si(CH_3)$_3$), 1.44–1.58 (m, 1H, 4-H), 1.78–1.96 (m, 3H, 3-H, 4-H), 2.82–3.02 (m, 2H, NCH$_2$CH_2Ph), 3.29 (s, 3H, OCH_3), 3.22–3.36 (m, 1H, NCH_2CH$_2$Ph), 3.82 (dd, J = 5.5/1.8 Hz, 1H, 5-H), 4.00 (s, 1H, 1-H), 4.09 (ddd, J = 13.6/8.3/7.2 Hz, 1H, NCH_2CH$_2$Ph), 4.39 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.68 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.18–7.41 (m, 10H, arom. H).

6.1.4. (1S,5S)-6-Benzyl-8-methyl-6,8-diazabicyclo-[3.2.2]nonane-2,7,9-trione (**7a**)

As described for **6a** the piperazinedione **5a** (8.28 g, 27.2 mmol) was reacted with LHMDS (30.0 mL, 30.0 mmol) and chlorotrimethylsilane (11.2 mL, 87.4 mmol, in 8 mL THF) to yield the mixed methyl silyl acetal **6a**. Without purification **6a** was dissolved in a mixture of THF (100 mL) and water (10 mL), *p*-toluenesulfonic acid (1.00 g, 5.25 mmol) was added and the mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by fc (8 cm, ethyl acetate, 100 mL, R_f = 0.41). Colorless solid, mp 183–184 °C, yield 6.70 g (90%, with regard to **5a**). $[\alpha]_{589}^{25}$ = +5.2 (c = 0.55, CH_2Cl_2). $C_{15}H_{16}N_2O_3$ (272.3). Calcd. C 66.2 H 5.92 N 10.3 found C 65.9 H 6.41 N 10.4. MS (EI): m/z (%) = 272 (M, 49), 215 (M − CO−NCH$_3$, 8), 181 (M − CH$_2$Ph, 97). MS (CI): m/z (%) = 273 (MH$^+$, 100), 181 (MH$^+$ − PhCH$_3$, 2). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3030 (w, $\nu_{CH\ arom.}$), 2975, 2935 (m, $\nu_{CH\ aliph.}$), 1728 (s, $\nu_{C=O,\ ketone}$), 1682 (s, $\nu_{C=O,\ tert.\ amides}$), 1253, 1177 (m, ν_{COC}), 732 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.84 (dddd, J = 14.5/8.8/7.2/3.3 Hz, 1H, 4-H), 2.28 (ddt, J = 14.5/8.4/4.1 Hz, 1H, 4-H), 2.46 (ddd, J = 15.5/7.3/4.3 Hz, 1H, 3-H), 2.67 (dt, J = 15.5/8.4 Hz, 1H, 3-H), 3.03 (s, 3H, NCH_3), 4.03 (t, J = 3.7 Hz, 1H, 5-H), 4.18 (s, 1H, 1-H), 4.53 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.66 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.21–7.36 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 29.2 (1C, C-4), 32.9 (1C, NCH_3), 36.9 (1C, C-3), 49.0 (1C, NCH_2Ph), 59.1 (1C, C-5), 73.5 (1C, C-1), 128.3 (2C, arom. CH), 128.4 (1C, arom. CH), 129.1 (2C, arom. CH), 135.3 (1C, arom. C), 163.3 (1C, C=O), 167.4 (1C, C=O), 199.2 (1C, C=O$_{ketone}$).

6.1.5. (1S,5S)-6-Benzyl-8-butyl-6,8-diazabicyclo[3.2.2]-nonane-2,7,9-trione (**7b**)

A solution of the mixed acetal **6b** (5.33 g, prepared from **5b**, 5.0 g, 14.5 mmol) and *p*-toluenesulfonic acid (550 mg, 2.9 mmol) in THF (90 mL) and H_2O (10 mL) was stirred for 16 h at room temperature. The mixture was concentrated in vacuo and the residue was purified by fc (5 cm, ethyl acetate, 20 mL, R_f = 0.53). Pale yellow solid, mp 89–93 °C, yield 2.41 g (53% with regard to the monocyclic piperazinedione **5b**). $[\alpha]_{589}^{20}$ = +22 (c = 1.13, CH_2Cl_2). $C_{18}H_{22}N_2O_3$ (314.2). HR-MS: Calcd. 314.163043 found 314.163155 (+0.4 ppm). MS (EI): m/z (%) = 314 (M, 14), 223 (M − CH$_2$Ph, 39), 195 (223-CO, 29). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3033 (w, $\nu_{CH\ arom.}$), 1727 (s, $\nu_{C=O,\ ketone}$), 1683 (s, $\nu_{C=O,\ tert.\ amides}$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.3 Hz, 3H, NCH$_2$CH$_2$CH$_2$CH_3), 1.26 (sext, J = 7.3 Hz, 2H, NCH$_2$CH$_2$CH_2CH$_3$), 1.35–1.57 (m, 2H, NCH$_2$CH_2CH$_2$CH$_3$), 1.81 (dddd, J = 14.4/9.7/7.0/2.5 Hz, 1H, 4-H), 2.29 (ddt, J = 14.6/8.5/4.2 Hz, 1H, 4-H), 2.43 (ddd, J = 15.5/7.1/3.8 Hz, 1H, 3-H), 2.75 (ddd, J = 15.6/9.2/8.6 Hz, 1H, 3-H), 3.36 (ddd, J = 14.1/8.4/5.9 Hz, 1H, NCH_2CH$_2$CH$_2$CH$_3$), 3.50 (ddd, J = 13.9/8.6/6.2 Hz, 1H, NCH_2CH$_2$CH$_2$CH$_3$), 4.05 (dd, J = 4.4/2.9 Hz, 1H, 5-H), 4.26 (s, 1H, 1-H), 4.53 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.63 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.19–7.43 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 13.5 (1C, NCH$_2$CH$_2$CH$_2$CH_3), 19.8 (1C, NCH$_2$CH$_2$CH_2CH$_3$), 28.8 (1C, C-4), 29.6 (1C, NCH$_2$CH_2CH$_2$CH$_3$), 36.9 (1C, C-3), 45.9 (1C, NCH_2CH$_2$CH$_2$CH$_3$), 49.0 (1C, NCH_2Ph), 59.2 (1C, C-5), 72.0 (1C, C-1), 128.2 (2C, arom. CH), 128.3 (1C, arom. CH), 129.0 (2C, arom. CH), 135.3 (1C, arom. C), 163.6 (1C, C=O), 167.0 (1C, C=O), 199.8 (1C, C=O$_{ketone}$).

6.1.6. (1S,5S)-6-Benzyl-8-(2-phenylethyl)-6,8-diazabicyclo-[3.2.2]nonane-2,7,9-trione (**7c**)

As described for the synthesis of **6c** the monocyclic piperazinedione **5c** (3.01 g, 7.62 mmol) was dissolved in THF (80 mL) and at −78 °C reacted with a 1 M LHMDS solution in THF (8.7 mL, 8.7 mmol) and after 45 min with a solution of chlorotrimethylsilane (3.0 mL, 23.4 mmol) in THF (5 mL). After stirring for 20 min at −78 °C and for 3 h at room temperature the reaction mixture was worked up as described for **6c**. The resulting residue was dissolved in a mixture of THF (100 mL) and H_2O (10 mL), *p*-toluenesulfonic acid (0.32 g, 1.7 mmol) was added and the mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo and the residue was purified by fc (4 cm, ethyl acetate, 20 mL, R_f = 0.48). Colorless solid, mp 164–166 °C, yield 2.47 g, 90% related to the monocyclic piperazinedione **5c**. $[\alpha]_{589}^{23}$ = +72 (c = 0.68, CH_2Cl_2). $C_{22}H_{22}N_2O_3$ (362.4). Calcd. C 72.91 H 6.12 N 7.73 found C 73.05 H 6.30 N

7.86. MS (EI): *m/z* (%) = 362 (M, 10), 271 (M − CH_2Ph, 18), 243 (M − NCH_2CH_2Ph, 38). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3055 (w, $\nu_{CH\ arom.}$), 1720 (m, $\nu_{C=O,\ ketone}$), 1688 (s, $\nu_{C=O,\ tert.\ amides}$). ^1H NMR ($CDCl_3$): δ = 1.79 (dddd, *J* = 14.3/9.5/6.9/2.7 Hz, 1H, 4-H), 2.24 (ddt, *J* = 14.3/8.2/4.1 Hz, 1H, 4-H), 2.37 (ddd, *J* = 15.7/7.1/3.6 Hz, 1H, 3-H), 2.57 (dt, *J* = 15.6/8.9 Hz, 1H, 3-H), 2.88 (t broad, *J* = 7.3 Hz, 2H, NCH_2CH_2Ph), 3.69 (dt, *J* = 14.0/7.2 Hz, 1H, NCH_2CH_2Ph), 3.85 (dt, *J* = 13.7/7.1 Hz, NCH_2CH_2Ph), 3.98 (dd, *J* = 4.3/3.2 Hz, 1H, 5-H), 4.21 (s, 1H, 1-H), 4.53 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 4.63 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 7.15–7.38 (m, 10H, arom. H).

*6.1.7. (1R,2S,5S)-6-Benzyl-8-methyl-6,8-diazabicyclo-[3.2.2]nonan-2-ol ((2S)-**8a**) and (1R,2R,5S)-6-benzyl-8-methyl-6,8-diazabicyclo[3.2.2]nonan-2-ol ((2R)-**8a**)*

Under N_2 a tablet of $LiAlH_4$ (800 mg, 21.1 mmol) was added to an ice-cold solution of **7a** (888 mg, 3.26 mmol) in THF (80 mL). The mixture was stirred for 30 min at 0 °C and for 68 h at reflux temperature. Then the excess of $LiAlH_4$ was carefully (ice bath, N_2) destroyed by addition of $Na_2SO_4 \cdot 10H_2O$ (4.8 g). The mixture was heated to reflux (30 min), filtered and the solvent was removed in vacuo. The residue ((2*S*)-**8a**:(2*R*)-**8a** = 27:73) was purified by fc (2 cm, ethyl acetate:C_2H_5OH = 9:1 + 1% dimethylethylamine, 5 mL).

(2*S*)-**8a** (R_f = 0.45): Pale yellow oil, yield 160 mg (20%). $[\alpha]_{589}^{20}$ = +24.2 (*c* = 0.55, CH_2Cl_2). $C_{15}H_{22}N_2O$ (246.2). HR-MS: Calcd. 246.173213 found 246.173131 (−0.3 ppm). MS (EI): *m/z* (%) = 246 (M, 9), 228 (M − H_2O, 1), 217 (M − NCH_3, 2), 187 (M − $CH_2CH_2CH_2OH$, 11), 155 (M − CH_2Ph, 22). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3371 (m, ν_{OH}), 3027 (w, $\nu_{CH\ arom.}$), 732, 698 (m, $\gamma_{monosubst.\ arom.}$). ^1H NMR ($CDCl_3$): δ = 1.54–1.70 (m, 2H, 4-H, 3-H), 1.71–1.83 (m, 1H, 4-H), 2.11 (dddd, *J* = 13.6/8.4/6.7/4.4 Hz, 1H, 3-H), 2.47 (s, 3H, NCH_3), 2.65 (dt, *J* = 4.9/2.1 Hz, 1H, 1-H), 2.73 (d broad, *J* = 2.4 Hz, 2H, 9-H), 2.80–2.93 (m, 3H, 5-H, 7-H), 3.68 (d, *J* = 13.4 Hz, 1H, NCH_2Ph), 3.73 (d, *J* = 13.4 Hz, 1H, NCH_2Ph), 3.80 (td, *J* = 4.8/1.8 Hz, 1H, 2-H), 4.40–4.57 (broad, 1H, CHO*H*), 7.19–7.36 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 27.9 (1C, C-4), 30.1 (1C, C-3), 44.9 (1C, NCH_3), 48.1 (1C, C-7), 53.8 (1C, C-9), 53.9 (1C, C-5), 60.6 (1C, NCH_2Ph), 61.8 (1C, C-1), 70.2 (1C, C-2), 126.8 (1C, arom. CH), 128.2 (2C, arom. CH), 128.3 (2C, arom. CH), 139.9 (1C, arom. C).

(2*R*)-**8a** (R_f = 0.34): Colorless oil, yield 422 mg (53%). $[\alpha]_{589}^{20}$ = +33.3 (*c* = 0.47, CH_2Cl_2). $C_{15}H_{22}N_2O$ (246.2). HR-MS: Calcd. 246.173213 found 246.173131 (−0.3 ppm). MS (EI): *m/z* (%) = 246 (M, 5), 228 (M − H_2O, 2), 187 (M − $CH_2CH_2CH_2OH$, 12), 155 (M − CH_2Ph, 20). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3358 (m, ν_{OH}), 3028 (w, $\nu_{CH\ arom.}$), 2927 (s, $\nu_{CH\ aliph.}$), 730, 698 (m, $\gamma_{monosubst.\ arom.}$). ^1H NMR ($CDCl_3$): δ = 1.61 (dddd, *J* = 15.7/11.0/4.9/1.7 Hz, 1H, 4-H), 1.77–1.90 (m, 2H, 4-H, 3-H), 2.09 (tdd, *J* = 10.7/4.7/1.8 Hz, 1H, 3-H), 2.27–2.36 (broad, 1H, CHO*H*), 2.41 (s, 3H, NCH_3), 2.64 (dt, *J* = 4.6/2.5 Hz, 1H, 1-H), 2.74 (d broad, *J* = 2.4 Hz, 2H, 9-H), 2.75 (dd, *J* = 11.3/2.7 Hz, 1H, 7-H), 2.84 (tt, *J* = 4.7/2.6 Hz, 1H, 5-H), 3.08 (dd, *J* = 11.3/2.4 Hz, 1H, 7-H), 3.67 (d, *J* = 13.4 Hz, 1H, NCH_2Ph), 3.73 (d, *J* = 13.4 Hz, 1H, NCH_2Ph), 4.02 (dt, *J* = 7.3/5.2 Hz, 1H, 2-H), 7.20–7.37 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 29.5 (1C, C-3), 29.8 (1C, C-4), 44.5 (1C, NCH_3), 46.1 (1C, C-7), 53.4 (1C, C-9), 53.9 (1C, C-5), 60.8 (1C, NCH_2Ph), 63.6 (1C, C-1), 74.8 (1C, C-2), 126.9 (1C, arom. CH), 128.2 (2C, arom. CH), 128.4 (2C, arom. CH), 139.6 (1C, arom. C).

*6.1.8. (1R,2S,5S)-6-Benzyl-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol ((2S)-**8c**) and (1R,2R,5S)-6-benzyl-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol ((2R)-**8c**)*

Under N_2 a solution of $LiAlH_4$ (1 M in THF, 5.0 mL, 5.0 mmol) was added to an ice-cold solution of the ketone **7c** (392 mg, 1.08 mmol) in THF (50 mL). The reaction mixture was stirred for 90 h at reflux temperature. The excess of $LiAlH_4$ was carefully (ice bath) destroyed by addition of 3 M NaOH (3 mL) and H_2O (3 mL) and subsequent warming for 30 min. The mixture was filtered and concentrated in vacuo. The residue ((2*S*)-**8c**:(2*R*)-**8c** = 30:70) was purified by fc (2 cm, petroleum ether:ethyl acetate = 3:7).

(2*S*)-**8c** (R_f = 0.44): Pale yellow oil, yield 71 mg (20%). $[\alpha]_{589}^{18}$ = +34.8 (*c* = 0.39, CH_2Cl_2). $C_{22}H_{28}N_2O$ (336.2). HR-MS: Calcd. 336.220163 found 336.220322 (+0.5 ppm). MS (EI): *m/z* (%) = 336 (M, 7), 277 (M − $CH_2CH_2CH_2OH$, 3) 245 (M − CH_2Ph, 100), 154 (M − 2× CH_2Ph, 10). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3380 (m, ν_{OH}), 3027 (w, $\nu_{CH\ arom.}$), 2925, 2807 (m, $\nu_{CH\ aliph.}$), 733, 700 (s, $\gamma_{monosubst.\ arom.}$). ^1H NMR ($CDCl_3$): δ = 1.50–1.64 (m, 2H, 4-H, 3-H), 1.72–1.84 (m, 1H, 4-H), 2.12 (ddt, *J* = 14.0/8.6/4.9 Hz, 1H, 3-H), 2.78–3.00 (m, 10H, 7-H (2H), 9-H (2H), NCH_2CH_2Ph (3H), 5-H, 1-H, CHO*H*) 3.06 (dt, *J* = 12.1/5.5 Hz, 1H, NCH_2CH_2Ph), 3.74 (s, 2H, NCH_2Ph), 3.77 (td, *J* = 5.5/1.8 Hz, 1H, 2-H), 7.20–7.39 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 27.9 (1C, C-4), 30.0 (1C, C-3), 34.5 (1C, NCH_2CH_2Ph), 49.3 (1C, C-7), 51.5 (1C, C-9), 53.7 (1C, C-5), 59.5 (1C, NCH_2CH_2Ph), 60.6 (1C, NCH_2Ph), 61.2 (1C, C-1), 67.5 (1C, C-2), 126.3 (1C, arom. CH), 126.9 (1C, arom. CH), 128.2 (2C, arom. CH), 128.3 (2C, arom. CH), 128.5 (4C, arom. CH), 139.7 (2C, arom. C).

(2*R*)-**8c** (R_f = 0.23): Pale yellow oil, yield 146 mg (40%). $[\alpha]_{589}^{18}$ = +23.5 (*c* = 0.95, CH_2Cl_2). $C_{22}H_{28}N_2O$ (336.2). HR-MS: Calcd. 336.220163 found 336.220322 (+0.5 ppm). MS (EI): *m/z* (%) = 336 (M, 7), 277 (M − $CH_2CH_2CH_2OH$, 5), 245 (M − CH_2Ph, 100), 154 (M − 2× CH_2Ph, 10). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3379 (m, ν_{OH}), 3026 (w, $\nu_{CH\ arom.}$), 2929, 2802 (m, $\nu_{CH\ aliph.}$), 732, 699 (s, $\gamma_{monosubst.\ arom.}$). ^1H NMR ($CDCl_3$): δ = 1.60–1.73 (m, 1H, 4-H), 1.80–1.95 (m, 2H, 4-H, 3-H), 2.10–2.20 (m, 1H, CHO*H*), 2.15 (dtd, *J* = 11.8/5.9/2.7 Hz, 1H, 3-H), 2.86–2.98 (m, 9H, NCH_2CH_2Ph (4H), 9-H (2H), 7-H, 5-H, 1-H), 3.19 (dd, *J* = 11.3/2.4 Hz, 1H, 7-H), 3.75 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 3.80 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 4.03 (dt, *J* = 6.7/5.4 Hz, 1H, 2-H), 7.20–7.45 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 29.4 (1C, C-3), 29.9 (1C, C-4), 34.7 (1C, NCH_2CH_2Ph), 47.2 (1C, C-7), 51.1 (1C, C-9), 54.0 (1C, C-5), 58.8 (1C, NCH_2CH_2Ph), 60.7 (1C, NCH_2Ph), 61.5 (1C, C-1), 75.0 (1C, C-2), 125.9 (1C, arom. CH), 126.9 (1C, arom. CH),

128.2 (4C, arom. CH), 128.4 (2C, arom. CH), 128.6 (2C, arom. CH), 139.4 (1C, arom. C), 140.4 (1C, arom. C).

In addition to the pure products a mixture of (2*S*)-**8c** and (2*R*)-**8c** was isolated by fc. Yield 82 mg (22%); total yield 299 mg (82%).

*6.1.9. (1S,2S,5S)-6-Benzyl-2-hydroxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**9a**) and (1S,2R,5S)-6-benzyl-2-hydroxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**9a**)*

$NaBH_4$ (0.83 g, 21.9 mmol) was added to a cooled (ice bath) solution of **7a** (1.95 g, 7.16 mmol) in a mixture of THF/propan-2-ol/H_2O (100 mL, 20 mL, 5 mL). After stirring for 16 h at room temperature the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (80 mL) and washed with H_2O (2 × 50 mL) and HCl (0.5 M, 1 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to yield a mixture of the diastereomeric alcohols (2*S*)-**9a** and (2*R*)-**9a** as a colorless solid. The diastereomers (2*S*)-**9a** and (2*R*)-**9a** (ratio 15:85 according to ^{1}H NMR spectrum) were separated by fc (4 cm, ethyl acetate:acetone = 1:1, 20 mL).

(2*S*)-**9a** (R_f = 0.45): Colorless solid, mp 171–173 °C, yield 0.20 g (10%). $[\alpha]_{589}^{23}$ = +88.1 (c = 0.50, CH_2Cl_2). $C_{15}H_{18}N_2O_3$ (274.3). Calcd. C 65.7 H 6.61 N 10.2 found C 65.4 H 6.61 N 10.2. MS (EI): *m/z* (%) = 274 (M, 79), 246 (M − CO, 6), 217 (M − CH_3NCO, 23), 183 (M − CH_2Ph, 52). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3394 (m, ν_{OH}), 3063, 3030 (w, $\nu_{CH\ arom.}$), 2934 (m, $\nu_{CH\ aliph.}$), 1668 (s, $\nu_{C=O,\ tert.\ amides}$), 737, 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.23–1.38 (m, 1H, 4-H), 1.49–1.71 (m, 1H, 3-H), 1.85–1.98 (m, 2H, 3-H, 4-H), 3.11 (s, 3H, NCH_3), 3.36–3.54 (broad, 1H, CHO*H*), 3.82 (dd, J = 4.9/2.4 Hz, 1H, 5-H), 4.05 (d, J = 1.8 Hz, 1H, 1-H), 4.14 (ddd, J = 8.5/4.8/1.9 Hz, 1H, 2-H), 4.43 (d, J = 14.6 Hz, 1H, NC*H*$_2$Ph), 4.58 (d, J = 14.6 Hz, 1H, NC*H*$_2$Ph), 7.11–7.35 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 24.5 (1C, C-4), 29.1 (1C, C-3), 34.5 (1C, N*C*H$_3$), 48.5 (1C, N*C*H$_2$Ph), 59.0 (1C, C-5), 67,2 (1C, C-2), 69.6 (1C, C-1), 128.1 (1C, arom. CH), 128.2 (2C, arom. CH), 128.9 (2C, arom. CH), 135.4 (1C, arom. C), 167.9 (1C, C=O), 168.3 (1C, C=O).

(2*R*)-**9a** (R_f = 0.38): Colorless solid, mp 165–167 °C, yield 0.53 g (27%). $[\alpha]_{589}^{25}$ = +166 (c = 1.06, CH_2Cl_2). $C_{15}H_{18}N_2O_3$ (274.3). Calcd. C 65.7 H 6.61 N 10.2 found C 65.7 H 6.55 N 10.1. MS (EI): *m/z* (%) = 274 (M, 35), 217 (M − CH_3NCO, 9), 183 (M − CH_2Ph, 39). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3419 (m, ν_{OH}), 3055 (w, $\nu_{CH\ arom.}$), 2976 (w, $\nu_{CH\ aliph.}$), 1678 (s, $\nu_{C=O,\ tert.\ amides}$), 737, 700 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.48–1.75 (m, 3H, 4-H, 3-H), 1.90–2.02 (m, 1H, 3-H), 2.99 (s, 3H, NC*H*$_3$), 3.35–3.45 (broad, 1H, CHO*H*), 3.82 (dt, J = 4.6/3.3 Hz, 1H, 2-H), 3.86 (dd, J = 5.4/2.4 Hz, 1H, 5-H), 4.00 (d, J = 3.1 Hz, 1H, 1-H), 4.50 (d, J = 14.3 Hz, 1H, NC*H*$_2$Ph), 4.68 (d, J = 14.6 Hz, 1H, NC*H*$_2$Ph), 7.22–7.36 (m, 5H, arom. H); ^{13}C NMR ($CDCl_3$): δ = 23.4 (1C, C-4), 29.1 (1C, C-3), 32.7 (1C, N*C*H$_3$), 48.7 (1C, N*C*H$_2$Ph), 59.0 (1C, C-5), 65.8 (1C, C-2), 67.7 (1C, C-1), 128.1 (1C, arom. CH), 128.4 (2C, arom. CH), 128.9 (2C, arom. CH), 135.6 (1C, arom. C), 167.7 (1C, C=O), 169.5 (1C, C=O).

Additionally a mixture of (2*S*)-**9a** and (2*R*)-**9a** was isolated. Colorless solid, yield 0.78 g (40%); total yield 1.51 g (77%).

*6.1.10. (1S,2S,5S)-6-Benzyl-8-butyl-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**9b** and (1S,2R,5S)-6-benzyl-8-butyl-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**9b**)*

$NaBH_4$ (370 mg, 9.7 mmol) was added to a cooled (ice bath) solution of **7b** (506 mg, 1.61 mmol) in a mixture of THF (45 mL) and H_2O (5 mL) and the mixture was stirred for 20 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate (80 mL), and the mixture was washed with H_2O (3 × 50 mL). After drying (Na_2SO_4) the solution was concentrated in vacuo to afford a mixture of the diastereomeric alcohols (2*S*)-**9b** and (2*R*)-**9b** (18:82). Colorless oil, yield 403 mg (80%), R_f = 0.46/0.43 with tailing (ethyl acetate:acetone = 1:1). $[\alpha]_{589}^{24}$ = +97.7 (18:82 diastereomeric mixture, c = 0.84, CH_2Cl_2). $C_{18}H_{24}N_2O_3$ (316.4). Calcd. C 68.33 H 7.65 N 8.85 found C 68.19 H 7.42 N 8.65. MS (CI): *m/z* (%) = 334 ($M + NH_4^+$, 11), 317 (MH^+, 100), 261 ($MH^+ - CH_2CH_2CH_2CH_3$, 2), 225 (M − CH_2Ph, 7). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3407 (s, ν_{OH}), 3064, 3031 (w, $\nu_{CH\ arom.}$), 2934, 2869 (each m, $\nu_{CH\ aliph.}$), 1667 (s, $\nu_{C=O,\ tert.\ amides}$), 732, 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.29 (sext, J = 7.3 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.47–1.76 (m, 5H, $NCH_2CH_2CH_2CH_3$ (2H), 4-H (2H), 3-H (1H)), 1.97 (ddd, J = 14.5/9.7/4.8 Hz, 0.8H, 3-H), 1.86–1.95* (m, 0.2H, 3-H), 2.49* (s broad, 0.2H, CHO*H*), 3.16 (dt, J = 13.9/6.9 Hz, 0.8H, NC*H*$_2$CH$_2$CH$_2$CH$_3$), 3.19* (dt, J = 13.9/7.0 Hz, 0.2H, NC*H*$_2$CH$_2$CH$_2$CH$_3$), 3.58 (dt, J = 13.6/7.5 Hz, 1H, NC*H*$_2$CH$_2$CH$_2$CH$_3$), 3.86 (dd, J = 5.5/2.6 Hz, 1H, 5-H), 3.78–3.84 (m, 1H, 2-H), 4.03 (d, J = 3.3 Hz, 0.8H, 1-H), 4.12* (d, J = 1.1 Hz, 0.2H, 1-H), 4.23 (d broad, J = 3.7 Hz, 0.8H, CHO*H*), 4.44* (d, J = 14.6 Hz, 0.2H, NC*H*$_2$Ph), 4.51 (d, J = 14.6 Hz, 0.8H, NC*H*$_2$Ph), 4.59* (d, J = 14.6 Hz, 0.2H, NC*H*$_2$Ph), 4.67 (d, J = 14.3 Hz, 0.82H, NC*H*$_2$Ph), 7.14–7.38 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 13.6 (1C, $NCH_2CH_2CH_2CH_3$), 19.8 (1C, $NCH_2CH_2CH_2CH_3$), 23.1 (0.8C, C-4), 24.5* (0.2C, C-4), 29.0* (0.2C, C-3), 29.1 (0.8C, C-3), 29.8 (1C, $NCH_2CH_2CH_2CH_3$), 45.2 (1C, $NCH_2CH_2CH_2CH_3$), 48.5* (0.2C, N*C*H$_2$Ph), 48.7 (0.8C, N*C*H$_2$Ph), 59.3 (1C, C-5), 65.9 (0.8C, C-1), 66.9* (0.2C, C-1), 66.7 (0.8C, C-2), 67.7* (0.2C, C-2), 128.0 (1C, arom. CH), 128.3 (2C, arom. CH), 128.8 (2C, arom. CH), 135.5* (0.2C, arom. C), 135.7 (0.8C, arom. C), 167.8* (0.2C, C=O), 167.9 (0.8C, C=O), 168.5* (0.2C, C=O), 169.1 (0.8C, C=O). * = Signals of the minor diastereomer.

*6.1.11. (1S,2S,5S)-6-Benzyl-2-hydroxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**9c**) and (1S,2R,5S)-6-benzyl-2-hydroxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**9c**)*

$NaBH_4$ (505 mg, 13.3 mmol) was added to a cooled (ice bath) solution of ketone **7c** (1.02 g, 2.81 mmol) in a mixture of THF (50 mL) and H_2O (5 mL) and the mixture was stirred

for 4 h at room temperature. The solvent was removed in vacuo and the residue was purified by fc (3 cm, ethyl acetate:acetone = 8:2, 20 mL, R_f = 0.43/0.38). Colorless solid, yield 0.93 g (91%), ratio of diastereomers (2*S*)-**9c**:(2*R*)-**9c** = 25:75. $C_{22}H_{24}N_2O_3$ (364.2). Calcd. C 72.51 H 6.64 N 7.68 found C 72.49 H 6.69 N 7.58. The diastereomers were separated by a second fc (3 cm, ethyl acetate:acetone = 8:2, 10 mL).

(2*S*)-**9c** (R_f = 0.43): Colorless solid, mp 157–161 °C, yield 61 mg (5.9%). $[\alpha]_{589}^{20} = +19.1$ (c = 0.48, CH_2Cl_2). $C_{22}H_{24}N_2O_3$ (364.2). HR-MS: Calcd. 364.178693 found 364.179092 (+1.1 ppm). MS (EI): *m/z* (%) = 364 (M, 23), 273 (M − CH_2Ph, 26), 245 (M − NCH_2CH_2Ph, 22). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3423 (s, ν_{OH}), 3030 (w, $\nu_{CH\ arom.}$), 2933 (w, $\nu_{CH\ aliph.}$), 1660 (s, $\nu_{C=O,\ tert.\ amides}$), 735, 700 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.23–1.40 (m, 1H, 4-H), 1.55–1.73 (m, 1H, 3-H), 1.86–2.02 (m, 2H, 3-H, 4-H), 2.65 (d broad, J = 4.3 Hz, 1H, CHO*H*), 2.95 (t, J = 7.5 Hz, 2H, NCH_2CH_2Ph), 3.46 (dt, J = 13.7/7.3 Hz, 1H, NCH_2CH_2Ph), 3.78 (dd, J = 5.3/2.3 Hz, 1H, 5-H), 4.00 (d, J = 1.5 Hz, 1H, 1-H), 4.03–4.13 (m, 1H, 2-H), 4.09 (dt, J = 13.7/7.3 Hz, 1H, NCH_2CH_2Ph), 4.40 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.60 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.13–7.40 (m, 10H, arom. H).

(2*R*)-**9c** (R_f = 0.37): Colorless solid, mp 152–156 °C, yield 113 mg (11%). $[\alpha]_{589}^{20} = +53.5$ (c = 0.51, CH_2Cl_2). $C_{22}H_{24}N_2O_3$ (364.2). HR-MS: Calcd. 364.178693 found 364.179092 (+1.1 ppm). MS (EI): *m/z* (%) = 364 (M, 33), 273 (M − CH_2Ph, 11). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3410 (s, ν_{OH}), 3058, 3024 (w, $\nu_{CH\ arom.}$), 2956 (w, $\nu_{CH\ aliph.}$), 1664 (s, $\nu_{C=O,\ tert.\ amides}$), 738, 700 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.46–1.78 (m, 3H, 3-H, 4-H), 1.95 (dq, J = 14.0/4.8 Hz, 1H, 3-H), 2.90 (t broad, J = 7.6 Hz, 2H, NCH_2CH_2Ph), 3.42 (ddd, J = 14.0/7.9/6.7 Hz, 1H, NCH_2CH_2Ph), 3.71–3.80 (m, 1H, 2-H), 3.83 (dd, J = 5.7/2.5 Hz, 1H, 5-H), 3.90 (dt, J = 13.7/7.6 Hz, 1H, NCH_2CH_2Ph), 4.02 (d, J = 3.4 Hz, 1H, 1-H), 4.52 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.64 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.18–7.37 (m, 10H, arom. H). A signal for the OH-proton was not found.

In addition to the pure products a mixture of (2*S*)-**9c** and (2*R*)-**9c** was isolated. Colorless solid, yield 0.72 g (70%); total yield 0.894 g (87%).

*6.1.12. (1S,2R,5S)-6-Benzyl-2-methoxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**10a**)*

A solution of (2*R*)-**9a** (250 mg, 0.91 mmol, with a little amount of the diastereomeric alcohol (2*S*)-**9a**) in THF (15 mL) was slowly added to a cooled (0 °C) suspension of NaH (165 mg, 6.7 mmol) prepared from NaH dispersion (80% in oil, 206 mg) in THF (10 mL). After stirring for 20 min a solution of CH_3I (0.17 mL, 2.73 mmol) in THF (0.8 mL) was added and the mixture was stirred for 16 h at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (60 mL) and the solution was washed with 0.5 M HCl (40 mL), 0.5 M NaOH (40 mL), and brine (40 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (3 cm, ethyl acetate:acetone = 1:1, 10 mL, R_f = 0.46). Colorless solid, mp 136–139 °C, yield 192 mg (73%). $[\alpha]_{589}^{23} = +151$ (c = 0.57, CH_2Cl_2). $C_{16}H_{20}N_2O_3$ (288.1). HR-MS: Calcd. 288.147393 found 288.147343 (−0.2 ppm). MS (EI): *m/z* (%) = 288 (M, 18), 256 (M − CH_3OH, 19), 197 (M − CH_2Ph, 44), 169 (M − $PhCH_2NCH_2$, 64). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3056 (w, $\nu_{CH\ arom.}$), 2937 (w, $\nu_{CH\ aliph.}$), 1682 (s, $\nu_{C=O,\ tert.\ amides}$), 736, 703 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.47–1.70 (m, 3H, 4-H, 3-H), 1.80–1.91 (m, 1H, 3-H), 2.96 (s, 3H, NCH_3), 3.29 (ddd, J = 8.1/4.8/3.2 Hz, 1H, 2-H), 3.40 (s, 3H, OCH_3), 3.82 (dd, J = 5.5/2.4 Hz, 1H, 5-H), 3.97 (d, J = 2.7 Hz, 1H, 1-H), 4.41 (d, J = 14.3 Hz, 1H, NCH_2Ph), 4.70 (d, J = 14.6 Hz, 1H, NCH_2Ph), 7.19–7.34 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 23.3 (1C, C-4), 26.4 (1C, C-3), 32.4 (1C, NCH_3), 48.6 (1C, NCH_2Ph), 57.0 (1C, OCH_3), 58.9 (1C, C-5), 64.4 (1C, C-1), 75.0 (1C, C-2), 127.9 (1C, arom. CH), 128.3 (2C, arom. CH), 128.7 (2C, arom. CH), 135.8 (1C, arom. C), 166.5 (1C, C=O), 169.5 (1C, C=O).

*6.1.13. (1S,2S,5S)-6-Benzyl-8-butyl-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**10b**) and (1S,2R,5S)-6-benzyl-8-butyl-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**10b**)*

NaH (270 mg, 11.3 mmol) prepared from NaH dispersion (80% in oil, 340 mg) was slowly added to a cooled (0 °C) solution of (2*S*)-**9b**/(2*R*)-**9b** (356 mg, 1.13 mmol) in THF (40 mL). After stirring for 15 min at 0 °C a solution of CH_3I (0.35 mL, 5.63 mmol) in THF (4.5 mL) was added and the mixture was stirred for 16 h at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (70 mL) and the solution was washed with H_2O (2 × 40 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate, 2 mL, R_f = 0.39-0.37). Colorless solid, mp 91–92 °C, yield 237 mg (64%), ratio of diastereomers (2*S*)-**10b**:(2*R*)-**10b** = 22:78. $[\alpha]_{589}^{25} = +126$ (22:78 diastereomeric mixture, c = 0.54, CH_2Cl_2). $C_{19}H_{26}N_2O_3$ (330.4). Calcd. C 69.07 H 7.93 N 8.47 found C 69.19 H 7.76 N 8.29. MS (EI): *m/z* (%) = 330 (M, 24), 298 (M − CH_3OH, 3), 259 (M − $NCH_2CH_2CH_2CH_3$, 41), 239 (M − CH_2Ph, 67). IR (film): $\tilde{\nu}$[cm^{-1}] = 2932, 2869 (m, $\nu_{CH\ aliph.}$), 1680 (s, $\nu_{C=O,\ tert.\ amides}$), 733, 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 0.93* (t, J = 7.2 Hz, 3× 0.2H, $NCH_2CH_2CH_2CH_3$), 0.95 (t, J = 7.2 Hz, 3× 0.8H, $NCH_2CH_2CH_2CH_3$), 1.32* (sext, J = 7.3 Hz, 2× 0.2H, $NCH_2CH_2CH_2CH_3$), 1.34 (sext, J = 7.3 Hz, 2× 0.8H, $NCH_2CH_2CH_2CH_3$), 1.50–1.77 (m, 5H, $NCH_2CH_2CH_2CH_3$ (2H), 4-H (2H), 3-H (1H)), 1.93 (ddt, J = 13.4/8.2/5.0 Hz, 0.8H, 3-H), 1.94–2.02* (m, 0.2H, 3-H), 3.12 (ddd, J = 13.9/7.5/6.4 Hz, 0.8H, $NCH_2CH_2CH_2CH_3$), 3.14* (ddd, J = 13.9/7.3/6.8 Hz, 0.2H, $NCH_2CH_2CH_2CH_3$), 3.34 (ddd, J = 7.9/4.3/3.5 Hz, 0.8H, 2-H), 3.39* (s, 3× 0.2H, OCH_3), 3.45 (s, 3× 0.8H, OCH_3), 3.52* (ddd, J = 9.6/4.9/1.2 Hz, 0.2H, 2-H), 3.62 (dt, J = 13.6/7.7 Hz, 0.8H, $NCH_2CH_2CH_2CH_3$), 3.68–3.79* (m, 0.2H, $NCH_2CH_2CH_2CH_3$), 3.81* (dd, J = 5.7/2.0 Hz, 0.2H, 5-H), 3.85

(dd, $J = 5.3/2.6$ Hz, 0.8H, 5-H), 4.05 (d, $J = 3.4$ Hz, 0.8H, 1-H), 4.12* (d, $J = 0.9$ Hz, 0.2H, 1-H), 4.46 (d, $J = 14.6$ Hz, 0.8H, NCH_2Ph), 4.48* (d, $J = 14.6$ Hz, 0.2H, NCH_2Ph), 4.59* (d, $J = 14.6$ Hz, 0.2H, NCH_2Ph), 4.76 (d, $J = 14.6$ Hz, 0.8H, NCH_2Ph), 7.20–7.38 (m, 5H, arom. H). * = Signals of the minor diastereomer.

*6.1.14. (1S,2S,5S)-6-Benzyl-2-methoxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**10c**) and (1S,2R,5S)-6-benzyl-2-methoxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**10c**)*

A solution of (2*S*)-**9c**/(2*R*)-**9c** (437 mg, 1.20 mmol) in THF (10 mL) was slowly added to a cooled (0 °C) suspension of NaH (370 mg, 15 mmol) prepared from NaH dispersion (80% in oil, 460 mg) in THF (20 mL). After stirring for 15 min a solution of CH_3I (0.38 mL, 6.1 mmol) in THF (1.6 mL) was added and the mixture was stirred for 7 h at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (80 mL), the solution was washed with H_2O (2 × 50 mL), dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate, 5 mL, $R_f = 0.43/0.38$). Colorless oil, yield 396 mg (87%), ratio of diastereomers (2*S*)-**10c**: (2*R*)-**10c** = 22:78. $[\alpha]_{589}^{20} = +78.9$ (22:78 diastereomeric mixture, $c = 0.29$, CH_2Cl_2). $C_{23}H_{26}N_2O_3$ (378.2). HR-MS: Calcd. 378.194343 found 378.194455 (+0.3 ppm). MS (EI): *m/z* (%) = 378 (M, 35), 307 (M − $CH_2CHCHOCH_3$, 21), 287 (M − CH_2Ph, 30), 202 (307-CH_2CH_2Ph, 30). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3055 (w, $\nu_{CH\ arom.}$), 2932 (w, $\nu_{CH\ aliph.}$), 1679 (s, $\nu_{C=O,\ tert.\ amides}$), 736, 695 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 1.20–1.35$* (m, 0.2H, 4-H), 1.46-1.72 (m, 2.6H, 4-H (2× 0.8H), 3-H (1H)), 1.75–2.02 (m, 1.2H, 3-H (1H), 4-H (0.2H)), 2.88 (t, $J = 7.3$ Hz, 2× 0.8H, NCH_2CH_2Ph), 2.90* (t, $J = 7.3$ Hz, 2× 0.2H, NCH_2CH_2Ph), 3.10–3.18 (m, 0.8H, NC$H_2$$CH_2Ph$), 3.30–3.42 (m, 1H, 2-H), 3.35 (s, 3H, OCH_3), 3.48* (ddd, $J = 9.7/4.9/1.1$ Hz, 0.2H, NC$H_2$$CH_2Ph$), 3.75* (dd, $J = 5.6/2.0$ Hz, 0.2H, 5-H), 3.79 (dd, $J = 5.3/2.7$ Hz, 0.8H, 5-H), 3.88 (dt, J = 13.7/7.7 Hz, 0.8H, NC$H_2$$CH_2Ph$), 3.95–4.05* (m, 0.2H, NC$H_2$$CH_2Ph$), 4.00 (d, $J = 3.7$ Hz, 0.8H, 1-H), 4.04* (d, $J = 0.9$ Hz, 0.2H, 1-H), 4.36* (d, $J = 14.6$ Hz, 0.2H, NCH_2Ph), 4.45 (d, $J = 14.6$ Hz, 0.8H, NCH_2Ph), 4.59* (d, $J = 14.9$ Hz, 0.2H, NCH_2Ph), 4.66 (d, $J = 14.6$ Hz, 0.8H, NCH_2Ph), 7.12–7.34 (m, 10H, arom. H). * = Signals of the minor diastereomer.

*6.1.15. (1S,2S,5S)-6-Benzyl-2-benzyloxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**11a**) and (1S,2R,5S)-6-benzyl-2-benzyloxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**11a**)*

A solution of (2*S*)-**9a**/(2*R*)-**9a** (247 mg, 0.91 mmol) in THF (6 mL) was slowly added to a cooled (0 °C) suspension of NaH (120 mg, 5 mmol) prepared from NaH dispersion (80% in oil, 153 mg) in THF (10 mL). After stirring for 20 min a solution of $Bu_4N^+I^-$ (43 mg, 0.12 mmol) and benzyl bromide (0.35 mL, 3.0 mmol) in THF (2 mL) was added and the mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (60 mL) and the solution was washed with H_2O (2 × 40 mL), 0.5 M HCl, (40 mL) and 0.5 M NaOH (40 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (2 cm, petroleum ether:ethyl acetate = 1:9, 20 mL).

(2*S*)-**11a** ($R_f = 0.50$): Colorless solid, mp 141–142 °C, yield 42 mg (13%). $[\alpha]_{589}^{23} = +43.1$ ($c = 0.31$, CH_2Cl_2). $C_{22}H_{24}N_2O_3$ (364.2). HR-MS: Calcd. 364.178693 found 364.179092 (+1.1 ppm). MS (EI): *m/z* (%) = 364 (M, 8), 273 (M − CH_2Ph, 24). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3030 (w, $\nu_{CH\ arom.}$), 2934 (m, $\nu_{CH\ aliph.}$), 1678 (s, $\nu_{C=O,\ tert.\ amides}$), 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 1.24–1.38$ (m, 1H, 4-H), 1.60–1.79 (m, 1H, 3-H), 1.89–2.01 (m, 2H, 3-H, 4-H), 3.10 (s, 3H, NCH_3), 3.79 (ddd, $J = 8.9/4.6/1.8$ Hz, 1H, 2-H), 3.83 (dd, $J = 5.2/2.1$ Hz, 1H, 5-H), 4.15 (d, $J = 1.5$ Hz, 1H, 1-H), 4.46 (d, $J = 14.6$ Hz, 1H, NCH_2Ph), 4.56 (d, $J = 11.9$ Hz, 1H, OCH_2Ph), 4.63 (d, $J = 11.9$ Hz, 1H, OCH_2Ph), 4.60 (d, $J = 14.6$ Hz, 1H, NCH_2Ph), 7.21–7.40 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): $\delta = 24.6$ (1C, C-4), 26.6 (1C, C-3), 33.9 (1C, NCH_3), 48.3 (1C, NCH_2Ph), 58.7 (1C, C-5), 66.3 (1C, C-1), 70.9 (1C, OCH_2Ph), 74.1 (1C, C-2), 127.3 (2C, arom. CH), 127.7 (1C, arom. CH), 127.9 (1C, arom. CH), 128.1 (2C, arom. CH), 128.3 (2C, arom. CH), 128.8 (2C, arom. CH), 135.4 (1C, arom. C), 137.3 (1C, arom. C), 167.3 (1C, C=O), 168.1 (1C, C=O).

(2R)-**11a** ($R_f = 0.32$): Colorless solid, mp 158–160 °C, yield 234 mg (71%). **1** $[\alpha]_{589}^{23} = +136$ ($c = 0.75$, CH_2Cl_2). $C_{22}H_{24}N_2O_3$ (364.2). HR-MS: Calcd. 364.178693 found 364.179092 (+1.1 ppm). MS (EI): *m/z* (%) = 364 (M, 6), 273 (M − CH_2Ph, 30), 245 (273-NCH_3, 21). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3030 (w, $\nu_{CH\ arom.}$), 2937 (m, $\nu_{CH\ aliph.}$), 2868 (w, ν_{NCH3}), 1681 (s, $\nu_{C=O,\ tert.\ amides}$), 733, 701 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 1.48–1.73$ (m, 3H, 4-H, 3-H), 1.79–1.92 (m, 1H, 3-H), 2.88 (s, 3H, NCH_3), 3.46–3.53 (m, 1H, 2-H), 3.84 (dd, $J = 5.3/2.6$ Hz, 1H, 5-H), 4.03 (d, $J = 3.4$ Hz, 1H, 1-H), 4.40 (d, $J = 14.6$ Hz, 1H, NC*H*2Ph), 4.57 (d, $J = 12.2$ Hz, 1H, OCH_2Ph), 4.71 (d, $J = 12.2$ Hz, 1H, OCH_2Ph), 4.79 (d, $J = 14.6$ Hz, 1H, NCH_2Ph), 7.22–7.42 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): $\delta = 23.5$ (1C, C-4), 27.0 (1C, C-3), 32.5 (1C, NCH_3), 48.9 (1C, NCH_2Ph), 59.2 (1C, C-5), 64.9 (1C, C-1), 71.2 (1C, OCH_2Ph), 72.2 (1C, C-2), 127.8 (2C, arom. CH), 128.0 (1C, arom. CH), 128.1 (1C, arom. CH), 128.5 (4 C, arom. CH), 128.8 (2C, arom. CH), 136.0 (1C, arom. C), 137.4 (1C, arom. C), 166.7 (1C, C=O), 169.6 (1C, C=O).

*6.1.16. (1S,2S,5S)-6-Benzyl-2-benzyloxy-8-butyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**11b**) and (1S,2R,5S)-6-benzyl-2-benzyloxy-8-butyl-6,8-diazabicyclo-[3.2.2]nonane-7,9-dione ((2R)-**11b**)*

NaH (ca. 300 mg, 12.5 mmol), which had been prepared by washing a NaH dispersion (80% in oil, 380 mg) with petroleum ether, was added to a cooled (0 °C) solution of (2*S*)-**9b**/(2*R*)-**9b** (400 mg, 1.26 mmol) in THF (15 mL). After

stirring for 15 min at 0 °C a solution of $Bu_4N^+I^-$ (190 mg, 0.5 mmol) and benzyl bromide (0.75 mL, 6.4 mmol) in THF (2 mL) was added and the mixture was stirred for 6 h at room temperature. Then the mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (100 mL), the organic layer was washed with H_2O (2 × 70 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by fc (4 cm, petroleum ether:ethyl acetate = 1:1, 20 mL, R_f = 0.43–0.45 with tailing). Colorless solid, mp 103–105 °C, yield 375 mg (73%). According to the ^{1}H NMR spectrum the ratio of diastereomers (2*S*)-**11b**:(2*R*)-**11b** = 22:78. $[\alpha]_{589}^{23}$ = +43.1 (22:78 mixture of diastereomers, *c* = 0.31, CH_2Cl_2). $C_{25}H_{30}N_2O_3$ (406.5). Calcd. C 73.87 H 7.44 N 6.89 found C 73.67 H 7.29 N 7.06. MS (CI): *m/z* (%) = 407 (MH^+, 70), 315 ($M - CH_2Ph$, 6), 287 ($MH^+ - CHOCH_2Ph$, 8). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3031 (w, $\nu_{CH\ arom.}$), 2932, 2868 (m, $\nu_{CH\ aliph.}$), 1678 (s, $\nu_{C=O,\ tert.\ amides}$), 735, 700 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.28 (sext, *J* = 7.3 Hz, 2× 0.8H, $NCH_2CH_2CH_2CH_3$), 1.30* (sext, *J* = 7.4 Hz, 2× 0.2H, $NCH_2CH_2CH_2CH_3$), 1.40–2.05 (m, 6H, $NCH_2CH_2CH_2CH_3$ (2H), 4-H (2H), 3-H (2H)), 2.99 (ddd, *J* = 13.6/8.0/6.1 Hz, 0.8H, $NCH_2CH_2CH_2CH_3$), 3.18* (dt, *J* = 13.7/7.0 Hz, 0.2H, $NCH_2CH_2CH_2CH_3$), 3.46–3.60 (m, 2× 0.8H, $NCH_2CH_2CH_2CH_3$, 2-H), 3.75* (dd broad, *J* = 4.7/1.4 Hz, 0.2H, 2-H), 3.76* (dt, *J* = 13.7/7.8 Hz, 0.2H, $NCH_2CH_2CH_2CH_3$), 3.81* (dd, *J* = 5.8/1.8 Hz, 0.2H, 5-H), 3.85 (dd, *J* = 5.3/2.6 Hz, 0.8H, 5-H), 4.07 (d, *J* = 3.4 Hz, 0.8H, 1-H), 4.17* (d, *J* = 1.2 Hz, 0.2H, 1-H), 4.42 (d, *J* = 14.6 Hz, 0.8H, NCH_2Ph), 4.45* (d, *J* = 14.6 Hz, 0.2H, NCH_2Ph), 4.57* (d, *J* = 11.6 Hz, 0.2H, OCH_2Ph), 4.60 (d, *J* = 11.9 Hz, 0.8H, OCH_2Ph), 4.61* (d, *J* = 14.3 Hz, 0.2H, NCH_2Ph), 4.63* (d, *J* = 11.9 Hz, 0.2H, OCH_2Ph), 4.73 (d, *J* = 12.2 Hz, 0.8H, OCH_2Ph), 4.82 (d, *J* = 14.3 Hz, 0.8H, NCH_2Ph), 7.20–7.42 (m, 10H, arom. H). * = Signals of the minor diastereomer.

*6.1.17. (1S,2S,5S)-6-Benzyl-2-benzyloxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2S)-**11c**) and (1S,2R,5S)-6-benzyl-2-benzyloxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione ((2R)-**11c**)*

NaH dispersion (80% in oil, 414 mg) was washed with petroleum ether and subsequently (ca. 330 mg, 13.7 mmol) suspended in THF (20 mL) at 0 °C. Then a solution of (2*S*)-**9c**/(2*R*)-**9c** (500 mg, 1.37 mmol) in THF (20 mL) was added. After stirring for 10 min at 0 °C a solution of $Bu_4N^+I^-$ (197 mg, 0.5 mmol) and benzyl bromide (0.8 mL, 6.9 mmol) in THF (4 mL) was added and the mixture was stirred for 15 min at 0 °C and for 16 h at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (80 mL) and the organic layer was washed with 0.5 M NaOH (50 mL), 0.5 M HCl (50 mL) and brine (mL). The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was purified by fc (3 cm, petroleum ether:ethyl acetate = 1:1, 20 mL, R_f = 0.31–0.34 with tailing). Colorless oil, yield 378 mg (61%). According to the ^{1}H NMR spectrum the ratio of diastereomers (2*S*)-**11c**:(2*R*)-**11c** = 23:77. $[\alpha]_{589}^{23}$ = +98.7 (23:77 mixture of diastereomers, *c* = 0.68, CH_2Cl_2). $C_{29}H_{30}N_2O_3$ (454.2). HR-MS: Calcd. 454.225643 found 454.225684 (+0.1 ppm). MS (EI): *m/z* (%) = 454 (M, 12), 363 ($M - CH_2Ph$, 62), 348 ($M - CH_3CH_2Ph$, 26), 257 (348-CH_2Ph, 4), 227 ($M - CH_2Ph - CH_3CH_2OCH_2Ph$, 37). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3060, 3029 (w, $\nu_{CH\ arom.}$), 2935, 2866 (m, $\nu_{CH\ aliph.}$), 1678 (s, $\nu_{C=O,\ tert.\ amides}$), 1251, 1082 (m, ν_{COC}), 733, 700 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.23–1.36* (m, 0.2H, 4-H), 1.49–1.72 (m, 3× 0.8H, 4-H, 3-H), 1.75–1.89 (m, 1H, 3-H), 1.90–2.02* (m, 2× 0.2H, 3-H, 4-H), 2.81 (t broad, *J* = 7.9 Hz, 2× 0.8H, NCH_2CH_2Ph), 2.87–2.95* (m, 2× 0.2H, NCH_2CH_2Ph), 3.25 (ddd, *J* = 13.9/7.9/6.1 Hz, 0.8H, NCH_2CH_2Ph), 3.33–3.40 (m, 0.8H, 2-H), 3.41–3.48* (m, 0.2H, NCH_2CH_2Ph), 3.70–3.88 (m, 2H, 5-H, NCH_2CH_2Ph (0.8H), 2-H (0.2H)), 4.00* (ddd, *J* = 13.7/8.1/7.0 Hz, 0.2H, NCH_2CH_2Ph), 4.06 (d, *J* = 3.7 Hz, 0.8H, 1-H), 4.11* (d, *J* = 1.2 Hz, 0.2H, 1-H), 4.37* (d, *J* = 14.6 Hz, 0.2H, NCH_2Ph), 4.41 (d, *J* = 14.6 Hz, 0.8H, NCH_2Ph), 4.52 (d, *J* = 11.9 Hz, 0.8H, OCH_2Ph), 4.56* (d, *J* = 11.0 Hz, 0.2H, OCH_2Ph), 4.61* (d, *J* = 11.9 Hz, 0.2H, OCH_2Ph), 4.62* (d, *J* = 15.2 Hz, 0.2H, NCH_2Ph), 4.67 (d, *J* = 11.9 Hz, 0.8H, OCH_2Ph), 4.77 (d, *J* = 14.6 Hz, 0.8H, NCH_2Ph), 7.13–7.44 (m, 15H, arom. H). * = Signals of the minor diastereomer.

*6.1.18. (1R,2R,5S)-6-Benzyl-2-methoxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane ((2R)-**12a**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (3.0 mL, 3.0 mmol) was added to a cold solution of (2*R*)-**10a** (175 mg, 0.61 mmol) in THF (60 mL). After 15 min the mixture was heated to reflux for 90 h. The excess of $LiAlH_4$ was destroyed by careful addition of $Na_2SO_4 \cdot 10H_2O$ (3.6 g), the suspension was heated to reflux for 30 min and filtered. The filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate + 1% ethyldimethylamine, 2 mL, R_f = 0.25). Colorless oil, yield 59 mg (37%). $[\alpha]_{589}^{22}$ = +58.9 (*c* = 0.38, CH_2Cl_2). $C_{16}H_{24}N_2O$ (260.2). HR-MS: Calcd. 260.188863 found 260.188372 (−1.9 ppm). MS (EI): *m/z* (%) = 260 (M, 100), 187 ($M - CH_2CH_2CH_2OCH_3$, 23), 169 ($M - CH_2Ph$, 50), 137 (169-CH_3OH, 15). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3028 (w, $\nu_{CH\ arom.}$), 2937, 2870 (s, $\nu_{CH\ aliph.}$), 2794 (m, ν_{OCH_3/NCH_3}), 1261, 1098 (m, ν_{COC}), 729, 697 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.52 (td broad, *J* = 13.0/5.2 Hz, 1H, 4-H), 1.84–2.05 (m, 3H, 4-H, 3-H), 2.48 (s, 3H, NCH_3), 2.61–2.70 (m, 2H, 1-H, 9-H), 2.80 (dd, *J* = 11.0/3.6 Hz, 1H, 9-H), 2.83 (dd, *J* = 11.6/1.7 Hz, 1H, 7-H), 2.86–2.90 (m, 1H, 5-H), 3.09 (dd, *J* = 11.3/2.1Hz, 1H, 7-H), 3.36 (s, 3H, OCH_3), 3.42 (ddd, *J* = 9.2/7.0/2.4 Hz, 1H, 2-H), 3.68 (d, *J* = 14.0 Hz, 1H, NCH_2Ph), 3.73 (d, *J* = 14.0 Hz, 1H, NCH_2Ph), 7.19–7.44 (m, 5H, arom. H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 26.4 (1C, C-3), 28.2 (1C, C-4), 44.3 (1C, NCH_3), 47.2 (1C, C-7), 53.0 (1C, C-5), 54.0 (1C, C-9), 56.4 (1C, OCH_3), 60.4 (1C, NCH_2Ph), 60.5 (1C, C-1), 84.3 (1C, C-2), 126.7 (1C, arom. CH), 128.1 (2C, arom. CH), 128.3 (2C, arom. CH), 140.0 (1C, arom. C).

*6.1.19. (1S,2S,5S)-6-Benzyl-8-butyl-2-methoxy-6,8-diazabicyclo[3.2.2]nonane ((2S)-**12b**) and (1S,2R,5S)-6-benzyl-8-butyl-2-methoxy-6,8-diazabicyclo[3.2.2]nonane ((2R)-**12b**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (4.0 mL, 4.0 mmol) was added to a cold solution of **10b** (168 mg, 0.51 mmol) in THF (40 mL). The mixture was stirred for 30 min at 0 °C and then it was heated to reflux for 140 h. After careful addition of 3 M NaOH (2 mL) and H_2O (2 mL) the mixture was heated to reflux for 15 min. It was filtered, the filtrate was concentrated in vacuo, the residue was dissolved in ethyl acetate (80 mL) and H_2O (50 ml), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate:acetone = 8:2, 2 mL, R_f = 0.51*/0.34 with tailing). Pale yellow oil, yield 73 mg (47.4%). According to the ^{1}H NMR spectrum the ratio of diastereomers (2*S*)-**12b**:(2*R*)-**12b** = 25:75. $[\alpha]_{589}^{20} = +35.3$ (25:75 mixture of diastereomers, $c = 0.52$, CH_2Cl_2). $C_{19}H_{30}N_2O$ (302.5). Calcd. C 75.45 H 10.00 N 9.26 found C 75.25 H 9.83 N 9.56. MS (EI): *m/z* (%) = 302 (M, 100), 259 (M − $CH_2CH_2CH_3$, 6), 229 (M − $H_2NCH_2CH_2CH_2CH_3$, 23), 211 (M − CH_2Ph, 90). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3027 (w, $\nu_{CH\ arom.}$), 2927, 2870, 2804 (s, $\nu_{CH\ aliph.}$), 1149, 1100 (m, ν_{COC}), 730, 698 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 0.91* (t, J = 7.1 Hz, 3× 0.25H, $CH_2CH_2CH_2CH_3$), 0.93 (t, J = 7.2 Hz, 3× 0.75H, $NCH_2CH_2CH_2CH_3$), 1.25−1.60 (m, 4.75H, $NCH_2CH_2CH_2CH_3$ (4H), 4-H (0.75H)), 1.65−1.73* (m, 2× 0.25H, 4-H), 1.78−2.01 (m, 2.75H, 3-H (2H), 4-H (0.75H)), 2.50−2.66 (m, 2.75H, $NCH_2CH_2CH_2CH_3$ (2H), 9-H (0.75H)), 2.68−2.96 (m, 4.5H, 7-H (0.75H, 2× 0.25H), 9-H (0.75H, 2× 0.25H), 1-H (1H), 5-H (1H)), 3.10 (dd, J = 12.7/3.5 Hz, 0.75H, 7-H), 3.31* (s, 3× 0.25H, OCH_3), 3.36 (s, 3× 0.75H, OCH_3), 3.32−3.40 (m, 0.75H, 2-H), 3.52* (q, J = 5.2 Hz, 0.25H, 2-H), 3.64−3.74 (m, 2H, NCH_2Ph (2H)), 7.18−7.39 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 14.0 (1C, $NCH_2CH_2CH_2CH_3$), 20.4 (1C, $NCH_2CH_2CH_2CH_3$), 26.0* (0.25C, C-3), 26.6 (0.75C, C-3), 28.4 (0.75C, C-4), 30.2 (0.75C, $NCH_2CH_2CH_2CH_3$), 30.5* (0.25C, $NCH_2CH_2CH_2CH_3$), 31.7* (0.25C, C-4), 48.1 (0.75C, C-7), 50.1* (0.25C, C-7), 51.2* (0.25C, C-9), 51.7 (0.75C, C-9), 53.2 (0.75C, C-5), 54.6* (0.25C, C-5), 55.9 (0.75C, OCH_3), 56.4* (0.25C, OCH_3), 56.6 (0.75C, $NCH_2CH_2CH_2CH_3$), 57.2* (0.25C, $NCH_2CH_2CH_2CH_3$), 58.1 (0.75C, C-1), 60.4* (0.25C, C-1), 60.6 (0.75C, NCH_2Ph), 61.1* (0.25C, NCH_2Ph), 85.2 (0.75C, C-2), 86.0* (0.25H, C-2), 126.6 (0.75C, arom. CH), 126.7* (0.25C, arom. CH), 128.1 (2C, arom. CH), 128.3 (2× 0.75C, arom. CH), 128.6* (2× 0.25C, arom. CH), 139.9* (0.25C, arom. C), 140.2 (0.75C, arom. C). * = Signals of the minor diastereomer.

*6.1.20. (1R,2S,5S)-6-Benzyl-2-methoxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane ((2S)-**12c**) and (1R,2R,5S)-6-benzyl-2-methoxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane ((2R)-**12c**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (1.5 mL, 1.5 mmol) was added to a cold solution of **10c** (136 mg, 0.36 mmol) in THF (30 mL). The mixture was stirred for 15 min at 0 °C and then it was heated to reflux for 75 h. After careful addition of 3 M NaOH (1 mL) and H_2O (1 mL) the mixture was heated to reflux for 15 min. It was filtered and the filtrate was concentrated in vacuo. Pale yellow oil, yield 124 mg (98%), R_f = 0.57*/0.48 ethyl acetate:acetone = 8:2, with tailing. According to the ^{1}H NMR spectrum the ratio of diastereomers (2*S*)-**12c**:(2*R*)-**12c** = 23:77. $[\alpha]_{589}^{20} = +20.3$ (23:77 mixture of diastereomers, $c = 0.67$, CH_2Cl_2). $C_{23}H_{30}N_2O$ (350.2). HR-MS: Calcd. 350.235813 found 350.236364 (+1.6 ppm). MS (EI): *m/z* (%) = 350 (M, 34), 259 (M − CH_2Ph, 100), 168 (M − 2× CH_2Ph, 6). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3060, 3026 (w, $\nu_{CH\ arom.}$), 2927 (s, $\nu_{CH\ aliph.}$), 2807 (m, ν_{OCH3}), 1255 (m, ν_{COC}), 1096 (s, ν_{COC}), 731, 699 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.48−1.60 (td broad, J = 12.4/5.8 Hz, 0.8H, 4-H), 1.65−1.77* (m, 2× 0.2H, 4-H), 1.82−2.05 (m, 2.8H, 4-H (0.8H), 3-H (2H)), 2.71 (dd, J = 10.1/2.7 Hz, 0.8H, 9-H), 2.76−2.94 (m, 7.4H, NCH_2CH_2Ph (4H), 7-H (1.2H), 5-H, 1-H (0.8H), 9-H (2× 0.2H)), 2.98 (dd, J = 10.1/2.7 Hz, 0.8H, 9-H), 2.99−3.05* (m, 0.2H, 1-H), 3.16 (dd, J = 14.0/4.5 Hz, 0.8H, 7-H), 3.34* (s, 3× 0.2H, OCH_3), 3.37 (s, 3× 0.8H, OCH_3), 3.33−3.41 (m, 0.8H, 2-H), 3.52−3.61* (m, 0.2H, 2-H), 3.65−3.78 (m, 2H, NCH_2Ph), 7.17−7.44 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 25.9* (0.2C, C-3), 26.5 (0.8C, C-3), 28.3 (0.8C, C-4), 31.3* (0.2C, C-4), 34.8 (0.8C, NCH_2CH_2Ph), 35.1* (0.2C, NCH_2CH_2Ph), 48.4 (0.8C, C-7), 50.3* (0.2C, C-7), 51.4* (0.2C, C-9), 51.7 (0.8C, C-9), 53.2 (0.8C, C-5), 54.5* (0.2C, C-5), 56.0* (0.2C, OCH_3), 56.4 (0.8C, OCH_3), 58.5 (0.8C, C-1), 58.8 (0.8C, NCH_2CH_2Ph), 59.4* (0.2C, NCH_2CH_2Ph), 60.5 (1C, NCH_2Ph), 61.0* (0.2C, C-1), 84.8 (0.8C, C-2), 85.9* (0.2C, C-2), 125.8* (0.2C, arom. CH), 125.9 (0.8C, arom. CH), 126.7 (0.8C, arom. CH), 126.8* (0.2C, arom. CH), 128.1 (2C, arom. CH), 128.3 (2× 0.8C + 2C, arom. CH), 128.6* (2× 0.2C, arom. CH), 128.7 (2× 0.8C, arom. CH), 128.8* (2× 0.2C, arom. CH), 139.7* (0.2C, arom. C), 140.0 (0.8C, arom. C), 140.5 (0.8C, arom. C), 140.8* (0.2C, arom. C). * = Signals of the minor diastereomer.

*6.1.21. (1R,2R,5S)-6-Benzyl-2-benzyloxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane ((2R)-**13a**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (2.5 mL, 2.5 mmol) was added to a cold solution of (2*R*)-**11a** (171 mg, 0.47 mmol) in THF (40 mL). The mixture was stirred for 10 min at 0 °C and then it was heated to reflux for 50 h. After careful addition of $Na_2SO_4 \cdot 10H_2O$ (1.5 g) the mixture was heated to reflux for 20 min. It was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, petroleum ether:ethyl acetate = 8:2 + 1% ethyldimethylamine, 2 mL, R_f = 0.22). Colorless oil, yield 100 mg (63%). $[\alpha]_{589}^{22} = +54.6$ ($c = 0.67$, CH_2Cl_2). $C_{22}H_{28}N_2O$ (336.2). HR-MS: Calcd. 336.220163 found 336.220322 (+0.5 ppm). MS (EI): *m/z* (%) = 336 (M, 16), 245 (M − CH_2Ph, 10), 187 (M − $CH_2CH_2CH_2OCH_2Ph$, 12), 154 (M − 2× CH_2Ph, 67). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3061, 3028 (w, $\nu_{CH\ arom.}$), 2926, 2867 (s, $\nu_{CH\ aliph.}$), 2791 (m, ν_{NCH3}),

1261, 1072 (m, ν_{COC}), 732, 697 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (td, $J = 12.8/5.2$ Hz, 1H, 4-H), 1.82–1.94 (m, 1H, 4-H), 1.95–2.12 (m, 2H, 3-H), 2.43 (s, 3H, NCH_3), 2.60–2.68 (m, 2H, 1-H, 9-H), 2.78–2.85 (m, 3H, 5-H, 7-H, 9-H), 3.18 (dd, $J = 11.3/1.8$ Hz, 1H, 7-H), 3.63 (ddd, $J = 9.5/7.2/2.4$ Hz, 1H, 2-H), 3.68 (d, $J = 14.9$ Hz, 1H, NCH_2Ph), 3.73 (d, $J = 14.9$ Hz, 1H, NCH_2Ph), 4.53 (d, $J = 11.9$ Hz, 1H, OCH_2Ph), 4.59 (d, $J = 11.9$ Hz, 1H, OCH_2Ph), 7.18–7.42 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): $\delta = 26.8$ (1C, C-3), 28.3 (1C, C-4), 44.3 (1C, NCH_3), 47.4 (1C, C-7), 53.0 (1C, C-5), 54.0 (1C, C-9), 60.5 (1C, NCH_2Ph), 61.0 (1C, C-1), 70.7 (1C, OCH_2Ph), 82.1 (1C, C-2), 126.7 (1C, arom. CH), 127.4 (1C, arom. CH), 127.5 (2C, arom. CH), 128.1 (2C, arom. CH), 128.3 (2C, arom. CH), 128.4 (2C, arom. CH), 139.1 (1C, arom. C), 140.1 (1C, arom. C).

*6.1.22. (1R,2S,5S)-6-Benzyl-2-benzyloxy-8-butyl-6,8-diazabicyclo[3.2.2]nonane ((2S)-**13b**) and (1R,2R,5S)-6-benzyl-2-benzyloxy-8-butyl-6,8-diazabicyclo[3.2.2]nonane ((2R)-**13b**) and (1R,2S,5S)-6-benzyl-8-butyl-6,8-diazabicyclo[3.2.2]nonane-2-ol ((2S)-**8b**) and (1R,2R,5S)-6-benzyl-8-butyl-6,8-diazabicyclo[3.2.2]nonane-2-ol ((2R)-**8b**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (4.0 mL, 4.0 mmol) was added to a cold solution of **11b** containing small amounts of **9b** (208 mg, 0.51 mmol in THF (40 mL). The mixture was stirred for 30 min at 0 °C and then it was heated to reflux for 140 h. After careful addition of 3 M NaOH (2 mL) and H_2O (2 mL) the mixture was heated to reflux for 15 min. It was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate, 2 mL).

Compound **13b** ($R_f = 0.64$*/0.53 with tailing): colorless oil, yield 47 mg (24%). According to the ^{1}H NMR spectrum the ratio of (2*S*)-**13b**:(2*R*)-**13b** = 36:64. $[\alpha]_{589}^{20} = +25.0$ (36:64 mixture of diastereomers, $c = 0.51$, CH_2Cl_2). $C_{25}H_{34}N_2O$ (378.3). HR-MS: Calcd. 378.267113 found 378.266927 (−0.5 ppm). MS (EI): *m/z* (%) = 378 (M, 90), 287 (M − CH_2Ph, 35), 229 (287-$CH_3CH_2CH_2CH_3$, 11), 196 (M − 2× CH_2Ph, 100). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3028 (w, $\nu_{CH\ arom.}$), 2927, 2867, 2800 (m, $\nu_{CH\ aliph.}$), 1072 (s, ν_{COC}), 733, 698 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 0.92$ (t broad, $J = 7.0$ Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.25–1.58 (m, 4.6H, $NCH_2CH_2CH_2CH_3$ (4H), 4-H (0.6H)), 1.60–1.78* (m, 2× 0.4H, 4-H), 1.80–2.14 (m, 2.6H, 3-H (2H), 4-H (0.6H)), 2.50–2.72 (m, 3H, $NCH_2CH_2CH_2CH_3$ (2H), 7-H (0.4H), 9-H (0.6H)), 2.72–3.00 (m, 4.4H, 7-H (1H), 9-H (0.6H, 2× 0.4H), 1-H (1H), 5-H (1H)), 3.22 (dd, $J = 12.5/3.7$ Hz, 0.6H, 7-H), 3.56 (ddd, $J = 9.3/7.2/1.5$ Hz, 0.6H, 2-H), 3.66* (d, $J = 13.4$ Hz, 0.4H, NCH_2Ph), 3.68 (d, $J = 14.9$ Hz, 0.6H, NCH_2Ph), 3.72* (d, $J = 13.3$ Hz, 0.4H, NCH_2Ph), 3.73 (d, $J = 14.9$ Hz, 0.6H, NCH_2Ph), 3.76* (q, $J = 5.0$ Hz, 0.4H, 2-H), 4.53* (s, 2× 0.4H, OCH_2Ph), 4.55 (d, $J = 11.9$ Hz, 0.6H, OCH_2Ph), 4.60 (d, $J = 11.9$ Hz, 0.6H, OCH_2Ph), 7.18–7.39 (m, 10H, arom. H). ^{13}C NMR ($CDCl_3$): $\delta = 14.1$ (1C, $NCH_2CH_2CH_2CH_3$), 20.4 (1C, $NCH_2CH_2CH_2CH_3$), 26.5* (0.4C, C-3), 26.9 (0.6C, C-3), 28.5 (0.6C, C-4), 30.2 (0.6C, $NCH_2CH_2CH_2CH_3$), 30.6* (0.4C, $NCH_2CH_2CH_2CH_3$), 31.6* (0.4C, C-4), 48.3 (0.6C, C-7), 50.1* (0.4C, C-7), 51.3* (0.4C, C-9), 51.8 (0.6C, C-9), 53.2 (0.6C, C-5), 54.6* (0.4C, C-5), 56.5 (0.6C, $NCH_2CH_2CH_2CH_3$), 56.9* (0.4C, $NCH_2CH_2CH_2CH_3$), 58.7 (0.6C, C-1), 60.6 (0.6C, NCH_2Ph), 60.7* (0.4C, NCH_2Ph), 61.0* (0.4C, C-1), 70.0* (0.4C, OCH_2Ph), 70.7 (0.6C, OCH_2Ph), 82.9* (0.4C, C-2), 83.9 (0.6H, C-2), 127.3 (2C, arom. CH), 127.5 (1C, arom. CH), 128.1 (2C, arom. CH), 128.2 (1C, arom. CH), 128.3 (4C, arom. CH), 139.2 (0.6C, arom. $C_{benzyl\ ether}$), 139.5* (0.4C, arom. $C_{benzyl\ ether}$), 139.9* (0.4 C, arom. $C_{benzylamine}$), 140.3 (0.6C, arom. $C_{benzylamine}$). * = Signals of the minor diastereomer.

Compound **8b** ($R_f = 0.22$*/0.19 with tailing): pale yellow oil, yield 58 mg (34%). According to the ^{1}H NMR spectrum the ratio of (2*S*)-**8b**:(2*R*)-**8b** = 23:77. $[\alpha]_{589}^{21} = +29.9$ (23:77 mixture of diastereomers, $c = 0.46$, CH_2Cl_2). $C_{18}H_{28}N_2O$ (288.2). HR-MS: Calcd. 288.220163 found 288.219629 (−1.9 ppm). MS (EI): *m/z* (%) = 288 (M, 36), 245 (M − $CH_2CH_2CH_3$, 9), 229 (M − $CH_2CH_2CH_2OH$, 28), 197 (M − CH_2Ph, 84), 179 (197-H_2O, 72). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3369 (m, ν_{OH}), 3028 (w, $\nu_{CH\ arom.}$), 2929, 2870, 2802 (m, $\nu_{CH\ aliph.}$), 1145, 1053 (m, ν_{CO}), 732, 698 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (t, $J = 7.0$ Hz, 3× 0.8H, $NCH_2CH_2CH_2CH_3$), 0.93 (t, $J = 7.0$ Hz, 3× 0.2H, $NCH_2CH_2CH_2CH_3$), 1.24–1.53 (m, 5H, $NCH_2CH_2CH_2CH_3$ (4H), CHO*H* (1H)), 1.54–1.68 (m, 1.2H, 4-H (1H), 3-H (0.2H)), 1.71–1.88 (m, 1.8H, 3-H (0.8H), 4-H (1H)), 2.04–2.19 (m, 1H, 3-H), 2.51 (t, $J = 7.2$ Hz, 2× 0.8H, $NCH_2CH_2CH_2CH_3$), 2.54* (t, $J = 7.0$ Hz, 2× 0.2H, $NCH_2CH_2CH_2CH_3$), 2.65–2.94 (m, 5.2H, 9-H (2H), 7-H (0.8H), 7-H (2× 0.2H), 5-H (1H), 1-H (1H)), 3.09 (dd, $J = 11.0/2.1$ Hz, 0.8H, 7-H), 3.67 (d, $J = 13.4$ Hz, 1H, NCH_2Ph), 3.72 (d, $J = 13.4$ Hz, 1H, NCH_2Ph), 3.79* (t broad, $J = 5.0$ Hz, 0.2H, 2-H), 3.97 (dt, $J = 7.0/5.2$ Hz, 0.8H, 2-H), 7.19–7.37 (m, 5H, arom. H). * = Signals of the minor diastereomer.

*6.1.23. (1R,2S,5S)-6-Benzyl-2-benzyloxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane ((2S)-**13c**) and (1R,2R,5S)-6-benzyl-2-benzyloxy-8-(2-phenylethyl)-6,8-diazabicyclo[3.2.2]nonane (((2R)-**13c**)*

Under N_2 a solution of 1 M $LiAlH_4$ in THF (3.5 mL, 3.5 mmol) was added to a cold solution of **11c** (316 mg, 0.70 mmol) in THF (60 mL). The mixture was stirred for 15 min at 0 °C and then it was heated to reflux for 65 h. After careful addition of $Na_2SO_4 \cdot 10H_2O$ (4 g) the mixture was heated to reflux for 30 min. It was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate, 2 mL, $R_f = 0.65$*/0.58 with tailing). Pale yellow oil, yield 219 mg (74%). According to the ^{1}H NMR spectrum the ratio of diastereomers (2*S*)-**13c**:(2*R*)-**13c** = 22:78. $[\alpha]_{589}^{20} = +25.9$ (22:78 mixture of diastereomers, $c = 0.51$, CH_2Cl_2). $C_{29}H_{34}N_2O$ (426.3). HR-MS: Calcd. 426.267113 found 426.267320 (+0.5 ppm). MS (EI): *m/z* (%) = 426 (M, 53), 335 (M − CH_2Ph, 93), 244 (M − 2× CH_2Ph, 55), 229 (335-CH_3CH_2Ph, 12), 153 (M − 3× CH_2Ph, 56). IR (film): $\tilde{\nu}$

[cm^{-1}] = 3061, 3027 (w, $\nu_{CH\ arom.}$), 2927, 2801 (m, $\nu_{CH\ aliph.}$), 1072 (s, ν_{COC}), 732, 697 (s, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.49 (td, J = 12.5/4.7 Hz, 0.8H, 4-H), 1.62–1.75* (m, 2× 0.2H, 4-H), 1.80–2.12 (m, 2.8H, 3-H (2H), 4-H (0.8H)), 2.62–3.08 (m, 9.2H, NCH_2CH_2Ph (4H), 9-H (2H), 7-H (1.2H), 5-H, 1-H), 3.23 (dd, J = 13.7/4.2 Hz, 0.8H, 7-H), 3.54 (t broad, J = 7.3 Hz, 0.8H, 2-H), 3.66–3.80 (m, 2.2H, NCH_2Ph (2H), 2-H (0.2H)), 4.47–4.60* (m, 2× 0.2H, OCH_2Ph), 4.51 (d, J = 12.1 Hz, 0.8H, OCH_2Ph), 4.58 (d, J = 12.1 Hz, 0.8H, OCH_2Ph), 7.14–7.41 (m, 15H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 26.4* (0.2C, C-3), 26.9 (0.8C, C-3), 28.4 (0.8C, C-4), 31.3* (0.2C, C-4), 34.7 (0.8C, NCH_2CH_2Ph), 35.1* (0.2C, NCH_2CH_2Ph), 48.6 (0.8C, C-7), 50.4* (0.2C, C-7), 51.5* (0.2C, C-9), 51.7 (0.8C, C-9), 53.2 (0.8C, C-5), 54.4* (0.2C, C-5), 58.7 (0.8C, NCH_2CH_2Ph), 59.1 (0.8C, C-1), 59.2* (0.2C, NCH_2CH_2Ph), 60.5 (0.8C, NCH_2Ph), 60.9* (2× 0.2C, C-1, NCH_2Ph), 70.1* (0.2C, OCH_2Ph), 70.8 (0.8C, OCH_2Ph), 82.7 (0.8C, C-2), 84.0* (0.2C, C-2), 125.8* (0.2C, arom. CH), 125.9 (0.8C, arom. CH), 126.7* (0.2C, arom. CH), 127.2* (0.2C, arom. CH), 127.4 (2× 0.8C, arom. CH), 127.5 (2× 0.8C, arom. CH), 128.2 (2C, arom. CH), 128.3 (4.4 C, arom. CH (4× 0.8C, 6× 0.2C)), 128.4 (2C, arom. CH), 128.7 (2× 0.8C, arom. CH), 128.8* (2× 0.2C, arom. CH), 139.2 (0.8C, arom. C), 139.4* (0.2C, arom. C), 140.1 (1C, arom. C), 140.5 (0.8C, arom. C), 140.9* (0.2C, arom. C). * = Signals of the minor diastereomer.

6.1.24. (1S,5S)-6-Benzyl-2,2-dimethoxy-8-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (**14a**)

A solution of **6a** (4.52 g, 12.0 mmol) and *p*-toluenesulfonic acid (450 mg, 2.4 mmol) in THF (80 mL) and CH_3OH (80 ml) was stirred for 16 h at room temperature. After evaporation of the solvent the residue was purified by fc (6 cm, ethyl acetate, 40 mL, R_f = 0.41). The isolated product (yield 2.19 g, 63%) was an inseparable mixture of ketone **7a** and dimethyl acetal **14a**. In order to get the pure dimethyl acetal **14a** the residue was dissolved in THF (80 mL) and H_2O (80 mL), $NaBH_4$ (1.47 g, 38.9 mmol) was added and the mixture was stirred for 16 h at room temperature. The organic part of the solvent was removed in vacuo, the aqueous layer was extracted with ethyl acetate (100 mL), the organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue (mixture of **14a** and **9a**) was purified by fc (6 cm, ethyl acetate:acetone = 1:1, 30 mL).

Compound **14a** (R_f = 0.58): colorless oil, yield 0.83 g (22%). $[\alpha]_{589}^{23}$ = +73.9 (c = 0.65, CH_2Cl_2). $C_{17}H_{22}N_2O_4$ (318.4). Calcd. C 64.14 H 6.97 N 8.79 found C 63.85 H 7.03 N 8.37. MS (EI): m/z (%) = 318 (M, 28), 303 (M − CH_3, 4), 287 (M − OCH_3, 12), 217 (M − CH_2CHC$(OCH_3)_2$, 17). IR (film): $\tilde{\nu}$ [cm^{-1}] = 2943 (m, $\nu_{CH\ aliph.}$), 2837 (w, ν_{OCH_3/NCH_3}), 1683 (s, $\nu_{C=O,\ tert.\ amides}$), 1260, 1104, 1041 (m, ν_{COC}), 736, 702 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.43 (dddd, J = 13.8/11.5/5.1/2.1 Hz, 1H, 4-H), 1.65 (ddd, J = 14.1/11.6/5.2 Hz, 1H, 3-H), 1.77–1.87 (m, 1H, 4-H), 1.92 (dt, J = 14.1/4.6 Hz, 1H, 3-H), 3.00 (s, 3H, NCH_3), 3.21 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.81 (dd, J = 5.6/2.0 Hz, 1H, 5-H), 4.06 (s, 1H, 1-H), 4.42 (d, J = 14.6 Hz, 1H, NCH_2Ph), 4.66 (d, J = 14.9 Hz, 1H, NCH_2Ph), 7.21–7.35 (m, 5H, arom. H).

(2*S*)-**9a** (R_f = 0.46): Colorless solid, yield 0.37 g (11%).

(2*R*)-**9a** (R_f = 0.39): Colorless solid, yield 0.99 g (30%).

6.1.25. (1R,5S)-6-Benzyl-8-methyl-6,8-diazabicyclo[3.2.2]nonane-2-one dimethyl acetal (**15a**)

Under N_2 a solution of 1 M $LiAlH_4$ in Et_2O (1.5 mL, 1.5 mmol) was added to a cold solution of **14a** (83 mg, 0.26 mmol) in THF (20 mL). The mixture was stirred for 30 min at 0 °C and then it was heated to reflux for 60 h. After careful addition of $Na_2SO_4 \cdot 10H_2O$ (2.5 g) the mixture was heated to reflux for 30 min. It was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (2 cm, ethyl acetate + 1% $NH_{3\ conc.}$, 2 mL, R_f = 0.45). Colorless solid, yield 55 mg (73%), mp 60–61 °C. $[\alpha]_{589}^{23}$ = +31.9 (c = 0.39, CH_2Cl_2). $C_{17}H_{26}N_2O_2$ (290.2). HR-MS: Calcd. 290.199428 found 290.198867 (−1.9 ppm). MS (EI): m/z (%) = 290 (M, 57), 259 (M − OCH_3, 14), 184 (M − $NHCH_2Ph$, 100), 167 (M − CH_3OH−CH_2Ph, 23). IR (film): $\tilde{\nu}$ [cm^{-1}] = 3026 (w, $\nu_{CH\ arom.}$), 2935 (s, $\nu_{CH\ aliph.}$), 2794 (m, ν_{OCH_3/NCH_3}), 1104, 1051 (m, ν_{COC}), 731, 698 (m, $\gamma_{monosubst.\ arom.}$). ^{1}H NMR ($CDCl_3$): δ = 1.55–1.68 (m, 1H, 4-H), 1.74–1.90 (m, 2H, 4-H, 3-H), 2.10–2.22 (m, 1H, 3-H), 2.50 (s, 3H, NCH_3), 2.62 (s broad, 1H, 1-H), 2.68–2.75 (m, 1H, 9-H), 2.77–2.88 (m, 3H, 9-H, 7-H, 5-H), 3.03 (dd, J = 10.1/1.5 Hz, 1H, 7-H), 3.23 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.65 (d, J = 13.4 Hz, 1H, NCH_2Ph), 3.72 (d, J = 13.7 Hz, 1H, NCH_2Ph), 7.22–7.36 (m, 5H, arom. H). ^{13}C NMR ($CDCl_3$): δ = 27.3 (1C, C-4), 30.3 (1C, C-3), 44.9 (1C, NCH_3), 47.2 (1C, C-7), 48.1 (1C, OCH_3), 48.4 (1C, OCH_3), 52.5 (1C, C-5), 53.6 (1C, C-9), 60.0 (1C, NCH_2Ph), 61.8 (1C, C-1), 105.0 (1C, C-2), 126.8 (1C, arom. CH), 128.2 (2C, arom. CH), 128.4 (2C, arom. CH), 139.9 (1C, arom. C).

6.2. Receptor binding studies, general

Teflon–glass-homogenizer: Potter®S (B. Braun Biotech International). Rotor/stator homogenizer: Ultraturrax® T25 basic (Ika Labortechnik). Centrifuge: high speed refrigerating centrifuge model J2-HS (Beckman). Filter: Whatman glass fibre filters GF/B, presoaked in 0.5% polyethylenimine (in water) for 2 h at 4 °C before use. Filtration was performed with a Brandel 24-well cell harvester. Scintillation cocktail: Rotiszint eco plus (Roth). Liquid scintillation analyzer: Tri-Carb 2100 TR (Canberra Packard), counting efficiency 66%. All experiments were carried out in triplicates. IC_{50}-values were determined from competition experiments with at least six concentrations of test compounds and were calculated with the curve-fitting program GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. K_i-values were calculated according to Cheng and Prusoff [18]. For compounds with high affinity (low K_i-values) mean values ± SEM from at least three independent experiments are given.

6.3. Investigation of σ_1 receptor affinity

[^{3}H]-(+)-Pentazocine binding to guinea pig brain membrane preparations was performed according to the procedure described in Ref. [14].

Membrane preparation: Thawed guinea pig brains (Dunkin Hartley, Harlan-Sera-Lab) were homogenized with an Ultraturrax (8000 rpm) in 10 volumes of cold 0.32 M sucrose. The homogenate was centrifuged at 1000 g for 10 min at 4 °C. The supernatant was separated and centrifuged at 22,000 g for 20 min at 4 °C. The pellet was resuspended in 10 volumes of buffer (50 mM Tris–HCl, pH 7.4) with an Ultraturrax (8000 rpm), incubated for 30 min at 25 °C and centrifuged at 22,000 g (20 min, 4 °C). The pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford [19] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 2 mg protein/mL.

Performance of the σ_1 assay: The test was performed with the radioligand [ring-1,3-^{3}H]-(+)-pentazocine (1036 GBq/mmol; NEN Life Science Products). The thawed membrane preparation (about 150 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-(+)-pentazocine and buffer (50 mM Tris–HCl, pH 7.4) in a total volume of 500 μL for 150 min at 37 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/B filters using a cell harvester. After washing four times with 2 mL of cold buffer 3 mL of scintillation cocktail were added to the filters. After at least 8 h bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Non-specific binding was determined with 10 μM haloperidol. The K_d-value of [^{3}H]-(+)-pentazocine is 2.9 nM.

6.4. Investigation of σ_2 receptor affinity

σ_2 Receptor affinity was determined using rat liver membranes with [^{3}H]-ditolylguanidine in the presence of 100 nM (+)-pentazocine to mask σ_1-binding sites. The assay was performed according to the procedure described in Ref. [14].

Membrane preparation: One frozen rat liver (Sprague Dawley, Harlan-Sera-Lab) was allowed to thaw slowly on ice. Then it was homogenized with a potter (800 rpm) in 10 volumes of cold buffer (10 mM Tris–HCl/0.32 M sucrose, pH 7.4). The homogenate was centrifuged at 1000 g for 10 min at 4 °C. The supernatant was separated and saved on ice. The pellet was resuspended in 30 mL of cold buffer and centrifuged again. Both supernatants were then centrifuged at 31,000 g for 20 min at 4 °C. The pellet was resuspended in 30 mL of buffer (10 mM Tris–HCl, pH 7.4) by vortexing and gentle potter homogenization. Then it was incubated for 15 min at 25 °C and centrifuged at 31,000 g (20 min, 4 °C). The pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford [19] using bovine serum albumin as standard, and subsequently the preparation was frozen (−83 °C) in 5 mL portions of about 2.5 mg protein/mL.

Performance of the σ_2 assay: The membrane preparation (about 60 μg protein) was incubated with 3 nM [^{3}H]-ditolylguanidine (di-[*p*-ring-^{3}H]-1,3-di-*o*-tolylguanidine, 2220 GBq/mmol; American Radiolabeled Chemicals Inc.) and different concentrations of test compounds in buffer (50 mM Tris–HCl, pH 8.0) in the presence of 100 nM (+)-pentazocine. The total volume was 250 μL. The incubation (120 min, 25 °C) was stopped by addition of 2 mL of ice cold buffer (10 mM Tris–HCl, pH 8.0) followed by rapid filtration through presoaked Whatman GF/B filters using a cell harvester. After washing three times with 2 mL of cold buffer 3 mL of scintillation cocktail were added to the filters. After at least 8 h bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Non-specific binding was determined with 10 μM non-radiolabeled ditolylguanidine. The K_d-value of [^{3}H]-ditolylguanidine is 17.9 nM.

6.5. Investigation of κ receptor affinity

[^{3}H]-U-69593 binding to guinea pig brain membrane preparations was performed according to standard procedure described in Ref. [16].

6.6. Investigation of μ receptor affinity

[^{3}H]-DAMGO binding to guinea pig brain membrane preparations was performed according to standard procedure described in Ref. [16].

6.7. Investigation of NMDA receptor-affinity

[^{3}H]-(+)-MK-801 binding to guinea pig brain membrane preparations was performed according to standard procedure described in Ref. [15].

Acknowledgement

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Wissenschaftliche Gesellschaft Freiburg is gratefully acknowledged. Thanks are also due to the Degussa AG, Janssen-Cilag GmbH, and Bristol-Myers Squibb for donation of chemicals and reference compounds.

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