Bioorganic & Medicinal Chemistry 17 (2009) 777–793

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Relationships between the structure of 6-allyl-6,8-diazabicyclo[3.2.2]nonane derivatives and their σ receptor affinity and cytotoxic activity

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ARTICLE INFO

Article history:
Received 20 August 2008
Revised 12 November 2008
Accepted 15 November 2008
Available online 24 November 2008

Keywords:
Sigma receptor ligands
6,8-Diazabicyclo[3.2.2]nonanes
Cytotoxicity
Structure–activity relationships

ABSTRACT

A series of bridged piperazine derivatives was prepared and the affinity toward σ_1 and σ_2 receptors by means of radioligand binding assays as well as the inhibition of the growth of six human tumor cell lines was investigated. All possible stereoisomers of the 2-hydroxy, 2-methoxy, 2,2-dimethoxy, 2-oxo, and 2-unsubstituted 6,8-diazabicyclo[3.2.2]nonanes were prepared in a chiral pool synthesis starting with (*S*)- and (*R*)-glutamate. A Dieckmann analogous cyclization was the key step in the synthesis of the bicyclic framework. The configuration in position 2 was established by a diastereoselective $LiBH_4$ reduction and subsequent Mitsunobu inversion. Structure–affinity relationships demonstrate that substituents in position 2 decrease σ_1 receptor affinity which might be due to unfavorable interactions with the σ_1 receptor protein. Without a substituent in position 2 high σ_1 affinity was obtained (**23a** ((+)-(1*S*,5*S*)-6-allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane): K_i = 11 nM). Experiments with six human tumor cell lines showed a weak but selective growth inhibition of the human small cell lung cancer cell line A-427 by the methyl ethers ent-**16b** (IC_{50} = 18.9 μM), **21a** (IC_{50} = 16.4 μM), ent-**21a** (IC_{50} = 20.4 μM), and **21b** (IC_{50} = 27.1 μM) and the unsubstituted compounds **23a** and **23b** (42% inhibition at 20 μM).

1. Introduction

Originally it was assumed that the σ receptor belongs to the opioid receptor family.[1] However, since most of the effects caused by activation of σ receptors are not sensitive to the opioid antagonist naloxone, this classification was discarded. Later it became clear that σ receptors represent an own class of haloperidol-sensitive, non-opioid, non-phencyclidine receptors with a characteristic binding profile. This family of receptors is subdivided into σ_1 and σ_2 receptors.[2]

The human σ_1 receptor has been cloned,[3] however cloning of the σ_2 receptor has not yet been reported. The amino acid sequence of the σ_1 receptor displays no similarity to any other known mammalian protein but shows 30% homology to the yeast enzyme sterol Δ^8/Δ^7-isomerase. The cloned receptor is postulated to possess two transmembrane domains[4] and neurosteroids such as progesterone are discussed to be the endogenous ligands for σ_1 receptors.[5] Although the biochemical and physiological role of σ receptors as well as their mechanism of signal transduction are not completely understood so far, they seem to play a crucial role in pathophysiological processes such as psychosis, depression, and uncontrolled cell proliferation. Therefore, high affinity σ_1 and σ_2 receptor ligands could be developed as atypical antipsychotics, antidepressants, and antitumor agents.[6]

The ethylenediamine substructure substituted with different residues at the nitrogen atoms represents a crucial pharmacophoric element of several σ_1 receptor ligands.[7] For example, the piperazine derivative **1** (Fig. 1) which contains the ethylenediamine substructure within the piperazine moiety represents a very potent σ_1 receptor ligand (K_i = 0.47 nM).[8]

In order to reduce the conformational flexibility of the ethylenediamine substructure the piperazine ring of **1** was bridged to obtain diazabicyclo[3.2.2]nonane derivatives like **2a** (K_i = 6.5 nM) and **2b** (K_i = 26 nM) which also bind with high affinity and selectivity to the σ_1 receptor.[9]

In this paper, we wish to report on the synthesis, σ_1 and σ_2 receptor affinity and growth inhibition of human tumor cell lines of a series of *N*-6-allyl substituted bridged piperazines **3** bearing different substituents in position 2. The introduction of the allyl group was stimulated by the prototypical σ receptor ligand (+)-SKF-10,047 which is also substituted by an allyl residue. Furthermore, the *N*-allyl group was envisaged in order to find out whether this group is able to replace bioisosterically the benzyl group of **2a** and **2b**. In addition, the electronic properties of the aromatic residue in position 8 were changed by introduction of a second methoxy group.

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doi:10.1016/j.bmc.2008.11.043

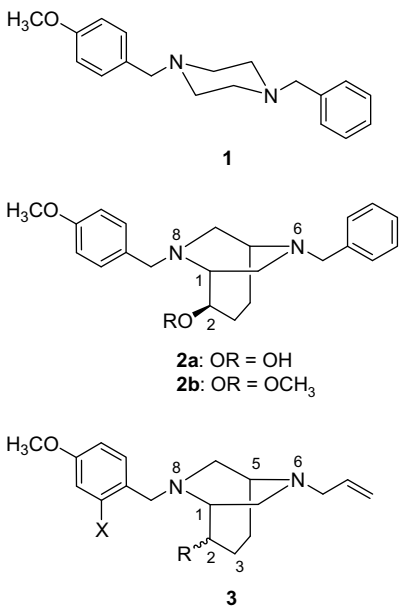


Figure 1. Lead compounds **1** and **2** compared with the structure of the planned ligands **3**.

2. Chemistry

The synthesis of the bicyclic ketone **9a** was performed according to a literature procedure.[10] Its 2,4-dimethoxybenzyl derivative **9b** was synthesized in an analogous manner. In this six step synthesis the proteinogenic amino acid (*S*)-glutamate was first esterified with methanol in the presence of trimethylsilyl chloride to give the hydrochloride of dimethyl glutamate **4**·HCl. Acylation of **4** with chloroacetyl chloride yielded the chloroacetamide **5**, which was subsequently reacted with 4-methoxybenzylamine and 2,4-dimethoxybenzylamine to provide the monocyclic piperazinediones **6a** and **6b**, respectively. The bislactams **6a** and **6b** were then allylated with allyl bromide and NaHMDS to give **7a** and **7b** (Scheme 1).

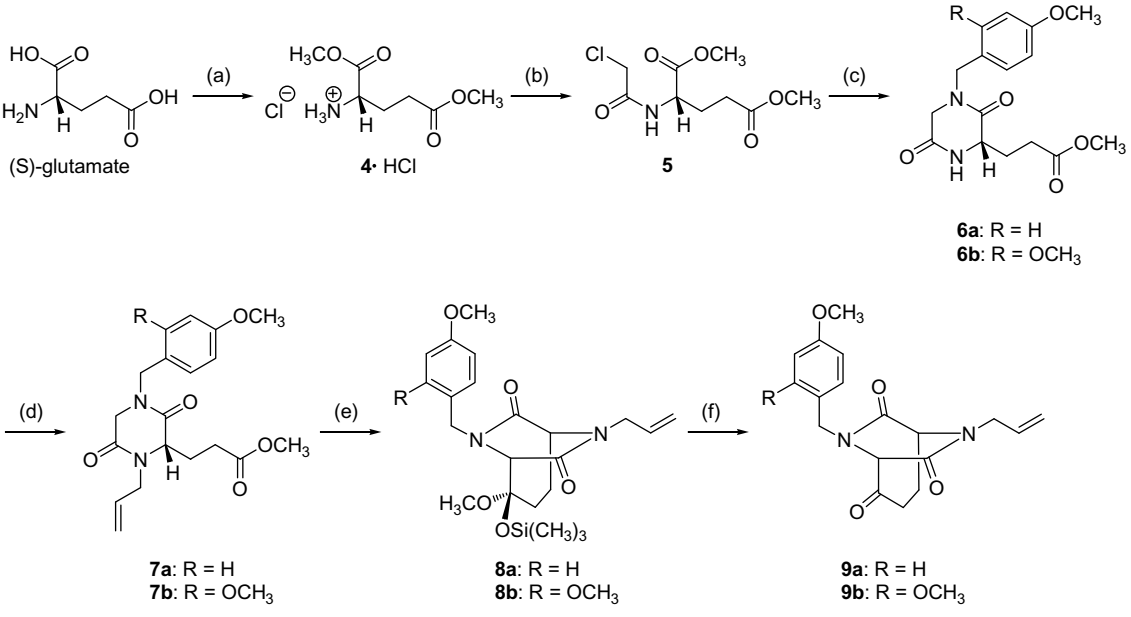
The desired 6,8-diazabicyclo[3.2.2]nonane scaffold was finally obtained by a Dieckmann analogous cyclization using LiHMDS and trapping of the resulting intermediates with chlorotrimethylsilane to form stereoselectively the mixed methyl/silyl acetals **8a** and **8b**, which were carefully hydrolyzed to give the bicyclic ketones **9a** and **9b**.

The bicyclic ketone **9a** was reacted with methanol in the presence of trimethyl orthoformate and *p*-toluenesulfonic acid to give the dimethyl acetal **10**. Both lactam groups of **10** were subsequently reduced with $LiAlH_4$ to yield the basic piperazine derivative **11**. After hydrolysis of the dimethyl acetal **11** the bicyclic ketone **12** was obtained (Scheme 2).

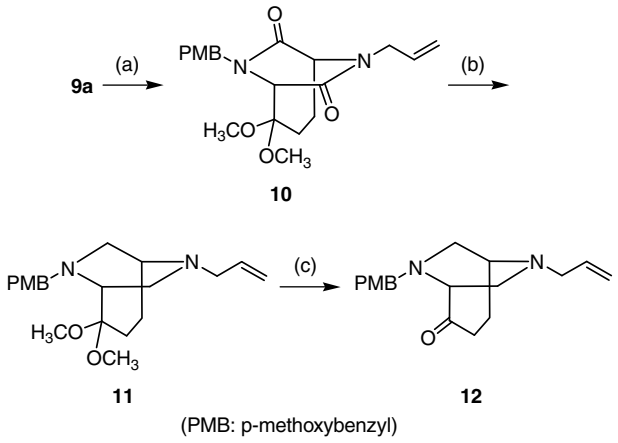
A diastereoselective reduction of the bicyclic ketones **9a** and **9b** with $LiBH_4$ in THF at −78 °C led to the (2*R*)-configured alcohols **13a** and **13b** (de > 90%).[9] The alcohols **13a** and **13b** were transformed into the corresponding methyl ethers **14a** and **14b** with methyl iodide and NaH. Reaction of the bicyclic alcohols **13** and methyl ethers **14** with $LiAlH_4$ led to reduction of both lactam carbonyl moieties to give the bridged piperazines **15** and **16** with a hydroxy and a methoxy group in position 2, respectively (Scheme 3).

The (2*S*)-configured diastereomers of **15** and **16** were obtained after inversion of the (2*R*)-configured alcohols **13** by a Mitsunobu reaction.[11] For this purpose **13a** and **13b** were reacted with 4-nitrobenzoic acid, diisopropyl azodicarboxylate (DIAD), and PPh_3 to yield the (2*S*)-configured 4-nitrobenzoates **17a** and **17b**. Cleavage of the 4-nitrobenzoates **17a** and **17b** with K_2CO_3 in methanol provided the inverted alcohols **18a** and **18b** (Scheme 4). Methylation of the alcohols **18** with methyl iodide and NaH gave the (2*S*)-configured methyl ethers **19**. Reduction of the alcohols **18** and methyl ethers **19** with $LiAlH_4$ resulted in the basic piperazine derivatives with a hydroxy (**20a** and **20b**) and a methoxy moiety (**21a** and **21b**) in position 2.

In order to obtain compounds **23a** and **23b** without a substituent in position 2 the (2*R*)-configured alcohols **13a** and **13b** were transformed into the mesylates **22a** and **22b** with methanesulfonyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP)



Scheme 1. Reagents and conditions: (a) Me_3SiCl, MeOH, rt, 16 h, 98%; (b) $ClCH_2COCl$, CH_2Cl_2, $NaHCO_3$, rt, 16 h, 66%; (c) 4-methoxybenzylamine, NEt_3, H_3CCN, Bu_4NI, reflux, 48 h, 83% (**6a**) or 2,4-dimethoxybenzylamine, NEt_3, H_3CCN, Bu_4NI, reflux, 48 h, 79% (**6b**); (d) NaHMDS, THF, allyl bromide, Bu_4NI, −78 °C, 1 h, rt, 2 h, 53% (**7a**), 59% (**7b**); (e) LiHMDS, THF, −78 °C, 40 min and then M_3SiCl, 82% (**8a**), 79% (**8b**); (f) 2 M HCl, THF, rt, 16 h, 80% (**9a**), 85% (**9b**). The compounds of the **a** series have been published in Ref. 10.



Scheme 2. Reagents and conditions: (a) $HC(OCH_3)_3$, MeOH, *p*-toluenesulfonic acid, reflux, 16 h, 98%; (b) $LiAlH_4$, THF, reflux, 16 h, 20%; (c) 1 M HCl, 3 h, 50% (over 2 steps).

and *N*,*N*-diisopropylethylamine (DIEA). The reaction of the mesylates **22a** and **22b** with $LiAlH_4$ led in addition to the reduction of the lactam carbonyl moieties to the substitution of the mesylate moieties by hydride to give the unsubstituted bridged piperazines **23a** and **23b** (Scheme 5).

The enantiomers of the dimethyl acetal **11**, ketone **12**, alcohols **15** and **20**, methyl ethers **16** and **21**, and 2-unsubstituted compounds **23** were prepared in the same manner, starting from (*R*)-glutamate. Therefore, all possible stereoisomers of the described compounds were available for pharmacological evaluation, respectively.

3. Pharmacological evaluation

3.1. Receptor binding studies

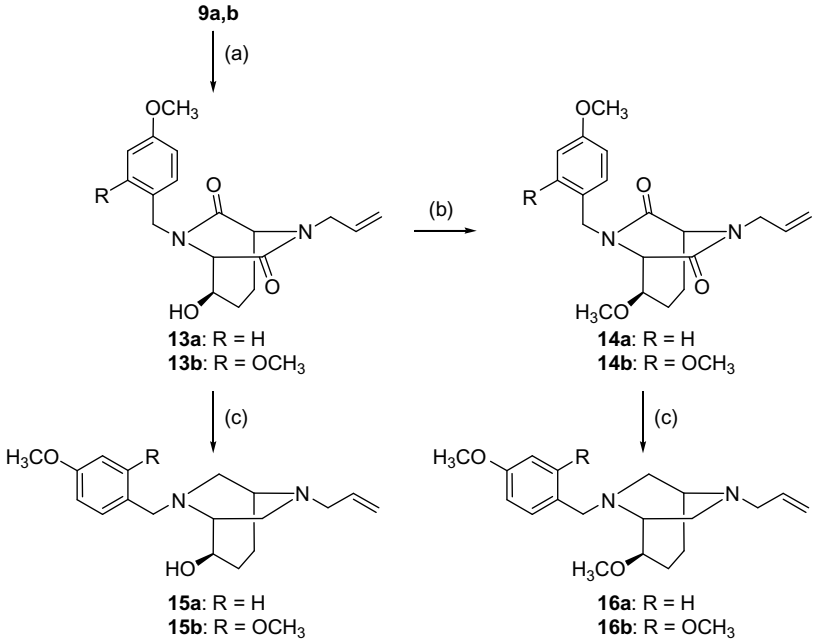
The σ receptor affinities of the synthesized compounds were determined in competition experiments with radioligands. Homogenates of guinea pig brains were used as receptor material in the σ_1 assay and the σ_1 selective ligand [^{3}H]-(+)-pentazocine was employed as radioligand. The non-specific binding was determined in the presence of a large excess of cold (+)-pentazocine. In the σ_2 assay homogenates of rat liver served as source for σ_2 receptors. The non-selective radioligand [^{3}H]-1,3-di(o-tolyl)guanidine was employed in the presence of an excess of non-tritiated (+)-pentazocine for selective occupation of σ_1 receptors. The non-specific binding of the radioligand was determined by performing the σ_2 assay in the presence of an excess of non-tritiated 1,3-di(o-tolyl)guanidine.[9,12,14]

3.2. Results and discussion

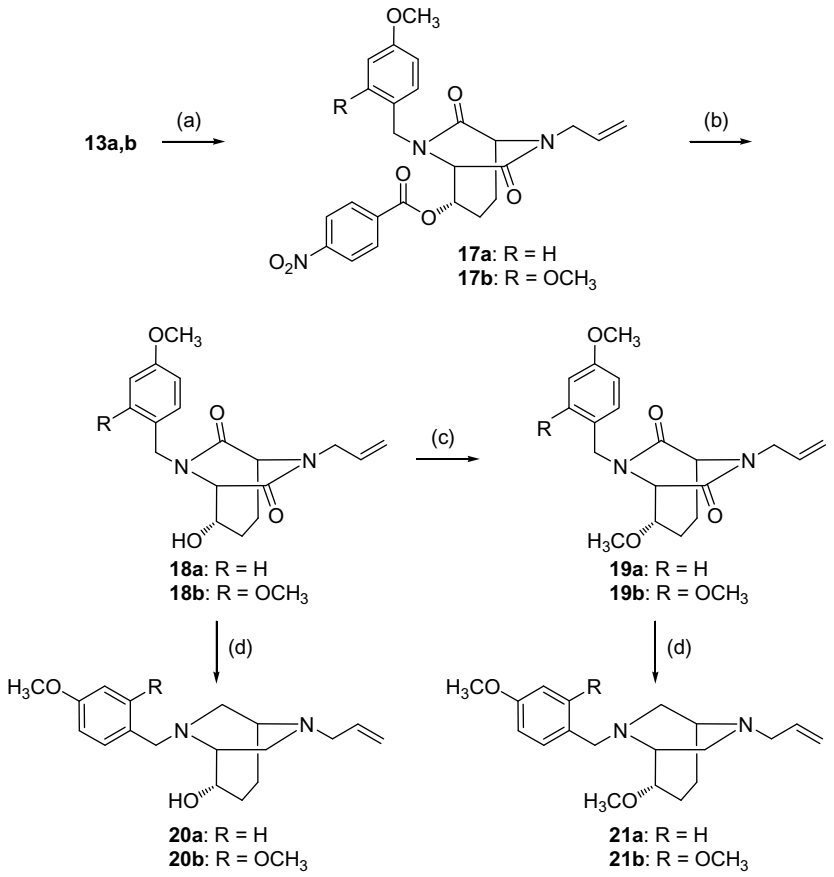
In Table 1, the σ_1 and σ_2 receptor affinity of the synthesized compounds is summarized. Compared to their *N*-6-benzyl counterparts **2a** and **2b**, the bicyclic alcohol **15a** and methyl ether **16a** with an allyl group in position 6 show a more than 100-fold reduced σ_1 receptor affinity. Obviously the allyl moiety is not able to replace bioisosterically the benzyl group. ent-**15a**, which is the most potent σ_1 ligand (K_i = 343 nM) within the series of bicyclic alcohols and methyl ethers, displays a considerable selectivity toward the σ_2 receptor (σ_1:$\sigma_2 \approx 4$).

The dimethyl acetals **11** and ent-**11** as well as the bicyclic ketones **12** and ent-**12** also interact with low affinity with σ_1 receptors. However, removal of the substituent in position 2 (**23**) led to a dramatic increase of the σ_1 affinity. In particular, the (*S*,*S*)-configured 4-methoxybenzyl derivative **23a** displays an affinity toward the σ_1 receptor in the low nanomolar range (K_i = 11 nM). The eudismic ratio (**23a**:ent-**23a**) is 25 and the selectivity against the σ_2 receptor is about 20.

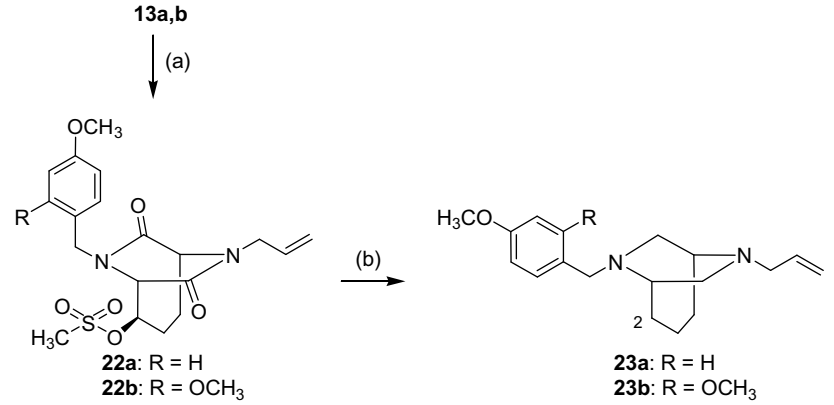
Introduction of a second methoxy moiety in position 2 of the 4-methoxybenzyl residue leads generally to a decreased σ_1 affinity. Typical pairs are ent-**15a** (K_i = 343 nM) and ent-**15b** (K_i = 9670 nM) as well as **23a** (K_i = 11 nM) and **23b** (K_i = 267 nM). In both examples the σ_1 affinity is 20- to 30-fold reduced by the second methoxy group. Obviously, increase of electron density of the N-8 substituent is not tolerated by the σ_1 receptor protein.



Scheme 3. Reagents and conditions: (a) $LiBH_4$, THF, −78 °C, 92% (**13a**), 92% (**13b**); (b) NaH, MeI, THF, rt, 16 h, 89% (**14a**), 77% (**14b**); (c) $LiAlH_4$, THF, reflux, 16 h, 58% (**15a**), 23% (**15b**), 27% (**16a**), 34% (**16b**).



Scheme 4. Reagents and conditions: (a) DIAD, PPh_3, *p*-nitrobenzoic acid, THF, rt, 6 h, 87% (**17a**), 78% (**17b**); (b) MeOH, K_2CO_3, rt, 16 h, 90% (**18a**), 92% (**18b**); (c) NaH, MeI, THF, rt, 16 h, 81% (**19a**), 97% (**19b**); (d) $LiAlH_4$, THF, reflux, 16 h, 35% (**20a**), 20% (**20b**), 55% (**21a**), 25% (**21b**).



Scheme 5. Reagents and conditions: (a) H_3CSO_2Cl, DMAP, DIEA, CH_2Cl_2, rt, 16 h, 96% (**22a**), 88% (**22b**); (b) $LiAlH_4$, THF, reflux, 16 h, 46% (**23a**), 36% (**23b**).

A hypothetical explanation for the surprisingly high σ_1 receptor affinity of **23a** can be deduced from the pharmacophore model, which has been proposed by Glennon et al.[13] According to this model a basic nitrogen atom with two hydrophobic residues in different distances from the nitrogen atom are required for a high σ_1 receptor affinity (Fig. 2).

The synthesized bridged piperazine derivatives can bind either with N-6 or N-8 to the postulated proton donor site of the receptor protein. Fig. 2b shows the situation for the 6,8-diazabicyclo[3.2.2]nonanes derived from (*S*)-glutamate with N-6 binding to the proton donor site. Most of the bicyclic compounds bearing an allyl moiety in position 6 show rather low σ_1 affinity compared to the lead compounds **2a** and **2b** with an *N*-6-benzyl moiety. Obviously the allyl group in position 6 is too small to interact fully with the secondary hydrophobic region (A) of the σ_1 receptor.

On the other hand, when N-8 binds to the proton donor site of the receptor protein (Fig. 2a) unfavorable interactions between the substituent in position 2 and the receptor protein prevent the compounds from binding to the σ_1 receptor with high affinity. This postulated unfavorable interaction between the substituent in position 2 and the σ_1 receptor is supported by the high affinity of the bridged piperazine **23a** (K_i = 11 nM) which does not bear a substituent in position 2.

Table 1
σ_1 and σ_2 receptor affinity of the 6,8-diazabicyclo[3.2.2]nonane derivatives and some reference compounds

Compound	Configuration	C-2 Substituents	K_i ± SEM [nM]	
			σ_1 affinity	σ_2 affinity
2a	(*R*,*R*,*S*)	H, OH	6.5 ± 0.7	806
2b	(*R*,*R*,*S*)	H, OCH_3	26 ± 9	573
11	(*R*,*S*)	OCH3, OCH_3	1250	0%[a]
ent-**11**	(*S*,*R*)	OCH3, OCH_3	588	19%[a]
12	(*R*,*S*)	=O	1600	9100
ent-**12**	(*S*,*R*)	=O	548	1900
15a	(*R*,*R*,*S*)	H, OH	2240	4780
ent-**15a**	(*S*,*S*,*R*)	H, OH	343	1210
15b	(*R*,*R*,*S*)	H, OH	9140	1460
ent-**15b**	(*S*,*S*,*R*)	H, OH	9670	5170
16a	(*R*,*R*,*S*)	H, OCH_3	4030	1690
ent-**16a**	(*S*,*S*,*R*)	H, OCH_3	16,100	1550
16b	(*R*,*R*,*S*)	H, OCH_3	51%[a]	2100
ent-**16b**	(*S*,*S*,*R*)	H, OCH_3	37%[a]	13,500
20a	(*R*,*S*,*S*)	H, OH	23,100 0	%[a]
ent-**20a**	(*S*,*R*,*R*)	H, OH	17,200	5%[a]
20b	(*R*,*S*,*S*)	H, OH	0%[a]	6%[a]
ent-**20b**	(*S*,*R*,*R*)	H, OH	22%[a]	35%[a]
21a	(*R*,*S*,*S*)	H, OCH_3	3500	2100
ent-**21a**	(*S*,*R*,*R*)	H, OCH_3	8280	22,400
21b	(*R*,*S*,*S*)	H, OCH_3	5740	7660
ent-**21b**	(*S*,*R*,*R*)	H, OCH_3	10,600	36%[a]
23a	(*S*,*S*)	H, H	11 ± 4.7	203
ent-**23a**	(*R*,*R*)	H, H	27	335
23b	(*S*,*S*)	H, H	267 ± 32	2340
ent-**23b**	(*R*,*R*)	H, H	561 ± 167	1850
(+)-Pentazocine	—	(*S*,*S*,*S*)	4.2 ±1.1	—
Ditolylguanidine	—	—	61 ± 18	42 ± 17
Haloperidol	—	—	3.9 ± 1.5	78 ± 2.3

[a] Inhibition of radioligand binding at a test compound concentration of 1 μM.

Therefore, we conclude that potent σ_1 ligands result when 6,8-diazabicyclo[3.2.2]nonanes are unsubstituted in position 2 (**23a**) or bear a relatively large lipophilic substituent in position 6 (**2a**, **2b**), which is able to interact with the secondary hydrophobic region of the σ_1 receptor.

Generally, the σ_2 receptor affinity of the bicyclic compounds is rather low. However, some compounds like the methyl ethers **16a** and **16b** show a small preference for the σ_2 receptor over the σ_1 receptor.

Since some σ receptor ligands show considerable affinity toward the NMDA receptor,[14] the affinity of the bridged piperazines toward the phencyclidine binding site of the NMDA receptor (pig brain cortex membrane preparations, radioligand [^{3}H]-MK801) was also determined. However, at a concentration of 1 μM the replacement of the radioligand by the synthesized compounds was always lower than 25% indicating a very low affinity toward the phencyclidine binding site of the NMDA receptor.

3.3. Inhibition of cell growth of human tumor cell lines

In the literature, it has been reported that some human tumor cell lines overexpress σ_1 and σ_2 receptors.[15] Furthermore, some σ_2 agonists and σ_1 antagonists showed antiproliferative and cytotoxic effects in tumor cell lines.[16] Therefore, the antiproliferative effects of the synthesized compounds were investigated in a panel of six human tumor cell lines, including the cell lines 5637 (bladder cancer), RT-4 (bladder cancer), A-427 (small cell lung cancer), LCLC-103H (large cell lung cancer), MCF-7 (breast cancer), and DAN-G (pancreas cancer).

In the primary screening the tumor cells were incubated with a 20 μM solution of the test compound at 37 °C. After 96 h the medium was removed and the density of adherent cells (living cells) was measured by staining with crystal violet.[17] In Table 2, the cell growth inhibiting activity of the test compounds is given as part of living cells (in %) in relation to a control without test compound.

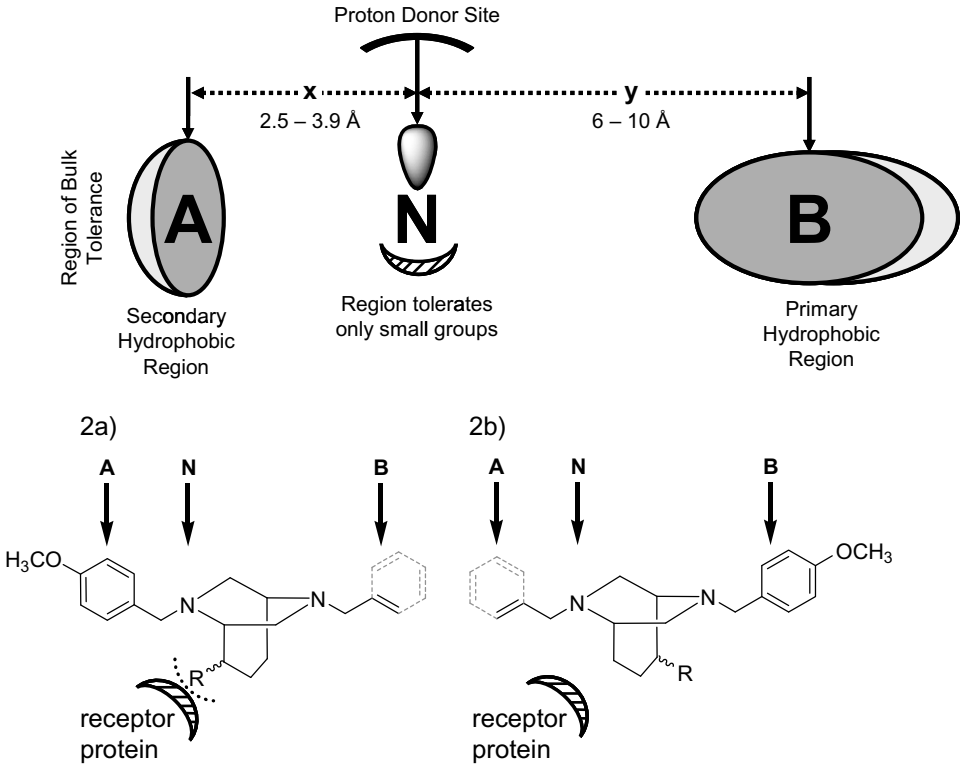


Figure 2. Pharmacophore model of σ_1 receptor ligands (modified according to Ref. 13) and hypothetical binding of the bridged piperazines to the σ_1 receptor.

Table 2
Cell growth inhibitory activity (% of untreated control) of the 6,8-diazabicyclo[3.2.2]nonane derivatives in six human cancer cell lines[a]

	Configuration	5637[b]	RT-4[c]	A-427[d]	LCLC-103H[e]	MCF-7[f]	DAN-G[g]
2a9	(1*R*,2*R*,5*S*)	88	93	46	94	91	–
2b9	(1*R*,2*R*,5*S*)	68	61	-8	72	21	–
11	(*R*,*S*)	83	86	37	101	62	102
ent-**11**	(*S*,*R*)	109	112	111	104	84	109
12	(*R*,*S*)	38	80	60	81	72	75
ent-**12**	(*S*,*R*)	19	76	50	64	65	69
15a	(*R*,*R*,*S*)	100	103	81	101	92	101
ent-**15a**	(*S*,*S*,*R*)	104	107	90	111	99	100
15b	(*R*,*R*,*S*)	100	103	78	103	86	92
ent-**15b**	(*S*,*S*,*R*)	98	100	77	105	100	94
16a	(*R*,*R*,*S*)	96	100	67	103	85	92
ent-**16a**	(*S*,*S*,*R*)	86	103	79	107	91	93
16b	(*R*,*R*,*S*)	61	88	60	90	61	82
ent-**16b**	(*S*,*S*,*R*)	63	87	49	98	79	84
20a	(*R*,*S*,*S*)	103	109	81	107	93	102
ent-**20a**	(*S*,*R*,*R*)	101	108	91	106	91	93
20b	(*R*,*S*,*S*)	100	103	79	103	84	87
ent-**20b**	(*S*,*R*,*R*)	105	109	87	103	102	91
21a	(*R*,*S*,*S*)	95	89	45	99	80	95
ent-**21a**	(*S*,*R*,*R*)	81	94	48	107	84	95
21b	(*R*,*S*,*S*)	102	68	36	78	84	101
ent-**21b**	(*S*,*R*,*R*)	84	79	62	86	87	85
23a	(*S*,*S*)	87	65	42	91	65	92
ent-**23a**	(*R*,*R*)	90	71	55	82	74	87
23b	(*S*,*S*)	73	66	42	74	61	83
ent-**23b**	(*R*,*R*)	75	65	77	59	67	82

[a] Relative cell growth (%) in relation to untreated control of the tumor cell lines after 96 h exposure to substance at 20 μM. Results are averages of two independent experiments.
[b] Bladder cancer.
[c] Bladder cancer.
[d] Small cell lung cancer.
[e] Large cell lung cancer.
[f] Breast cancer.
[g] Pancreas Cancer.

3.4. Results and discussion

TheThe resulting data are summarized in Table 2. Compared with their *N*-6-benzyl analogues,[9] the alcohols **15**, **20** and methyl ethers **16**, **21** led to a considerably decreased inhibition of cell growth. The growth of the cell line 5637 was selectively inhibited by the bicyclic ketones **12** and ent-**12**. On the other hand the bicyclic acetal **11**, the methyl ethers ent-**16b**, **21a**, ent-**21a**, and **21b** as well as the 2-unsubstituted compounds **23a** and **23b** show cell growth inhibiting activity selectively for the small cell lung cancer cell line A-427. The growth of the other cell lines was reduced to a lower extent by these compounds. Exemplarily the IC_{50}-values for the methyl ethers ent-**16b** (IC_{50} = 18.9 ± 7.0 μM), **21a** (IC_{50} = 16.4 ± 2.0 μM), ent-**21a** (IC_{50} = 20.4 ± 12.6 μM), and **21b** (IC_{50} = 27.1 μM) were recorded. The low potency in this assay is correlating with low σ_1 and σ_2 receptor affinity. However, the selective growth inhibition of only few cell lines (5637, A-427) by few compounds clearly indicates that the cell growth inhibiting activity is not simply due to an unspecific toxicity, but is mediated by a specific mechanism.

The unsubstituted bridged piperazine **23a** with the highest affinity toward σ_1 and σ_2 receptors does not show significantly higher cell growth inhibiting activity than its enantiomer ent-**23a** and its methoxy derivative **23b**, which possess considerably lower σ affinity. This might be due to the different (partial) σ_1 agonistic and/or σ_2 antagonistic properties of the compounds or the different penetration of the compounds through the cell membrane to reach their site of action at the σ_1 receptor.

4. Conclusion

6,8-Diazabicyclo[3.2.2]nonanes bearing a *N*-6-allyl moiety without a substituent in position 2 interact with high affinity (**23a**: K_i = 11 nM), high enantioselectivity (eudismic ratio **23a**:ent-**23a** = 25) and high selectivity over σ_2 receptors (**23a**: K_i = 203 nM) and NMDA receptors with σ_1 receptors. Substituents in position 2 such as a hydroxy, an oxo or one or two methoxy groups decrease σ_1 receptor affinity, since these substituents lead to unfavorable interactions with the σ_1 receptor protein (compare Fig. 2a). When such a substituent is present in position 2 a large lipophilic moiety like a benzyl group is required in position 6 to achieve high σ_1 receptor affinity (compounds **2a**, **2b**). This observation is explained by a reversed binding mode (compare Fig. 2b). Altogether, the allyl moiety is too small to replace bioisosterically the *N*-benzyl group and to interact efficiently with the secondary hydrophobic region.

Furthermore, in a screening some of the synthesized bridged piperazine derivatives show a moderate cell growth inhibition of the human small cell lung cancer cell line A-427. Since the σ_1 receptor affinity of the new *N*-allyl derivatives is significantly lower than the σ_1 affinity of the corresponding *N*-benzyl derivatives **2a** and **2b**, the growth inhibition of the human tumor cell lines, in particular the A-427 cell line, is also considerably reduced.

5. Experimental

5.1. Chemistry: General

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (TLC): Silica gel 60 F254 plates (Merck). Flash column chromatography (FC): Silica gel 60, 40–64 μM (Merck); parentheses include: diameter of the column, length of the silica gel bed, eluent, fraction size, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity Mercury Plus 400 spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC: method 1: Merck Hitachi Equipment; UV detector: L-7400; autosampler:L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μM); LiCroCART® 250-4 mm cartridge; flow rate: 1.000 mL/min; injection volume: 5.0 μL; detection at λ = 210 nM; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: 0.0 min: 90.0% of A, 10.0% of B; 4.0 min: 90.0% of A, 10.0% of B; 29.0 min: 0.0% of A, 100.0% of B; 31.0 min: 0.0% of A, 100.0% of B; 31.5 min: 90.0% of A, 10.0% of B; 40.0 min: 90.0% of A, 10.0% of B. method 2: Equipment: pump: HPLC pump 64 (Knauer); UV-Detector: Variable Wavelength Monitor (Knauer); data acquisition: D-2500 Chromato-Integrator (Merck Hitachi); injection volume: 20.0 μL; stop time: 2× t_R; (a) column: LiChroCART® 250-4 with Superspher® 100 RP-18; flow rate: 1.0 mL/min; detection: wavelength: 235 nM; solvent: methanol/water = 60:40 + 0.1% triethylamine; (b) column: LiChroCART® 250-4 with Superspher® 100 RP-18; flow rate: 0.6 mL/min; detection: wavelength: 235 nM; solvent: methanol/water = 85:15 + 0.1% triethylamine; (c) column LiChroCART® 250-4 with Superspher® 100 RP-18; flow rate: 0.6 mL/min; detection: wavelength: 235 nM; solvent: methanol/water = 75:25 + 0.1% triethylamine; (d) column: LiChroCART® 250-4 with Superspher® 100 RP-18; flow rate: 0.6 mL/min; detection: wavelength: 235 nM; solvent: methanol/water = 65:35 + 0.1% triethylamine; (e) column: LiChroCART® 250-4 with LiChrospher® RP-8e (5 μM); flow rate: 1.0 mL/min;

detection: wavelength: 254 nM; solvent: acetonitrile/water = 50:50 + 0.1% triethylamine; (f) column: LiChroCART® 250-4 with LiChrospher® RP-8e (5 μM); flow rate: 1.0 mL/min; detection: wavelength: 254 nM; solvent: acetonitrile/water = 40:60 + 0.1% triethylamine; (g) column: LiChroCART® 250-4 with LiChrospher® RP-8e (5 μM); flow rate: 1.0 mL/min; detection: wavelength: 254 nM; solvent: acetonitrile/water = 35:65 + 0.1% triethylamine; (h) column: Hibar® RT 250-4 with LiChrospher® 100 RP-18 (5 μM); flow rate: 1.0 mL/min; detection: wavelength: 254 nM; solvent: acetonitrile/water = 60:40 + 0.1% triethylamine; (i) column: Hibar® RT 250-4 with LiChrospher® 100 RP-18 (5 μM); flow rate: 1.0 mL/min; detection: wavelength: 254 nM; solvent: acetonitrile/water = 50:50 + 0.1% triethylamine.

5.2. (−)-Methyl (*S*)-3-[4-(2,4-dimethoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (6b)

The chloroacetamide **5** (1.51 g, 6.0 mmol) was dissolved in acetonitrile (50 mL) and 2,4-dimethoxybenzylamine hydrochloride (1.83 g, 9.0 mmol), triethylamine (2.53 mL, 1.84 g, 18.2 mmol) and tetrabutylammonium iodide (222 mg, 0.60 mmol) were added. The mixture was heated to reflux for 48 h. Then 2/3 of the solvent was removed in vacuo. The residue was filtered and poured into 0.5 M HCl. The mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by FC (Ø = 6 cm, *h* = 15 cm, petroleum ether/acetone = 1:1, V = 30 mL, R_f = 0.27) to give **6b** as a colorless solid, mp 123 °C, yield 1.67 g (79%). $C_{17}H_{22}N_2O_6$ (350.4). Purity by HPLC: method 1: t_R = 14.6 min, purity 98.1%. $[\alpha]_D^{20}$ −4.1 (*c* 0.64; CH_2Cl_2). MS (EI): *m/z* [%] = 350 (M, 25), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.15–2.21 (m, 2H, C*H*$_2$CH$_2$CO$_2$CH$_3$), 2.39–2.53 (m, 2H, CH$_2$C*H*$_2$CO$_2$CH$_3$), 3.67 (s, 3H, CO$_2$C*H*$_3$), 3.80 (s, 3H, ArOC*H*$_3$), 3.81 (s, 3H, ArOC*H*$_3$), 3.89 (s, 2H, O=CC*H*$_2$N), 4.05–4.10 (m, 1H, C*H*CH$_2$CH$_2$CO$_2$CH$_3$), 4.47 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 4.63 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 6.43–6.47 (m, 2H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 6.70 (s, 1H, N*H*), 7.20 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3209 (m br, ν_{N-H}), 3075 (w, $\nu_{C-H\ arom.}$), 2951 (m, $\nu_{C-H\ aliph.}$), 1729 (m, $\nu_{C=O\ ester}$), 1673 (s, $\nu_{C=O\ amide}$), 1615 (m)/1585 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1456 (m, $\delta_{C-H\ aliph.}$), 1216 (m)/1161 (m)/1033 (m, ν_{C-O}), 818 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.3. (+)-Methyl (*R*)-3-[4-(2,4-dimethoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (ent-6b)

As described for the preparation of **6b**, the enantiomer ent-**5** (1.07 g, 4.25 mmol) was reacted with 2,4-dimethoxybenzylamine hydrochloride (1.30 g, 6.38 mmol), triethylamine (1.95 mL, 1.42 g, 14.0 mmol) and tetrabutylammonium iodide (157 mg, 0.43 mmol) in acetonitrile (40 mL) to give ent-**6b** as a colorless solid, mp 125 °C, yield 750 mg (50%). $C_{17}H_{22}N_2O_6$ (350.4). Purity by HPLC: method 1: t_R = 14.6 min, purity 99.5%. $[\alpha]_D^{20}$ +4.6 (*c* 0.57; CH_2Cl_2).

5.4. (+)-Methyl (*S*)-3-[1-allyl-4-(2,4-dimethoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (7b)

Under N_2 a solution of **6b** (520 mg, 1.48 mmol) and tetrabutylammonium iodide (110 mg, 0.30 mmol) in THF (60 mL) was cooled to −78 °C. Then a 2.0 M solution of sodium hexamethyldisilazane in THF (0.82 mL, 1.63 mmol) was added dropwise. After stirring the mixture at −78 °C for 40 min, allyl bromide (0.65 mL, 898 mg, 7.42 mmol) was added. The mixture was stirred at −78 °C for 1 h and was then allowed to warm to rt. After stirring the mixture at ambient temperature for 2 h, water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 3 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, 20 mL, R_f = 0.28) to give **7b** as a yellow oil, yield 340 mg (59%). $C_{20}H_{26}N_2O_6$ (390.4). Purity by HPLC: method 1: t_R = 17.6 min, purity 96.1%. $[\alpha]_D^{20}$ +30.9 (*c* 0.69; CH_2Cl_2). MS (EI): *m/z* [%] = 390 (M, 16), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.95–2.05 (m, 1H, C*H*$_2$CH$_2$CO$_2$CH$_3$), 2.18–2.27 (m, 1H, C*H*$_2$CH$_2$CO$_2$CH$_3$), 2.32–2.49 (m, 2H, CH$_2$C*H*$_2$CO$_2$CH$_3$), 3.49 (dd, *J* = 15.7/7.8 Hz, 1H, NC*H*$_2$CH=CH$_2$), 3.67 (s, 3H, CO$_2$C*H*$_3$), 3.80 (s, 6H, ArOC*H*$_3$), 3.89 (s, 2H, O=CC*H*$_2$N), 3.99 (dd, *J* = 8.6/3.9 Hz, 1H, C*H*CH$_2$CH$_2$CO$_2$CH$_3$), 4.37 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 4.52–4.59 (m, 1H, NC*H*$_2$CH=CH$_2$), 4.71 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 5.20–5.26 (m, 2H, NCH$_2$CH=C*H*$_2$), 5.67–5.78 (m, 1H, NCH$_2$C*H*=CH$_2$), 6.43–6.47 (m, 2H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.19 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3080 (w, $\nu_{C-H\ arom.}$), 2951 (w, $\nu_{C-H\ aliph.}$), 1733 (m, $\nu_{C=O\ ester}$), 1658 (s, νC=O amide), 1612 (m)/1587 (m)/1508 (m, $\nu_{C=C\ arom.}$), 1464 (m, $\delta_{C-H\ aliph.}$), 1208 (m)/1157 (m)/1032 (m, ν_{C-O}), 835 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.5. (-)-Methyl (*R*)-3-[1-allyl-4-(2,4-dimethoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (ent-7b)

As described for the preparation of **7b**, the enantiomer ent-**6** (600 mg, 1.71 mmol), tetrabutylammonium iodide (127 mg, 0.34 mmol), 2 M solution of sodium hexamethyldisilazane in THF (0.94 mL, 1.88 mmol) and allyl bromide (0.75 mL, 1.04 g, 8.56 mmol) were reacted in THF (30 mL) to give ent-**7b** as a yellow oil, yield 380 mg (57%). $C_{20}H_{26}N_2O_6$ (390.4). Purity by HPLC: method 1: t_R = 17.5 min, purity 98.1%. $[\alpha]_D^{20}$ −32.1 (*c* 0.68; CH_2Cl_2).

5.6. (+)-(1*S*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (8b)

Under N_2 **7b** (5.76 g, 14.8 mmol) was dissolved in THF (150 mL) and cooled to −78 °C. Then a 1 M solution of lithium hexamethyldisilazane in THF (22.1 mL, 22.1 mmol) was added dropwise. After stirring at −78 °C for 40 min, chlorotrimethylsilane (6.79 mL, 5.77 g, 53.1 mmol) was slowly added. The mixture was stirred at −78 °C for 1 h and at rt for 2 h. Then a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 8 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:1, V = 30 mL, R_f = 0.30) to give **8b** as a yellow oil, yield 5.41 g (79%). $C_{23}H_{34}N_2O_6Si$ (462.6). $[\alpha]_D^{20}$ +28.7 (*c* 0.71; CH_2Cl_2). MS (EI): *m/z* [%] = 462 (M, 25), 311 (M−2,4-dimethoxybenzyl, 12), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.19 (s, 9H, OSi(C*H*$_3$)$_3$), 1.74–1.83 (m, 1H, 4-H), 1.87–1.98 (m, 2H, 3-H), 2.00–2.09 (m, 1H, 4-H), 3.22 (s, 3H, OC*H*$_3$), 3.78 (s, 6H, 2× ArOC*H*$_3$), 3.81 (dd, *J* = 5.5/2.3 Hz, 1H, 5-H), 3.93 (d, *J* = 6.3 Hz, 2H, NC*H*$_2$CH=CH$_2$), 4.10 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 4.13 (s, 1H, 1-H), 4.96 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 5.12–5.19 (m, 2H, NCH$_2$CH=C*H*$_2$), 5.71 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.39–6.44 (m, 2H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.14 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2956 (m, $\nu_{C-H\ aliph.}$), 1683 (s, $\nu_{C=O\ amide}$), 1612 (m)/1588 (m)/1507 (m, $\nu_{C=C\ arom.}$), 1453 (m, $\delta_{C-H\ aliph.}$), 1249 (m)/1207 (m, ν_{C-O}), 1106 (m, ν_{Si-O}), 872 (m, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.7. (−)-(1*R*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-8b)

As described for the preparation of **8b**, the enantiomer ent-**7b** (9.0 g, 23.1 mmol) was reacted with a 1 M solution of lithium hex-

amethyldisilazane in THF (34.6 mL, 34.6 mmol) and chlorotrimethylsilane (10.6 mL, 9.02 g, 83.0 mmol) in THF (200 mL) to give ent-**8b** as a yellow oil, yield 8.09 g (76%). $C_{23}H_{34}N_2O_6Si$ (462.6). $[\alpha]_D^{20}$ −30.1 (*c* 0.73; CH_2Cl_2).

5.8. (+)-(1*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (9b)

Under N_2 **8b** (518 mg, 1.12 mmol) was dissolved in a degassed mixture of THF/2 M HCl (9:1, 70 mL) and the mixture was stirred at rt for 2 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 3 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, V = 20 mL, R_f = 0.26) to give **9b** as a colorless solid, mp 119 °C, yield 340 mg (85%). $C_{19}H_{22}N_2O_5$ (358.4). Calculated C, 63.68; H, 6.19; N, 7.82; found: C, 63.58; H, 6.01; N, 7.69. $[\alpha]_D^{20}$ +96.8 (*c* 0.26; CH_2Cl_2). MS (EI): *m/z* [%] = 358 (M, 45), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.00–2.10 (m, 1H, 4-H), 2.22–2.30 (m, 1H, 3-H), 2.38–2.54 (m, 2H, 3-H (1H), 4-H (1H)), 3.70 (s, 3H, ArOC*H*$_3$), 3.78 (s, 3H, ArOC*H*$_3$), 3.83 (dd, *J* = 15.1/6.4 Hz, 1H, NC*H*$_2$CH=CH$_2$), 3.93–3.96 (m, 1H, 5-H), 4.15 (dd, *J* = 15.1/6.4 Hz, 1H, NC*H*$_2$CH=CH$_2$), 4.29 (d, *J* = 13.5 Hz, 1H, NC*H*$_2$Ar), 4.47 (s, 1H, 1-H), 4.83 (d, *J* = 13.5 Hz, 1H, NC*H*$_2$Ar), 5.18–5.26 (m, 2H, NCH$_2$CH=C*H*$_2$), 5.66–5.77 (m, 1H, NCH$_2$C*H*=CH$_2$), 6.37 (d, *J* = 2.4 Hz, 1H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$), 6.43 (dd, *J* = 8.8/2.4 Hz, 1H, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.32 (d, *J* = 8.8 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 30.6 (1C, C-4), 36.8 (1C, C-3), 46.0 (1C, NC*H*$_2$Ar), 48.0 (1C, NC*H*$_2$CH=CH$_2$), 55.2 (1C, ArOC*H*$_3$), 55.6 (1C, ArOC*H*$_3$), 59.2 (1C, C-5), 73.6 (1C, C-1), 98.5 (1C, C-3′$_{2,4\text{-dimethoxybenzyl}}$), 104.7 (1C, C-5′$_{2,4\text{-dimethoxybenzyl}}$), 115.8 (1C, C-1′$_{2,4\text{-dimethoxybenzyl}}$), 120.0 (1C, NCH$_2$CH=*C*H$_2$), 131.7 (1C, NCH$_2$*C*H=CH$_2$), 133.1 (1C, C-6′$_{2,4\text{-dimethoxybenzyl}}$), 158.5 (1C, C-4′$_{2,4\text{-dimethoxybenzyl}}$), 161.5 (1C, C-2′$_{2,4\text{-dimethoxybenzyl}}$), 163.7 (1C, C=O), 167.1 (1C, C=O), 201.4 (1C, C=O$_{ketone}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3007 (w, $\nu_{C-H\ arom.}$), 2934 (w, $\nu_{C-H\ aliph.}$), 1721 (m, $\nu_{C=O\ ketone}$), 1678 (s, $\nu_{C=O\ amide}$), 1610 (m)/1509 (m, $\nu_{C=C\ arom.}$), 1456 (m, $\delta_{C-H\ aliph.}$), 1210 (m)/1027 (m, ν_{C-O}), 836 (m, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.9. (−)-(1*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (ent-9b)

As described for the preparation of **9b**, the enantiomer ent-**8b** (9.0 g, 23.1 mmol) was reacted in a degassed mixture of THF/2 M HCl (9:1, 200 mL) to give ent-**9b** as a colorless solid, mp 119 °C, yield 4.62 g (75%). $C_{19}H_{22}N_2O_5$ (358.4). Calculated C, 63.68; H, 6.19; N, 7.82; found: C, 63.62; H, 6.08; N, 7.78. $[\alpha]_D^{20}$ −96.1 (*c* 0.27; CH_2Cl_2).

5.10. (+)-(1*S*,5*S*)-6-Allyl-2,2-dimethoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (10)

Under N_2 trimethyl orthoformate (1.2 mL, 1.17 g, 11.1 mmol) was added to a solution of **9a** (330 mg, 1.00 mmol) and *p*-toluenesulfonic acid (381 mg, 2.21 mmol) in methanol (50 mL). The mixture was heated to reflux for 16 h. Then a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by FC (Ø = 2 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 2/1, *V* = 10 mL, R_f = 0.10) to give **10** as a colorless oil, yield 368 mg (98%). $C_{20}H_{26}N_2O_5$ (374.4). Purity by HPLC: method 1: t_R = 18.3 min, purity 97.7%. $[\alpha]_D^{20}$ +11.7 (*c* 0.66; CH_2Cl_2). MS (EI): *m/z* [%] = 374 (M, 2), 343 (M−OCH$_3$, 1), 121 (CH$_2$PhOCH$_3$, 31), 101 (H$_2$CCHC(OCH$_3$)$_2$, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.73–1.88 (m, 2H, 3-H), 2.00–2.11 (m, 2H, 4-H), 3.18 (s, 3H, OC*H*$_3$), 3.27 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, ArOC*H*$_3$), 3.87 (ddt, *J* = 15.7/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH$_2$), 3.89–3.92 (m, 1H, 5-H), 3.96 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 3.99 (s, 1H, 1-H), 4.11 (ddt, *J* = 15.7/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH$_2$), 5.18–5.25 (m, 2H, NCH$_2$CH=C*H*$_2$), 5.20 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 5.73 (ddt, *J* = 16.4/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.84 (d, *J* = 8.6 Hz, 2H, 3′-H$_{4\text{-methoxybenzyl}}$, 5′-H$_{4\text{-methoxybenzyl}}$), 7.12 (d, *J* = 8.6 Hz, 2H, 2′-H$_{4\text{-methoxybenzyl}}$, 6′-H$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2938 (m, $\nu_{C-H\ aliph.}$), 1677 (s, $\nu_{C=O\ amide}$), 1612 (m)/1512 (m, $\nu_{C=C\ arom.}$), 1453 (m, $\delta_{C-H\ aliph.}$), 1243 (m)/1035 (m, ν_{C-O}), 808 (w, $\Gamma_{p\text{-}subst.\ arom.}$).

5.11. (−)-(1*R*,5*R*)-6-Allyl-2,2-dimethoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-10)

As described for the preparation of **10**, the enantiomer ent-**9a** (400 mg, 1.22 mmol) was reacted with trimethyl orthoformate (1.7 mL, 1.42 g, 13.4 mmol) and *p*-toluenesulfonic acid (461 mg, 2.68 mmol) in methanol (60 mL) to give ent-**10** as a colorless oil, yield 450 mg (99%). $C_{20}H_{26}N_2O_5$ (374.4). Purity by HPLC: method 1: t_R = 18.3 min, purity 97.2%. $[\alpha]_D^{20}$ −11.8 (*c* 0.55; CH_2Cl_2).

5.12. (+)-(1*R*,5*S*)-6-Allyl-2,2-dimethoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-one dimethyl acetal (11)

Under N_2 $LiAlH_4$ (66 mg, 1.74 mmol) was added to an ice-cooled solution of **10** (130 mg, 0.35 mmol) in THF (30 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL, R_f = 0.04) to give **11** as a colorless oil, yield 24 mg (20%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 24.0 min, purity 97.9%; method 1: t_R = 16.7 min, purity 97.6%. $[\alpha]_D^{20}$ +45.1 (*c* 0.24; CH_2Cl_2). MS (EI): *m/z* [%] = 346 (M, 48), 315 (M−OCH$_3$, 6), 225 (M−CH$_2$PhOCH$_3$, 6), 121 (CH$_2$PhOCH$_3$, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.57–1.67 (m, 1H, 4-H), 1.76–1.91 (m, 2H, 3-H (1H), 4-H (1H)), 1.95–2.04 (m, 1H, 3-H), 2.61–2.69 (m, 2H, 9-H), 2.74 (dd, *J* = 11.7/3.9 Hz, 1H, 7-H), 2.84–2.87 (m, 1H, 1-H), 2.90–2.95 (m, 1H, 5-H), 3.07 (dd, *J* = 11.7/1.6 Hz, 1H, 7-H), 3.11 (s, 3H, OC*H*$_3$), 3.12–3.19 (m, 2H, NC*H*$_2$CH=CH$_2$), 3.20 (s, 3H, OC*H*$_3$), 3.76 (s, 2H, NC*H*$_2$Ar), 3.79 (s, 3H, ArOC*H*$_3$), 5.08 (d, *J* = 10.2 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.16 (dd, *J* = 17.2/1.6 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.85 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.84 (d, *J* = 8.6 Hz, 2H, 3′-H$_{4\text{-methoxybenzyl}}$, 5′-H$_{4\text{-methoxybenzyl}}$), 7.31 (d, *J* = 8.6 Hz, 2H, 2′-H$_{4\text{-methoxybenzyl}}$, 6′-H$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3071 (w, $\nu_{C-H\ arom.}$), *2932 (m, $\nu_{C-H\ aliph.}$), 1611 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1442 (m, $\delta_{C-H\ aliph.}$), 1243 (m)/1038 (m, ν_{C-O}), 829 (m, $\Gamma_{p\text{-}subst.\ arom.}$).*

5.13. (−)-(1*S*,5*R*)-6-Allyl-2,2-dimethoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-one dimethyl acetal (ent-11)

As described for the preparation of **11**, the enantiomer ent-**10** (176 mg, 0.47 mmol) was reacted with $LiAlH_4$ (89 mg, 2.35 mmol) in THF (40 mL) to give ent-**11** as a colorless oil, yield 30 mg (18%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 25.0 min, purity 96.8%; method 1: t_R = 16.4 min, purity 98.4%. $[\alpha]_D^{20}$ −45.1 (*c* 0.49; CH_2Cl_2).

5.14. (−)-(1*R*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-one (12)

Under N_2 a 1.0 M solution of $LiAlH_4$ in THF (2.13 mL, 2.13 mmol) was added to an ice-cooled solution of **10** (200 mg, 0.53 mmol) in

THF (60 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then 1.0 M HCl (10 mL) was added under ice-cooling and the mixture was stirred at 0 °C for 10 min and then heated to reflux for 3 h. After cooling down the mixture was alkalized with a saturated aqueous solution of $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by FC (Ø = 2 cm, h = 15 cm, CH_2Cl_2/methanol = 100:1, V = 10 mL, R_f = 0.15) to give **12** as a colorless oil, yield 80 mg (50%). $C_{18}H_{24}N_2O_2$ (300.4). Purity by HPLC: method 2d: t_R = 24.5 min, purity 98.0%; method 1: t_R = 15.6 min, purity 98.6%. $[\alpha]_D^{20}$ −73.7 (*c* 0.59; CH_2Cl_2). MS (EI): *m/z* [%] = 301 (MH, 2), 272 (M−CO, 16), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66–1.76 (m, 1H, 4-H), 1.83–1.92 (m, 1H, 4-H), 2.28 (ddd, J = 13.3/8.6/1.6 Hz, 1H, 3-H), 2.78–2.87 (m, 3H, piperazine-H), 2.92 (dd, J = 11.0/2.3 Hz, 1H, piperazine-H), 3.05–3.21 (m, 4H, NCH_2CH=CH_2, piperazine-H), 3.27 (ddd, J = 13.3/10.2/8.6 Hz, 1H, 3-H), 3.60 (d, J = 12.5 Hz, 1H, NCH_2Ar), 3.64 (d, J = 12.5 Hz, 1H, NCH_2Ar), 3.79 (s, 3H, ArOCH_3), 5.09 (dd, J = 10.2/1.6 Hz, 1H, NCH_2CH=CH_2), 5.15 (ddd, J = 17.2/3.1/1.6 Hz, 1H, NCH_2CH=CH_2), 5.75–5.86 (m, 1H, NCH_2CH=CH_2), 6.83 (d, J = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.18 (d, J = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3067 (w, $\nu_{C-H\ arom.}$), 2911 (m, $\nu_{C-H\ aliph.}$), 1708 (s, $\nu_{C=O\ ketone}$), 1611 (m)/1510 (s, $\nu_{C=C\ arom.}$), 1441 (m, $\delta_{C-H\ aliph.}$), 1243 (m)/1033 (m, ν_{C-O}), 820 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.15. (+)-(1*S*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-one (ent-12)

As described for the preparation of **12**, the enantiomer ent-**10** (357 mg, 0.95 mmol) was reacted with $LiAlH_4$ (3.81 mL of a 1.0 M solution in THF, 3.81 mmol) in THF (80 mL) and afterward hydrolyzed with 1.0 M HCl (20 mL) to give ent-**12** as a colorless oil, yield 95 mg (33%). $C_{18}H_{24}N_2O_2$ (300.4). Purity by HPLC: method 2d: t_R = 24.5 min, purity 98.0%; method 1: t_R = 15.6 min, purity 99.5%. $[\alpha]_D^{20}$ +76.1 (*c* 0.73; CH_2Cl_2).

5.16. (+)-(1*S*,2*R*,5*S*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (13a)

Under N_2 **9a** (1.3 g, 4.0 mmol) was dissolved in THF (70 mL) and the solution was cooled to −78 °C. Then a 2 M solution of $LiBH_4$ in THF (8.0 mL, 16.0 mmol) was slowly added. The reaction mixture was stirred for 3 h at −78 °C. Then the mixture was warmed to rt and carefully hydrolyzed with 1 M HCl (70 mL). The resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 4 cm, h = 15 cm, ethyl acetate, V = 30 mL, R_f = 0.30) to give **13a** as a colorless solid, mp 109 °C, yield 1.2 g (92%). $C_{18}H_{22}N_2O_4$ (330.4). Calculated C, 65.44; H, 6.71; N, 8.48; found: C, 65.30; H, 6.66; N, 8.29. $[\alpha]_D^{20}$ +120 (*c* 1.41; CH_2Cl_2). MS (EI): *m/z* [%] = 330 (M, 100), 209 (M−CH_2PhOCH_3, 7), 121 (CH_2PhOCH_3, 72). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.50–1.64 (m, 1H, 3-H), 1.78–2.06 (m, 3H, 3-H (1H), 4-H (2H)), 2.54 (d br, J = 3.9 Hz, 1H, O*H*), 3.43–3.49 (m, 1H, 2-H), 3.78 (s, 3H, ArOCH_3), 3.90–4.00 (m, 3H, 1-H, 5-H, NCH_2CH=CH_2), 4.08 (dd, J = 15.7/6.3 Hz, 1H, NCH_2CH=CH_2), 4.40 (d, J = 14.1 Hz, 1H, NCH_2Ar), 4.60 (d, J = 14.1 Hz, 1H, NCH_2Ar), 5.20–5.28 (m, 2H, NCH_2CH=CH_2), 5.70–5.82 (m, 1H, NCH_2CH=CH_2), 6.84 (d, J = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.19 (d, J = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 23.5 (1C, C-4), 29.5 (1C, C-3), 47.9 (1C, NCH_2CH=CH_2), 48.7 (1C, NCH_2Ar), 55.5 (1C, $ArOCH_3$), 59.1 (1C, C-5), 65.4 (1C, C-1), 66.3 (1C, C-2), 114.6 (2C, C-3′$_{4\text{-methoxybenzyl}}$, C-5′$_{4\text{-methoxybenzyl}}$), 119.8 (1C, NCH_2CH=CH_2), 128.0 (1C, C-1′$_{4\text{-methoxybenzyl}}$), 130.1 (2C, C-2′$_{4\text{-methoxybenzyl}}$, C-6′$_{4\text{-methoxybenzyl}}$), 132.0 (1C, NCH_2CH=CH_2), 159.7 (1C, C-4′$_{4\text{-methoxybenzyl}}$), 167.6 (1C, C=O), 169.1 (1C, C=O). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3567 (m br, ν_{O-H}), 2932 (w, $\nu_{C-H\ aliph.}$), 1652 (s, $\nu_{C=O\ amide}$), 1612 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1453 (m, $\delta_{C-H\ aliph.}$), 1241 (m)/1079 (m, ν_{C-O}), 839 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.17. (−)-(1*R*,2*S*,5*R*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-13a)

As described for the preparation of **13a**, the enantiomer ent-**9a** (510 mg, 1.6 mmol) was reacted with a 2 M solution of $LiBH_4$ in THF (3.1 mL, 6.4 mmol) in THF (50 mL) to give ent-**13a** as a colorless solid, mp 109 °C, yield 451 mg (88%). $C_{18}H_{22}N_2O_4$ (330.4). Calculated C, 65.44; H, 6.71; N, 8.48; found: C, 65.12; H, 6.58; N, 8.31. $[\alpha]_D^{20}$ −122 (*c* 0.28; CH_2Cl_2).

5.18. (+)-(1*S*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (13b)

Under N_2 **9b** (1.8 g, 5.0 mmol) was dissolved in THF (100 mL) and the solution was cooled to −78 °C. Then a 2 M solution of $LiBH_4$ in THF (10.0 mL, 20.0 mmol) was slowly added. The reaction mixture was stirred for 3 h at −78 °C. Then the mixture was warmed to rt and carefully hydrolyzed with 1 M aq HCl (80 mL). The resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 5 cm, h = 15 cm, ethyl acetate, V = 30 mL, R_f = 0.22) to give **13b** as a colorless oil, yield 1.7 g (92%). $C_{19}H_{24}N_2O_5$ (360.4). $[\alpha]_D^{20}$ +119 (*c* 0.67; CH_2Cl_2). MS (EI): *m/z* [%] = 360 (M, 65), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.50–1.60 (m, 1H, 3-H), 1.78–1.87 (m, 1H, 4-H), 1.89–2.02 (m, 2H, 3-H (1H), 4-H (1H)), 2.26 (s br, 1H, O*H*), 3.48–3.56 (m, 1H, 2-H), 3.79 (s, 3H, ArOCH_3), 3.81 (s, 3H, ArOCH_3), 3.87 (dd, J = 5.5/2.3 Hz, 1H, 5-H), 3.95 (dd, J = 14.9/6.3 Hz, 1H, NCH_2CH=CH_2), 4.05–4.12 (m, 2H, 1-H, NCH_2CH=CH_2), 4.46 (d, J = 14.1 Hz, 1H, NCH_2Ar), 4.60 (d, J = 14.1 Hz, 1H, NCH_2Ar), 5.20–5.28 (m, 2H, NCH_2CH=CH_2), 5.71–5.82 (m, 1H, NCH_2CH=CH_2), 6.42–6.46 (m, 2H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.22 (d, J = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 23.5 (1C, C-4), 29.6 (1C, C-3), 44.0 (1C, NCH_2Ar), 47.8 (1C, NCH_2CH=CH_2), 55.6 (1C, $ArOCH_3$), 55.7 (1C, $ArOCH_3$), 59.2 (1C, C-5), 65.8 (1C, C-1), 66.6 (1C, C-2), 98.8 (1C, C-3′$_{2,4\text{-dimethoxybenzyl}}$), 104.7 (1C, C-5′$_{2,4\text{-dimethoxybenzyl}}$), 116.5 (1C, C-1′$_{2,4\text{-dimethoxybenzyl}}$), 119.6 (1C, NCH_2CH=CH_2), 132.1 (1C, NCH_2CH=CH_2), 132.2 (1C, C-6′$_{2,4\text{-dimethoxybenzyl}}$), 158.9 (1C, C-4′$_{2,4\text{-dimethoxybenzyl}}$), 161.2 (1C, C-2′$_{2,4\text{-dimethoxybenzyl}}$), 167.7 (1C, C=O), 169.1 (1C, C=O). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3381 (m br, ν_{O-H}), 2938 (m, $\nu_{C-H\ aliph.}$), 1660 (s, $\nu_{C=O\ amide}$), 1611 (m)/1507 (m, $\nu_{C=C\ arom.}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1208 (m)/1030 (m, ν_{C-O}), 833 (w, $\Gamma_{tri\text{-subst. arom.}}$).

5.19. (−)-(1*R*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-13b)

As described for the preparation of **13b**, the enantiomer ent-**9b** (3.0 g, 8.4 mmol) was reacted with a 2 M solution of $LiBH_4$ in THF (16.8 mL, 33.6 mmol) in THF (150 mL) to give ent-**13b** as a colorless oil, yield 2.3 g (76%). $C_{19}H_{24}N_2O_5$ (360.4). Purity by HPLC: method 1: t_R = 15.6 min, purity 99.5%. $[\alpha]_D^{20}$ −119 (*c* 0.49; CH_2Cl_2).

5.20. (+)-(1*S*,2*R*,5*S*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (14a)

Under N_2 and ice-cooling 60% NaH suspension in paraffin oil (75 mg, ca. 45 mg NaH, 1.87 mmol) was added to a solution of **13a** (103 mg, 0.31 mmol) in THF (30 mL). After 20 min methyl io-

dide (0.06 mL, 132 mg, 0.94 mmol) was added dropwise and the mixture was stirred at rt for 16 h. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and washed with water (2×), 0.5 M HCl (1×) and 0.5 M NaOH (1×). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 1 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, V = 5 mL, R_f = 0.18) to give **14a** as a colorless solid, mp 127 °C, yield 96 mg (89%). $C_{19}H_{24}N_2O_4$ (344.4). Calculated C, 66.26; H, 7.02; N, 8.13; found: C, 66.36; H, 6.97; N, 8.00. $[\alpha]_D^{20}$ +149.0 (*c* 0.22; CH_2Cl_2). MS (EI): *m/z* [%] = 344 (M, 30), 303 (M−$CH_2CH{=}CH_2$, 4), 223 (M−CH_2PhOCH_3, 7), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.55–1.65 (m, 1H, 3-H), 1.80–1.91 (m, 2H, 3-H (1H), 4-H (1H)), 1.92–2.01 (m, 1H, 4-H), 2.86–2.92 (m, 1H, 2-H), 3.16 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, ArOC*H*$_3$), 3.92 (dd, *J* = 5.5/2.3 Hz, 1H, 5-H), 3.94–4.01 (m, 2H, 1-H, NC*H*$_2$CH=CH_2 (1H)), 4.08 (dd, *J* = 14.9/6.3 Hz, 1H, NC*H*$_2$CH=CH_2), 4.29 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 4.75 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 5.21–5.27 (m, 2H, $NCH_2CH{=}CH_2$), 5.76 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.86 (d, *J* = 8.6 Hz, 2H, 3′-H$_{4\text{-methoxybenzyl}}$, 5′-H$_{4\text{-methoxybenzyl}}$), 7.21 (d, *J* = 8.6 Hz, 2H, 2′-H$_{4\text{-methoxybenzyl}}$, 6′-H$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3080 (w, $\nu_{C-H\ arom.}$), 2951 (w, $\nu_{C-H\ aliph.}$), 1663 (s, $\nu_{C=O\ amide}$), 1609 (m)/1508 (m, $\nu_{C=C\ arom.}$), 1459 (m, $\delta_{C-H\ aliph.}$), 1242 (m)/1096 (m, ν_{C-O}), 835 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.21. (−)-(1*R*,2*S*,5*R*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-14a)

As described for the preparation of **14a**, the enantiomer ent-**13a** (81 mg, 0.25 mmol), 60% NaH suspension in paraffin oil (59 mg, ca. 35 mg NaH, 1.47 mmol) and methyl iodide (0.05 mL, 104 mg, 0.74 mmol) were reacted in THF (30 mL) to give ent-**14a** as a colorless solid, mp 128 °C, yield 70 mg (83%). $C_{19}H_{24}N_2O_4$ (344.4). Calculated C, 66.26; H, 7.02; N, 8.13; found: C, 66.18; H, 7.07; N, 8.04. $[\alpha]_D^{20}$ −149.4 (*c* 0.33; CH_2Cl_2).

5.22. (+)-(1*S*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (14b)

Under N_2 and ice-cooling 60% NaH suspension in paraffin oil (54 mg, ca. 32 mg NaH, 1.35 mmol) was added to a solution of **13b** (81 mg, 0.31 mmol) in THF (20 mL). After 20 min methyl iodide (0.04 mL, 96 mg, 0.67 mmol) was added dropwise and the mixture was stirred at rt for 16 h. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and washed with water (2×), 0.5 M HCl (1×) and 0.5 M NaOH (1×). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 1 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, *V* = 5 mL, R_f = 0.18) to give **14b** as a colorless oil, yield 65 mg (77%). $C_{20}H_{26}N_2O_5$ (374.4). $[\alpha]_D^{20}$ +141.1 (*c* 0.40; CH_2Cl_2). MS (EI): *m/z* [%] = 374 (M, 24), 343 (M−OCH_3, 8), 223 (M−2,4-dimethoxybenzyl, 2), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.54–1.65 (m, 1H, 3-H), 1.77–1.98 (m, 3H, 3-H (1H), 4-H (2H)), 2.95–3.00 (m, 1H, 2-H), 3.20 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, ArOC*H*$_3$), 3.81 (s, 3H, ArOC*H*$_3$), 3.87 (dd, *J* = 5.5/3.1 Hz, 1H, 5-H), 3.96 (ddt, *J* = 15.7/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH_2), 4.06 (ddt, *J* = 14.9/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH_2), 4.15 (d, *J* = 3.9 Hz, 1H, 1-H), 4.42 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 4.66 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 5.18–5.25 (m, 2H, $NCH_2CH{=}CH_2$), 5.75 (ddt, *J* = 16.4/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.41–6.47 (m, 2H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.22 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3081 (w, $\nu_{C-H\ arom.}$), 2937 (w, $\nu_{C-H\ aliph.}$), 1673 (s, $\nu_{C=O\ amide}$), 1611 (m)/1587 (m)/1507 (m, $\nu_{C=C\ arom.}$), 1452 (m, $\delta_{C-H\ aliph.}$), 1208 (m)/1091 (m, ν_{C-O}), 834 (w, $\Gamma_{tri\text{-subst. arom.}}$).

5.23. (−)-(1*R*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-14b)

As described for the preparation of **14b**, the enantiomer ent-**13b** (148 mg, 0.41 mmol), 60% NaH suspension in paraffin oil (99 mg, ca. 59 mg NaH, 2.46 mmol) and methyl iodide (0.08 mL, 175 mg, 1.23 mmol) were reacted in THF (30 mL) to give ent-**14b** as a colorless oil, yield 136 mg (88%). $C_{20}H_{26}N_2O_5$ (374.4). $[\alpha]_D^{20}$ −144.7 (*c* 0.18; CH_2Cl_2).

5.24. (+)-(1*R*,2*R*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (15a)

Under N_2 $LiAlH_4$ (40 mg, 1.1 mmol) was added to an ice-cooled solution of the **13a** (70 mg, 0.21 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 1 cm, *h* = 15 cm, CH_2Cl_2/methanol = 9.5:0.5, V = 5 mL, R_f = 0.12) to give **15a** as a yellow oil, yield 37 mg (58%). $C_{18}H_{26}N_2O_2$ (302.4). Purity by HPLC: method 2a: t_R = 19.9 min, purity 99.9%; method 2g: t_R = 17.4 min, purity 97.2%. $[\alpha]_D^{20}$ +14.3 (*c* 0.30; CH_2Cl_2). MS (EI): *m/z* [%] = 302 (M, 14), 181 (M−CH_2PhOCH_3, 24), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.65–1.78 (m, 2H, 3-H (1H), 4-H (1H)), 1.88–1.98 (m, 1H, 4-H), 2.14–2.24 (m, 1H, 3-H), 2.68–2.80 (m, 3H, 7-H (1H), 9-H), 2.86–2.91 (m, 1H, 1-H), 2.92–2.98 (m, 1H, 5-H), 3.12–3.27 (m, 3H, 7-H (1H), NC*H*$_2$CH=CH_2), 3.60 (d, *J* = 17.2 Hz, 1H, NC*H*$_2$Ar), 3.63 (d, *J* = 17.2 Hz, 1H, NC*H*$_2$Ar), 3.79 (s, 3H, ArOC*H*$_3$), 4.00 (q, *J* = 5.7 Hz, 1H, 2-H), 5.12–5.24 (m, 2H, $NCH_2CH{=}CH_2$), 5.83–5.95 (m, 1H, $NCH_2CH{=}CH_2$), 6.84 (d, *J* = 8.5 Hz, 2H, 3′-H$_{4\text{-methoxybenzyl}}$, 5′-H$_{4\text{-methoxybenzyl}}$), 7.23 (d, *J* = 8.5 Hz, 2H, 2′-H$_{4\text{-methoxybenzyl}}$, 6′-H$_{4\text{-methoxybenzyl}}$). The signal for the proton of the OH group could not be detected. ^{13}C NMR ($CDCl_3$): δ [ppm] = 29.3 (1C, C-4), 30.6 (1C, C-3), 46.6 (1C, C-7), 51.2 (1C, C-9), 54.7 (1C, C-5), 55.5 (1C, ArOC*H*$_3$), 59.7 (1C, NC*H*$_2$CH=CH_2), 59.8 (1C, C-1), 60.5 (1C, NC*H*$_2$Ar), 74.5 (1C, C-2), 113.9 (2C, C-3′$_{4\text{-methoxybenzyl}}$, C-5′$H_{4\text{-methoxybenzyl}}$), 118.1 (1C, $NCH_2CH{=}CH_2$), 129.0 (1C, C-1′$_{4\text{-methoxybenzyl}}$), 129.9 (2C, C-2′$_{4\text{-methoxybenzyl}}$, C-6′$_{4\text{-methoxybenzyl}}$), 135.7 (1C, $NCH_2CH{=}CH_2$), 158.9 (1C, C-4′$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3362 (m br, ν_{O-H}), 2919 (m, $\nu_{C-H\ aliph.}$), 1610 (w)/1510 (m, $\nu_{C=C\ arom.}$), 1242 (m)/1036 (m, ν_{C-O}), 830 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.25. (−)-(1*S*,2*S*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (ent-15a)

As described for the preparation of **15a**, the enantiomer ent-**13a** (110 mg, 0.33 mmol) was reacted with $LiAlH_4$ (63 mg, 1.7 mmol) in THF (30 mL) to give ent-**15a** as a yellow oil, yield 41 mg (41%). $C_{18}H_{26}N_2O_2$ (302.4). Purity by HPLC: method 2a: t_R = 20.0 min, purity 97.6%; method 2g: t_R = 17.4 min, purity 96.7%. $[\alpha]_D^{20}$ −14.4 (*c* 0.28; CH_2Cl_2).

5.26. (+)-(1*R*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (15b)

Under N_2 $LiAlH_4$ (58 mg, 1.53 mmol) was added to an ice-cooled solution of **13b** (110 mg, 0.31 mmol) in THF (30 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL,

R_f = 0.03) to give **15b** as a yellow oil, yield 23 mg (23%). $C_{19}H_{28}N_2O_3$ (332.5). Purity by HPLC: method 2d: t_R = 19.6 min, purity 97.4%; method 2g: t_R = 16.6 min, purity 95.6%. $[\alpha]_D^{20}$ +12.1 (*c* 0.28; CH_2Cl_2). MS (EI): *m/z* [%] = 332 (M, 7), 181 (M−2,4-dimethoxybenzyl, 21), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66–1.75 (m, 2H, 3-H (1H), 4-H (1H)), 1.85–1.94 (m, 1H, 4-H), 2.14–2.22 (m, 1H, 3-H), 2.72 (dd, *J* = 11.7/3.1 Hz, 1H, 7-H), 2.78 (dd, *J* = 11.7/3.1 Hz, 1H, 9-H), 2.84 (dd, *J* = 11.7/3.1 Hz, 1H, 9-H), 2.87–2.93 (m, 2H, 1-H, 5-H), 3.11 (dd, *J* = 11.7/2.3 Hz, 1H, 7-H), 3.13–3.23 (m, 2H, NC*H*$_2$CH=CH$_2$), 3.62 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 3.68 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 3.78 (s, 3H, ArOC*H*$_3$), 3.79 (s, 3H, ArOC*H*$_3$), 4.03 (q, *J* = 5.5 Hz, 1H, 2-H), 5.11 (dd, *J* = 10.2/1.6 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.18 (dd, *J* = 17.2/1.6 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.86 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.43 (d, *J* = 2.3 Hz, 1H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$), 6.46 (dd, *J* = 8.6/2.3 Hz, 1H, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.27 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). The signal for the proton of the OH group could not be detected. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3367 (m br, ν_{O-H}), 2919 (m, $\nu_{C-H\ aliph.}$), 1610 (m)/1587 (m)/1505 (m, $\nu_{C=C\ arom.}$), 1205 (m)/1037 (m, ν_{C-O}), 831 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.27. (−)-(1*S*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (ent-15b)

As described for the preparation of **15b**, the enantiomer ent-**13b** (95 mg, 0.26 mmol) was reacted with $LiAlH_4$ (50 mg, 1.32 mmol) in THF (30 mL) to give ent-**15b** as a yellow oil, yield 27 mg (26%). $C_{19}H_{28}N_2O_3$ (332.5). Purity by HPLC: method 2d: t_R = 19.4 min, purity 99.1%; method 2g: t_R = 16.4 min, purity 98.1%. $[\alpha]_D^{20}$ −12.3 (*c* 0.26; CH_2Cl_2).

5.28. (+)-(1*R*,2*R*,5*S*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (16a)

Under N_2 $LiAlH_4$ (34 mg, 0.89 mmol) was added to an ice-cooled solution of **14a** (61 mg, 0.17 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 1 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 5 mL, R_f = 0.05) to give **16a** as a yellow oil, yield 15 mg (27%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2c: t_R = 21.8 min, purity 96.3%; method 2e: t_R = 14.4 min, purity 96.6%. $[\alpha]_D^{20}$ +6.7 (*c* 0.95; CH_2Cl_2). MS (EI): *m/z* [%] = 316 (M, 100), 275 (M–$CH_2CH{=}CH_2$, 11), 195 (M−CH_2PhOCH_3, 47), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.53–1.63 (m, 1H, C*H*$_2$C*H*$_2$), 1.70–1.82 (m, 1H, C*H*$_2$C*H*$_2$), 1.86–1.94 (m, 2H, C*H*$_2$C*H*$_2$), 2.61–2.67 (m, 1H, piperazine-H), 2.68–2.78 (m, 2H, piperazine-H), 2.79–2.86 (m, 1H, piperazine-H), 2.90–2.96 (m, 1H, piperazine-H), 2.99–3.10 (m, 1H, piperazine-H), 3.08 (s, 3H, OC*H*$_3$), 3.13–3.18 (m, 2H, NC*H*$_2$CH=CH$_2$), 3.25–3.31 (m, 1H, 2-H), 3.64 (d, *J* = 13.3 Hz, 1H, NC*H*$_2$Ar), 3.72 (d, *J* = 13.3 Hz, 1H, NC*H*$_2$Ar), 3.79 (s, 3H, ArOC*H*$_3$), 5.06 (d, *J* = 10.2 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.17 (dd, *J* = 17.2/1.6 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.85 (ddt, *J* = 17.2/10.2/5.5 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.84 (d, *J* = 8.6 Hz, 2H, 3′-H$_{4\text{-methoxybenzyl}}$, 5′-H$_{4\text{-methoxybenzyl}}$), 7.26 (d, *J* = 8.6 Hz, 2H, 2′-H$_{4\text{-methoxybenzyl}}$, 6′-H$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3073 (w, $\nu_{C-H\ arom.}$), 2924 (m, $\nu_{C-H\ aliph.}$), 1611 (w)/1510 (m, $\nu_{C=C\ arom.}$), 1462 (w, $\delta_{C-H\ aliph.}$), 1243 (m)/1098 (m, ν_{C-O}), 830 (w, $\Gamma_{p\text{-}subst.\ arom.}$).

5.29. (−)-(1*S*,2*S*,5*R*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (ent-16a)

As described for the preparation of **16a**, the enantiomer ent-**14a** (109 mg, 0.32 mmol) was reacted with $LiAlH_4$ (60 mg, 1.6 mmol) in THF (30 mL) to give ent-**16a** as a yellow oil, yield 13 mg (13%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2c: t_R = 20.1 min, purity 95.7%; method 2e: t_R = 15.8 min, purity 97.6%. $[\alpha]_D^{20}$ −6.4 (*c* 0.57; CH_2Cl_2).

5.30. (+)-(1*R*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-iazabicyclo[3.2.2]nonane (16b)

Under N_2 $LiAlH_4$ (67 mg, 1.76 mmol) was added to an ice-cooled solution of **14b** (132 mg, 0.35 mmol) in THF (30 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL, R_f = 0.05) to give **16b** as a yellow oil, yield 41 mg (34%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 19.3 min, purity 96.4%; method 2e: t_R = 15.1 min, purity 99.1%. $[\alpha]_D^{20}$ +12.6 (*c* 0.43; CH_2Cl_2). MS (EI): *m/z* [%] = 346 (M, 80), 195 (M−2,4-dimethoxybenzyl, 81), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.53–1.63 (m, 1H, C*H*$_2$C*H*$_2$), 1.70–1.81 (m, 1H, C*H*$_2$C*H*$_2$), 1.86–1.94 (m, 2H, C*H*$_2$C*H*$_2$), 2.65–2.77 (m, 2H, piperazine-H), 2.82 (s br, 1H, piperazine-H), 2.88–2.97 (m, 2H, piperazine-H), 3.06 (d, *J* = 11.0 Hz, 1H, piperazine-H), 3.13–3.18 (m, 2H, NC*H*$_2$CH=CH$_2$), 3.14 (s, 3H, OC*H*$_3$), 3.30–3.36 (m, 1H, 2-H), 3.70 (d, *J* = 13.3 Hz, 1H, NC*H*$_2$Ar), 3.73–3.83 (m, 7H, NC*H*$_2$Ar (1H), Ar(OC*H3*)$_2$ (6H)), 5.07 (d, *J* = 10.2 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.17 (d, *J* = 17.2 Hz, 1H, NCH$_2$CH=C*H*$_2$), 5.80–5.91 (m, 1H, NCH$_2$C*H*=CH$_2$), 6.43 (d, *J* = 2.3 Hz, 1H, 3′-H$_{2,4\text{-dimethoxybenzyl}}$), 6.46 (dd, *J* = 8.6/2.3 Hz, 1H, 5′-H$_{2,4\text{-dimethoxybenzyl}}$), 7.31 (d, *J* = 8.6 Hz, 1H, 6′-H$_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3075 (w, $\nu_{C-H\ arom.}$), 2925 (m, $\nu_{C-H\ aliph.}$), 1611 (m)/1587 (m)/1505 (m, $\nu_{C=C\ arom.}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1206 (m)/1097 (m, ν_{C-O}), 832 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.31. (−)-(1*S*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane (ent-16b)

As described for the preparation of **16b**, the enantiomer ent-**14b** (87 mg, 0.23 mmol) was reacted with $LiAlH_4$ (44 mg, 1.16 mmol) in THF (30 mL) to give ent-**16b** as a yellow oil, yield 39 mg (48%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 19.3 min, purity 96.6%; method 2e: t_R = 14.7 min, purity 98.4%. $[\alpha]_D^{20}$ −12.0 (*c* 0.09; CH_2Cl_2).

5.32. (+)-[(1*S*,2*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]non-2-yl] 4-nitrobenzoate (17a)

Under N_2 atmosphere **13a** (503 mg, 1.52 mmol), triphenylphosphine (2.00 g, 7.61 mmol) and 4-nitrobenzoic acid (1.27 g, 7.61 mmol) were dissolved in THF (70 mL). Under ice-cooling diisopropyl azodicarboxylate (1.51 mL, 1.54 g, 7.61 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min and then at rt for 6 h. Thereafter the solvent was removed in vacuo and the residue was purified by FC (Ø = 6 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 2:1, V = 30 mL, R_f = 0.11) to give **17a** as a colorless solid, mp 173 °C, yield 634 mg (87%). $C_{25}H_{25}N_3O_7$ (479.5). $[\alpha]_D^{20}$ +101 (*c* 0.53; CH_2Cl_2). MS (EI): *m/z* [%] = 479 (M, 92), 313 (M−O_2CPhNO_2, 73), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.76–1.86 (m, 1H, C*H*$_2$C*H*$_2$), 1.89–2.00 (m, 1H, C*H*$_2$C*H*$_2$), 2.18–2.30 (m, 2H, C*H*$_2$C*H*$_2$), 3.74 (s, 3H, ArOC*H*$_3$), 3.88 (dd, *J* = 14.9/6.3 Hz, 1H, NC*H*$_2$CH=CH$_2$), 4.01 (dd, *J* = 4.7/2.3 Hz, 1H, 5-H), 4.14–4.22 (m, 2H, 1-H, NC*H*$_2$CH=CH$_2$ (1H)), 4.44 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 4.82 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 5.22–5.35 (m, 3H, 2-H, NCH$_2$CH=C*H*$_2$), 5.59–5.70 (ddt, *J* = 16.4/10.2/

6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.78 (m, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.12 (m, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$), 7.92 (m, 2H, 2′-$H_{4\text{-nitrobenzoate}}$, 6′-$H_{4\text{-nitrobenzoate}}$), 8.27 (m, 2H, 3′-$H_{4\text{-nitrobenzoate}}$, 5′-$H_{4\text{-nitrobenzoate}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3076 (m, $\nu_{C-H\ arom.}$), 2964 (w, $\nu_{C-H\ aliph.}$), 1715 (s, $\nu_{C=O\ ester}$), 1692 (s)/1679 (s, $\nu_{C=O\ amide}$), 1614 (m, $\nu_{C=C\ arom.}$), 1514 (s, $\nu_{N=O}$), 1452 (s, $\delta_{C-H\ aliph.}$), 1344 (m, $\nu_{N=O}$), 1233 (s)/1110 (m, ν_{C-O}), 824 (m, $\Gamma_{p\text{-subst. arom.}}$).

5.33. (−)-[(1*R*,2*R*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]non-2-yl] 4-nitrobenzoate (ent-17a)

As described for the preparation of **17a**, the enantiomer ent-**13a** (250 mg, 0.76 mmol) was reacted with triphenylphosphine (992 mg, 3.78 mmol), 4-nitrobenzoic acid (632 mg, 3.78 mmol) and diisopropyl azodicarboxylate (0.75 mL, 765 mg, 3.78 mmol) in THF (50 mL) to give ent-**17a** as a colorless solid, mp 172 °C, yield 275 mg (76%). $C_{25}H_{25}N_3O_7$ (479.5). $[\alpha]_D^{20}$ −98 (*c* 0.13; CH_2Cl_2).

5.34. (+)-[(1*S*,2*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]non-2-yl] 4-nitrobenzoate (17b)

Under N_2 **13b** (1.70 g, 4.72 mmol), triphenylphosphine (4.95 g, 18.9 mmol) and 4-nitrobenzoic acid (3.15 g, 18.9 mmol) were dissolved in THF (300 mL). Under ice-cooling diisopropyl azodicarboxylate (3.74 mL, 3.82 g, 18.9 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min and then at rt for 6 h. Thereafter the solvent was removed in vacuo and the residue was purified by FC (Ø = 8 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:1, V = 30 mL, R_f = 0.16) to give **17b** as a colorless solid, mp 169 °C, yield 1.87 g (78%). $C_{26}H_{27}N_3O_8$ (509.5). $[\alpha]_D^{20}$ +79.5 (*c* 0.51; CH_2Cl_2). MS (EI): *m/z* [%] = 509 (M, 44), 343 (M−O_2CPhNO_2, 26), 151 (2,4-dimethoxybenzyl, 100). ^1H NMR ($CDCl_3$): δ [ppm] = 1.73–1.83 (m, 1H, CH_2CH_2), 1.90–2.01 (m, 1H, CH_2CH_2), 2.18–2.28 (m, 2H, CH_2CH_2), 3.67 (s, 3H, $ArOCH_3$), 3.74 (s, 3H, $ArOCH_3$), 3.84 (dd, *J* = 14.9/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 3.94 (m, 1H, 5-H), 4.16 (dd, *J* = 14.9/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 4.34 (d, *J* = 14.1 Hz, 1H, NCH_2Ar), 4.38 (d, *J* = 1.6 Hz, 1H, 1-H), 4.94 (d, *J* = 14.9 Hz, 1H, NCH_2Ar), 5.18–5.24 (m, 2H, $NCH_2CH{=}CH_2$), 5.35 (ddd, *J* = 9.4/4.7/1.6 Hz, 1H, 2-H), 5.74 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.33 (d, *J* = 2.3 Hz, 1H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$), 6.38 (dd, *J* = 8.6/2.3 Hz, 1H, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.13 (d, *J* = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$), 8.08 (d, *J* = 8.6 Hz, 2H, 2′-$H_{4\text{-nitrobenzoate}}$, 6′-$H_{4\text{-nitrobenzoate}}$), 8.30 (d, *J* = 8.6 Hz, 2H, 3′-$H_{4\text{-nitrobenzoate}}$, 5′-$H_{4\text{-nitrobenzoate}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3076 (w, $\nu_{C-H\ arom.}$), 2934 (m, $\nu_{C-H\ aliph.}$), 1720 (s, $\nu_{C=O\ ester}$), 1685 (s, $\nu_{C=O\ amide}$), 1608 (m, $\nu_{C=C\ arom.}$), 1523 (s, $\nu_{N=O}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1347 (m, $\nu_{N=O}$), 1269 (s)/1103 (m, ν_{C-O}), 824 (m, $\Gamma_{tri\text{-subst. arom.}}$).

5.35. (−)-[(1*R*,2*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]non-2-yl] 4-nitrobenzoate (ent-17b)

As described for the preparation of **17b**, the enantiomer ent-**13b** (513 mg, 1.42 mmol) was reacted with triphenylphosphine (1.87 g, 7.12 mmol), 4-nitrobenzoic acid (1.19 g, 7.12 mmol) and diisopropyl azodicarboxylate (1.41 mL, 1.44 g, 7.12 mmol) in THF (70 mL) to give ent-**17b** as a colorless solid, mp 168 °C, yield 574 mg (79%). $C_{26}H_{27}N_3O_8$ (509.5). $[\alpha]_D^{20}$ −79.1 (*c* 0.27; CH_2Cl_2).

5.36. (+)-(1*S*,2*S*,5*S*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (18a)

The ester **17a** (634 mg, 1.32 mmol) and potassium carbonate (457 mg, 3.31 mmol) were suspended in methanol (70 mL) and the mixture was stirred at rt for 16 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 3 cm, *h* = 15 cm, ethyl acetate, *V* = 20 mL, R_f = 0.30) to give **18a** as a colorless solid, mp 111 °C, yield 393 mg (90%). $C_{18}H_{22}N_2O_4$ (330.4). Calculated C, 65.44; H, 6.71; N, 8.48; found: C, 65.17; H, 6.62; N, 8.30. $[\alpha]_D^{20}$ +31.5 (*c* 0.26; CH_2Cl_2). MS (EI): *m/z* [%] = 330 (M, 100), 209 (M−CH_2PhOCH_3, 7), 121 (CH_2PhOCH_3, 83). ^1H NMR ($CDCl_3$): δ [ppm] = 1.56–1.69 (m, 2H, 3-H (1H), 4-H (1H)), 1.93–2.03 (m, 1H, 3-H), 2.05–2.17 (m, 1H, 4-H), 2.31 (d br, *J* = 5.5 Hz, 1H, O*H*), 3.71–3.80 (m, 4H, $ArOCH_3$ (3H), $NCH_2CH{=}CH_2$ (1H)), 3.88 (dd, *J* = 5.5/1.8 Hz, 1H, 5-H), 3.96–4.03 (m, 2H, 1-H, 2-H), 4.14 (ddt, *J* = 15.7/6.4/1.8 Hz, 1H, $NCH_2CH{=}CH_2$), 4.38 (d, *J* = 14.6 Hz, 1H, NCH_2Ar), 4.91 (d, *J* = 14.6 Hz, 1H, NCH_2Ar), 5.18–5.26 (m, 2H, $NCH_2CH{=}CH_2$), 5.65–5.76 (m, 1H, $NCH_2CH{=}CH_2$), 6.82–6.87 (m, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.16–7.21 (m, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3337 (m br, ν_{OH}), 2931 (m, $\nu_{C-H\ aliph.}$), 1672 (s)/1652 (s, $\nu_{C=O\ amide}$), 1613 (m)/1515 (m, $\nu_{C=C\ arom.}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1241 (m)/1066 (m, ν_{C-O}), 829 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.37. (−)-(1*R*,2*R*,5*R*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-18a)

As described for the preparation of **18a**, the enantiomer ent-**17a** (275 mg, 0.57 mmol) was reacted with potassium carbonate (198 mg, 1.43 mmol) in methanol (50 mL) to give ent-**18a** as a colorless solid, mp 111 °C, yield 158 mg (83%). $C_{18}H_{22}N_2O_4$ (330.4). Calculated C, 65.44; H, 6.71; N, 8.48; found: C, 65.21; H, 6.67; N, 8.33. $[\alpha]_D^{20}$ −29.3 (*c* 0.18; CH_2Cl_2).

5.38. (+)-(1*S*,2*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (18b)

The ester **17b** (1.87 g, 3.67 mmol) and potassium carbonate (1.27 g, 9.18 mmol) were suspended in methanol (200 mL) and the mixture was stirred at rt for 16 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 5 cm, *h* = 15 cm, ethyl acetate, *V* = 30 mL, R_f = 0.22) to give **18b** as a colorless solid, mp 159 °C, yield 1.22 g (92%). $C_{19}H_{24}N_2O_5$ (360.4). Calculated C, 63.32; H, 6.71; N, 7.77; found: C, 63.44; H, 6.76; N, 7.42. $[\alpha]_D^{20}$ +41.6 (*c* 0.20; CH_2Cl_2). MS (EI): *m/z* [%] = 360 (M, 38), 151 (2,4-dimethoxybenzyl, 100). ^1H NMR ($CDCl_3$): δ [ppm] = 1.56–1.71 (m, 2H, 3-H (1H), 4-H (1H)), 1.92–2.02 (m, 1H, 3-H), 2.04–2.14 (m, 1H, 4-H), 3.70–3.80 (m, 7H, $ArOCH_3$ (6H), $NCH_2CH{=}CH_2$ (1H)), 3.84 (dd, *J* = 5.5/2.3 Hz, 1H, 5-H), 3.98–4.03 (m, 1H, 2-H), 4.06–4.16 (m, 2H, 1-H, $NCH_2CH{=}CH_2$ (1H)), 4.40 (d, *J* = 14.1 Hz, 1H, NCH_2Ar), 4.87 (d, *J* = 14.1 Hz, 1H, NCH_2Ar), 5.13–5.23 (m, 2H, $NCH_2CH{=}CH_2$), 5.69 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.42–6.47 (m, 2H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.19 (d, *J* = 7.8 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). The signal for the proton of the OH group could not be detected. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3419 (m br, ν_{O-H}), 2945 (m, $\nu_{C-H\ aliph.}$), 1675 (s)/1652 (s, $\nu_{C=O\ amide}$), 1615 (m)/1585 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1454 (m, $\delta_{C-H\ aliph.}$), 1211 (m)/1129 (m, ν_{C-O}), 819 (w, $\Gamma_{tri\text{-subst. arom.}}$).

5.39. (−)-(1*R*,2*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-hydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-18b)

As described for the preparation of **18b**, the enantiomer ent-**17b** (512 mg, 1.00 mmol) was reacted with potassium carbonate (347 mg, 2.51 mmol) in methanol (70 mL) to give ent-**18b** as a colorless solid, mp 159 °C, yield 343 mg (95%). $C_{19}H_{24}N_2O_5$ (360.4). Calculated C, 63.32; H, 6.71; N, 7.77; found: C, 63.47; H, 6.67; N, 7.65. $[\alpha]_D^{20}$ −40.4 (*c* 0.23; CH_2Cl_2).

5.40. (−)-(1*S*,2*S*,5*S*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (19a)

Under N_2 and ice-cooling 60% NaH suspension in paraffin oil (52 mg, ca. 31 mg NaH, 1.31 mmol) was added to a solution of **18a** (72 mg, 0.22 mmol) THF (20 mL). After 20 min methyl iodide (0.04 mL, 93 mg, 0.65 mmol) was added dropwise and the mixture was stirred at rt for 16 h. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and washed with water (2×), 0.5 M HCl (1×) and 0.5 M NaOH (1×). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 1 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 2:1, V = 5 mL, R_f = 0.04) to give **19a** as a colorless solid, mp 118 °C, yield 61 mg (81%). $C_{19}H_{24}N_2O_4$ (344.4). Calculated C, 66.26; H, 7.02; N, 8.13; found: C, 66.27; H, 6.89; N, 8.00. $[\alpha]_D^{20}$ −9.9 (*c* 0.18; CH_2Cl_2). MS (EI): *m/z* [%] = 344 (M, 32), 303 (M−$CH_2CH{=}CH_2$, 4), 223 (M−CH_2PhOCH_3, 10), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.55–1.75 (m, 2H, 3-H (1H), 4-H (1H)), 2.03–2.18 (m, 2H, 3-H (1H), 4-H (1H)), 3.31 (s, 3H, OC*H*$_3$), 3.48 (ddd, *J* = 8.6/5.5/1.6 Hz, 1H, 2-H), 3.72–3.79 (m, 4H, ArOC*H*$_3$, NC*H*$_2$CH=CH_2 (1H)), 3.88 (dd, *J* = 5.5/1.6 Hz, 1H, 5-H), 3.97 (d, *J* = 14.1 Hz, 1H, NC*H*$_2$Ar), 4.02 (d, *J* = 1.6 Hz, 1H, 1-H), 4.15 (ddt, *J* = 14.9/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH_2), 5.18–5.28 (m, 3H, NC*H*$_2$Ar (1H), $NCH_2CH{=}CH_2$), 5.71 (ddt, *J* = 16.4/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.85 (d, *J* = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.14 (d, *J* = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3086 (w, $\nu_{C-H\ arom.}$), 2969 (w, $\nu_{C-H\ aliph.}$), 1676 (s, $\nu_{C=O\ amide}$), 1609 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1456 (m, $\delta_{C-H\ aliph.}$), 1250 (m)/1093 (m, ν_{C-O}), 837 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.41. (+)-(1*R*,2*R*,5*R*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-19a)

As described for the preparation of **19a**, the enantiomer ent-**18a** (112 mg, 0.34 mmol), 60% NaH suspension in paraffin oil (81 mg, ca. 49 mg NaH, 2.03 mmol) and methyl iodide (0.06 mL, 144 mg, 1.02 mmol) were reacted in THF (30 mL) to give ent-**19a** as a colorless solid, mp 118 °C, yield 97 mg (83%). $C_{19}H_{24}N_2O_4$ (344.4). Calculated C, 66.26; H, 7.02; N, 8.13; found: C, 66.23; H, 6.96; N, 8.03. $[\alpha]_D^{20}$ +9.7 (*c* 0.33; CH_2Cl_2).

5.42. (+)-(1*S*,2*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (19b)

Under N_2 and ice-cooling 60% NaH suspension in paraffin oil (55 mg, ca. 33 mg NaH, 1.37 mmol) was added to a solution of **18b** (82 mg, 0.23 mmol) in THF (20 mL). After 20 min methyl iodide (0.04 mL, 97 mg, 0.68 mmol) was added dropwise and the mixture was stirred at rt for 16 h. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and washed with water (2×), 0.5 M HCl (1×) and 0.5 M NaOH (1×). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 1 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 2:1, V = 5 mL, R_f = 0.03) to give **19b** as a colorless solid, mp 116 °C, yield 83 mg (97%). $C_{20}H_{26}N_2O_5$ (374.4). Calculated C, 64.16; H, 7.00; N, 7.48; found: C, 63.77; H, 6.81; N, 7.32. $[\alpha]_D^{20}$ +5.8 (*c* 0.37; CH_2Cl_2). MS (EI): *m/z* [%] = 374 (M, 42), 343 (M−OCH_3, 9), 223 (M−2,4-dimethoxybenzyl, 2), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.52–1.76 (m, 2H, 3-H (1H), 4-H (1H)), 2.00–2.16 (m, 2H, 3-H (1H), 4-H (1H)), 3.31 (s, 3H, OC*H*$_3$), 3.43–3.48 (m, 1H, 2-H), 3.71 (ddt, *J* = 15.7/6.3/1.6 Hz, 1H, NC*H*$_2$CH=CH_2), 3.77–3.83 (m, 7H, 5-H, ArOC*H*$_3$ (6H)), 4.10–4.19 (m, 2H, NC*H*$_2$CH=CH_2 (1H), NC*H*$_2$Ar (1H)), 4.20 (s, 1H, 1-H), 5.05 (d, *J* = 14.9 Hz, 1H, NC*H*$_2$Ar), 5.12–5.22 (m, 2H, $NCH_2CH{=}CH_2$), 5.69 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.41–6.45 (m, 2H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.14 (d, *J* = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3102 (w, $\nu_{C-H\ arom.}$), 2952 (w, $\nu_{C-H\ aliph.}$), 1672 (s, $\nu_{C=O\ amide}$), 1617 (m)/1591 (m)/1506 (m, $\nu_{C=C\ arom.}$), 1456 (m, $\delta_{C-H\ aliph.}$), 1210 (m)/1096 (m, ν_{C-O}), 831 (w, $\Gamma_{tri\text{-subst. arom.}}$).

5.43. (−)-(1*R*,2*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-19b)

As described for the preparation of **19b**, the enantiomer ent-**18b** (102 mg, 0.28 mmol), 60% NaH suspension in paraffin oil (68 mg, ca. 41 mg NaH, 1.70 mmol) and methyl iodide (0.05 mL, 121 mg, 0.85 mmol) were reacted in THF (20 mL) to give ent-**19b** as a colorless solid, mp 116 °C, yield 85 mg (80%). $C_{20}H_{26}N_2O_5$ (374.4). Calculated C, 64.16; H, 7.00; N, 7.48; found: C, 64.21; H, 6.99; N, 7.32. $[\alpha]_D^{20}$ −5.9 (*c* 0.48; CH_2Cl_2).

5.44. (+)-(1*R*,2*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (20a)

Under N_2 $LiAlH_4$ (68 mg, 1.78 mmol) was added to an ice-cooled solution of **18a** (118 mg, 0.36 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL, R_f = 0.11) to give **20a** as a yellow oil, yield 38 mg (35%). $C_{18}H_{26}N_2O_2$ (302.4). Purity by HPLC: method 2d: t_R = 23.3 min, purity 97.0%; method 2f: t_R = 16.6 min, purity 98.8%. $[\alpha]_D^{20}$ +27.4 (*c* 0.39; CH_2Cl_2). MS (EI): *m/z* [%] = 302 (M, 37), 181 (M−CH_2PhOCH_3, 31), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.52–1.64 (m, 2H, 3-H (1H), 4-H (1H)), 1.71–1.80 (m, 1H, 4-H), 1.93–2.03 (m, 1H, 3-H), 2.57 (dd, *J* = 11.0/2.3 Hz, 1H, 7-H or 9-H), 2.62 (dd, *J* = 11.0/2.3 Hz, 1H, 7-H or 9-H), 2.79 (dd, *J* = 11.0/3.9 Hz, 1H, 7-H or 9-H), 2.84–2.94 (m, 3H, 1-H, 5-H, 7-H or 9-H), 3.13 (d, *J* = 6.3 Hz, 2H, NC*H*$_2$CH=CH_2), 3.67 (d, *J* = 12.5 Hz, 1H, NC*H*$_2$Ar), 3.72 (d, *J* = 12.5 Hz, 1H, NC*H*$_2$Ar), 3.75–3.80 (m, 1H, 2-H), 3.79 (s, 3H, ArOC*H*$_3$), 5.07 (dd, *J* = 10.2/1.6 Hz, 1H, $NCH_2CH{=}CH_2$), 5.16 (dd, *J* = 17.2/2.3 Hz, 1H, $NCH_2CH{=}CH_2$), 5.80 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.85 (d, *J* = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.23 (d, *J* = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). The signal for the proton of the OH group could not be detected. ^{13}C NMR ($CDCl_3$): δ (ppm) = 28.1 (1C, C-4), 30.1 (1C, C-3), 49.1 (1C, C-7 or C-9), 51.9 (1C, C-9 or C-7), 53.7 (1C, C-5), 55.5 (1C, ArOCH_3), 59.5 (1C, $NCH_2CH{=}CH_2$), 60.2 (1C, C-1), 61.6 (1C, NCH_2Ar), 70.6 (1C, C-2), 114.1 (2C, C-3′$_{4\text{-methoxybenzyl}}$, C-5′$_{4\text{-methoxybenzyl}}$), 117.0 (1C, $NCH_2CH{=}CH_2$), 130.4 (2C, C-2′$_{4\text{-methoxybenzyl}}$, C-6′$_{4\text{-methoxybenzyl}}$), 130.6 (1C, C-1′$_{4\text{-methoxybenzyl}}$), 136.7 (1C, $NCH_2CH{=}CH_2$), 159.2 (1C, C-4′$_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379 (m br, ν_{O-H}), 2922 (m, $\nu_{C-H\ aliph.}$), 1611 (w)/1510 (m, $\nu_{C=C\ arom.}$), 1244 (m)/1035 (w, ν_{C-O}), 829 (w, $\Gamma_{p\text{-subst. arom.}}$).

5.45. (−)-(1*S*,2*R*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (ent-20a)

As described for the preparation of **20a**, the enantiomer ent-**18a** (98 mg, 0.30 mmol) was reacted with $LiAlH_4$ (56 mg, 1.48 mmol) in THF (20 mL) to give ent-**20a** as a yellow oil, yield 27 mg (30%). $C_{18}H_{26}$-N_2O_2 (302.4). Purity by HPLC: method 2d: t_R = 22.6 min, purity 99.6%; method 2f: t_R = 16.6 min, purity 99.0%. $[\alpha]_D^{20}$ −26.7 (*c* 0.13; CH_2Cl_2).

5.46. (+)-(1*R*,2*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (20b)

Under N_2 $LiAlH_4$ (63 mg, 1.65 mmol) was added to an ice-cooled solution of **18b** (119 mg, 0.33 mmol) in THF (30 mL). The mixture

was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL, R_f = 0.11) to give **20b** as a yellow oil, yield 22 mg (20%). $C_{19}H_{28}N_2O_3$ (332.5). Purity by HPLC: method 2d: t_R = 38.3 min, purity 98.8%; method 2g: t_R = 31.2 min, purity 97.3%. $[\alpha]_D^{20}$ +25.5 (*c* 0.54; CH_2Cl_2). MS (EI): *m/z* [%] = 332 (M, 27), 181 (M−2,4-dimethoxybenzyl, 48), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.47–1.60 (m, 2H, 3-H (1H), 4-H (1H)), 1.67–1.77 (m, 1H, 4-H), 1.93–2.02 (m, 1H, 3-H), 2.43 (d, *J* = 9.4 Hz, 1H, 7-H or 9-H), 2.60 (d, *J* = 10.2 Hz, 1H, 7-H or 9-H), 2.77–2.98 (m, 4H, 1-H, 5-H, 7-H (1H), 9-H (1H)), 3.14 (d, *J* = 6.3 Hz, 2H, NCH_2CH=CH_2), 3.65 (d, *J* = 11.7 Hz, 1H, NCH_2Ar), 3.75–3.85 (m, 2H, 2-H, NCH_2Ar, (1H)), 3.80 (s, 3H, ArOCH_3), 3.83 (s, 3H, ArOCH_3), 5.02 (d, *J* = 10.2 Hz, 1H, NCH$_2$CH=CH_2), 5.17 (dd, *J* = 17.2/1.6 Hz, 1H, NCH$_2$CH=CH_2), 5.81 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.40 (dd, *J* = 8.6/2.3 Hz, 1H, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 6.46 (d, *J* = 2.3 Hz, 1H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.08 (d, *J* = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). The signal for the proton of the OH group could not be detected. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3373 (m br, ν_{O-H}), 2921 (m, $\nu_{C-H\ aliph.}$), 1612 (m)/1587 (m)/1506 (m, $\nu_{C=C\ arom.}$), 1207 (m)/1033 (m, ν_{C-O}), 833 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.47. (−)-(1*S*,2*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (ent-20b)

As described for the preparation of **20b**, the enantiomer ent-**18b** (110 mg, 0.31 mmol) was reacted with $LiAlH_4$ (58 mg, 1.53 mmol) in THF (30 mL) to give ent-**20b** as a yellow oil, yield 30 mg (30%). $C_{19}H_{28}N_2O_3$ (332.5). Purity by HPLC: method 2d: t_R = 34.6 min, purity 99.7%; method 2g: t_R = 34.1 min, purity 97.3%. $[\alpha]_D^{20}$ −26.1 (*c* 0.69; CH_2Cl_2).

5.48. (−)-(1*R*,2*S*,5*S*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (21a)

Under N_2 $LiAlH_4$ (72 mg, 1.9 mmol) was added to an ice-cooled solution of **19a** (130 mg, 0.38 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 10 mL, R_f = 0.07) to give **21a** as a yellow oil, yield 66 mg (55%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2c: t_R = 18.8 min, purity 97.8%; method 2f: t_R = 23.9 min, purity 98.0%. $[\alpha]_D^{20}$ −6.5 (*c* 0.38; CH_2Cl_2). MS (EI): *m/z* [%] = 316 (M, 96), 275 (M−CH_2CH=CH_2, 6), 195 (M−CH_2PhOCH_3, 44), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.59–1.69 (m, 1H, CH_2CH_2), 1.73–1.81 (m, 1H, CH_2CH_2), 1.82–1.90 (m, 1H, CH_2CH_2), 1.99–2.11 (m, 1H, CH_2CH_2), 2.65–2.71 (m, 1H, piperazine-H), 2.74–2.86 (m, 4H, piperazine-H), 2.99–3.02 (m, 1H, piperazine-H), 3.11–3.22 (m, 2H, NCH_2CH=CH_2), 3.15 (s, 3H, OCH_3), 3.52 (dd, *J* = 11.0/4.7 Hz, 1H, 2-H), 3.65 (d, *J* = 13.3 Hz, 1H, NCH_2Ar), 3.70 (d, *J* = 13.3 Hz, 1H, NCH_2Ar), 3.79 (s, 3H, ArOCH_3), 5.10 (d, *J* = 10.2 Hz, 1H, NCH$_2$CH=CH_2), 5.17 (dd, *J* = 17.2/1.6 Hz, 1H, NCH$_2$CH=CH_2), 5.86 (ddt, *J* = 17.2/10.2/6.3 Hz, 1H, NCH$_2$C*H*=CH$_2$), 6.83 (d, *J* = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.30 (d, *J* = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3072 (w, $\nu_{C-H\ arom.}$), 2925 (m, $\nu_{C-H\ aliph.}$), 1611 (w)/1510 (m, $\nu_{C=C\ arom.}$), 1463 (w, $\delta_{C-H\ aliph.}$), 1242 (m)/1097 (m, ν_{C-O}), 828 (w, $\Gamma_{p\text{-}subst.\ arom.}$).

5.49. (+)-(1*S*,2*R*,5*R*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (ent-21a)

As described for the preparation of **21a**, the enantiomer ent-**19a** (97 mg, 0.28 mmol) was reacted with $LiAlH_4$ (54 mg, 1.4 mmol) in THF (20 mL) to give ent-**21a** as a yellow oil, yield 19 mg (21%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2c: t_R = 18.1 min, purity 98.8%; method 2f: t_R = 24.0 min, purity 100%. $[\alpha]_D^{20}$ +6.8 (*c* 0.58; CH_2Cl_2).

5.50. (−)-(1*R*,2*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane (21b)

Under N_2 $LiAlH_4$ (41 mg, 1.08 mmol) was added to an ice-cooled solution of **19b** (81 mg, 0.22 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished. The mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 1 cm, *h* = 15 cm, CH_2Cl_2/methanol = 50:1, V = 5 mL, R_f = 0.03) to give **21b** as a yellow oil, yield 19 mg (25%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 19.2 min, purity 100%; method 2i: t_R = 16.3 min, purity 97.2%. $[\alpha]_D^{20}$ −12.7 (*c* 0.26; CH_2Cl_2). MS (EI): *m/z* [%] = 346 (M, 100), 195 (M−2,4-dimethoxybenzyl, 68), 151 (2,4-dimethoxybenzyl, 80). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.60–1.92 (m, 3H, CH_2CH_2), 2.03–2.15 (m, 1H, CH_2CH_2), 2.76–2.90 (m, 4H, piperazine-H), 2.92–2.99 (m, 1H, piperazine-H), 3.02–3.09 (m, 1H, piperazine-H), 3.14–3.24 (m, 2H, NCH_2CH=CH_2), 3.18 (s, 3H, OCH_3), 3.56 (dd, *J* = 10.2/4.7 Hz, 1H, 2-H), 3.69–3.74 (m, 2H, NCH_2Ar), 3.79 (s, 3H, ArOCH_3), 3.80 (s, 3H, ArOCH_3), 5.11–5.22 (m, 2H, NCH$_2$CH=CH_2), 5.83–5.96 (m, 1H, NCH$_2$C*H*=CH$_2$), 6.43 (d, *J* = 2.3 Hz, 1H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$), 6.49 (dd, *J* = 7.8/2.3 Hz, 1H, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.43–7.49 (m, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3075 (w, $\nu_{C-H\ arom.}$), 2926 (m, $\nu_{C-H\ aliph.}$), 1611 (m)/1588 (m)/1506 (m, $\nu_{C=C\ arom.}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1206 (m)/1097 (m, ν_{C-O}), 831 (w, $\Gamma_{tri\text{-}subst.\ arom.}$).

5.51. (+)-(1*S*,2*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-2-methoxy-6,8-diazabicyclo[3.2.2]nonane (ent-21b)

As described for the preparation of **21b**, the enantiomer ent-**19b** (90 mmg, 0.24 mmol) was reacted with $LiAlH_4$ (46 mg, 1.21 mmol) in THF (20 mL) to give ent-**21b** as a yellow oil, yield 22 mg (26%). $C_{20}H_{30}N_2O_3$ (346.5). Purity by HPLC: method 2c: t_R = 18.9 min, purity 98.2%; method 2i: t_R = 18.0 min, purity 97.4%. $[\alpha]_D^{20}$ +13.2 (*c* 0.79; CH_2Cl_2).

5.52. (+)-[(1*S*,2*R*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]nonan-2-yl] methanesulfonate (22a)

The alcohol **13a** (247 mg, 0.75 mmol), 4-(dimethylamino)pyridine (183 mg, 1.50 mmol) and *N*,*N*-diisopropylethylamine (0.62 mL, 483 mg, 3.74 mmol) were dissolved in CH_2Cl_2 (20 mL). Under ice-cooling methanesulfonyl chloride (0.12 mL, 171 mg, 1.50 mmol) was slowly added and the mixture was stirred at 0 °C for 2 h and at rt for 16 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 3 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, V = 20 mL, R_f = 0.28) to give **22a** as a colorless solid, mp 110 °C, yield 292 mg (96%). $C_{19}H_{24}N_2O_6S$ (408.5). $[\alpha]_D^{20}$ +97.8 (*c* 0.72; CH_2Cl_2). MS (EI): *m/z* [%] = 408 (M, 100), 121 (CH_2PhOCH_3, 46). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.80–2.08 (m, 4H, 3-H, 4-H), 3.02 (s, 3H, CH_3), 3.80 (s, 3H, ArOCH_3), 3.95 (dd, *J* = 4.7/3.1 Hz, 1H, 5-H), 3.97–4.08 (m, 2H, NCH_2CH=CH$_2$), 4.17 (d, *J* = 3.9 Hz, 1H, 1-H),

4.43–4.48 (m, 1H, 2-H), 4.53 (s, 2H, NCH_2Ar), 5.23–5.29 (m, 2H, $NCH_2CHH{=}CH_2$), 5.75 (ddt, J = 17.2/9.4/6.3 Hz, 1H, $NCH_2CHH{=}CH_2$), 6.87 (d, J = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.22 (d, J = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3012 (w, $\nu_{C-H\ arom.}$), 2935 (m, $\nu_{C-H\ aliph.}$), 1675 (s, $\nu_{C=O\ amide}$), 1612 (m)/1512 (m, $\nu_{C=C\ arom.}$), 1455 (m, $\delta_{C-H\ aliph.}$), 1244 (m, $\nu_{C\text{-}O}$), 1170 (m, $\nu_{S=O}$), 829 (m, $\Gamma_{p\text{-subst. arom.}}$).

5.53. (−)-[(1*R*,2*S*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]nonan-2-yl] methanesulfonate (ent-22a)

As described for the preparation of **22a**, the enantiomer ent-**13a** (296 mg, 0.90 mmol) was reacted with 4-(dimethylamino)pyridine (219 mg, 1.79 mmol), *N*,*N*-diisopropylethylamine (0.74 mL, 580 mg, 4.49 mmol) and methanesulfonyl chloride (0.14 mL, 214 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) to give ent-**22a** as a colorless solid, mp 111 °C, yield 256 mg (70%). $C_{19}H_{24}N_2O_6S$ (408.5). $[\alpha]_D^{20}$ −98.5 (*c* 0.33; CH_2Cl_2).

5.54. (+)-[(1*S*,2*R*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]nonan-2-yl] methanesulfonate (22b)

The alcohol **13b** (192 mg, 0.53 mmol), 4-(dimethylamino)pyridine (130 mg, 1.07 mmol) and *N*,*N*-diisopropylethylamine (0.44 mL, 344 mg, 2.66 mmol) were dissolved in CH_2Cl_2 (20 mL). Under ice-cooling methanesulfonyl chloride (0.08 mL, 122 mg, 1.07 mmol) was slowly added and the mixture was stirred at 0 °C for 2 h and at rt for 16 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 3 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, V = 20 mL, R_f = 0.24) to give **22b** as a yellow oil, yield 205 g (88%). $C_{20}H_{26}N_2O_7S$ (438.5). Purity by HPLC: method 1: t_R = 18.4 min, purity 99.1%. $[\alpha]_D^{20}$ +99.8 (*c* 0.64; CH_2Cl_2). MS (EI): *m*/*z* [%] = 438 (M, 30), 343 (M−O_3SCH_3, 8), 287 (M−2,4-dimethoxybenzyl, 7), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.80–1.96 (m, 4H, 3-H, 4-H), 3.02 (s, 3H, CH_3), 3.80 (s, 3H, ArOCH_3), 3.83 (s, 3H, ArOCH_3), 3.87–3.90 (m, 1H, 5-H), 3.96 (ddt, J = 14.9/6.3/1.6 Hz, 1H, NCH_2CH=CH_2), 4.05 (ddt, J = 14.9/6.3/1.6 Hz, 1H, NCH_2CH=CH_2), 4.36 (d, J = 4.7 Hz, 1H, 1-H), 4.44 (d, J = 14.1 Hz, 1H, NCH_2Ar), 4.55–4.59 (m, 1H, 2-H), 4.66 (d, J = 14.1 Hz, 1H, NCH_2Ar), 5.20–5.25 (m, 2H, $NCH_2CH{=}CH_2$), 5.74 (ddt, J = 18.0/9.4/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.43–6.46 (m, 2H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.25 (d, J = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2937 (m, $\nu_{C-H\ aliph.}$), 1679 (s, $\nu_{C=\ O\ amide}$), 1612 (m)/1508 (m, $\nu_{C=C\ arom.}$), 1454 (m, $\delta_{C-H\ aliph.}$), 1171 (m, $\nu_{S=O}$), 1030 (m, ν_{C-O}), 830 (m, $\Gamma_{tri\text{-subst. arom.}}$).

5.55. (−)-[(1*R*,2*S*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-7,9-dioxo-6,8-diazabicyclo[3.2.2]nonan-2-yl] methanesulfonate (ent-22b)

The alcohol ent-**13b** (725 mg, 2.01 mmol) and triethylamine (1.1 mL, 814 mg, 8.05 mmol) were dissolved in CH_2Cl_2 (30 mL). Under ice-cooling methanesulfonyl chloride (0.31 mL, 461 mg, 4.02 mmol) was slowly added and the mixture was stirred at 0 °C for 2 h and at rt for 16 h. Then water was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by FC (Ø = 4 cm, *h* = 15 cm, cyclohexane/ethyl acetate = 1:2, V = 30 mL, R_f = 0.24) to give ent-**22b** as a yellow oil, yield 572 mg (65%). $C_{20}H_{26}N_2O_7S$ (438.5). $[\alpha]_D^{20}$ −96.8 (*c* 0.66; CH_2Cl_2).

5.56. (+)-(1*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (23a)

Under N_2 $LiAlH_4$ (172 mg, 4.53 mmol) was added to an ice-cooled solution of **22a** (370 mg, 0.91 mmol) in THF (50 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished, the mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 2 cm, *h* = 15 cm, CH_2Cl_2/methanol = 9.5:0.5, V = 10 mL, R_f = 0.24) to give **23a** as a yellow oil, yield 120 mg (46%). $C_{18}H_{26}N_2O$ (286.4). Purity by HPLC: method 2b: t_R = 18.4 min, purity 95.8%; method 2h: t_R = 15.6 min, purity 96.1%. $[\alpha]_D^{20}$ +10.8 (*c* 0.18; CH_2Cl_2). MS (EI): *m*/*z* [%] = 286 (M, 35), 245 (M−$CH_2CH{=}CH_2$, 11), 165 (M−CH_2PhOCH_3, 81), 121 (CH_2PhOCH_3, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.58–1.94 (m, 6H, 2-H, 3-H, 4-H), 2.74–2.79 (m, 2H, piperazine-H), 2.88–2.97 (m, 4H, piperazine-H), 3.17–3.26 (m, 2H, NC*H2*CH=CH_2), 3.65 (s, 2H, NCH_2Ar), 3.79 (s, 3H, ArOCH_3), 5.10 (m, 1H, $NCH_2CH{=}CH_2$), 5.19 (m, 1H, $NCH_2CH{=}CH_2$), 5.92 (ddt, J = 16.4/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.84 (d, J = 8.6 Hz, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.28 (d, J = 8.6 Hz, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3073 (w, $\nu_{C-H\ arom.}$), 2913 (m, $\nu_{C-H\ aliph.}$), 1611 (m)/1510 (m, $\nu_{C=C\ arom.}$), 1452 (m, $\delta_{C-H\ aliph.}$), 1241 (m)/1037 (m, ν_{C-O}), 826 (m, $\Gamma_{p\text{-subst. arom.}}$).

5.57. (−)-(1*R*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (ent-23a)

As described for the preparation of **23a**, the enantiomer ent-**22a** (240 mg, 0.59 mmol) was reacted with $LiAlH_4$ (112 mg, 2.94 mmol) in THF (40 mL) to give ent-**23a** as a yellow oil, yield 60 mg (36%). $C_{18}H_{26}N_2O$ (286.4). Purity by HPLC: method 2b: t_R = 18.9 min, purity 95.8%; method 2h: t_R = 15.6 min, purity 96.8%. $[\alpha]_D^{20}$ −10.9 (*c* 0.29; CH_2Cl_2).

5.58. (+)-(1*S*,5*S*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (23b)

Under N_2 $LiAlH_4$ (287 mg, 7.56 mmol) was added to an ice-cooled solution of **22b** (663 mg, 1.51 mmol) in THF (80 mL). The mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Then water was added under ice-cooling until H_2 formation was finished and the mixture was stirred at 0 °C for 10 min and then heated to reflux for 30 min. After cooling down the mixture was filtered, the solvent was removed in vacuo and the residue was purified by FC (Ø = 3 cm, *h* = 15 cm, CH_2Cl_2/methanol = 9.5/0.5, *V* = 20 mL, R_f = 0.12) to give **23b** as a yellow oil, yield 170 mg (36%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2b: t_R = 18.2 min, purity 99.2%; method 2h: t_R = 15.4 min, purity 95.3%. $[\alpha]_D^{20}$ +6.5 (*c* 0.17; CH_2Cl_2). MS (EI): *m*/*z* [%] = 316 (M, 26), 275 (M−$CH_2CH{=}CH_2$, 3), 165 (M−2,4-dimethoxybenzyl, 74), 151 (2,4-dimethoxybenzyl, 100). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.59–1.99 (m, 6H, 2-H, 3-H, 4-H), 2.74 (d, J = 9.4 Hz, 1H, piperazine-H), 2.80 (d, J = 10.1 Hz, 1H, piperazine-H), 2.88–3.00 (m, 4H, piperazine-H), 3.15–3.25 (m, 2H, NC*H2*CH=CH_2), 3.63 (d, J = 14.9 Hz, 1H, NCH_2Ar), 3.71 (d, J = 14.9 Hz, 1H, NCH_2Ar), 3.79 (s, 3H, ArOCH_3), 3.80 (s, 3H, ArOCH_3), 5.08 (d, J = 10.2 Hz, 1H, $NCH_2CH{=}CH_2$), 5.18 (dd, J = 17.2/1.6 Hz, 1H, $NCH_2CH{=}CH_2$), 5.90 (ddt, J = 17.2/10.2/6.3 Hz, 1H, $NCH_2CH{=}CH_2$), 6.43 (d, J = 2.3 Hz, 1H, 3′-$H_{2,4\text{-dimethoxybenzyl}}$), 6.47 (dd, J = 8.6/2.3 Hz, 1H, 5′-$H_{2,4\text{-dimethoxybenzyl}}$), 7.36 (d, J = 8.6 Hz, 1H, 6′-$H_{2,4\text{-dimethoxybenzyl}}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3073 (w, $\nu_{C-H\ arom.}$), 2917 (m, $\nu_{C-H\ aliph.}$), 1611 (m)/1588 (m)/1505 (m, $\nu_{C=C\ arom.}$), 1453 (m, $\delta_{C-H\ aliph.}$), 1206 (m)/1037 (m, ν_{C-O}), 831 (m, $\Gamma_{tri\text{-subst. arom.}}$).

5.59. (−)-(1*R*,5*R*)-6-Allyl-8-(2,4-dimethoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane (ent-23b)

As described for the preparation of **23b**, the enantiomer ent-**22b** (572 mg, 1.30 mmol) was reacted with $LiAlH_4$ (248 mg, 6.52 mmol) in THF (70 mL) to give ent-**23b** as a yellow oil, yield 65 mg (16%). $C_{19}H_{28}N_2O_2$ (316.5). Purity by HPLC: method 2b: t_R = 17.1 min, purity 98.8%; method 2h: t_R = 14.9 min, purity 96.6%. $[\alpha]_D^{20}$ −6.3 (*c* 0.29; CH_2Cl_2).

6. Receptor binding studies

6.1. Materials and general procedures

The guinea pig brains and rat livers were commercially available (Harlan-Winkelmann, Germany). Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo-Finnigan). Filter: Printed Filtermat Typ B (Perkin-Elmer), presoaked in 0.5% aqueous polyethylenimine for 2 h at rt before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin-Elmer). The scintillation analysis was performed using Meltilex (Typ A) solid scintillator (Perkin-Elmer). The solid scintillator was melted on the filtermat at a temperature of 95 °C for 5 min. After solidification of the scintillator at rt, the scintillation was measured using a MicroBeta Trilux scintillation analyzer (Perkin-Elmer). The counting efficiency was 20%.

6.2. Membrane preparation for the σ_1 assay (modified according to Ref. 9)

Five guinea pig brains were homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in six volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500*g* for 20 min at 4 °C. The pellet was resuspended in 5–6 volumes of buffer (50 mM Tris, pH 7.4) and centrifuged again at 23,500*g* (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5–6 volumes of buffer, the protein concentration was determined according to the method of Bradford[18] using bovine serum albumin as standard, and subsequently the preparation was frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

6.3. Performing of the σ_1 assay (modified according to Ref. 9)

The test was performed with the radioligand [^{3}H]-(+) pentazocine (42.5 Ci/mmol; Perkin-Elmer). The thawed membrane preparation (about 75 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and buffer (50 mM Tris, pH 7.4) in a total volume of 200 μL for 180 min at 37 °C. The incubation was terminated by rapid filtration through the presoaked filtermats by using the cell harvester. After washing each well five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM unlabeled (+) pentazocine. The K_d-value of the radioligand [^{3}H]-(+)-pentazocine is 2.9 nM.[19]

6.4. Membrane preparation for the σ_2 assay (modified according to Ref. 9)

Two rat livers were cut into smaller pieces and homogenized with a potter (500–800 rpm, 10 up-and-down strokes) in six volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200*g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000*g* for 20 min at 4 °C. The pellet was resuspended in buffer (50 mM Tris, pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000*g* for 20 min at 4 °C. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[18] using bovine serum albumin as standard, and subsequently the preparation was frozen (−80 °C) in 1.5 mL portions containing about 2 mg protein/mL.

6.5. Performing of the σ_2 assay (modified according to Ref. 9)

The test was performed with the radioligand [^{3}H]-ditolylguanidine (50 Ci/mmol; ARC). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-ditolylguanidine, 500 nM (+)-pentazocine, and buffer (50 mM Tris, pH 8.0) in a total volume of 200 μL for 180 min at room temperature. The incubation was terminated by rapid filtration through the presoaked filtermats using a cell harvester. After each well was washed five times with 300 μL of water, the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The non-specific binding was determined with 10 μM unlabeled ditolylguanidine. The K_d-value of the radioligand [^{3}H]-ditolylguanidine is 17.9 nM.[20]

6.6. NMDA assay

The preparation of the receptor material and the assay were performed according to a literature procedure.[14]

6.7. Data analysis

All experiments were carried out in triplicates using standard 96-well multiplates (Diagonal). The IC_{50}-values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism 3.0 (GraphPad Software) by nonlinear regression analysis. The K_i-values were calculated according to Cheng and Prusoff.[21] The K_i-values are given as mean value ± SEM from three independent experiments.

6.8. Cytotoxicity assay

All cell lines were obtained from the German Collection of Microbiology and Cell Culture (DSZK, Braunschweig, FRG). Cytotoxicity testing was done by using a microtiter assay based on staining cells with crystal violet as described in detail elsewhere.[17] To determine the IC_{50}-values, five serially diluted stock solutions of test substance in DMF were used in the studies; concentrations giving T/C values between 10% and 90% were used to estimate the IC_{50}-values, which were calculated by least-squares analysis of the dose–response curves.

Acknowledgments

This work was performed within the International Research Training Group 'Complex Functional Systems in Chemistry: Design, Synthesis and Applications' in collaboration with the University of Nagoya. Financial support of this IRTG by the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

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