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Synthesis and pharmacological evaluation of bicyclic SNC80 analogues with separated benzhydryl moiety

Bettina Jung,[a] Werner Englberger,[b] Roland Fröhlich,[c] Dirk Schepmann,[a] Kirstin Lehmkuhl[a] and Bernhard Wünsch[a,*]

[a]*Institut für Pharmazeutische und Medizinische Chemie, Westfälische Wilhelms-Universität, Hittorfstraße 58-62, D-48149 Münster, Germany*
[b]*Grünenthal GmbH, Zieglerstraße 6, D-52078 Aachen, Germany*
[c]*Organisch-chemisches Institut, Corrensstraße 40, D-48149 Münster, Germany*

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Abstract—Directed by molecular modeling studies the pharmacophoric benzhydryl moiety of the δ opioid receptor agonist SNC80 was separated and the two phenyl residues were attached to different positions of the conformationally constrained 6,8-diazabicyclo[3.2.2]nonane framework in order to find novel δ agonists. The crucial reaction step in the chiral pool synthesis was the establishment of the three carbon bridge by a Dieckmann analogous cyclization of the allyl and propyl derivatives **6** and **7** to yield the mixed methyl silyl acetals **8** and **9**, respectively. Stereoselective Grignard reaction, dehydration, and introduction of the pharmacophoric (*N*,*N*-diethylcarbamoylbenzyl) residue led to the designed δ receptor agonists **3**, ent-**3**, and **20** with a double bond in the bicyclic framework. Hydrogenation of the allyl derivative **14** was performed with ammonium formate and Pd/C to yield the saturated ligands **24a** and **24b**. Removal of the allyl substituent with $RhCl_3$, hydrogenation of the ring system, and re-attachment of the allyl moiety provided the allyl derivatives **4a** and **4b**. In receptor binding studies with the radioligand [^{3}H]-deltorphine II only ent-**3** showed considerable δ receptor affinity (K_i = 740 nM). Since ent-**3** also interacts with μ receptors (K_i = 250 nM) it belongs to the very interesting compound class of mixed δ/μ ligands.

1. Introduction

The opioid receptor family consists of four subtypes termed μ (morphine), κ (ketocyclazocine), δ (vas deferens), and ORL1 (opioid receptor like 1) receptors. Whereas activation of the three classical opioid receptors (μ, κ, δ) leads to strong analgesia, which is antagonized by naloxone,[1] activation of the ORL1-receptor by the endogenous agonist nociceptin induces hyperalgesia depending on the region in the central nervous system.[2] The clinically used opioid analgesics predominantly activate μ-opioid receptors and are therefore associated with undesirable side effects, that is, respiratory depression, euphoria, physical dependence, tolerance, and constipation. High affinity κ agonists also display analgesic effects in animal models and in humans but their clinical use is limited by strong diuresis, dysphoria, and sedation.[3,4]

In terms of side effects δ receptors represent an attractive target, because their activation leads to strong analgesia without the typical side effects caused by μ and/or κ receptor agonists. Therefore, δ agonists are considered as safe analgesics. Furthermore, it has been shown that δ agonists are able to potentate the analgesic effect of morphine in subanalgesic doses. In addition to their analgesic activity δ agonists show further pharmacological effects, including immunoregulatory properties, antisecretory activity in bronchial diseases, and gastroprotective effects.[3,4]

In order to identify novel δ opioid receptor agonists a molecular modeling study based on the highly potent δ agonists SNC80 (**1**) and BW373U86 (**2**) has been performed. The basic idea was to separate the aromatic residues of the benzhydryl moiety of **1** and **2** and attach these phenyl residues to a conformationally restricted bicyclic system with a definite orientation to each other.

Keywords: δ Receptor agonists; Bicyclic SNC80 analogues; Bridged piperazines; Dieckmann cyclization.
* Corresponding author. Tel.: +49 251 8333311; fax: +49 251 32144; e-mail: wuensch@uni-muenster.de

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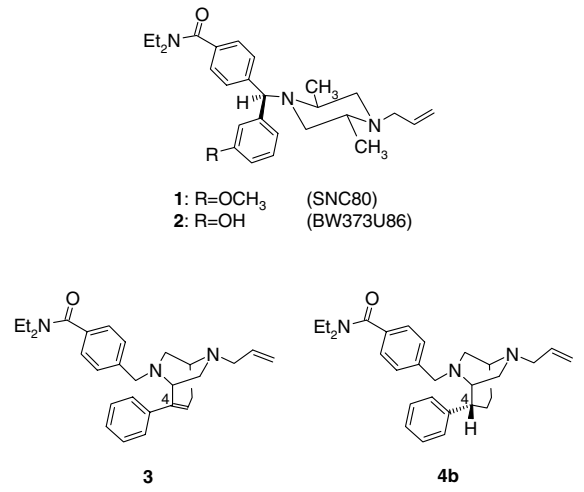


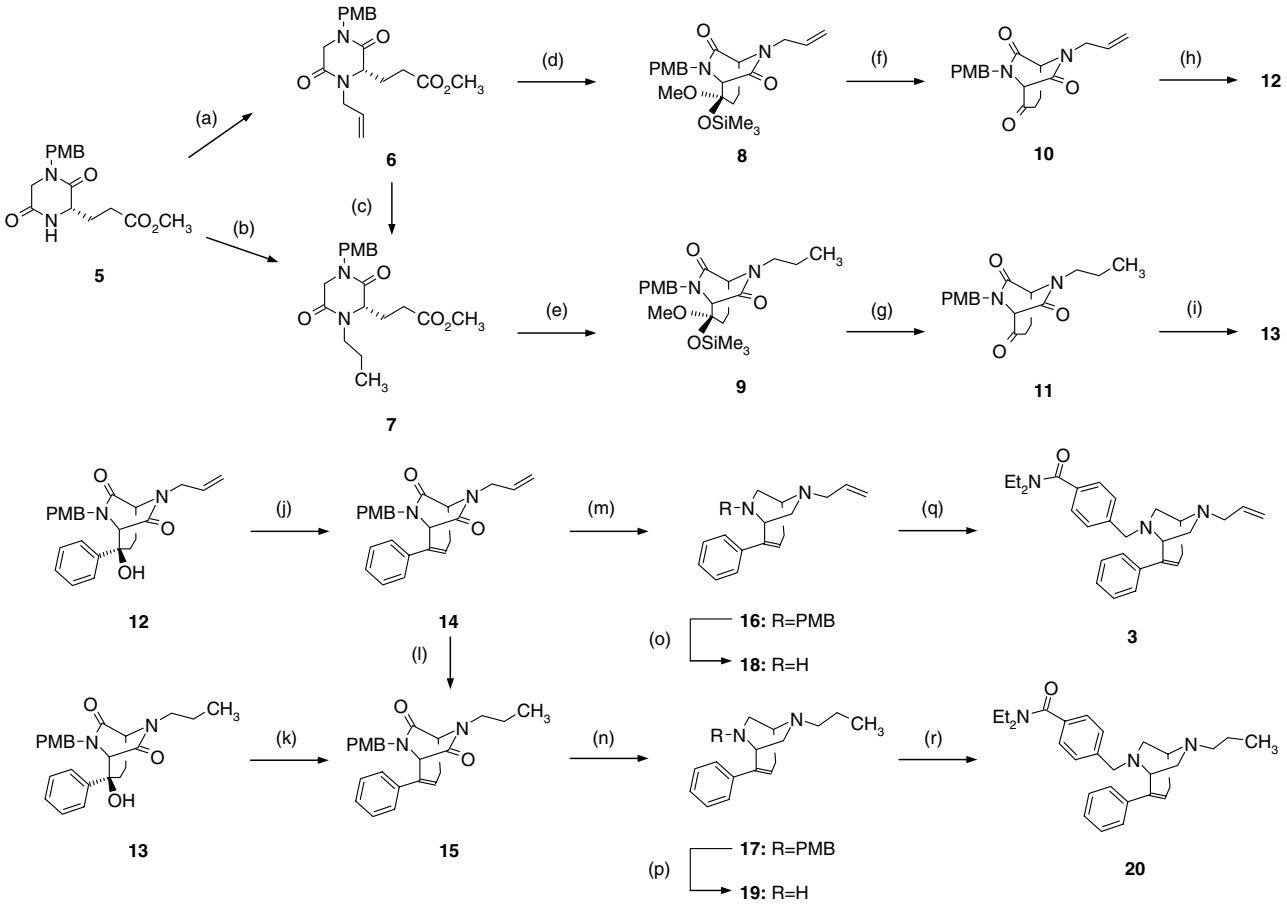
Figure 1. Lead compounds with high δ receptor affinity.

These calculations resulted in the bridged piperazines **3** and **4b** showing high similarity to SNC80 (**1**, low multifit energy). In the original manuscript the synthesis and pharmacological evaluation of the first example of this new class of δ agonists, the allylic derivative **3** with a double bond within the bicyclic framework, was detailed.[5] The synthesis started from (*S*)-glutamate, a product readily available from the chiral pool of nature. At first the piperazinedione **5** was prepared in a three step sequence. Allylation of **5** led to the piperazinedione **6**, which was converted via the bicyclic ketone **10** and the phenylalkene **16** into the bridged compound **3**.[5] (Fig. 1, see also Scheme 1).

Herein we wish to report on the synthesis and opioid receptor affinity of bridged piperazines with the phenyl residue directly attached to position 4 of the bicyclic system (compare compounds **3** and **4b** in Fig. 1). The possible diastereomers, the corresponding propyl derivatives (bearing a propyl instead of the allyl residue at the nitrogen atom in position 8) as well as the enantiomer of **3** are envisaged.

2. Chemistry

The synthesis started with the bicyclic piperazinedione **5**, which was prepared from (*S*)-glutamic acid by esterifica-



Scheme 1. Reagents and conditions: (a) NaHMDS, allyl bromide, Bu_4NI, THF, −78 °C, 67% (Ref. 5); (b) NaHMDS, propyl bromide, THF, 0 °C, 13%; (c) NH_4HCO_2, Pd/C, MeOH, 65 °C, 94%; (d) LiHMDS, THF, −78 °C, after 40 min Me_3SiCl, −78 °C, 88% (Ref. 5); (e) LiHMDS, THF, −78 °C, after 40 min Me_3SiCl, −78 °C, 86%; (f) 2 M HCl, THF, rt, 100% (Ref. 5); (g) 2 M HCl, THF, rt, 97%; (h) PhMgBr, THF, 0 °C, 90% (Ref. 5); (i) PhMgBr, THF, 0 °C, 100%; (j) P_4O_{10}, toluene, 90 °C, 67% (Ref. 5); (k) P_4O_{10}, toluene, 95 °C, 57%; (l) NH_4HCO_2, $RhCl(PPh_3)_3$, THF, 66 °C, 89%; (m) $LiAlH_4$, THF, 66 °C, 26% (Ref. 5); (n) $LiAlH_4$, THF, 65 °C, 30%; (o) CF_3CO_2H, reflux, 77% (Ref. 5); (p) CF_3CO_2H, reflux, 96%; (q) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (=*p*-(*N*,*N*-diethylcarbamoyl)benzyl chloride = DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 63% (Ref. 5); (r) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 40%. PMB, *p*-methoxybenzyl.

tion, chloroacetylation, and reaction with *p*-methoxybenzylamine (PMB-NH_2).[5] After introduction of the *N*-allyl moiety (**6**) the bicyclic ketone **10** was prepared according to our modified Dieckmann cyclization via the mixed methyl/silyl acetal **8**.[5–8] Nucleophilic addition of phenylmagnesium bromide to the ketone **10** provided diastereoselectively the tertiary alcohol **12**, which was heated with P_4O_{10} to afford the alkene **14** in 67% yield. Selective hydrogenation of the allylic double bond proceeded with ammonium formate in the presence of Wilkinson's catalyst [$RhCl(PPh_3)_3$][9] to give the propyl derivative **15** in 47% yield (calculated from **10**). The dilactam **15** was reduced with $LiAlH_4$ to afford the basic bicyclic system **17**. In the last step the *p*-(diethylcarbamoyl)benzyl (DCB) residue was introduced by trifluoroacetic acid cleavage[10] of the *p*-methoxybenzyl protective group and subsequent alkylation of the secondary amine **19** with DCB-Cl to yield the propyl substituted bicyclic receptor ligand **20**.

In order to reduce the number of reaction steps and to improve the yield the propyl residue of **20** was alternatively introduced at the beginning of the reaction sequence. For this purpose the piperazinedione **5** was deprotonated with NaHMDS and subsequently alkylated with propyl bromide to obtain the propyl derivative **7**. In contrast to the corresponding allylation (67% yield of **6**) the yield of **7** did not exceed 13% despite several optimization attempts. Alternatively, the allyl derivative **6** was hydrogenated with ammonium formate in the presence of Pd/C to give the propyl derivative **7** in almost quantitative yield. Cyclization of the piperazinedione **7** with LiHMDS and subsequent trapping of the intermediate with Me_3SiCl provided diastereoselectively[8] the mixed methyl/silyl acetal **9** with (*R*)-configuration of the new center of chirality. Careful hydrolysis of the mixed acetal **9** afforded the ketone **11**, which reacted diastereoselectively with phenylmagnesium bromide to give the tertiary alcohol **13**. Elimination of water with P_4O_{10} yielded the alkene **15**, which was also available by selective hydrogenation of the *N*-allyl residue of **14**.

For the synthesis of bicyclic SNC80 analogues without double bond in the bicyclic framework the phenylalkene **14** was hydrogenated with ammonium formate in the presence of Pd/C. Heating of this mixture in methanol led to saturation of both double bonds, the double bond in the allyl side chain as well as the double bond in the ring system. The diastereomers **21a** and **21b** were formed in the ratio 75:25 and separated by flash chromatography. Since various NMR spectroscopic methods did not lead to an unambiguous assignment of the configuration of the novel center of chirality in position 2, the main diastereomer **21a** was recrystallized from *i*-Pr_2O to yield colorless crystals, which were suitable for an X-ray crystal structure analysis. The X-ray crystal structure analysis of **21a**, which is shown in Figure 2, proves the (*S*)-configuration of the novel center of chirality in position 2 (Scheme 2).

The conversion of the diastereomers **21a** and **21b** into the target compounds **24a** and **24b** was performed in the same way. At first the dilactams **21a** and **21b** were

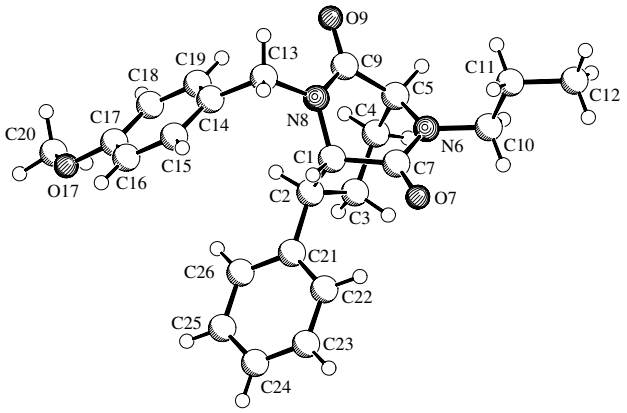


Figure 2. X-ray crystal structure analysis of **21a**.

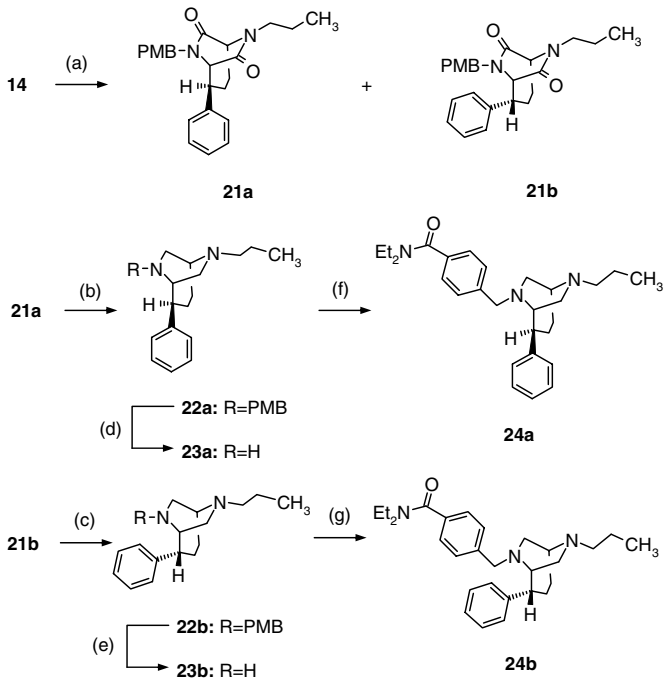
reduced with $LiAlH_4$ to provide the basic systems **22a** and **22b**. Removal of the *p*-methoxybenzyl protective group with trifluoroacetic acid and subsequent alkylation with *p*-(diethylcarbamoyl)benzyl chloride (DCB-Cl) led to the diastereomeric benzamides **24a** and **24b**.

The synthesis of SNC80 analogues with a saturated bicyclic framework and an *N*-allyl residue, that is, **4a** and **4b** (compare Fig. 1), proved to be difficult, since it was not possible to remove the hydroxy moiety of **12** directly by reductive methods (i.e., Barton–McCombie reduction,[11] reduction with Et_3SiH/BF_3,[12] and reduction with $NaBH_4$/TFA).[13] All attempts led to the elimination product **14** as main product.

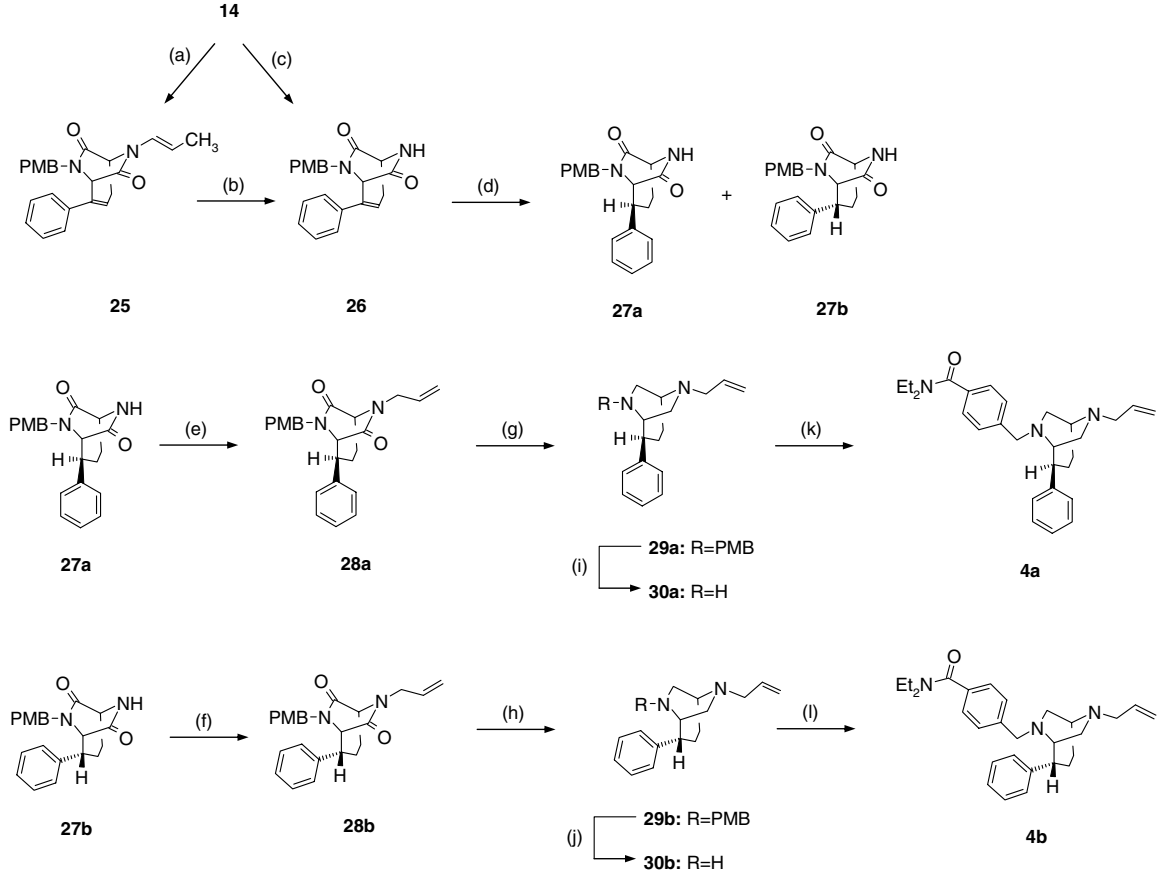
Therefore, it was planned to remove the allyl residue, hydrogenate the trisubstituted cyclic double bond, and reattach the allyl moiety. Thus, heating of an ethanolic solution of the allyl derivative **14** with $RhCl_3$ and DABCO[14] led to isomerization of the allylic double bond resulting in the enamine derivative **25** in 60% yield. Hydrolysis of the enamine **25** was performed with aqueous HCl in methanol to afford the secondary amide **26** in 95% yield. The overall yield of the secondary amide **26** was improved by a consecutive procedure. After isomerization of the double bond with $RhCl_3$ the intermediate enamine **25** was directly treated with 1 M HCl to give the desired secondary amide **26** in 88% yield. Hydrogenation of the double bond of **26** with ammonium formate and Pd/C led to the diastereomeric bicyclic compounds **27a** and **27b** in the ratio 83:17 (Scheme 3).

The allyl residue was re-attached by deprotonation of the secondary amides **27a** and **17b** with NaHMDS and subsequent reaction with allyl bromide to furnish the saturated (ring system) allyl derivatives **28a** and **28b**. Both diastereomers **28a** and **28b** were transformed into the benzamides **4a** and **4b** by $LiAlH_4$ reduction, trifluoroacetic acid removal of the *p*-methoxybenzyl protective group, and alkylation with *p*-(*N*,*N*-diethylcarbamoyl)benzyl chloride (DCB-Cl).

According to the molecular modeling study[5] compounds with the enantiomeric bicyclic framework show lower similarity to the lead compound SNC80 (**1**) than



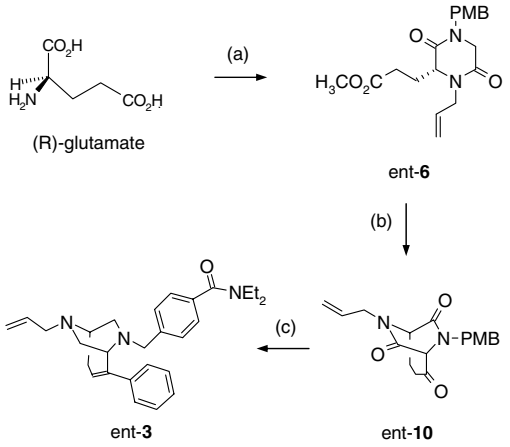
Scheme 2. Reagents and conditions: (a) NH_4HCO_2, Pd/C, MeOH, 65 °C, yield (**21a**) 28%, yield (**21b**) 15%; (b) $LiAlH_4$ THF, 65 °C, 93%; (c) CF_3CO_2H, reflux, 76%; (d) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 49%; (e) $LiAlH_4$ THF, 65 °C, 69%; (f) CF_3CO_2H, reflux, 78%; (g) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 74%. PMB, *p*-methoxybenzyl.



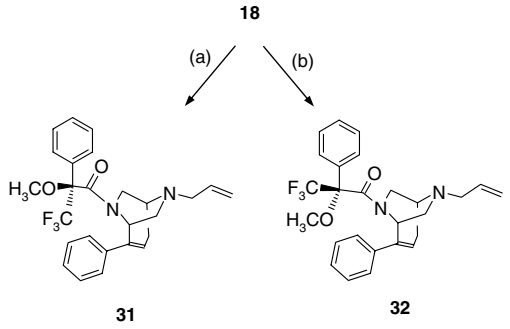
Scheme 3. Reagents and conditions: (a) $RhCl_3{\cdot}3H_2O$, DABCO, EtOH, 78 °C, 60%; (b) 1 M HCl, MeOH, reflux, 95%; (c) $RhCl_3{\cdot}3H_2O$, DABCO, EtOH, 78 °C, then 1 M HCl, reflux, 88%; (d) NH_4HCO_2, Pd/C, MeOH, 65 °C, yield (**27a**) 35%, yield (**27b**) 11%; (e) NaHMDS, allyl bromide, Bu_4NI, THF, −78 °C, 92%; (f) NaHMDS, allyl bromide, Bu_4NI, THF, −78 °C, 83%; (g) $LiAlH_4$ THF, 65 °C, 59%; (h) $LiAlH_4$ THF, 65 °C, 91; (i) CF_3CO_2H, reflux, 59%; (j) CF_3CO_2H, reflux, 71%; (k) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 42%; (l) 4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 71%. PMB, *p*-methoxybenzyl.

the described compounds **3** or **4b** derived from (*S*)-glutamate. In order to prove or disprove this hypothesis we decided to synthesize and biologically evaluate at least one enantiomer, in particular the enantiomer of **3**. The synthesis is outlined in Scheme 4. The enantiomeric piperazinedione ent-**6** was prepared in four steps starting from (*R*)-glutamate. Establishment of the bridge proceeded by deprotonation with LiHMDS, trapping of the intermediate with Me_3SiCl, and careful hydrolysis of the resulting mixed methyl/silyl acetal ent-**8** to obtain the bicyclic ketone ent-**10**. Stereoselective addition of PhMgBr and subsequent elimination of water led to the phenylalkene ent-**14**. In order to improve the yield of the reduction product ent-**16** RedAl® (sodium-dihydridobis(2-methoxyethoxy)aluminum) was employed instead of $LiALH_4$. In fact, the milder reducing agent RedAl® raised the yield from 26% (for **16**) to 45% for ent-**16**. The final step of the synthesis comprises the introduction of the δ-pharmacophoric (*N*,*N*-diethylcarbamoyl)benzyl residue after cleavage of the PMB protective group.

Exemplarily, the enantiomeric purity of the final compounds was shown by acylation of the secondary amine **18** with (*R*)- and (*S*)-Mosher acid chloride[15] to yield the



Scheme 4. Synthesis of the enantiomer. Reagents and conditions: (a) 1—MeOH, Me_3SiCl; 2—$ClCH_2COCl$, CH_2Cl_2, $NaHCO_3$; 3—PMB-NH_2, Bu_4NI, CH_3CN, NEt_3, reflux; 4—NaHMDS, allyl bromide, Bu_4NJ, THF, −78 °C. Overall yield of ent-**6** 21%; (b) 1—LiHMDS, THF, −78 °C, after 40 min Me_3SiCl, −78 °C, 92%; 2—2 M HCl, THF, rt, 98%; (c) 1—PhMgBr, THF, 0 °C, 87%; 2—P_4O_{10}, toluene, 90 °C, 58%; 3—RedAL®, THF, toluene, reflux, 45%; 4—CF_3CO_2H, reflux, 38%; 5—4-(chloromethyl)-*N*,*N*-diethylbenzamide (DCB-Cl), Bu_4NI, K_2CO_3, CH_3CN, reflux, 48%. PMB, *p*-methoxybenzyl.



Scheme 5. Reagents and conditions: (a) (*R*)-Mosher acid chloride, NEt_3, DMAP, CH_2Cl_2, 40 °C; (b) (*S*)-Mosher acid chloride, NEt_3, DMAP, CH_2Cl_2, 40 °C.

Mosher esters **31** and **32**, respectively (Scheme 5). The ratio of diastereomers **31**:ent-**32** and **32**:ent-**31** in the crude reaction products was determined by ^{19}F NMR spectroscopy, achiral HPLC, and capillary electrophoresis. According to these investigations the enantiomeric purity of the secondary amine **18** is greater than 99.0% ee, since the ratio of diastereomers is greater than 99.0% de (i.e., ratio **32**:ent-**32** = 99.5:0.5 (^{19}F NMR), 99.8: 0.2 (HPLC), 99.6:0.4 (CE)).

3. Receptor binding studies

The affinity of the bridged piperazines with *N*-allyl and *N*-propyl residue **3**, ent-**3**, **4a**, **4b**, **20**, **24a**, and **24b** toward δ, μ, κ, and ORL1 receptors was investigated in receptor binding studies using tritium labeled radioligands. The following radioligands were used: [^{3}H]-deltorphine II in the δ assay, [^{3}H]-naloxone in the μ assay, [^{3}H]-Cl-977 in the κ assay, and [^{3}H]-nociceptin in the ORL1 assay. Transfected CHO-K_1 cell lines expressing the human δ and μ opioid receptors and HEK-293 cell lines expressing the human κ and ORL1 receptors were employed as receptor material.

At first the inhibition of radioligand binding at a test compound concentration of 10 μM was measured (Table 1). For compounds showing a more than 50% inhibition of the radioligand binding the K_i-values were determined (Table 2).

All compounds derived from (*S*)-glutamate reveal very low affinity to the δ receptor. However, ent-**3** with the enantiomeric ring system displays considerable δ receptor affinity. The corresponding K_i value of 740 nM

Table 1. Inhibition of radioligand binding at a test compound concentration of 10 μM

Compound	δ ([^{3}H]-deltorphine II) (%)	μ ([^{3}H]-naloxone) (%)	κ ([^{3}H]-Cl-977) (%)	ORL1 ([^{3}H]-nociceptin) (%)
3	14	56	76	9
ent-**3**	87	91	31	<10
20	20	55	22	45
24a	4	61	63	1
24b	4	44	49	3
4a	6	56	73	7
4b	34	58	76	14

Table 2. K_i values [μM] of promising test compounds

Compound	δ ([^{3}H]-deltorphine II)	μ ([^{3}H]-naloxone)	κ ([^{3}H]-Cl-977)	ORL1 ([^{3}H]-nociceptin)
3	—	6.8 μM	0.89 μM	—
ent-**3**	0.74 μM	0.25 μM	—	—
20	—	—	—	—
24a	—	5.7 μM	2.4 μM	—
24b	—	—	—	—
4a	—	7.3 μM	1.7 μM	—
4b	—	6.32 μM	1.1 μM	—
SNC80 (**1**)	0.0017 μM	—	—	—

represents a promising starting point for the development of δ receptor agonists with a novel ring system.

In the μ assay most of the compounds showed considerable inhibition of the radioligand [^{3}H]-naloxone at a concentration of 10 μM. However, with exception of ent-**3** the corresponding K_i-values are rather high (>5 μM) indicating low μ receptor affinity. Within this series of compounds ent-**3** possesses the highest μ affinity (K_i = 250 nM), which exceeds its δ affinity threefold. Obviously, ent-**3** belongs to the very interesting class of compounds, which are able to interact with both, μ and δ receptors.

The allyl substituted derivatives **3**, **4a**, and **4b** were active in the κ assay, displaying moderate affinity in the range of 1 μM. Since the interaction with δ, μ, and ORL1 receptors is very low, the κ receptor selectivity of these κ ligands should be noticed.

A considerable interaction with the ORL1 receptor was not detected.

4. Discussion

According to the molecular modeling studies the allyl derivative **3** showed high structural and electronic similarity to the lead δ agonist SNC80 (**1**), whereas its enantiomer ent-**3** was less similar to SNC80. The higher similarity of **3** to SNC80 in comparison to ent-**3** should lead to a higher δ receptor affinity of **3**. However, the experiments showed the opposite result, since the enantiomer ent-**3** was the better δ ligand. Obviously the δ receptor protein is able to tolerate small structural and electronic variations of ligands, which are not properly recognized by the theoretical methods.

5. Conclusion

The promising δ receptor affinity of the allyl derivative ent-**3** derived from (*R*)-glutamate represents a stimulating starting point for the synthesis of further δ receptor ligands based on the bridged piperazine system. In particular introduction of a longer spacer (e.g., CH_2, OCH_2) between the phenyl moiety in position 4 and the heterocyclic framework will result in a better adaptation of the phenyl moiety to the binding pocket of the δ receptor protein.

6. Experimental

6.1. Chemistry, General

Thin-layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc)[16]: Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL], R_f. Melting points: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation: Polarimeter 341 (PerkinElmer); 1.0 dm tube; concentration *c* [g/100 mL]; temperature 20 °C. Elemental analyses: Vario EL (Elementaranalysesysteme GmbH). MS: MAT GCQ (Thermo-Finnigan); TSQ 7000 (Thermo-Finnigan); LCQ MAT (Thermo-Finnigan); EI = electron impact; CI = chemical ionization, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376.7 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques. HPLC: L-6200A Intelligent pump Merck Hitachi, Variable Wavelength Monitor Knauer, D-2000 Chromato Integrator Merck Hitachi, injection volume 20 μL, flow rate 1 mL/min. Column 1: LiChroCART® 250-4 Merck with LiChrospher® 100 RP-8 endcapped (5 μm); Column 2: Hibar® RT 250-4 Merck with LiChrospher® 100 RP-18 (5 μm).

6.2. Synthetic procedures

6.2.1. (+)-Methyl (*R*)-[4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (ent-5).

6.2.1.1. Dimethyl (*R*)-2-aminopentanedioate hydrochloride. Chlorotrimethylsilane (75 mL, 594 mmol) was added dropwise during 90 min to an ice-cooled suspension of (*R*)-glutamate (25.1 g, 171 mmol) in methanol (350 mL). The mixture was stirred for 16 h at rt. Workup, purification, and spectroscopic data are given in Ref. 5 for the (*S*)-enantiomer. Colorless solid, yield 36.4 g (100%).

6.2.1.2. Dimethyl (*R*)-2-(2-chloroacetylamino)pentanedioate. A solution of chloroacetyl chloride (9.3 mL, 117 mmol) in CH_2Cl_2 (50 mL) was added dropwise to an ice-cooled solution of dimethyl (*R*)-2-aminopentanedioate hydrochloride (8.0 g, 37.8 mmol) in CH_2Cl_2 (240 mL) and the mixture was stirred for 40 min. Workup, purification, and spectroscopic data are given in Ref. 5 for the (*S*)-enantiomer. Colorless oil, yield 6.8 g

(71.6%). $[\alpha]_{589}$ −17.9 (*c* 1.2, CH_2Cl_2). $C_9H_{14}ClNO_5$ (251.7). Calcd C, 42.9; H, 5.61; N, 5.56. Found: C, 42.9; H, 5.50; N, 5.46.

6.2.1.3. Methyl (*R*)-[4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate. 4-Methoxybenzylamine (4.6 mL, 35.6 mmol), triethylamine (5.0 mL, 36.1 mmol) and tetrabutylammonium iodide (0.88 g, 2.38 mmol) were added to a stirred solution of dimethyl (*R*)-2-(2-chloroacetylamino)pentanedioate (6.0 g, 23.8 mmol) in acetonitrile (200 mL). The mixture was refluxed for 48 h. Workup, purification, and spectroscopic data are given in Ref. 5 for ent-**5**. Colorless solid, mp 93.5 °C, yield 3.8 g (50%). $[\alpha]_{589}$ +16.5 (*c* 0.56, CH_2Cl_2). $C_{16}H_{20}N_2O_5$ (320.3). Calcd C, 60.0; H, 6.29; N, 8.74. Found: C, 60.0; H, 6.17; N, 8.72. The spectroscopic data of **5** are given in Ref. 5.

6.2.2. (−)-Methyl (*R*)-3-[1-allyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (ent-6). Under N_2 atmosphere a 1 M solution of sodium hexamethyldisilazane in THF (17.2 mL, 17.2 mmol) was added dropwise to a cooled solution (−78 °C) of ent-**5** (5.0 g, 15.6 mmol) and tetrabutylammonium iodide (1.0 g, 2.70 mmol) in THF (150 mL). The mixture was stirred at −78 °C for 40 min then a solution of allyl bromide (6.7 mL, 78 mmol) in THF (15 mL) was added. The mixture was stirred at −78 °C for 1 h and then allowed to warm to rt (2 h). Workup, purification, and spectroscopic data are given in Ref. 5 for the (*S*)-enantiomer. Pale yellow oil, yield 3.2 g (61%). $[\alpha]_{589}$ −18.9 (*c* 0.71, CH_2Cl_2). $C_{19}H_{24}N_2O_5$ (360.4). Calcd C, 63.3; H, 6.71; N, 7.77. Found C, 62.9; H, 6.86; N, 7.90. The spectroscopic data of **6** are given in Ref. 5.

6.2.3. (+)-Methyl 3-[(2*S*)-4-(4-methoxybenzyl)-1-propyl-3,6-dioxopiperazin-2-yl]propanoate (7).
Method A—Synthesis by alkylation of **5**:

Under N_2 a solution of NaHMDS in THF (1 M, 6.25 mL, 6.25 mmol) was added to a cooled (ice bath) solution of **5** (0.87 g, 2.72 mmol) in THF (30 mL). After 40 min a solution of 1-bromopropane (2.54 mL, 27.2 mmol) in THF (10 mL) was added. The mixture was stirred for 1 h at 0 °C and 16 h at rt. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (3 cm, petroleum ether/ethyl acetate = 3:7, 20 mL, R_f = 0.25). Colorless oil, yield 125 mg (13%).

Method B—Synthesis by hydrogenation of the allyl derivative **6**:

Under N_2 dry ammonium formate (70 mg, 1.40 mmol) was added to a suspension of **6** (100 mg, 0.28 mmol) and 10% Pd/C (10 mg) in MeOH (30 mL). The mixture was heated to reflux for 5 h, then filtered through Celite. The solvent was removed in vacuo and the residue was purified by fc (2 cm, petroleum ether/ethyl acetate = 3:7, 5 mL, R_f = 0.25). Colorless oil, yield 94.3 mg (94%). $C_{19}H_{26}N_2O_5$ (362.4). Calcd C, 62.9; H, 7.23; N, 7.73. Found: C, 62.6; H, 7.24; N, 7.64. $[\alpha]_{589}$ +70.4 (*c* 0.61, CH_2Cl_2). MS (EI): *m*/*z* (%) = 362 (M, 69), 241 (M−CH_2PhOCH_3, 90), 121 (CH_2PhOCH_3, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1734 (m, $\nu_{C=Oester}$), 1654 (s, $\nu_{C=Oamide}$), 1244, 1172 (m, ν_{COC}), 1031 (w, ν_{COC}), 764 (s, *p*-disubst. aromat.). ^1H NMR ($CDCl_3$): δ (ppm) = 0.90 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.52–1.74 (m, 2H, $NCH_2CH_2CH_3$), 1.99 (ddd, *J* = 14.4/8.6/6.3 Hz, 1H, $CH_2CH_2CO_2CH_3$), 2.17–2.28 (m, 1H, $CH_2CH_2CO_2CH_3$), 2.36–2.53 (m, 2H, $CH_2CH_2CO_2CH_3$), 2.84 (ddd, *J* = 14.1/8.6/5.7, 1H, $NCH_2CH_2CH_3$), 3.68 (s, 3H, CO_2CH_3), 3.75 (d, *J* = 17.2 Hz, 1H, O=C–CH_2N), 3.80 (s, 3H, OCH_3), 3.82 (ddd, *J* = 14.1/8.6/5.7 Hz, 1H, $NCH_2CH_2CH_3$), (d, *J* = 17.2 Hz, 1H, O=C–CH_2N), 4.00 (dd, *J* = 8.6/3.9 Hz,1H, CHNPropyl), 4.39 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 4.61 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 6.85 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.18 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]).

6.2.4. (+)-(1*S*,2*R*,5*S*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (8)[5]. Under N_2 a solution of **6** (3.25 g, 13.5 mmol) in THF (130 mL) was cooled to −78 °C. A solution of LiHMDS in THF (1 M, 13.5 mL, 13.5 mmol) and after 40 min a solution of chlorotrimethylsilane (4.1 mL, 32.5 mmol) in THF (10 mL) were slowly added. The mixture was stirred for 1 h at −78 °C and for 2 h at rt. Then a saturated solution of $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 150 mL). The combined organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (6 cm, petroleum ether/ethyl acetate = 6:4, 30 mL, R_f = 0.27). Colorless solid, mp 93–94 °C, yield 3.4 g (88%). $C_{22}H_{32}N_2O_5Si$ (432.6). Calcd C, 61.1; H, 7.46; N, 6.48. Found: C, 60.6; H, 7.30; N, 6.38. $[\alpha]_{589}$ +22.1 (*c* 0.95, CH_2Cl_2). The spectroscopic data of **8** are given in Ref. 5.

6.2.5. (−)-(1*R*,2*S*,5*R*)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-8). The synthesis was performed as described for **8** using ent-**6** (5.0 g, 20.8 mmol) in THF (150 mL), LiHMDS in THF (1 M, 258 mL, 258 mmol), and chlorotrimethylsilane (6.4 mL, 50 mmol) in THF (15 mL). Colorless solid, mp 94 °C, yield 5.5 g (92%). $C_{22}H_{32}N_2O_5Si$ (432.6). Calcd C, 61.1; H, 7.46; N, 6.48. Found: C, 61.0; H, 7.38; N, 6.30. $[\alpha]_{589}$ −20.2, (*c* 0.49, CH_2Cl_2).

6.2.6. (1*S*,2*R*,5*S*)-2-Methoxy-8-(4-methoxybenzyl)-6-propyl-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (9). The synthesis was performed as described for **8** using **7** (2.39 g, 6.6 mmol) in THF (100 mL), LiHMDS in THF (10.0 mL, 10.0 mmol), and chlorotrimethylsilane (3.25 mL, 25.7 mmol) in THF (10 mL). Workup and fc purification (5 cm, petroleum ether/ethyl acetate = 6:4, 30 mL, R_f = 0.25) gave a yellow resin, yield 2.50 g (86%). $C_{22}H_{34}N_2O_5Si$ (434.6). MS (EI): *m*/*z* (%) = 434 (M, 84), 313 (M−CH_2PhOCH_3, 57), 121 (CH_2PhOCH_3, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1680 (s, $\nu_{C=Oamide}$), 1246 (s, ν_{COC}), 843 (s, *p*-disubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.01 (s, 9H, $Si(CH_3)_3$), 0.73 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.37–1.40 (m, 2H, $NCH_2CH_2CH_3$), 1.59–1.63 (m, 1H, 4-H), 1.78–1.81

(m, 2H, 3-H), 1.90–2.01 (m, 1H, 4-H), 3.10 (s, 3H, OCH_3), 3.10 (ddd, J = 14.1/8.6/7.0, 1H, $NCH_2CH_2CH_3$), 3.18 (ddd, J = 14.1/8.6/7.0, 1H, $NCH_2CH_2CH_3$), 3.63 (s, 3H, $PhOCH_3$), 3.70 (dd, J = 6.3/2.4 Hz,1H, 5-H), 3.71 (s, 1H, 1-H), 3.81 (d, J = 14.7 Hz,1H, $CH_2PhO CH_3$), 4.99 (d, J = 14.7 Hz, 1H, CH_2PhOCH_3), 6.68 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.95 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]).

6.2.7. (+)-(1*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (10)[5]. Under N_2 a solution of **8** (1.12 g, 2.59 mmol) in THF (45 mL) and 2 N HCl (5 mL) was stirred for 2 h at rt. Then, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layer was dried (Na_2SO_4), concentrated in vacuo to yield a colorless solid, mp 195–196 °C, yield 0.85 g (100%). $C_{18}H_{20}N_2O_4$ (328.4). Calcd C, 65.8; H, 6.14; N, 8.53. Found: C, 65.6; H, 5.95; N, 8.25. $[\alpha]_{589}$ +120 (*c* 0.49, CH_2Cl_2). The spectroscopic data of **10** are given in Ref. 5.

6.2.8. (−)-(1*R*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (ent-10). The synthesis was performed as described for **10** using ent-**8** (4.4 g, 10.2 mmol) in THF (90 mL) and 2 N HCl (10 mL). Colorless solid, mp 196.5 °C, yield 3.26 g (98%). $C_{18}H_{20}N_2O_4$ (328.4). Calcd C, 65.8; H, 6.14; N, 8.53. Found: C, 65.7; H, 6.03; N, 8.42. $[\alpha]_{589}$ −115 (*c* 0.29, CH_2Cl_2).

6.2.9. (+)-(1*S*,5*S*)-8-(4-Methoxybenzyl)-6-propyl-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (11). The synthesis was performed as described for **10** using **9** (713 mg, 1.64 mmol) in THF (27 mL) and 2 N HCl (3 mL). Workup and removal of the solvent afforded a colorless solid, mp 198.5 °C, yield 525 mg (97%). $C_{18}H_{22}N_2O_4$ (330.4). $[\alpha]_{589}$ +124.5 (*c* 0.43, CH_2Cl_2). MS (EI): *m*/*z* (%) = 330 (M, 10), 209 (M−CH_2PhOCH_3, 5), 121 (CH_2PhOCH_3, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1727 (s, $\nu_{C=Oketone}$), 1684 (s, $\nu_{C=Oamide}$), 823 (w, *p*-disubst. Ar). ^1H NMR($CDCl_3$): δ (ppm) = 0.83 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.47–1.56 (m, 2H, $NCH_2CH_2CH_3$), 2.03–2.10 (m, 1H, 4-H), 2.24–2.31 (m, 1H, 3-H), 2.36–2.49 (m, 2H, 3-H, 4-H), 3.07 (ddd, J = 14.1/8.6/7.0 Hz, 1H, $NCH_2CH_2CH_3$), 3.50 (ddd, J = 14.1/8.6/7.0 Hz, 1H, $NCH_2CH_2CH_3$), 3.71 (s, 3H, $PhOCH_3$), 3.97 (dd, J = 4.7/2.3 Hz, 1H, 5-H), 4.18 (s, 1H, 1-H), 4.24 (d, J = 14.1 Hz, 1H, CH_2PhOCH_3), 4.76 (d, J = 14.1 Hz, 1H, CH_2PhOCH_3) 6.76 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.13 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]).

6.2.10. (1*S*,2*S*,5*S*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (12)[5]. Under N_2 a solution of **10** (2.2 g, 6.7 mmol) in THF (100 mL) was added to an ice-cooled solution of phenylmagnesium bromide prepared from bromobenzene (4.2 mL, 40.0 mmol) and magnesium tunings (1.0 g, 40.7 mmol) in THF (10 mL). After stirring for 2 h at 0–5 °C the mixture was poured into a cold saturated solution of NH_4Cl (200 mL). The mixture was extracted four times with CH_2Cl_2 (4× 150 mL), the organic layer was dried, the solvent was removed in vacuo and the residue was purified by fc (4 cm, petroleum ether/ethyl acetate 2:8, 20 mL, R_f = 0.25) to give a yellow oil, yield 2.5 g (90%). $[\alpha]_{589}$ +3.96 (*c* 1.0, CH_2Cl_2). $C_{24}H_{26}N_2O_4$ (406.5). The spectroscopic data of **12** are given in Ref. 5.

6.2.11. (−)-(1*R*,2*R*,5*R*)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (ent-12). The synthesis was performed as described for **12** using ent-**10** (3.0 g, 9.14 mmol) in THF (100 mL), Mg (1.34 g, 54.8 mmol), and a solution of bromobenzene (5.7 mL, 54.6 mmol) in THF (15 mL). Colorless solid, yield 3.21 g (87%). $C_{24}H_{26}N_2O_4$ (406.5). $[\alpha]_{589}$ −3.30 (*c* 6.0, CH_2Cl_2).

6.2.12. (+)-(1*S*,2*S*,5*S*)-2-Hydroxy-8-(4-methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (13). The synthesis was performed as described for **12** using **11** (1.71 g, 5.2 mmol) in THF (30 mL), Mg (0.63 g, 25.6 mmol) in THF (2 mL), and a solution of bromobenzene (4.2 mL, 28.8 mmol) in THF (8 mL). Workup and fc purification (4 cm, petroleum ether/acetone = 6:4, 20 mL, R_f = 0.24) gave a pale yellow oil, yield 2.12 g (100%). $C_{24}H_{28}N_2O_4$ (408.5). Calcd C, 70.5; H, 6.91; N, 6.86. Found: C, 70.0; H, 6.85; N, 6.66. $[\alpha]_{589}$ +23.4 (*c* 0.52, CH_2Cl_2). MS (EI): *m*/*z* (%) = 408 (M, 41), 287 (M−CH_2PhOCH_3, 100), 259 (M−CH_2PhOCH_3−OH, 8), 121 (CH_2PhOCH_3, 65). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3384 (w, ν_{O-H}), 1660 (s, $\nu_{C=Oamide}$), 1245, 1137, 1080 (s, ν_{COC}), 829 (s, *p*-disubst. Ar), 727, 700 (m, monosubst. Ar). ^1H NMR($CDCl_3$): δ (ppm) = 1.78 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.51–1.71 (m, 2H, $NCH_2CH_2CH_3$), 1.99–2.01 (m, 1H, 3-H), 2.20–2.38 (m, 2H, 4-H), 2.57–2.64 (m, 1H, 3-H), 2.82 (d, J = 14.9 Hz, 1H, CH_2PhOCH_3), 3.19 (ddd, J = 14.1/8.6/5.5 Hz, 1H, $NCH_2CH_2CH_3$), 3.59 (ddd, J = 14.1/8.6/5.5 Hz, 1H, $NCH_2CH_2CH_3$), 3.74 (s, 3H, OCH_3), 3.93 (s, 1H, 1-H), 4.01 (dd, J = 4.7/3.9 Hz, 1H, H-5), 4.91 (d, J = 14.7 Hz, 1H, CH_2PhOCH_3), 6.70 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.75 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.33–7.54 (m, 5H, aromat. H). A signal for the proton of the OH group was not found.

6.2.13. (1*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene-7,9-dione (14)[5]. Under N_2 atmosphere P_4O_{10} (3 g, 21 mmol) was added to a solution of **12** (1.0 g, 2.46 mmol) in toluene (70 mL). The mixture was heated at 90 °C for 48 h, filtered, and concentrated in vacuo. The residue was purified by fc (3 cm, petroleum ether/ethyl acetate 3:7, 10 mL, R_f = 0.43). Colorless solid, yield 0.54 g (67%), mp 142–143 °C. $[\alpha]_{589}$ +184 (*c* 0.57, CH_2Cl_2). $C_{24}H_{24}N_2O_3$ (388.5). Calcd C, 74.2; H, 6.23; N, 7.21. Found: C, 73.7; H, 6.13; N, 6.92. The spectroscopic data of **14** are given in Ref. 5.

6.2.14. (−)-(1*R*,5*R*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene-7,9-dione (ent-14). The synthesis was performed as described for **14** using ent-**12** (3.0 g, 7.4 mmol) and P_4O_{10} (5.0 g, 35 mmol) in toluene (100 mL). Analogous workup provided a colorless solid, mp 142 °C, yield 1.67 g (58%). $C_{24}H_{24}N_2O_3$ (388.5). Calcd C, 74.2; H, 6.23; N, 7.21. Found: C, 74.2; H, 6.13; N, 7.20. $[\alpha]_{589}$ −188 (*c* 0.74, CH_2Cl_2).

6.2.15. (+)-(1*S*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]non-2-ene-7,9-dione (15). Method A—Dehydration of **13**:

Under N_2 atmosphere P_4O_{10} (4 g, 28 mmol) was added to a solution of **13** (2.0 g, 4.9 mmol) in toluene (100 mL) and the mixture was heated to 95 °C for 48 h. The mixture was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (6 cm, petroleum ether/ethyl acetate = 3:7, 10 mL, R_f = 0.45). Colorless solid, mp 147 °C, yield 1.10 g (57%).

Method B—Hydrogenation of **14**:

A solution of **14** (300 mg, 0.77 mmol), dried NH_4HCO_2 (243 mg, 3.86 mmol), and $(PPh_3)_3RhCl$ (5 mg, 0.005 mmol) in THF (50 mL) was heated to reflux for 16 h. Then 0.5 N HCl (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 150 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (3 cm, petroleum ether/ethyl acetate = 1:1, 10 mL). Colorless solid, mp 147 °C, yield 269 mg (89%). $C_{24}H_{26}N_2O_3$ (390.5). Calcd C, 73.8; H, 6.71; N, 7.17. Found: C, 73.6; H, 6.21; N, 6.99. $[\alpha]_{589}$ +237 (*c* 0.49, CH_2Cl_2). MS (EI): *m*/*z* (%) = 390 (M, 57), 227 (MH-propyl-CH_2PhOCH_3, 65), 121 (CH_2PhOCH_3, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1670 (s, $\nu_{C=Oamide}$), 1244, 1174, 1032 (m, ν_{COC}), 809 (w, *p*-disubst. Ar), 728, 699 (m, monosubst. Ar). ^1H NMR($CDCl_3$): δ (ppm) = 0.93 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.56–1.68 (m, 2H, $NCH_2CH_2CH_3$), 2.69 (ddd, *J* = 19.6/4.7/3.1 Hz, 1H, 4-H), 2.82 (ddd, *J* = 19.6/4.7/3.1 Hz, 1H, 4-H), 3.30 (ddd, *J* = 14.1/8.6/6.3 Hz, 1H, $NCH_2CH_2CH_3$), 3.54 (ddd, *J* = 14.1/8.6/6.3 Hz, 1H, $NCH_2CH_2CH_3$), 3.72 (s, 3H, OCH_3), 4.10 (t, *J* = 3.1 Hz, 1H, 5-H), 4.32 (d, *J* = 14.7 Hz, 1H, CH_2PhOCH_3), 4.44 (d, *J* = 1.6 Hz, 1H, 1-H), 4.66 (d, *J* = 14.7 Hz, 1H, CH_2PhOCH_3), 5.71 (m, 1H, 3-H), 6.61 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.95 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.03–7.23 (m, 5H, aromat. H).

6.2.16. (+)-(1*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene (16)[5]. Under N_2 $LiAlH_4$ (0.464 g, 12.23 mmol) was added to a cooled solution (ice bath) of **14** (0.95 g, 2.45 mmol) in THF (90 mL). The mixture was stirred for 30 min with cooling and for 6 h under reflux. Then water (0.88 mL, 48.9 mmol) was added dropwise under cooling (ice bath) and the mixture was stirred for 30 min at rt and for 30 min under reflux. Subsequently, it was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (3 cm, CH_2Cl_2/CH_3OH = 9.5:0.5, 10 mL, R_f = 0.15). Pale yellow oil, yield 0.23 g (26%). $C_{24}H_{28}N_2O$ (360.5). $[\alpha]_{589}$ +43 (*c* 0.48, CH_2Cl_2).- The spectroscopic data of **16** are given in Ref. 5.

6.2.17. (−)-(1*R*,5*R*)-6-Allyl-2-phenyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]non-2-ene (ent-16). The synthesis was performed as described for **16** using ent-**14** (300 mg, 0.77 mmol) in THF (50 mL) and a solution of sodium-dihydridobis(2-methoxyethoxy)aluminum (Red-Al®) in toluene (0.7 mL, 0.21 mmol). Analogous workup afforded a pale yellow oil, yield 125 mg (45%). $C_{24}H_{28}N_2O$ (360.5). $[\alpha]_{589}$ −45 (*c* 0.64, CH_2Cl_2).

6.2.18. (+)-(1*S*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]non-2-ene (17). The synthesis was performed as described for **16** using **15** (500 mg, 1.38 mmol) in THF (75 mL) and $LiAlH_4$ (250 mg, 6.58 mmol). Usual workup and purification by fc (3 cm, CH_2Cl_2/methanol = 9:1, 10 mL, R_f = 0.22) provided a pale yellow oil, yield 137 mg (30%). $C_{24}H_{30}N_2O$ (362.5). $[\alpha]_{589}$ +42.6 (*c* 0.75, CH_2Cl_2). MS (EI): *m*/*z* (%) = 362 (M, 24), 241 (M−CH_2PhOCH_3, 100), 121 (CH_2PhOCH_3, 24). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1510 (m, $\nu_{C=C}$), 1243 (s, ν_{COC}), 1103, 1032 (m, ν_{COC}), 830 (w, *p*-disubst. Ar), 730, 669 (m, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.78 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.53–1.69 (m, 2H, $NCH_2CH_2CH_3$), 2.33–2.40 (m, 1H, 4-H), 2.62–2.65 (m, 1H, 9-H), 2.67–2.74 (m, 2H, $NCH_2CH_2CH_3$), 2.91–3.15 (m, 2H, 4-H, 7-H), 3.24–3.31 (m, 1H, 5-H), 3.24–3.42 (m, 2H, 7-H, 9-H), 3.47 (d, *J* = 13.3 Hz, 1H, CH_2PhOCH_3), 3.51 (d, *J* = 13.3 Hz, 1H, CH_2PhOCH_3), 3.62–3.65 (m, 1H, 1-H), 3.70 (s, 3H, OCH_3), 5.91–5.93 (m, 1H, 3-H), 6.67 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.94 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.05–7.20 (m, 5H, aromat. H).

6.2.19. (1*S*,5*S*)-6-Allyl-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene (18)[5]. Under N_2 a solution of **16** (0.145 g, 0.4 mmol) in trifluoroacetic acid (40 mL) was heated to reflux for 16 h. Then a 10 M solution of KOH (50 mL) was slowly added and the mixture was extracted with CH_2Cl_2 (5× 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, CH_2Cl_2/CH_3OH = 8.5:1.5, 5 mL, R_f = 0.27). Yellow oil, yield 0.075 g (77%). $C_{16}H_{20}N_2$ (240.3). The spectroscopic data of **18** are given in Ref. 5.

6.2.20. (1*R*,5*R*)-6-Allyl-2-phenyl-6,8-diazabicyclo[3.2.2]-non-2-ene (ent-18). The synthesis was performed as described for **18** heating ent-**16** (100 mg, 0.28 mmol) in trifluoroacetic acid (40 mL) to reflux. Analogous workup provided a yellow oil, yield 25 mg (38%).

6.2.21. (1*S*,5*S*)-2-Phenyl-6-propyl-6,8-diazabicyclo[3.2.2]-non-2-ene (19). The synthesis was performed as described for **18** heating **17** (26.0 mg, 0.072 mmol) in trifluoroacetic acid (30 mL) to reflux. After workup the residue was purified by fc (1 cm, CH_2Cl_2/CH_3OH = 8.5:1.5, 5 mL, R_f = 0.18). Yellow oil, yield 16.8 mg (96%). $C_{16}H_{22}N_2$ (242.3). MS (EI): *m*/*z* (%) = 242 (M, 68), 184 (M−Npropyl, 61), 170 (M−CH_2Npropyl, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3274 (w, ν_{N-H}), 1506 (m, δ_{N-H}), 756, 689 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.87 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.53, (sext., *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 2.41 (ddd, *J* = 18.8/3.9/3.1 Hz, 1H, 4-H), 2.59–2.63 (m, 2H, 4-H, 7-H), 2.67 (s, 1H, N*H*), 2.78–2.89 (m, 1H, 9-H), 3.01–3.04 (m, 1H, 5-H), 3.10–3.13 (m, 2H, 7-H, 9-H), 3.31–3.53 (m, 2H, $NCH_2CH_2CH_3$), 3.99–4.05 (m, 1H, 1-H), 5.90–5.93 (m,1H, 3-H), 7.08–7.33 (m, 5H, aromat. H).

6.2.22. (+)-4-{[(1*S*,5*S*)-8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]nonan-3-en-6-yl]methyl}-*N*,*N*-diethylbenzamide (3)[5]. Under N_2 K_2CO_3 (39 mg, 0.28 mmol), Bu_4NI (7.0 mg, 0.019 mmol), and 4-(chloromethyl)-*N*,*N*-diethylbenzamide (47 mg, 0.21 mmol) were successively added to a solution of **18** (45 mg, 0.19 mmol) in acetonitrile (20 mL) and the mixture was heated to reflux for 9 h. Then it was filtered, the filtrate was concentrated in vacuo and the residue was dissolved in 1 M HCl (10 mL). The acidic solution was washed with ethyl acetate (2× 10 mL), then 2 M NaOH (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 15 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (1 cm, CH_2Cl_2/CH_3OH = 9.5:0.5, 3 mL, R_f = 0.07). Colorless oil, yield 51 mg (63%). $C_{28}H_{35}N_3O$ (429.6). $[\alpha]_{589}$ +70.1 (*c* 0.65, CH_2Cl_2). The spectroscopic data of **3** are given in Ref. 5. Purity: HPLC, column 2, CH_3CN/H_2O = 50:50 + 0.1%, NEt_3; λ = 254 nm, t_R = 17 min, purity 99.0%.

6.2.23. (−)-4-[(1*R*,5*R*)-8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]nonane-3-en-6-ylmethyl]-*N*,*N*-diethylbenzamide (ent-3). The synthesis was performed as described for **3** using 4-(chloromethyl)-*N*,*N*-diethylbenzamide (20 mg, 0.08 mmol), ent-**18** (21 mg, 0.09 mmol), Bu_4NI (3 mg, 0.008 mmol), and K_2CO_3 (23 mg, 0.16 mmol) in acetonitrile (20 mL). Analogous workup afforded a colorless oil, yield 17 mg (48%). $C_{28}H_{35}N_3O$ (429.6). $[\alpha]_{589}$ −68.4 (*c* 0.62, CH_2Cl_2). Purity: HPLC, column 1, CH_3CN/H_2O = 50: 50 + 0.1%, NEt_3; λ = 254 nm, t_R = 17 min, purity 98.3%; column 2, MeOH/H_2O = 70:30 + 0.1% NEt_3; λ = 235 nm, t_R = 26 min, purity 98.7%.

6.2.24. (+)-4-*N*,*N*-Diethyl-4-{[(1*S*,5*S*)-4-phenyl-8-propyl-6,8-diazabicyclo[3.2.2]nonane-3-en-6-yl]methyl}benzamide (20). The synthesis was performed as described for **3** heating a mixture of 4-(chloromethyl)-*N*,*N*-diethylbenzamide (21 mg, 0.09 mmol), **19** (20 mg, 0.08 mmol), Bu_4NI (3.0 mg, 0.008 mmol) and K_2CO_3 (23 mg, 0.17 mmol) in acetonitrile (15 mL) to reflux. Analogous workup and fc purification (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.23) gave a colorless oil, yield 14 mg (40%). $C_{28}H_{37}N_3O$ (431.6). $[\alpha]_{589}$ +74.6 (*c* 0.10, CH_2Cl_2). MS (EI): *m*/*z* (%) = 431 (M, 31), 241 (M−$CH_2PhCONEt_2$, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3058 (w, $\upsilon_{C-Haromat.}$), 1631 (s, $\upsilon_{C=Oamide}$), 1285, 1093, 1021 (m, υ_{COC}), 842 (w, *p*-disubst. Ar) 756, 699 (m, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.85 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.01–1.21 (m, 6H, $N(CH_2CH_3)_2$), 1.47 (sext., *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 2.24 (dt, *J* = 18.8/3.9 Hz, 1H, 2-H), 2.51–2.55 (m, 2H, $NCH_2CH_2CH_3$), 2.58–2.61 (m, 1H, 7-H), 2.78–2.85 (m, 2H, 2-H, 9-H), 3.06–3.14 (m, 3H, 1-H, $N(CH_2CH_3)_2$), 3.29–3.36 (m, 2H, 7-H, 9-H), 3.38–3.45 (m, 2H, $N(CH_2CH_3)_2$), 3.50 (d, *J* = 13.3 Hz, 1H, $CH_2PhCONEt_2$), 3.53–3.55 (m, 1H, 5-H), 3.58 (d, *J* = 13.3 Hz, 1H, $CH_2PhCONEt_2$), 5.93–5.95 (m, 1H, 3-H), 7.06–7.19 (m, 9H, aromat. H). Purity: HPLC, column 1, CH_3CN/H_2O = 50: 50 + 0.1%, NEt_3, λ = 254 nm, t_R = 22 min, purity 98.8%, column 2, MeOH/H_2O = 75:25 + 0.1% NEt_3; λ = 235 nm, t_R = 19 min, purity 97.8%.

6.2.25. (+)-(1*S*,2*S*,5*S*)- and (+)-(1*S*,2*R*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]-nonane-7,9-dione (21a) and (21b). Under N_2 ammonium formate (722 mg, 14.2 mmol) was added to a stirred suspension of **14** (550 mg, 1.42 mmol) and 20% Pd/C (25.4 mg) in methanol (50 mL). The mixture was refluxed for 3 h. Then it was filtered through Celite, the solvent was removed in vacuo and the residue was purified by fc (3 cm, petroleum ether/ethyl acetate = 1:1, 10 mL). The product (colorless solid, yield 533 mg, 96%, mixture **21a**/**21b** = 75:25) was purified once more by fc (4 cm, petroleum ether/ethyl acetate = 6:4, 10 mL).

6.2.25.1. Data of compound 21a. Compound **21a** (R_f = 0.25): colorless solid, mp 112 °C (*i*-Pr_2O), yield 201 mg (28%). $C_{24}H_{28}N_2O_3$ (392.5). Calcd C, 73.4; H, 7.19; N, 7.13. Found: C, 73.3; H, 7.06; N, 7.09. $[\alpha]_{589}$ +96.9 (*c* 0.61, CH_2Cl_2). MS (EI): *m*/*z* (%) = 392 (M, 4), 121 (CH_2PhOCH_3, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1672 (s, $\upsilon_{C=Oamide}$), 1245 (m, υ_{C-O}), 1194, 1074 (w, υ_{C-O}), 800 (w, *p*-disubst. Ar), 752, 699 (m, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.96 (t, *J* = 7.2 Hz, 3H, $NCH_2CH_2CH_3$), 1.53–1.75 (m, 2H, $NCH_2CH_2CH_3$), 1.79–1.99 (m, 3H, 3-H, 4-H), 2.12–2.23 (m, 1H, 4-H), 2.43 (dd, *J* = 11.3/5.5 Hz, 1H, 2-H), 3.46 (ddd, *J* = 13.5/9.0/6.6 Hz, 1H, $NCH_2CH_2CH_3$), 3.51 (ddd, *J* = 13.5/9.0/6.6 Hz, 1H, $NCH_2CH_2CH_3$), 3.80 (s, 3H, OCH_3), 3.93 (s, 1H, 1-H), 4.04 (d, *J* = 7.8 Hz, 1H, 5-H), 4.33 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 4.71 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 6.85 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.98 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.15–7.26 (m, 5H, aromat. H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.8 (1C, $NCH_2CH_2CH_3$), 21.8 (1C, $NCH_2CH_2CH_3$), 26.4 (1C, C-4), 29.6 (1C, C-3), 45.9 (1C, C-2), 48.1 (1C, $NCH_2CH_2CH_3$), 49.3 (1C, CH_2PhOCH_3), 55.7 (1C, OCH_3), 60.5 (1C, C-1), 65.3 (1C, C-5), 114.3 (2C, C-3′ and C-5′[H_3COPh]), 127.1 (1C, C-1′[H_3COPh]),127.3 (2C, C-2′ and C-6′[H_3COPh]), 128.1 (1C, C-4′[phenyl]), 128.7 (2C, C-2′ and C-6′[phenyl]), 130.2 (2C, C-3′ and C-5′[phenyl]), 142.7 (1C, C-1′[phenyl]), 159.5 (1C, C-4′[H_3COPh]), 167.5 (1C, C=O), 170.4 (1C, C=O). Further recrystallization from *i*-Pr_2O gave colorless needles, which were suitable for X-ray crystal structure analysis.

6.2.25.2. X-ray crystal structure analysis of 21a. Formula $C_{24}H_{28}N_2O_3$, *M* = 395.5, *T* = 198 K, colorless needles, crystal size 0.45 × 0.30 × 0.25 nm, *a* = 10.244(1) [Å], *b* = 8.237(1) [Å], *c* = 13.520(1) [Å], β = 104.90(1) [°], *V* = 1102.5 [$Å^3$] (2), $Å^3$, ρ_{calc} = 1.182 g cm^{-3}, μ = 0.078 mm^{-1}, empirical absorption correction ($0.966 \leqslant T \leqslant 0.981$), *Z* = 2, monoclinic, space group $P2_1$ (No. 4), λ = 0.71073 Å, ω and φ scans, 7634 reflections collected ($\pm h$, $\pm k$, $\pm l$), [$(\sin\theta)/\lambda_{max}$] = 0.66 $Å^{-1}$, 4833 independent (R_{int} = 0.034) and 3980 observed reflections [$I \geqslant 2\ \sigma(I)$], 264 refined parameters, *R* = 0.044, wR^2 = 0.104, max. residual electron density 0.12 (−0.13) e $Å^{-3}$, Flack parameter 1.1(10), hydrogens calculated and refined as riding atoms. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT,[17] data reduction Denzo-SMN,[18] absorption correction Den-

zo,[19] structure solution SHELXS-97,[20] structure refinement SHELXL-97,[21] and graphics SCHAKAL.[22]

CCDC-658780 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336 033, E-mail: deposit@ccdc.cam.ac.uk].

6.2.25.3. Data of compound 21b. Compound **21b** (R_f = 0.13): colorless solid, mp 146 °C, yield 119 mg (15%). $C_{24}H_{28}N_2O_3$ (392.5). $[\alpha]_{589}$ +93.3 (*c* 1.20, CH_2Cl_2). MS (ESI): *m/z* (%) = 415 ($M+Na^+$, 100), 393 (MH^+, 11). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1676 (s, $\nu_{C=Oamide}$), 1245 (m, ν_{C-O}), 1174, 1032 (w, ν_{C-O}), 800 (w, *p*-disubst. Ar), 753, 700 (m, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.91 (t, *J* = 7.2 Hz, 3H, $NCH_2CH_2CH_3$), 1.50–1.67 (m, 2H, $NCH_2CH_2CH_3$), 1.76–1.86 (m, 1H, 4-H), 2.03–2.12 (m, 1H, 3-H), 2.16–2.28 (m, 1H, 4-H), 2.29–2.38 (m, 1H, 3-H), 3.11 (ddd, *J* = 14.1/8.6/5.5 Hz, 1H, $NCH_2CH_2CH_3$), 3.20 (ddd, *J* = 8.9/5.1/1.2 Hz,1H, 2-H), 3.26 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 3.61 (ddd, *J* = 14.1/8.6/5.5 Hz, 1H, $NCH_2CH_2CH_3$), 3.74 (s, 3H, OCH_3), 3.91 (d, *J* = 1.2 Hz, 1H, 1-H), 3.99 (d, *J* = 5.1/2.7 Hz, 1H, 5-H), 5.04 (d, *J* = 14.5 Hz, 1H, CH_2PhOCH_3), 6.69 (d, *J* = 8.9 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.75 (d, *J* = 8.9 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.21–7.38 (m, 5H, aromat. H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.8 (1C, $NCH_2CH_2CH_3$), 21.6 (1C, $NCH_2CH_2CH_3$), 25.2 (1C, C 4), 26.9 (1C, C-3), 41.3 (1C, $NCH_2CH_2CH_3$), 47.1 (1C, C-2), 46.9 (1C, CH_2PhOCH_3), 55.4 (1C, OCH_3), 59.9 (1C, C-5), 66.3 (1C, C-1), 114.3 (2C, C-3′ and C-5′[H_3COPh]), 127.5 (2C, C-2′ and C-6′[phenyl]), 127.9 (1C, C-1′[H_3COPh]), 129.4 (2C, C-2′ and C-6′[H_3COPh]), 129.7 (2C, C-3′ and C-5′[phenyl]), 129.9 (1C, C-4′[phenyl]), 142.8 (1C, C-1′[phenyl]), 159.1 (1C, C-4′[H_3COPh]), 168.8 (1C, C=O), 171.5 (1C, C=O).

6.2.26. (−)-(1*S*,2*S*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]nonane (22a). Under N_2 $LiAlH_4$ (25 mg, 0.64 mmol) was added to a solution (0 °C) of **21a** (50 mg, 0.13 mmol) in THF (15 mL). The mixture was stirred at 0 °C for 30 min and then under reflux temperature for 48 h. Then H_2O (0.1 mL) was carefully added and the mixture was heated to reflux for 30 min. After filtration the solvent was removed in vacuo. The residue was dissolved in 1 M HCl (10 mL), the aqueous layer was washed with ethyl acetate (2× 10 mL), then 2 M NaOH (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The CH_2Cl_2 layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (1 cm, ethyl acetate/acetone = 9:1, 3 mL, R_f = 0.32). Colorless oil, yield 43 mg (93%). $C_{24}H_{32}N_2O$ (364.5). $[\alpha]_{589}$ = −71.5 (*c* 0.75, CH_2Cl_2). MS (ESI): *m/z* (%) = 365 (MH^+, 100), 243 ($M-CH_2PhOCH_3$, 9). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1509 (m, $\nu_{C=Caromat.}$), 1242 (s, ν_{COC}), 1102, 1035 (m, ν_{COC}), 829 (w, *p*-disubst. Ar), 746, 699 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.86 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.41 (sext., *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 1.60–1.74 (m, 2H, 3-H, 4-H), 2.04–2.27 (m, 2H, 3-H, 4-H), 2.44 (t, *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 2.55–2.63 (m, 3H, 1-H, 7-H, 9-H), 2.91–2.93 (m, 3H, 5-H, 7-H, 9-H), 5.77 (dd, *J* = 12.9/5.5 Hz, 1H, 2-H), 3.57 (d, *J* = 13.1 Hz, 1H, CH_2PhOCH_3), 3.69 (d, *J* = 13.1 Hz, 1H, CH_2PhOCH_3), 3.73 (s, 3H, OCH_3), 6.77 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.97 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.02–7.23 (m, 5H, aromat. H). Purity: HPLC, column 2, CH_3OH/H_2O = 85:15 + 0.1% NEt_3; λ = 235 nm, t_R = 21 min, purity 97.9%.

6.2.27. (1*S*,2*R*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-propyl-6,8-diazabicyclo[3.2.2]nonane (22b). The synthesis was performed as described for **22a** refluxing a mixture of **21b** (122 mg, 0.31 mmol) and $LiAlH_4$ (60 mg, 1.55 mmol) in THF (50 mL). After workup the residue was purified by fc (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.24). Colorless oil, yield 78 mg (69%). $C_{24}H_{32}N_2O$ (364.5). MS (ESI): *m/z* (%) = 365 (MH^+, 100), 243 ($M-CH_2PhOCH_3$, 5). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1510 (m, $\nu_{C=Caromat.}$), 1244 (s, ν_{COC}), 1105, 1036 (m, ν_{COC}), 831 (w, *p*-disubst. Ar), 758 (m, monosubst. Ar), 700 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.88 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.54–1.59 (m, 2H, $NCH_2CH_2CH_3$), 1.63–1.84 (m, 4H, 3-H, 4-H), 2.21–2.36 (m, 1H, 2-H), 2.45–2.64 (m, 2H, $NCH_2CH_2CH_3$), 2.71–2.91 (m, 3H, 1-H, 7-H, 9H), 3.01–3.12 (m, 3H, 5-H, 7-H, 9-H), 3.51 (d, *J* = 12.5 Hz, 1H, CH_2PhOCH_3), 3.68 (d, *J* = 12.5 Hz, 1H, CH_2PhOCH_3), 3.76 (s, 3H, OCH_3), 6.78 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.18 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.21–7.33 (m, 5H, aromat. H).

6.2.28. (1*S*,2*S*,5*S*)-2-Phenyl-6-propyl-6,8-diazabicyclo[3.2.2]-nonane (23a). Under N_2 a solution of **22a** (0.20 g, 0.55 mmol) in trifluoroacetic acid (50 mL) was heated to reflux for 24 h. Then a solution of KOH (10 M, 70 mL) was added dropwise during cooling with ice. The mixture was extracted with CH_2Cl_2 (5× 100 mL), the organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, CH_2Cl_2/CH_3OH = 9:1, 5 mL, R_f = 0.28). Pale yellow oil, yield 0.102 g (76%). $C_{16}H_{24}N_2$ (244.4). MS (EI): *m/z* (%) = 244 (M, 49), 200 (M−H-propyl, 25), 125 (M−H-propyl-phenyl, 100). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3368 (w, ν_{N-H}), 749, 700 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.96 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.73 (sext., *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 1.98–2.20 (m, 3H, 3-H, 4-H), 2.48–2.60 (m, 1H, 4-H), 3.06 (m, 2H, $NCH_2CH_2CH_3$), 3.56–3.69 (m, 3H, 1-H, 7-H, 9-H), 3.73–3.78 (m, 3H, 5-H, 7-H, 9-H), 3.88 (m, 1H, 2-H), 7.12–7.27 (m, 5H, aromat. H).

6.2.29. (1*S*,2*R*,5*S*)-2-Phenyl-6-propyl-6,8-diazabicyclo[3.2.2]nonane (23b). As described for **23a** a solution of the methoxybenzyl derivative **22b** (39 mg, 0.01 mmol) in trifluoroacetic acid (30 mL) was heated to reflux. After workup and purification by fc (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.34) **23b** was isolated as pale yellow oil, yield 19 mg (78%). $C_{16}H_{24}N_2$ (244.4). MS (ESI): *m/z* (%) = 245 (MH^+, 100). IR (neat): $\tilde{\nu}$

[cm^{-1}] = 3365 (w, ν_{N-H}), 754, 701 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.87 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 1.15–1.19 (m, 1H, 4-H), 1.51 (sext., J = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 1.75–1.94 (m, 3H, 3-H, 4-H), 2.04–2.18 (m, 1H, 2-H), 2.56 (m, 2H, $NCH_2CH_2CH_3$), 2.93–3.18 (m, 4H, 7-H, 9H), 3.29–3.32 (m, 1H, 5-H), 3.38–3.47 (m, 1H, 1-H), 7.07–7.29 (m, 5H, aromat. H). A signal for the NH proton could not be detected.

6.2.30. (−)-4-{[(1*S*,4*S*,5*S*)–4-Phenyl-8-propyl-6,8-diazabicyclo[3.2.2]nonan-6-yl]methyl}-*N*,*N*-diethylbenzamide (24a). Under N_2 K_2CO_3 (99 mg, 0.72 mmol), Bu_4NI 15.0 mg, 0.041 mmol, and 4-(chloromethyl)-*N*,*N*-diethylbenzamide (108 mg, 0.48 mmol) were successively added to a solution of **23a** (100 mg, 0.41 mmol) in acetonitrile (25 mL)and the mixture was heated to reflux for 4 h. Then it was filtered, the filtrate was concentrated in vacuo and the residue was dissolved in 1 M HCl (10 mL). The mixture was washed with ethyl acetate (2× 15 mL), then 2 M NaOH (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 20 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (1 cm, CH_2Cl_2/CH_3OH = 9.5:0.5, 3 mL, R_f = 0.26). Colorless oil, yield 85 mg (49%). $C_{28}H_{39}N_3O$ (433.6). $[\alpha]_{589}$ −74.0 (c 0.40, CH_2Cl_2). MS (ESI): m/z (%) = 434 (MH^+, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1629 (s, $\nu_{C=Oamide}$), 1284, 1092 (m, ν_{C-O}), 838 (w, *p*-disubst. Ar), 749 (m, monosubst. Ar), 699 (s, monosubst. Ar). ^1H NMR (d_5-nitrobenzene, 51 °C): δ (ppm) = 0.63 (t, J = 7.4 Hz, 3H, $NCH_2CH_2CH_3$), 0.96 (t, J = 7.0 Hz, 6H, $N(CH_2CH_3)_2$), 1.19 (sext., J = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 1.38–1.50 (m, 1H, 2-H), 1.53 (dt, J = 13.3/5.4 Hz, 1H, 3-H), 1.82–1.95 (m, 1H, 3-H), 2.10–2.23 (m, 3H, 2-H, 9-H), 2.35 (t, J = 7.4 Hz, 2H, $NCH_2CH_2CH_3$), 2.48 (dd, J = 9.7/2.4 Hz, 1H, 7-H), 2.62–2.76 (m, 3H, 1-H, 5-H, 7-H), 2.90 (dd, J = 12.1/5.4 Hz, 1H, 4-H), 3.23 (q, J = 7.0 Hz, 4H, $N(CH_2CH_3)_2$), 3.48 (d, J = 13.9 Hz, 1H, $CH_2PhCONEt_2$), 3.63 (d, J = 13.9 Hz, 1H, $CH_2PhCONEt_2$), 6.85–7.06 (m, 5H, aromat. H), 7.29 (d, J = 8.2 Hz, 2H, 2′-H and 6′-H [$PhCONEt_2$]), 7.31 (d, J = 8.2 Hz, 2H, 3′-H and 5′-H [$PhCONEt_2$]). Purity: HPLC, column 1, CH_3CN/H_2O = 60:40 + 0.1%, NEt_3; λ = 254 nm, t_R = 21 min, purity 98.2%; column 2, CH_3OH/H_2O = 80:20 + 0.1% NEt_3; λ = 235 nm, t_R = 17 min, purity 96.8%.

6.2.31. (−)-4-{[(1*S*,4*R*,5*S*)-4-Phenyl-8-propyl-6,8-diazabicyclo[3.2.2]nonan-6-yl]methyl}-*N*,*N*-diethylbenzamide (24b). The synthesis was performed as described for **24a** by alkylation of **23b** (30 mg, 0.12 mmol) with 4-(chloromethyl)-*N*,*N*-diethylbenzamide (30 mg, 0.13 mmol) in the presence of K_2CO_3 (35 mg, 0.25 mmol) and Bu_4NI (10 mg, 0.027 mmol) in acetonitrile (20 mL). After workup and fc purification (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.17) **24b** was isolated as colorless oil, yield 39.8 mg (74%). $C_{28}H_{39}N_3O$ (433.6). $[\alpha]_{589}$ = −12.9 (c 0.35, CH_2Cl_2). MS (ESI): m/z (%) = 434 (M, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1629 (s, $\nu_{C=Oamide}$), 1285, 1093 (m, ν_{C-O}), 838 (w, *p*-disubst. Ar), 756 (m, monosubst. Ar), 701 (s, monosubst. Ar). ^1H NMR ($CDCl_3$): δ (ppm) = 0.83 (t, J = 7.3 Hz, 3H, $NCH_2CH_2CH_3$), 1.01–1.22 (m, 6H, $(NCH_2CH_3)_2$), 1.43–1.72 (m, 4H, 2-H. 3-H), 1.79–1.91 (m, 2H, $NCH_2CH_2CH_3$), 2.24–2.38 (m, 1H, 4-H), 2.45–2.58 (m, 2H, $NCH_2CH_2CH_3$), 2.76–2.84 (m, 3H, 1-H,7-H, 9-H), 2.99–3.17 (m, 3H, 5-H, 7-H, 9-H), 3.19–3.28 (m, 4H, $(NCH_2CH_3)_2$), 3.59 (d, J = 13.0 Hz, 1H, $CH_2PhCONEt_2$), 3.78 (d, J = 13.0 Hz, 1H, $CH_2PhCONEt_2$), 7.03–7.22 (m, 5H, aromat. H),7.25 (d, J = 8.0 Hz, 2H, 2′-H and 6′-H [$PhCONEt_2$]), 7.31 (d, J = 8.0 Hz, 2H, 3′-H and 5′-H [$PhCONEt_2$]). Purity: HPLC, column 1, CH_3CN/H_2O = 60:40 + 0.1%, NEt_3; λ = 254 nm, t_R = 23 min, purity 99.9%; column 2, CH_3OH/H_2O = 80:20 + 0.1% NEt_3; λ = 235 nm, t_R = 23 min, purity 99.9%.

6.2.32. (1*S*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6-prop-1-en-1-yl-6,8-diazabicyclo[3.2.2]non-2-ene-7,9-dione (25). Under N_2 1,4-diazabicyclooctane (29 mg, 0.26 mmol) and $RhCl_3{\cdot}3H_2O$ (10 mg, 0.004 mmol) were added to a solution of **14** (0.1 g, 0.26 mmol) in EtOH 90% (10 mL) and the mixture was heated to reflux for 5 h. Then it was filtered with Celite, 1 M HCl (20 mL) was added to the filtrate, and the mixture was extracted with CH_2Cl_2 (4× 50 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, petroleum ether/ethyl acetate = 1:1, 5 mL, R_f = 0.35). Colorless oil, yield 60 mg (60%). $C_{24}H_{24}N_2O_3$ (388.5). MS (ESI): m/z (%) = 411 ($M+Na^+$, 100), 389 (MH^+, 9). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3010 (w, $\nu_{C-Haromat.}$), 1676 (s, $\nu_{C=Oamide}$), 1245 (m, ν_{COC}), 1175, 1032 (w, ν_{COC}), 809 (w, *p*-disubst. Ar), 754, 698 (m, monosubst. Ar). ^1H NMR($CDCl_3$): δ (ppm) = 1.76 (dd, J = 6.6/2.0 Hz, 3H, $NCH{=}CHCH_3$), 2.70 (ddd, J = 19.5/4.3/2.7 Hz, 1H, 4-H), 2.84 (ddd, J = 19.5/4.3/3.9 Hz, 1H, 4-H), 3.71 (s, 3H, OCH_3), 4.40 (d, J = 14.5 Hz, 1H, CH_2PhOCH_3), 4.74 (d, J = 1.2 Hz, 1H, 1-H), 4.62 (m, 1H, 5-H), 4.63 (d, J = 14.5 Hz, 1H, CH_2PhOCH_3), 5.25 (dq, J = 13.3/6.4 Hz, 1H, $NCH{=}CHCH_3$), 5.75 (ddd, J = 3.9/2.7/1.2 Hz, 1H, 3-H), 6.63 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.88 (qd, J = 13.3/2.0 Hz, 1H, $NCH{=}CHCH_3$), 6.97(d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 6.99–7.23 (m, 5H, aromat. H).

6.2.33. (+)-(1*S*,5*S*)-8-(4-Methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene-7,9-dione (26). Under N_2 a solution of 1,4-diazabicyclooctane (0.57 g, 5.1 mmol) and $RhCl_3{\cdot}3H_2O$ (0.19 g, 0.07 mmol) was added to a solution of **14** (1.97 g, 5.1 mmol) in EtOH 90% (25 mL) and the mixture was heated to reflux for 6 h. Then 1 N HCl in MeOH (50 mL) was added and the mixture was heated to reflux for further 16 h. After addition of 1 N HCl (50 mL) the mixture was extracted with CH_2Cl_2 (4× 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (5 cm, petroleum ether/ethyl acetate = 2:8, 20 mL, R_f = 0.13). Colorless solid, mp 156.8 °C, yield 1.56 g (88%). $C_{21}H_{20}N_2O_3$ (348.4). $[\alpha]_{589}$ +115 (c 0.40, CH_2Cl_2). MS (EI): m/z (%) = 348 (M,72), 241 ($M-PhOCH_3$, 100), 227 ($M-CH_2PhOCH_3$, 5), 121 (CH_2PhOCH_3, 67). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3262 (w, ν_{N-H}), 1668,1650 (s, $\nu_{C=Oamide}$), 1239 (s, ν_{COC}), 1176, 1028 (m, ν_{COC}), 807 (m, *p*-disubst. Ar), 763, 701 (m, monos-

ubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.56 (ddd, J = 19.5/4.3/2.7 Hz, 1H, 4-H), 2.79 (ddd, J = 19.5/4.3/3.9 Hz, 1H, 4-H), 3.65 (s, 3H, OCH_3), 4.02–4.07 (m, 1H, 5-H), 4.31–4.33 (m, 1H, 1-H), 4.33 (d, J = 14.5 Hz, 1H, CH_2PhOCH$_3$), 4.63 (d, J = 14.5 Hz, 1H, CH_2PhOCH$_3$), 5.70 (ddd, J = 3.9/2.7/1.2 Hz, 1H, 3-H), 6.57 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.70 (s, 1H, NH), 6.91 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 6.95–7.17 (m, 5H, aromat. H).

6.2.34. (+)-(1*S*,2*S*,5*S*)- and (+)-(1*S*,2*R*,5*S*)-8-(-Methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (27a) and (27b). Under N_2 ammonium formate (1.35 g, 26.6 mmol) was added to a suspension of **26** (1.50 g, 3.9 mmol) and 20% Pd/C (0.3 g) in MeOH (150 mL) and the mixture was heated to reflux for 3 h. Then it was filtered with Celite, the filtrate was concentrated in vacuo and the residue was purified by fc (5 cm, ethyl acetate/acetone = 8:2, 20 mL). The product (colorless solid, yield 1.31 g, 87%, mixture **27a**/**27b** = 83:17) was purified once more by fc (4 cm, ethyl acetate, 10 mL).

Compound **27a** (R_f = 0.11, ethyl acetate): colorless solid, mp 196.6 °C, yield 472 mg (35%). $C_{21}H_{22}N_2O_3$ (350.5). Calcd C, 71.9; H, 6.33; N, 7.99. Found: C, 71.7; H, 6.33; N, 7.89. $[\alpha]_{589}$ +118 (c 0.66, CH_2Cl_2). MS (ESI): m/z (%) = 723 (2M+Na$^+$, 52), 373 (M+Na$^+$, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3322 (w, ν_{N-H}), 1669,1657 (s, $\nu_{C=Oamide}$), 1511 (m, δ_{N-H}), 1243 (s, ν_{COC}), 1168, 1030 (m, ν_{COC}), 802 (m, p-disubst. Ar), 751, 700 (m, monosubst. Ar). ^{1}H NMR($CDCl_3$): δ (ppm) = 1.88–2.18 (m, 4H, 3-H, 4-H), 2.49 (dd, J = 12.1/4.7 Hz, 1H, 2-H), 3.80 (s, 3H, OCH_3), 3.87 (s, 1H, 1-H), 4.10 (dd, J = 7.6/5.5 Hz, 1H, 5-H), 4.42 (d, J = 14.5 Hz, 1H, CH_2PhOCH$_3$), 4.67 (d, J = 14.5 Hz, 1H, CH_2PhOCH$_3$), 6.51 (d, J = 5.5 Hz, 1H, NH), 6.84 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.01 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.16–7.26 (m, 5H, aromat. H).

Compound **27b** (R_f = 0.08, ethyl acetate): colorless solid, mp 192.1 °C, yield 170 mg (11%). $C_{21}H_{22}N_2O_3$ (350.5). Calcd C, 71.9; H, 6.33; N, 7.99. Found: C, 71.6; H, 6.32; N, 7.44. $[\alpha]_{589}$ +71 (c 0.58, CH_2Cl_2). MS (ESI): m/z (%) = 1073 (3M+Na$^+$, 100), 723 (2M+Na$^+$, 98), 373 (M+Na$^+$, 4), 351 (MH$^+$, 13). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3329 (w, ν_{N-H}), 1675 (s, $\nu_{C=Oamide}$), 1512 (m, δ_{N-H}), 1245 (s, ν_{COC}), 1174, 1031 (m, ν_{COC}), 810 (m, p-disubst. Ar), 757, 701 (m, monosubst. Ar). ^{1}H NMR($CDCl_3$): δ (ppm) = 1.77–1.87 (m, 1H, 4-H), 2.11–2.27 (m, 1H, 3-H), 2.18–2.26 (m, 1H, 4-H), 2.33–2.41 (m, 1H, 3-H), 3.26 (ddd, J = 9.1/4.3/1.2 Hz, 1H, 2-H), 3.32 (d, J = 14.8 Hz, 1H, CH_2PhOCH$_3$), 3.74 (s, 3H, OCH_3), 3.83 (d, J = 1.2 Hz, 1H, 1-H), 4.07 (ddd, J = 7.8/5.1/2.7 Hz, 1H, 5-H), 5.06 (d, J = 14.8 Hz, 1H, CH_2PhOCH$_3$), 6.70 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.77 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 6.88 (d, J = 2.7 Hz, 1H, NH), 7.20–7.37(m, 5H, aromat. H).

6.2.35. (+)-(1*S*,2*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2. 2]nonane-7,9-dione (28a). Under N_2 a solution of **27a** (50.0 mg, 0.14 mmol) and Bu_4NI (10.5 mg, 0.028 mmol) in THF (20 mL) was cooled down to −78 °C. Then a solution of NaHMDS in THF (1 M, 0.2 mL, 0.2 mmol) and 40 min later a solution of allyl bromide (0.1 mL, 1.15 mmol) in THF (0.5 mL) were slowly added. The mixture was stirred for 1 h at −78 °C and for 2 h at rt. H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 50 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (1 cm, petroleum ether/ethyl acetate = 3:7, 3 mL, R_f = 0.24). Colorless oil, yield 50.9 mg (92%). $C_{24}H_{26}N_2O_3$ (390.5). $[\alpha]_{589}$ +135 (c 0.20, CH_2Cl_2). MS (ESI): m/z (%) = 803 (2M+Na$^+$, 58), 413 (M+Na$^+$, 100), 391 (MH$^+$, 8). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1670 (s, $\nu_{C=Oamide}$), 1243 (m, ν_{COC}), 1174, 1031 (w, ν_{COC}), 836 (w, p-disubst. Ar), 752, 700 (m, monosubst. Ar). ^{1}H NMR($CDCl_3$): δ (ppm) = 1.65–1.90 (m, 3H, 3-H, 4-H), 2.03–2.12 (m, 1H, 3-H), 2.36 (dd, J = 11.7/4.7 Hz, 1H, 2-H), 3.73 (s, 3H, OCH_3), 3.87 (s, 1H, 1-H), 3.97 (d, J = 7.8 Hz, 1H, 5-H), 4.02–4.06 (m, 2H, NCH_2CH=CH_2), 4.27 (d, J = 14.6 Hz, 1H, CH_2PhOCH$_3$), 4.64 (d, J = 14.6 Hz, 1H, CH_2PhOCH$_3$), 5.17–5.25 (m, 2H, NCH$_2$CH=CH_2), 5.70–5.81 (m, 1H, NCH$_2$CH=CH$_2$), 6.76 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.91 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.07–7.19 (m, 5H, aromat. H).

6.2.36. (−)-(1*S*,2*R*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (28b). As described for **28a** the diastereomer **27b** (60.0 mg, 0.17 mmol) was allylated with NaHMDS (1 M in THF, 0.2 mL, 0.2 mmol) and allyl bromide (0.2 mL, 2.30 mmol) in the presence of Bu_4NI (6.3 mg, 0.017 mmol) in THF (20 mL). After workup the residue was purified by fc (1 cm, petroleum ether/ethyl acetate = 3:7, 3 mL, R_f = 0.18). Colorless oil, yield 52.7 mg (83%). $C_{24}H_{26}N_2O_3$ (390.5). $[\alpha]_{589}$ −6.0 (c 0.29, CH_2Cl_2). MS (EI): m/z (%) = 390 (M, 52), 349 (M-allyl, 3), 273 (MH$^+$-allyl-phenyl, 31), 269 (M−CH$_2$PhOCH$_3$, 3), 121 (CH$_2$PhOCH$_3$, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1679 (s, $\nu_{C=Oamide}$), 1246 (m, ν_{COC}), 751 (m, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.73 (dddd, J = 7.0/5.5/3.1/1.6 Hz, 1H, 4-H), 1.95–2.05 (m, 1H, 3-H), 2.09–2.18 (m, 1H, 4-H), 2.19–2.26 (m, 1H, 3-H), 3.14 (ddd, J = 7.8/4.7/1.6 Hz,1H, 2-H), 3.19 (d, J = 14.9 Hz, 1H, CH_2PhOCH$_3$), 3.67 (s, 3H, OCH_3), 3.76 (ddd, J = 14.1/6.3/1.6 Hz, 1H, NCH_2CH=CH_2), 3.87 (d, J = 1.6 Hz, 1H, 1-H), 3.93 (dd, J = 5.5/1.6 Hz, 1H, 5-H), 4.14 (dddd, J = 14.1/6.3/3.1/1.6 Hz, 1H, NCH_2CH=CH$_2$), 4.97 (d, J = 14.9 Hz, 1H, CH_2PhOCH$_3$), 4.93–5.24 (m, 2H, NCH$_2$CH=CH_2), 5.64–5.75 (m, 1H, NCH$_2$CH=CH$_2$), 6.63 (d, J = 8.9 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.68 (d, J = 8.9 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.15–7.30 (m, 5H, aromat. H).

6.2.37. (−)-(1*S*,2*S*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane (29a). Under N_2 a mixture of $LiAlH_4$ (200 mg, 5.26 mmol) and **28a** (400 mg, 1.02 mmol) in THF (60 mL) was heated to reflux for 48 h. Then H_2O (0.4 mL) was cautiously added and the mixture was heated to reflux for 30 min. Then it was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in 1 M HCl (30 mL), the solution was washed with ethyl acetate (2× 20 mL), then 2 M NaOH (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 50 mL). The CH_2Cl_2 layer

was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by (3 cm, CH_2Cl_2/CH_3OH = 9.5:0.5, 10 mL, R_f = 0.08). Colorless oil, yield 222 mg (59%). $C_{24}H_{30}N_2O$: (362.5). $[\alpha]_{589}$ −44.7 (*c* 0.43, CH_2Cl_2). MS (ESI):*m*/*z* (%) = 363 (MH^+, 100), 241 (M−CH_2PhO CH_3, 14). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1243 (s, υ_{COC}), 1169, 1035 (w, υ_{COC}), 829 (w, *p*-disubst. Ar), 745 (m, monosubst. Ar), 700 (s, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.64–1.72 (m, 2H, 3-H, 4-H), 2.02–2.27 (m, 2H, 3-H, 4-H), 2.57–2.71 (m, 3H, 1-H, 7-H, 9-H), 2.88–2.99 (m, 3H, 5-H, 7-H, 9-H), 5.77 (dd, *J* = 13.3/5.5 Hz, 1H, 2-H), 3.13 (dd, *J* = 12.9/5.8 Hz, 1H, NCH_2 CH=CH_2), 3.16 (dd, *J* = 12.9/6.3 Hz, 1H, NCH_2 CH=CH_2), 3.56 (d, *J* = 12.9 Hz, 1H, CH_2PhO CH_3), 3.67 (d, *J* = 12.9 Hz, 1H, CH_2PhOCH_3), 3.73 (s, 3H, OCH_3), 5.01 (dd, *J* = 10.2/1.6 Hz, 1H, NCH_2CH=CH_2), 5.13 (dd, *J* = 17.2/1.9 Hz, 1H, NCH_2CH=CH_2), 5.88 (dddd, *J* = 17.2/10.2/6.3/5.8 Hz, 1H, NCH_2C*H*=CH_2), 6.77 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.98 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.10–7.26 (m, 5H, aromat. H). Purity: HPLC, column 2, CH_3OH/H_2O = 85:15 + 0.1% NEt_3; λ = 235 nm, t_R = 16 min, purity 96.5%.

6.2.38. (−)-(1*S*,2*R*,5*S*)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]nonane (29b). As described for **29a** the diastereomer **28b** (60 mg, 0.15 mmol) was reduced with $LiAlH_4$ (32 mg, 0.41 mmol) in THF (30 mL). After workup the residue was purified by fc (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.35). Colorless oil, yield 51 mg (91%). $C_{24}H_{30}N_2O$: (362.5). $[\alpha]_{589}$ −3.1 (*c* 0.64, CH_2Cl_2). MS (EI): *m*/*z* (%) = 362 (M, 100), 241 (M−H_2PhOCH_3, 43), 200 (M-allyl-phenyl, 31), 121 (CH_2PhOCH_3, 49). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1268, 1169, 1036 (m, υ_{COC}), 751, 701 (w, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.56–1.81 (m, 3H, 3-H, 4-H), 2.22–2.35 (m, 1H, 3-H), 2.50 (dd, *J* = 11.0/3.1 Hz, 1H, 2-H), 2.78–2.83 (m, 3H, 1-H, 7-H, 9H), 2.92–3.04 (m, 3H, 5-H, 7-H, 9-H), 3.14 (dd, *J* = 13.3/7.0 Hz, 1H, NCH_2CH=CH_2), 3.21 (dd, *J* = 13.3/5.5 Hz, 1H, NCH_2 CH=CH_2), 3.47 (d, *J* = 12.5 Hz, 1H, CH_2PhOCH_3), 3.67 (d, *J* = 12.5 Hz, 1H, CH_2PhOCH_3), 3.74 (s, 3H, OCH_3), 5.07–5.16 (m, 2H, NCH_2CH=CH_2), 5.84–5.94 (m, 1H, NCH_2C*H*=CH_2), 6.80 (d, *J* = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.01 (d, *J* = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.13–7.27 (m, 5H, aromat. H).

6.2.39. (1*S*,2*S*,5*S*)-6-Allyl-2-phenyl-6,8-diazabicyclo[3.2.2]-nonane (30a). Under N_2 a solution of **29a** (0.20 g, 0.55 mmol) in trifluoroacetic acid (40 mL) was heated to reflux for 24 h. After addition of 10 M KOH (70 mL) the mixture was extracted with CH_2Cl_2 (5× 100 mL), the organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by fc (2 cm, CH_2Cl_2/CH_3OH = 8.5:1.5, 5 mL, R_f = 0.28). Pale yellow oil, yield 0.079 g (59%). $C_{16}H_{22}N_2$ (242.4). MS (ESI): *m*/*z* (%) = 243 (MH^+, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3352 (w, υ_{N-H}), 748, 700 (m, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.64–1.85 (m, 3H, 3-H, 4-H), 2.48–2.60 (m, 1H, 4-H), 2.19 (dd, *J* = 12.1/5.5 Hz, 1H, NCH_2 CH=CH_2), 2.23 (dd, *J* = 12.1/6.3 Hz, 1H, NCH_2 CH=CH_2), 2.83 (dd, *J* = 12.3/4.1 Hz, 1H 2-H), 3.04–3.22 (m, 4H, 7-H, 9-H), 3.36–3.46 (m, 2H, 1-H, 5-H), 5.10 (dd, *J* = 10.2/1.9 Hz, 1H, NCH_2CH=CH_2), 5.18 (ddd, *J* = 17.2/3.1/1.6 Hz, 1H, NCH_2CH=CH_2), 5.78 (dddd, *J* = 17.2/10.2/6.3/4.1 Hz, 1H, NCH_2C*H*=CH_2), 7.12–7.26 (m, 5H, aromat. H). A signal for the NH proton was not found.

6.2.40. (1*S*,2*R*,5*S*)-6-Allyl-2-phenyl-6,8-diazabicyclo[3.2.2]nonan (30b). As described for **30a** the methoxybenzyl group was removed by refluxing of **29b** (40 mg, 0.11 mmol) in trifluoroacetic acid (40 mL). Workup and fc purification (1 cm, CH_2Cl_2/CH_3OH = 9:1, 3 mL, R_f = 0.24) gave a pale yellow oil, yield 19 mg (71%). $C_{16}H_{22}N_2$ (242.4). MS (EI): *m*/*z* (%) = 242 (M, 100), 124 (M-allyl-phenyl, 42). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 3362 (w, υ_{N-H}), 1110 (m, υ_{COC}), 758, 702 (m, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.76–1.89 (m, 4H, 3-H, 4-H), 2.04–2.16 (m, 1H, 2-H), 2.92–2.98 (m, 2H, 7-H, 9-H), 3.03–3.24 (m, 4H, 7-H, 9H, NCH_2CH=CH_2), 3.27–3.30 (m, 1H, 5-H), 3.40 (dd, *J* = 12.5/3.9 Hz, 1H, 1-H), 5.10–5.20 (m, 2H, NCH_2CH=CH_2), 5.81–5.92 (m, 1H, NCH_2C*H*=CH_2), 7.10–7.28 (m, 5H, aromat. H). A signal for the NH proton was not seen.

6.2.41. (−)-4-{[(1*S*,4*S*,5*S*)-8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]nonan-6-yl]methyl}-*N*,*N*-diethylbenzamide (4a). The synthesis was performed as described for **24a** by alkylation of **30a** (79 mg, 0.33 mmol) with 4-(chloromethyl)-*N*,*N*-diethylbenzamide (81 mg, 0.36 mmol) in the presence of K_2CO_3 (90 mg, 0.65 mmol) and Bu_4NI (12 mg, 0.033 mmol) in acetonitrile (20 mL). After workup and fc purification (1 cm, CH_2Cl_2/CH_3OH = 9.5:0.5, 3 mL, R_f = 0.10) **4a** was isolated as colorless oil, yield 59 mg (42%). $C_{28}H_{37}N_3O$ (431.6). $[\alpha]_{589}$ −61.1 (*c* 0.40, CH_2Cl_2). MS (ESI): *m*/*z* (%) = 432 (MH^+, 100). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1629 (s, $\upsilon_{C=Oamide}$), 1285, 1093, 1021 (m, υ_{COC}), 841 (w, *p*-disubst. Ar) 756, 701 (m, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.93–1.35 (m, 6H, $N(CH_2CH_3)_2$), 1.59–1.76 (m, 2H, 2-H, 3-H), 2.03–2.13 (m, 1H, 2-H), 2.21 (ddd, *J* = 13.7/11.7/4.7 Hz, 1H, 3-H), 2.62–2.68 (m, 3H, 1-H, 7-H, 9-H) 2.92–2.99 (m, 3H, 5-H, 7-H, 9-H), 3.04 (dd, *J* = 12.9/4.7 Hz, 1H, 4-H), 3.11 (dd, *J* = 13.7/6.3 Hz, 1H, NCH_2CH=CH_2), 3.18 (dd, *J* = 13.7/5.9 Hz, 1H, NCH_2CH=CH_2), 3.16–3.21 (m, 2H, $N(CH_2CH_3)_2$), 3.42–3.50 (m, 2H, $N(CH_2CH_3)_2$), 3.66 (d, *J* = 13.9 Hz, 1H, CH_2PhCONEt_2), 3.76 (d, *J* = 13.9 Hz, 1H, CH_2PhCONEt_2), 5.01–5.03 (dd, *J* = 10.2/1.6 Hz, 1H, NCH_2CH=CH_2), 5.14 (ddd, *J* = 17.2/3.1/1.9 Hz, 1H, NCH_2CH=CH_2), 5.82 (dddd, *J* = 17.2/10.2/6.3/1.9 Hz, 1H, NCH_2C*H*=CH_2), 6.97–7.16 (m, 5H, aromat. H), 7.24 (d, *J* = 8.2 Hz, 2H, 2′-H and 6′-H [PhCONEt_2]), 7.34 (d, *J* = 8.2 Hz, 2H, 3′-H and 5′-H [PhCONEt_2]). Purity: HPLC, column 1, CH_3CN/H_2O = 60:40 + 0.1%, NEt_3; λ = 254 nm, t_R = 16 min, purity 95.2%; column 2 CH_3OH/H_2O = 75:25 + 0.1% NEt_3; λ = 235 nm, t_R = 35 min, purity 95.9%.

6.2.42. (−)-4-{[(1*S*,4*R*,5*S*)-8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]nonan-6-yl]methyl}-*N*,*N*-diethylbenzamide (4b). The synthesis was performed as described for **24a** by alkylation of **30b** (18 mg, 0.08 mmol) with 4-(chloromethyl)-*N*,*N*-diethylbenzamide (19 mg, 0.08 mmol) in the presence of K_2CO_3 (21 mg, 0.15 mmol) and Bu_4NI

(3 mg, 0.008 mmol) in acetonitrile (15 mL). After workup the residue was purified by fc (1 cm, ethyl acetate/acetone 7:3 + 1% NEt_3, 3 mL, $R_f = 0.32$). Colorless oil, yield 22 mg (71%). $C_{28}H_{37}N_3O$ (431.6). $[\alpha]_{589}$ −5.2 (*c* 0.30, CH_2Cl_2). MS (EI): *m/z* (%) = 431 (M, 100), 241 (M−CH_2PhCONEt_2, 42), 200 (M−CH_2PhCONEt_2-allyl, 31). IR (neat): $\tilde{\upsilon}$ [cm^{-1}] = 1631 (s, $\nu_{C=Oamid}$), 1285, 1093, (m, ν_{COC}), 841 (w, *p*-disubst. Ar) 757, 701 (m, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.07–1.18 (m, 6H, (NCH_2CH_3)$_2$), 1.57–1.86 (m, 3H, 2-H. 3-H), 2.23–2.40 (m, 1H, 3-H), 2.48 (dd, *J* = 11.0/1.6 Hz, 1H, 4-H), 2.78–2.92 (m, 4H, 1-H, 7-H, 9-H), 2.97–3.04 (m, 2H, 5-H, 9-H), 3.14 (dd, *J* = 13.3/7.0 Hz, 1H, NCH_2CH=CH_2), 3.19 (dd, *J* = 13.3/5.5 Hz, 1H, NCH_2CH=CH_2), 3.10–3.49 (m, 4H, N(CH_2CH_3)$_2$), 3.56 (d, *J* = 13.3 Hz, 1H, CH_2PhCONEt_2), 3.77 (d, *J* = 13.0 Hz, 1H, CH_2PhCONEt_2), 5.02–5.23 (m, 2H, NCH_2CH=CH_2), 5.81–5.91 (m, 1H, NCH_2C*H*=CH_2), 7.05–7.35 (m, 9H, aromat. H). Purity: HPLC, column 1, CH_3CN/H_2O = 60:40 + 0.1%, NEt_3; λ = 254 nm, t_R = 18 min, purity 97.7%; column 2, CH_3OH/H_2O = 75:25 + 1% NEt_3; λ = 235 nm, t_R = 19 min, purity 98.1%.

6.2.43. (2*S*)-1-{(1*S*,5*S*)-(8-Allyl-4-phenyl-6,8-diazabicyclo-[3.2.2]non-3-en-6-yl)-3,3,3-trifluoro-2-methoxy-3-phenylpropan-1-one (31). Under N_2 NEt_3 (25 μL, 0.18 mmol), 4-(dimethylamino)pyridine (20 mg, 0.15 mmol), and (*R*)-Mosher's acid chloride (28 μL, 0.15 mmol) were added to a solution of **18** (35 mg, 0.15 mmol) in CH_2Cl_2 (5 mL). After stirring under ice cooling for 15 min the mixture was heated to reflux for 5 h. The mixture was washed with a saturated solution of $NaHCO_3$ (5 mL) and H_2O (5 mL), dried (Na_2SO_4), and concentrated in vacuo. About one-third of the unpurified residue was used for determination of the diastereomeric ratio by ^{19}F NMR spectroscopy, HPLC, and CE. In order to get a pure reference compound for the analytical investigations the residual amount of the product was purified by fc (1 cm, petroleum ether/ethyl acetate = 6:4, 3 mL, R_f = 0.31). Colorless oil. $C_{26}H_{27}N_2O_3$ (456.5). MS (EI): *m/z* (%) = 456 (M, 15), 441 (M-methyl, 7), 267 (M−PhC(OCH_3)(CF_3), 100). IR (neat): $\tilde{\upsilon}$ (cm^{-1}) = 1652 (s, $\nu_{C=Oamide}$), 1177, 1152 (s, C–F), 752, 681 (s, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.39–2.44 (m, 1H, 2-H), 2.69–2.78 (m, 3H, 2-H, 9-H), 2.88–3.19 (m, 4H, 7-H, NCH_2CH=CH_2), 3.58 (s, 3H, OCH_3), 3.67–3.70 (m, 1H, 1-H), 4.98–5.03 (m, 2H, NCH_2CH=CH_2), 5.28–5.32 (m, 1H, 5-H), 5.63–5.72 (m, 1H, NCH_2C*H*=CH_2), 5.81–5.83 (m, 1H, 3-H), 7.19–7.67 (m, 10H, aromat. H). ^{19}F NMR (d_6-DMSO, 70 °C): δ (ppm) = −70.25 (s, 3F, CF_3, 99.5% intensity), −69.17 (s, 3F, CF_3, 0.5% intensity).

6.2.44. (2*R*)-1-{(1*S*,5*S*)-(8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]non-3-en-6-yl)-3,3,3-trifluoro-2-methoxy-3-phenylpropan-1-one (32). As described for **31** the secondary amine **18** (28 mg, 0.12 mmol) was acylated with (*S*)-Mosher's acid chloride (23 μL, 0.20 mmol) in the presence of NEt_3 (21 μL, 0.15 mmol), 4-(dimethylamino)pyridine (16 mg, 0.12 mmol) in CH_2Cl_2 (5 mL). After workup about one-third of the product was used for analysis of the diastereomeric ratio, the residual amount was purified by fc (1 cm, petroleum ether/ethyl acetate = 6:4, 3 mL, R_f = 0.31). Colorless oil. $C_{26}H_{27}N_2O_3$ (456.5). MS (EI): *m/z* (%) = 456 (M, 14), 441 (M-methyl, 6), 267 (M−PhC(OCH_3)(CF_3), 100). IR (neat): $\tilde{\upsilon}$ (cm^{-1}) = 1652 (s, $\nu_{C=Oamide}$), 1179, 1157 (s, C–F), 729, 700 (s, monosubst. Ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.35–1.53 (m, 1H, 2-H), 2.26–2.39 (m, 1H, 2-H), 2.77–3.12 (m, 4H, 7-H, 9-H), 3.27–3.32 (m, 2H, NCH_2CH=CH_2), 3.56–3.68 (m, 1H, 1-H), 3.70 (s, 3H, OCH_3), 5.02–5.07 (m, 2H, NCH_2CH=CH_2), 5.07–5.12 (m, 1H, 5-H), 5.66–5.82 (m, 2H, NCH_2C*H*=CH_2, 3-H), 7.15–7.73 (m, 10H, aromat. H). ^{19}F NMR (d_6-DMSO, 70 °C): δ (ppm) = −70.26 (s, 3F, CF_3, 1.0% intensity), −69.55 (s, 3F, CF_3, 99.0% intensity).

6.3. Receptor binding studies

6.3.1. δ Assay

6.3.1.1. General. Receptor material: Fa. Receptor Biology: human δ_2 opioid receptor (RB-HOD); transfected CHO-K_1-cells. Buffer: Buffer for incubation 50 mmol/L Tris–HCl, 5 mmol/L $MgCl_2$, pH 7.4; buffer for soaking of the filter plates 50 mmol/L Tris–HCl, 5 mmol/L $MgCl_2$, 0.5% polyethylenimine, pH 7.4. Filter: Glass fiber MT-filterplates (Whatman GF/B). Cell harvester: Brandel Cell Harvester Typ MPRI-96T. Liquid scintillation analyzer: 1450 Microbeta Trilux, Fa. Wallac. Scintillation cocktail: Ultima Gold MV, Fa. Packard. Radioligand: [^{3}H]-Deltorphine II (2-D-Ala) (NET-1087, Fa. NEN, specific activity 53 Ci/mmol).

6.3.1.2. Performance of the δ assay. The thawed membrane preparation was diluted with the incubation buffer 1:87 and pottered. In each well of a microtiter plate the test compound solution (5 μL), the radioligand solution (25 μL, 10 nmol/L), and the receptor preparation (220 μL) were given. Naloxone–HCl (5 μL, 500 μmol/L) was employed for the determination of the non-specific binding and an aqueous solution of DMSO 0.5% (5 μL) was used for the determination of the total binding. (The solutions of the test compounds, the radioligand, and naloxone contain 0.5% DMSO.) The components were mixed with a minishaker and incubation was performed at rt for 120 min. Subsequently, the samples were filtered through the filters, which were prepared with buffer (50 mmol/L Tris–HCl, 5 mmol/L $MgCl_2$, and 0.5% PEI, pH 7.4) and the filters were washed three times with cold incubation buffer. The filtermates were dried for 1 h at 55 °C, then the scintillation cocktail was added and the bound radioactivity trapped on the filters was counted with the liquid scintillation analyzer for 90 min.

6.3.2. μ Assay

6.3.2.1. General. Receptor material: human μ-opioid Receptor/CHO-K_1-Zellen (RB-HOM) Fa. PerkinElmer Life Sciences. Beads: Wheatgerm agglutinin SPA beads, Fa. Amersham, RPNQ0001. Buffer: Buffer for the assay 50 mmol/L Tris–HCl, pH 7.4; membrane buffer 50 mmol/L Tris–HCl, pH 7.4 + 0.06% BSA (bovine serum albumin Fa. Sigma). Luminescence plates: SPA-Plates Fa. Costar. Scintillation analyzer: 1450 Microbe-

ta Trilux, Firma Wallac. Radioligand: [^{3}H]-Naloxone (*N*-allyl-2,3) (NET719, Fa. NEN, specific activity ca. 60 Ci/mmol). Centrifuge: Microtiterplate centrifuge GS6 Fa. Beckmann.

6.3.2.2. Performance of the μ assay. The thawed membrane preparation was diluted with membrane buffer and pottered. The assay buffer (100 mL) was added to the beads (500 mg beads) and the mixture was stirred on a magnetic stirrer for 1 h. In the wells of a SPA-plate the test compound solution (5 μL), the radioligand solution (25 μL, 10 nmol/L), and 220 μL of an incubated mixture of receptor membrane (20 μL) and bead suspension (200 μL) were given. The non-specific binding was determined with naloxone–HCl (5 μL, 500 μmol/L) and the total binding was determined with an aqueous solution of DMSO 25% (5 μL). (The solutions of the test compounds, the radioligand, and naloxone contain about 25% of DMSO). The components were mixed with a minishaker and afterwards incubated for 150 min at rt. Then the samples were centrifuged for 20 min at 500 rpm, the bound radioactivity was counted with the liquid scintillation analyzer.

6.3.3. κ Assay

6.3.3.1. General. Receptor material: human κ opioid Receptor (RB-HOKM), HEK-293-Zellen, Fa. PerkinElmer Life Sciences. Beads: Wheatgerm agglutinin SPA beads, Fa. Amersham, RPNQ0001. Buffer: Buffer for the assay 50 mmol/L Tris–HCl, pH 7.4, 0.05% NaN_3; buffer for the homogenate 50 mmol/L Tris–HCl, 0.05% NaN_3, 0.02% BSA (bovine serum albumin Fa. Sigma), pH 7.4; buffer for the beads 50 mmol/L Tris–HCl, 0.05% NaN_3, pH 7.4. Luminescence plates: SPA plates Fa. Costar. Scintillation analyzer: 1450 Microbeta Trilux, Firma Wallac. Radioligand: [^{3}H]-CI-977, (TRK945, Fa. Amersham, specific activity ca. 48 Ci/mmol). Centrifuge: Microtiterplate centrifuge GS6 Fa. Beckmann.

6.3.3.2. Performance of the κ assay. The thawed membrane preparation was diluted with assay buffer in the ratio 1:34. The κ assay was performed in analogy to the μ assay as described above.

6.3.4. ORL1 Assay

6.3.4.1. General. Receptor material: Fa. Receptor Biology: human ORL1-Orphanine Receptor (RB-HORL), HEK-293-cells. Beads: Wheatgerm agglutinin SPA beads, Fa. Amersham, RPNQ0001. Buffer: Buffer for the assay 50 mmol/L Hepes, 10 mmol/L $MgCl_2$, 1 mmol/L EDTA, pH 7.4. Luminescence pates: SPA-Platten Fa. Costar. Scintillation analyzer: 1450 Microbeta Trilux, Firma Wallac. Radioligand: [*leucyl*-^{3}H]-nociceptin (TRK1047, Fa. Amersham, specific activity ca. 150 Ci/mmol). Centrifuge: Microtiterplate centrifuge GS6 Fa. Beckmann.

6.3.4.2. Performance of the PRL1 assay. The ORL1 assay was performed as described above for the μ assay. The non-specific binding was determined with nociceptin (5 μL, 100 nmol/L).

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References and notes

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