Molecular modeling directed synthesis of a bicyclic analogue of the δ opioid receptor agonist SNC 80

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In order to find novel δ opioid receptor agonists, the pharmacophoric benzhydryl moiety of the lead compound SNC 80 (**1**) was dissected and the phenyl residues were attached to different positions of the 6,8-diazabicyclo[3.2.2]nonane core system (**4**). The position of the carboxamido group, the stereochemistry, the C3/C4 bond order and the kind and length of the spacer X were considered. The resulting compounds were compared with the four energetically most favourable conformations of SNC 80 by a multifit analysis. These calculations led to the structures **5**-**10**, which fit best to SNC 80. Herein the synthesis of one of these compounds (**9**) is described. Starting from (S)-glutamate two alternative routes are detailed to obtain the key intermediate **14**. A variation of the Dieckmann cyclization, which uses trapping of the first cyclization product with $ClSiMe_3$ provided the mixed acetal **20**, which was carefully hydrolyzed to yield the bicyclic ketone **17**. Stereoselective addition of phenylmagnesium bromide, dehydration, $LiAlH_4$ reduction and exchange of the N-6 residue afforded the designed compound **9**. The affinities of **9** towards δ, μ, κ and ORL1 receptors were determined in receptor binding studies with radioligands. Only moderate receptor affinity was found.

Keywords: δ receptor agonists; ligand based molecular modeling; multifit analysis; bridged piperazines; bicyclic SNC 80 analogues; Dieckmann cyclization

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Introduction

Strong analgesics (i.e. morphine) mediate their effects by activating opioid receptors, which belong to the superfamily of G-protein coupled receptors (GPR). They transmit their information via G_i proteins inhibiting adenylyl cyclase, opening K^+ channels and closing Ca^{2+} channels. In the last three decades the opioid receptor class has been subdivided into three different subtypes named μ (MOP), κ (KOP) and δ (DOP)opioid receptor. The recently identified ORL1 receptor (NOP) is also classified in the opioid receptor family. The amino acid sequence of the ORL1 receptor is about 60% homologous to that of the μ, κ and δ receptors and about 80% homologous in the 2nd, 3rd and 7th transmembrane domains [1]. However, nociceptin the endogenous agonist of the ORL1 receptor induces hyperalgesia instead of analgesia [2].

The opioid analgesics used in clinical practice activate predominantly the μ receptor. However, their strong analgesic activity is associated with undesirable side effects including respiratory depression, physical dependency and constipation. High affinity κ agonists also display analgesic effects in animal models and in man but their clinical use is limited by strong diuresis, dysphoria and sedation [3, 4].

δ agonists also induce strong analgesia with no or little liability to induce the typical side effects of μ and κ agonists. Moreover, they potentiate the analgesic effect of morphine in subanalgesic doses [3]. Because of their antinociceptive potency and the lack of side effects δ agonists are considered as safe analgesics [3,4]. In addition to their analgesic activity δ agonists possess further pharmacological effects e.g. immunoregulatory properties, antisecretory activity in bronchial diseases and gastroprotective effects [4].

In literature some highly potent and selective non-peptide δ agonists have been described. They are subdivided into three major types: morphine derived compounds (e.g. SIOM) isoquinoline derivatives (e.g. TAN 67) and piperazine based compounds (e.g. SNC 80 (**1**), BW 373U86 (**2**)) [3, 4]. Intensive structure activity relationship studies based on SNC 80 (**1**) showed that the carboxamido moiety [3] and a cyclic amine [5] are required for strong δ receptor interaction. Removal of the piperazine methyl groups decreased the δ receptor affinity [6] and replacement of the N-allyl moiety by a proton or by alkyl or other alkenyl residues resulted in less potent δ agonists [6].

In order to develop novel δ agonists derived from the piperazine derivative SNC 80 (**1**) we replaced the mono-

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cyclic piperazine ring by the conformationally restricted diazabicyclo [3.2.2]nonane system as shown in structure **4**. The benzhydryl moiety should be imitated by two separated phenyl residues attached to different ring positions of the bicyclic core system. The propano bridge of the bicyclic system represents the methyl groups of SNC 80 (**1**). Several variations of the bicyclic structure were considered: The position of the carboxamido group, the stereochemistry, the binding order of the C_3/C_4 bond and the kind and the length of the spacer X. Ligand based molecular modeling should provide an idea, which of the possible variations might have similar steric and electronic properties as **1**.

Results

Molecular modeling

We assume that similarity of novel compounds to the lead compound SNC 80 (**1**) corresponds with high δ receptor affinity. Therefore in a molecular modeling study the bicyclic compounds **4** were compared with SNC 80 (**1**). In order to find energetically favorable conformations of the flexible benzhydryl moiety of SNC 80 (**1**), a systematic conformational analysis was performed. For this purpose, the bonds indicated with a) and b) of **1** in Figure 1 were rotated by increments of 30° and the resulting conformations were minimized and filtered to select the nonrepetitive conformations. The bond c) of the remaining eight conformations was rotated by an increment of 10° and after minimizing and filtering the resulting 12 conformations were ranked according to their energy. These conformations were grouped into four families (see Table 1) using the family option.

The conformation 4 (family 2) corresponds to the crystal structure of the fluoro derivative **3** [7]. In Figure 2 the similarity of conformation 4 of SNC 80 and the crystal structure of the fluoro derivative **3** is shown.

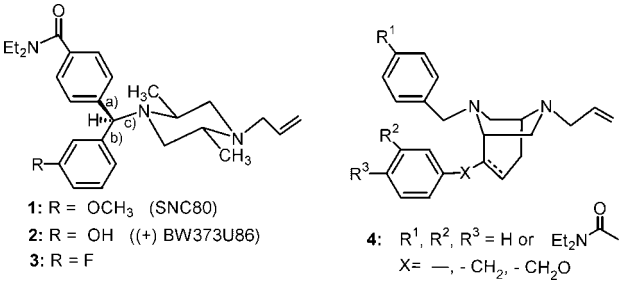


Figure 1. Lead compounds **1**–**3** and designed bicyclic δ agonists **4**.

Table 1. Calculated conformations of SNC 80 (**1**).

Conformation	Energy [kcal/mol]	Family
1	15.7	1
2	16.1	1
3	16.4	1
4	17.5	2
5	18.5	3
6	19.1	3
7	19.3	3
8	19.5	3
9	20.1	3
10	21.0	4
11	21.3	4
12	21.5	4

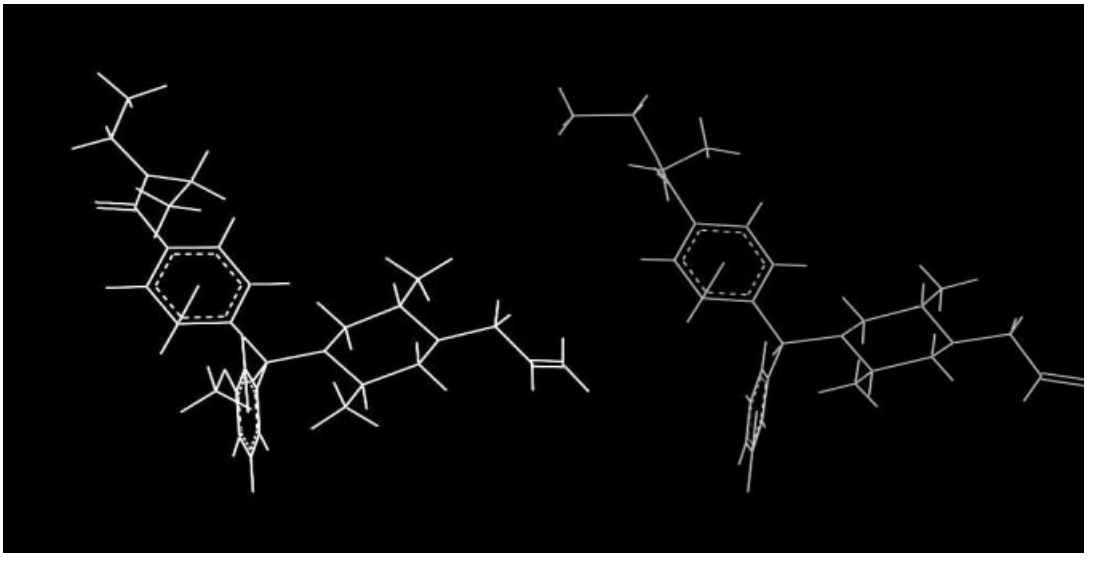
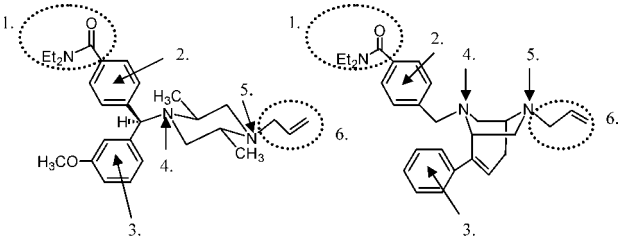


Figure 2. Conformation 4 of SNC 80 (**1**) (left) and the crystal structure of **3** (right).

The conformations with the lowest energy (conformations 1-4 = family 1,2) were chosen as templates and were compared with the planned bicyclic analogues **4** by multifit analysis that combines an atom-by-atom superposition with an energy minimization [8]. The pharmacophoric elements carboxamido moiety, allyl residue, the centroids of the phenyl residues and both piperazine nitrogen atomes were used as atom pairs for the superposition. The corresponding superposed anchoring points of the lead compound SNC 80 (**1**) and the synthesized compound **9** are demonstrated in Figure 3.

The superposition of the molecules was analyzed by calculating the multifit energy. The multifit energy is the energy that is necessary to adjust two molecules to each other.



1.: carboxamido moiety
2., 3.: centroids of the phenyl residues
4., 5.: piperazine nitrogen atoms
6.: allyl residue

Figure 3. Pharmacophoric elements.

Therefore it represents the quality of the fit: the lower the energy the better the fit. Careful analysis of the multifit energies of more than 100 superpositions led to the following general rules:

1. Compounds with the N,N-diethylcarbamoylbenzyl residue at the nitrogen atom generally revealed lower multifit energies than the analogues with this residue in position 4. The six compounds among this group with the lowest multifit energy are shown in Table 2.

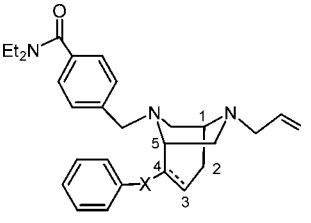
2. The most favorable configuration is (1S,4S,5R) for the 2-benzyloxy derivatives (**5**, X= CH2O) and (1S,4R,5S) for the 2-phenyl (**7**, X = bond) and 2-benzyl derivatives (**10**, X = CH_2). However, the enantiomers **6** and **8** of these compounds do also give low multifit energies. The best configuration for compounds with a C_3/C_4 double bond is (1S,5S) (compound **9**).

3. The benzyl derivatives (e.g. **10**) yielded the highest multifit energies in this group indicating low correlation with SNC 80 (**1**).

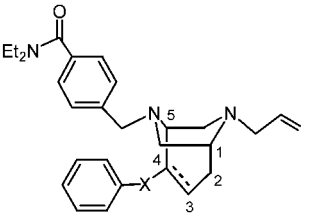
The multifit energy of 112 calculated superpositions ranged from 1.1 kcal/mol to 18.1 kcal/mol. Therefore, it was postulated that the compounds in Table 2 represent good correlates to the lead structure SNC 80 (**1**) displaying similar pharmacological activities.

We started the project with the synthesis and pharmacological evaluation of compound **9**. Since **9** possesses a double bond between C_3 and C_4, stereoisomers at C_4 are not to be

Table 2. Ten superpositions with low multifit energy.



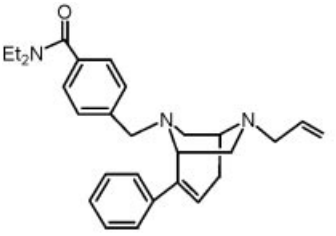
5,7,9,10



6,8

Compound	Fit on conformation (Table 1)	Spacer X	Configuration	C_3/C_4 bond order	Multifit-energy [kcal/mol]
5	2	-CH_2O-	1S, 4S, 5R	single	1.1
6	4	bond	1R, 4S, 5R	"	1.4
7	4	bond	1S, 4R, 5S	"	2.0
8	4	-CH_2O-	1R, 4R, 5S	"	2.2
9	4	bond	1S, 5S	double	2.4
7	1	bond	1S, 4R, 5S	single	2.7
5	3	-CH_2O-	1S, 4S, 5R	"	3.2
10	1	-CH_2-	1S, 4R, 5S	"	3.4
10	2	-CH_2-	1S, 4R, 5S	"	3.7
10	4	-CH_2-	1S, 4R, 5S	"	3.7

considered. The multifit energy of 2.4 kcal/mol resulting from the superposition of **9** with conformation 4 of SNC 80 (**1**), which is shown in Figure 4, indicates a quite good correlation.



9

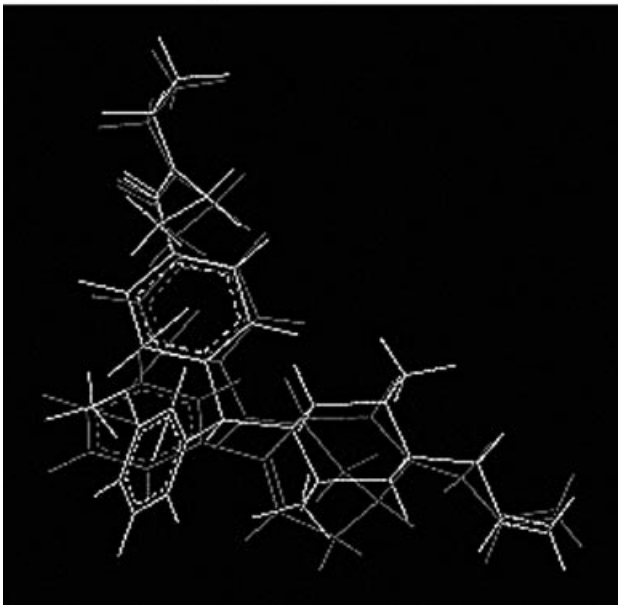


Figure 4. Superposition of compound **9** (dark gray) with conformation 4 (gray) of SNC 80 (**1**).

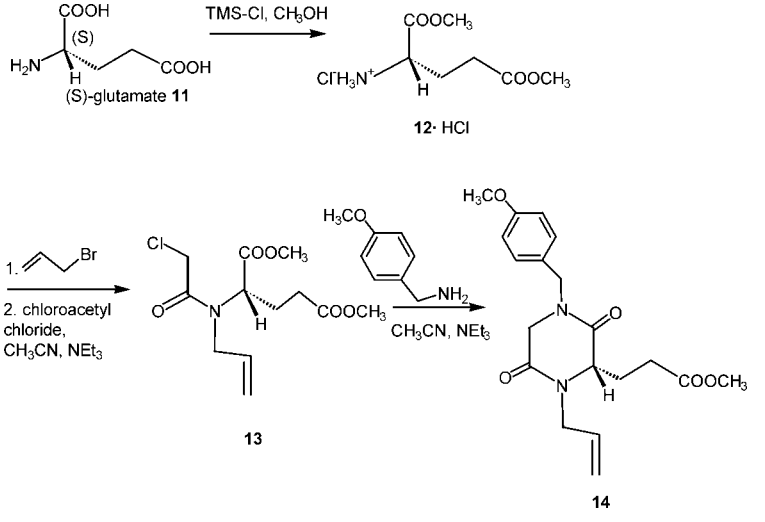
Chemistry

The synthesis of the 6,8-diazabicyclononane **9** started with the proteinogenic amino acid (S)-glutamate (**11**). (Scheme 1) Esterification of (S)-glutamate with methanol and chlorotrimethylsilane (TMSCl) [9] furnished the dimethyl ester **12**·HCl [10,11]. A one-pot reaction [12,13] comprising allylation and subsequent chloroacetylation of the amino moiety of **12** gave the N-allylchloroacetamide **13** only in poor yields (25%). The reaction of **13** with 4-methoxybenzylamine combines a S_N2 substitution with an intramolecular aminolysis leading to the monocyclic piperazinedione **14** in 17% yield over three steps from (S)-glutamate.

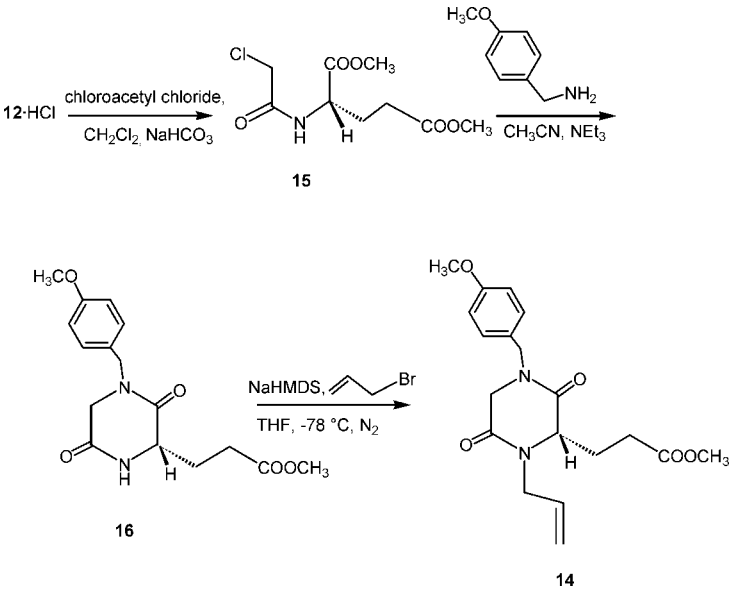
In order to improve the yield the reaction sequence was changed: Chloroacetylation of **12**·HCl followed by reaction of the formed chloroacetamide **15** with 4-methoxybenzylamine gave the piperazinedione **16,** which was allylated whith NaHMDS and allyl bromide to furnish the piperazinedione **14** in 42% yield over 4 steps from (S)-glutamate (Scheme 2).

A Dieckmann analogous cyclization (Scheme 3) was planned as the next step of the synthesis of the bicyclic scaffold **17**. However, reaction of **14** with LiHMDS or LDA failed to give the bicyclic ketone **17**. Surprisingly, the reaction of **14** with phenylmagnesium bromide led to the bicyclic ketone in 10% yield and the allyl derivative **18** (15%) which results from a [3,3]-sigmatropic rearrangement. Careful analysis of the ^{1}H NMR spectrum of the LDA experiment proved, that **18** had also been formed in this experiment.

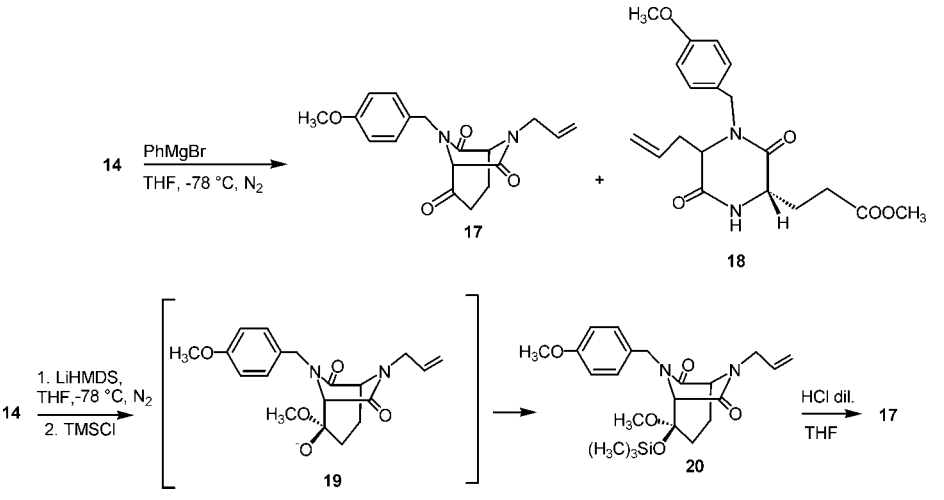
Finally, the cyclization was successfully performed by trapping of the intermediate product **19** formed by deprotonation with LiHMDS with chlorotrimethylsilane to furnish the mixed methyl/silyl acetal **20** [14] that was carefully hydrolyzed to obtain the ketone **17** in 88% yield.



Scheme 1. Synthesis of methyl 3-(dioxopiperazin-2-yl)propionate **14**.



Scheme 2. Improved synthesis of **14**.



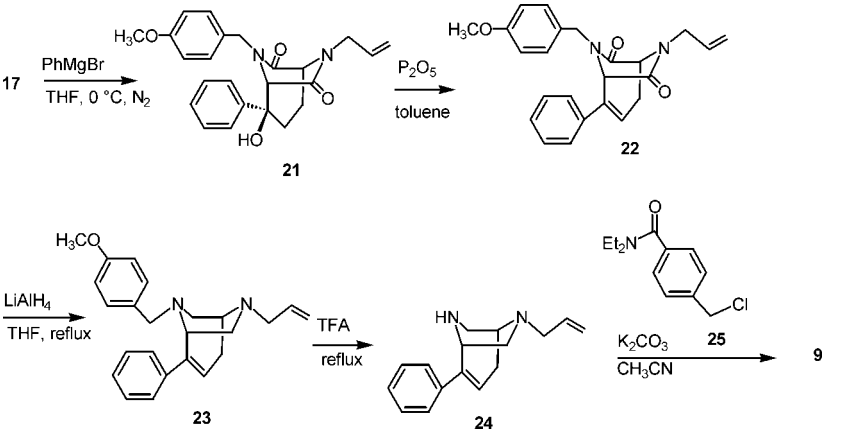
Scheme 3. Dieckmann cyclization of **14** to afford **17**.

The phenyl residue was introduced by a diastereoselective Grignard reaction of the ketone **17** with phenylmagnesium bromide (Scheme 4). The (2S)-configuration of the generated center of chirality was determined by a positive NOE between the phenyl residue and one proton of the benzyl CH_2-moiety. Dehydratation of the tertiary alcohol **21** with diphosphorpentoxide yielded the alkene **22**.

Reaction of the bicyclic piperazinedione **22** with LiAlH4 led to reduction of both lactam carbonyl moieties to give **23**. Removal of the N-(4-methoxybenzyl) protective group with CF_3COOH [15] provided the secondary amine **24**, which was alkylated with 4-(chloromethyl)-N,N-diethylbenzamide (**25**) to yield the target compound **9**. The building block **25** was synthesized by reaction of 4-(chloromethyl)benzoyl chloride with diethylamine [16].

Receptor binding studies

The affinity of the bridged piperazine **9** towards δ, μ, κ, and ORL1 receptors was investigated in receptor binding studies using tritiated deltorphine II (δ), naloxone (μ), Cl-977 (κ), and nociceptin (ORL1) as radioligands. CHO-K 1 cell lines expressing the corresponding human opioid receptors were employed as receptor material. The results of the receptor binding studies are summarized in Table 3. At a test concen-



Scheme 4. Synthesis route to **9**.

tration of 10 μM compound **9** shows less than 20% inhibition of radioligand binding at δ, κ and ORL1 receptors. Only moderate affinity toward μ receptors (K_i = 6.18 μM) was found.

Table 3. Affinity of compound **9** towards δ, μ, κ, and ORL1 receptors.

Assay	Receptor affinity of compound **9**
δ (DOP) ([^{3}H]-deltorphine II)	15.2%†
μ (MOP) ([^{3}H]-naloxone)	K_i = 6.18 μM
κ (KOP) ([^{3}H]-Cl−977)	15.3%†
ORL1 (NOP) ([^{3}H]-nociceptin)	9.3%†

† inhibition at a concentration of 10 μM of **9**.

Discussion

Molecular modeling studies have demonstrated structural similarity of the novel bicyclic piperazine **9** with the highly potent δ agonist SNC 80 (**1**). After synthesis of **9** receptor binding studies have revealed only moderate δ receptor affinity.

In the lead structure SNC 80 (**1**) the phenyl residues are connected in a benzhydryl moiety. Compared with SNC 80 the conformational freedom of the phenyl residue in positon 4 of **9** is restricted by attachment to an sp^2 hybridized carbon atom and the single bonds of the N-6 residue lead to rotational flexibility of the carbamoylbenzyl moiety. We assume that the combination of enhanced conformational flexibility of the N-6 benzyl residue with reduced conformational flexibility of the C-4 phenyl residue is responsible for low δ receptor interaction. Obviously, the pharmacophoric phenyl residues cannot adopt an arrangement, which imitates the benzhydryl moiety at the δ opioid receptor.

Acknowledgments

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Experimental

Molecular modeling

The molecular modeling studies were performed with Sybyl 6.8.version of Tripos® on a silicon graphics IRIS workstation. All molecules were geometry optimized *in vacuo* (ε = 1) with the implemented Tripos force field using the quasi Newton algorithm BFGS until the convergence criterion of 0.05 kcal//mol change in energy between successive iterations was reached. The charges were calculated by the Gasteiger Hückel method and the non bond interaction cut off was set at 50 Å. For the conformational analysis we used the tool grid search. Multifit analyses were performed by the program multifit and with a spring constant of 2 kcal/mol·Å.

Chemistry

General

Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash column chromatography (fc)[17]: Silica gel 60, 0.040−0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL], Rf. Melting points: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. Optical rotation: Polarimeter 341 (Perkin Elmer); 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 ionisation. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane, 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, columns: LiChroCART® 250-4 Merck with LiChrospher® 100 RP-8 endcapped (5 μm) and Hibar® RT 250-4 Merck with LiChrospher® 100 RP-18 (5 μm), injection volume: 20 μL, flow: 1 mL/min.

Dimethyl (S)-2-aminopentanedioate hydrochloride (12·HCl) [10, 11]

Chlorotrimethylsilane (75 mL, 594 mmol) was added dropwise during 90 min to an ice cooled suspension of **11** (25.1 g, 171 mmol) in methanol. The mixture was stirred for 16 h at room temperature. Then the solvent and all volatile components were removed under reduced pressure. The residue was suspended with methanol (50 mL) and the mixture was concentrated *in vacuo*. Then diethyl ether (3 × 60 mL) was added and the mixture was concentrated *in vacuo* to yield a colorless solid, yield 35.4 g (98%), mp 85°C (reference [11]: mp 88–90°C. $[\alpha]_{589}$ = +22.4, (*c* 0.53, 6 N HCl) (reference [11]: $[\alpha]_{589}$ = +26.0 (*c* 5.0, H_2O). IR (neat): ν [cm^{-1}] 2878 (m, $\nu_{CHaliph.}$), 1730 (s, $\nu_{C=O\ ester}$), 1505 (w, $\delta_{NH_3^+}$) 1441 (m, $\delta_{CHaliph}$), 1209, 1144 (m, ν_{COC}). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.29–2.41 (m, 2H, CH_2CH_2CO$_2$CH$_3$), 2.53–2.72 (m, 2H, CH_2CH_2CO$_2$CH$_3$), 3.61 (s, 3H, CH$_2$CO$_2$CH_3), 3.76 (s, 3H, CHCO$_2$CH_3), 4.22–4.32 (t, J = 6.3 Hz, 1H, CHCO$_2$CH$_3$), 8.65 (s, 3H, NH_3^+).

*Dimethyl (S)-2-[N-allyl-N-(2-chloroacetyl)amino]pentanedioate (**13**)*

Under N_2 atmosphere a solution of allyl bromide (2.5 mL, 28.9 mmol) in acetonitrile (7.5 mL) was added dropwise to an ice cooled solution of **12**·HCl (4.0 g, 18.9 mmol), triethylamine (5.3 mL, 38.0 mmol) and tetrabutylammonium iodide (1.3 g, 3.6 mmol) in acetonitrile (100 mL). Then the mixture was stirred for 2 h at 0–5°C and for 16 h at room temperature. Subsequently, the mixture was cooled with ice and triethylamine (2.7 mL, 19.4 mmol) and a solution of chloroacetyl chloride (4.5 mL, 56.6 mmol) in acetonitrile (12 mL) was added. The mixture was stirred for 2 h at 0–5°C and for 1 h at room temperature. 2/3 of the solvent were removed *in vacuo* and CH_2Cl_2 (50 mL) was added. The mixture was washed with 0.5 N HCl (50 mL) and 0.5 N NaOH (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (6 cm, petroleum ether/ethyl acetate 6:4, fractions 30 mL, Rf = 0.42) to give a yellow oil, yield 1.4 g (25%). $C_{12}H_{18}ClNO_5$ (291.8). MS (CI) *m/z* (%) = 294 (MH$^+$ (Cl^{37}), 34), 292 (MH$^+$ (Cl^{35}), 100), 262 (M (Cl^{37}) − OCH$_3$, 10), 260 (M (Cl^{35}) −OCH$_3$, 43). IR (neat): ν [cm^{-1}] = 2954 (w, $\nu_{C\text{-}Haliph.}$), 1732 (s, $\nu_{C=Oester}$), 1656 (m, $\nu_{C=Oamide}$), 1258, 1204,1 169 (m, ν_{COC}). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.95–2.15 (m, 1H, CH_2CH_2CO$_2$CH$_3$), 2.2–2.39 (m, 3H, CH_2CH_2CO$_2$CH$_3$), 3.61 (s, 3H, CO$_2$CH_3), 3.64 (s, 3H, CHCO$_2$CH_3) ,4.02 (s, 2H, ClCH_2), 3.98–4.07 (m, 2H, NCH_2CH=CH$_2$), 4.45–4.57 (m,1H, CHCO$_2$CH$_3$), 5.17–5.23 (m, 2H, NCH$_2$CH=CH_2), 5.76–5.89 (m, 1H, NCH$_2$C**H**=CH$_2$).

*Methyl (S)-3-[1-allyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (**14**)*

a) To a solution of **13** (1.5 g, 5.14 mmol) in acetonitrile (100 mL) 4-methoxybenzylamine (1.0 mL, 7.74 mmol), triethylamine (1.1 mL, 7.94 mmol) and tetrabutylammonium iodide (0.19 g, 0.514 mmol) were added. The mixture was stirred at room temperature for 16 h. 2/3 of the solvent were removed *in vacuo* and the residue was filtered and poured into 0.5 N HCl (60 mL). The mixture was extracted four times with CH_2Cl_2 (60 mL), the organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (3 cm, CH_2Cl_2/ethyl acetate 1:1, 10 mL, Rf = 0.39) to give a yellow oil, yield 1.4 g (70%). b) Under N2 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 **16** (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 (6.75 mL, 78.0 mmol) in THF (15 mL) was added. The mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature (2 h). Then water (100 mL) was added and the mixture was extracted twice with CH_2Cl_2 (150 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (8 cm, petroleum ether/ethyl acetate 3:7, 30 mL, Rf = 0.23) to give a yellow oil, yield 3.5 g (67%). $[\alpha]_{589}$ = +20.44, (*c* 0.50, CH_2Cl_2). $C_{19}H_{24}N_2O_5$ (360.4). Calcd. C 63.3, H 6.71, N 7.77, found C 62.8, H 6.86, N 7.57. MS (EI): *m/z* (%) = 360 (M, 43), 239 (M − CH_2PhOCH_3, 30), 121 (CH_2PhOCH_3, 100). IR (neat): ν [cm^{-1}] = 2951 (w, $\nu_{C\text{-}Halip.}$), 1733 (m, $\nu_{C=Oester}$) 1657 (s, $\nu_{C=Oamide}$), 1244, 1171 (m, ν_{COC}), 769 (s, p-disubst. ar.). ^{1}H NMR(CDCl3): δ (ppm) = 1.97–2.06 (m, 1H, $CH_2CH_2CO_2CH_3$), 2.18–2.28 (m, 1H, CH_2CH_2CO$_2$CH$_3$), 2.33–2.49 (m, 2H, CH_2CH_2CO$_2$CH$_3$), 3.43–3.53 (m, 1H, NCH_2CH=CH$_2$), 3.65 (s, 3H, CO$_2$CH_3), 3.77 (d, J = 18.0 Hz, 1H, O=C-CH_2N), 3.79 (s, 3H, OCH_3), 3.89 (d, J = 18.0 Hz, 1H, O=C-CH_2N), 4.02 (dd, J = 8.6/3.9 Hz, 1H, CHNAllyl), 4.41 (d, J = 14.1 Hz, 1H, CH_2PhOCH$_3$), 4.52–4.54 (m, 1H, NCH_2CH=CH_2), 4.58 (d, J = 14.1 Hz, 1H, CH$_2$PhOCH_3), 5.18–5.27 (m, 2H, NCH$_2$CH=CH_2), 5.68–5.74 (m, 1H, NCH$_2$CH=CH$_2$), 6.86 (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]).

*Dimethyl (S)-2-(2-chloroacetylamino)pentanedioate (**15**)*

A solution of chloroacetyl chloride (9.3 mL, 117 mmol) in CH_2Cl_2 (60 mL) was added dropwise to an ice cooled solution of **12**·HCl (8.0 g, 37.8 mmol) in CH_2Cl_2 (240 mL). After 40 min a saturated solution of sodium hydrogen carbonate (100 mL) was added and the mixture was stirred at room temperature for 16 h. Then the organic layer was separated and washed with 0.5 N NaOH (2 × 150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (8 cm, petroleum ether/ ethyl acetate 6:4, 30 mL, Rf = 0.38) to give **15** as a colorless oil, yield 6.8 g (71.6%). $[\alpha]_{589}$ = +18.1 (*c* 0.6, CH_2Cl_2). $C_9H_{14}ClNO_5$ (251.7). Calcd. C 42.9, H 5.61, N 5.56, found C 42.6, H 5.86, N 5.35. MS (CI, NH3): *m/z* (%) = 269 (M + NH_4^+, 22), 254 (MH$^+$ (Cl^{37}), 34), 252 (MH$^+$ (Cl^{35}, 100). IR (neat): ν (cm^{-1}) = 3317 (w, $\nu_{N\text{-}H}$), 2956 (w, $\nu_{C\text{-}H}$), 1733 (s, $\nu_{C=Oester}$), 1667 (s, $\nu_{C=Oamide}$), 1528 (m, $\delta_{N\text{-}H}$), 1206, 1170 (s, $\nu_{C\text{-}O}$). ^{1}H NMR ($CDCl_3$): δ = 2.00–2.44 (m, 4 H, CH_2CH_2CO$_2$CH$_3$), 3.68 (s, 3 H, CO$_2$CH_3), 3.77 (s, 3 H, CHCO$_2$CH_3), 4.06 (s, 2H, ClCH_2), 4.63 (ddd, J = 15.7/5.5/2.4 Hz, 1H , CHCO$_2$CH$_3$), 7.22 (d, J = 5.5 Hz,1 H, NH).

*Methyl (S)-[4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]propanoate (**16**)*

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 **15** (6.0 g, 23.8 mmol) in acetonitrile (200 mL). The mixture was refluxed for 48 h. 2/3 of the solvent were removed *in vacuo*. The residue was filtered, poured into

0.5 N HCl (200 mL), the mixture was extracted with CH_2Cl_2 (3 × 200 mL), the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (8 cm, petroleum ether/ethyl acetate/acetone 3:2:6, 30 mL, Rf = 0.32) to give a colorless solid, yield 6.7 g (88%), mp 93-94°C. $[\alpha]_{589}$ = −14.7, (*c* 0.51, CH_2Cl_2). $C_{16}H_{20}N_2O_5$ (320.3). Calcd. C 60.0, H 6.29, N 8.74, found C 59.7, H 6.54, N 8.63. MS (EI): *m/z* (%) = 320 (M, 11), 288 (M −$HOCH_3$, 2), 199 (M − CH_2PhOCH_3, 2), 121 (CH_2PhOCH_3, 100). IR (neat): ν [cm^{-1}] 3267 (w, ν_{N-H}), 2963 (w, $\nu_{C-Halip.}$), 1733 (m, $\nu_{C=Oester}$) 1661(s, $\nu_{C=Oamide}$), 1534 (w, $\delta_{N-Hamide}$), 1217, 1176 (m, ν_{COC}), 785 (s, p-disubst. ar.). ^{1}H NMR($CDCl_3$): δ (ppm) = 2.13−2.27 (m, 2H, $CH_2CH_2CO_2CH_3$), 2.41−2.53 (m, 2H, $CH_2CH_2CO_2CH_3$), 3.67 (s, 3H, CO_2CH_3), 3.78 (d, J = 17.6 Hz, 1H, CH_2PhOCH_3), 3.79 (s, 3H, OCH_3), 3.84 (d, J = 17.6 Hz, 1H, CH_2PhOCH_3), 4.12 (dd, J = 6.3/3.5 Hz, 1H, CHNH), 4.51 (s, 2H, O=C-CH_2N), 6.87 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.98 (s, 1H, NH), 7.18 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]).

*Methyl (S)-3-[5-allyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]-propanoate (**18**)*

Under N_2 atmosphere a solution of phenylmagnesium bromide prepared from bromobenzene (0.064 mL, 0.61 mmol) and magnesium tunings (0.015 g, 0.61 mmol) in THF (2 mL) was added to a cooled (−78°C) solution of 1**4** (0.20 g, 0.55 mmol) in THF (20 mL). After stirring at −78°C for 2 h and at room temperature for 1 h the mixture was poured into an ice cooled saturated solution of NH_4Cl (30 mL). The mixture was extracted four times with CH_2Cl_2, the organic layer was dried, the solvent was removed in vacuo and the residue was purified by flash column chromatography (2 cm, CH_2Cl_2 /ethyl acetate 7:3, 5 mL) to give **17** (Rf = 0.31) as a colorless solid, yield 18.8 mg (10%) and **18** (Rf = 0.18) as a pale yellow oil, yield 29.3 mg, (15%). **18**: $C_{19}H_{22}N_2O_5$ (360.4). MS (ESI): *m/z* (%) = 383 (M + Na^+, 100). IR (neat): ν [cm^{-1}] = 3233 (w, ν_{N-H}), 2951 (w, $\mu n_{C-Haliph.}$), 1734 (m, $\nu_{C=Oester}$), 1681 (m, $\nu_{C=Osec.amide}$), 1654 (m, $\nu_{C=Otert.amide}$), 1512 (m, δ_{N-H}),1245, 1174 (m, ν_{COC}), 807 (w, p-disubst. ar.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.13−2.38 (m, 2H, $CH_2CH_2CO_2CH_3$), 2.33−2.45 (m, 2H, $CH_2CH_2CO_2CH_3$), 2.49−2.58 (m, 2H, $CH_2CH{=}CH_2$), 3.60 (s, 3H, CO_2CH_3), 3.73 (s, 3H, OCH_3), 3.83 (m, 1H, O=C-CHN), 3.86 (d, J = 14.5 Hz, 1H, CH_2PhOCH_3), 4.14 (t, J = 4.7 Hz, 1H, CHNH), 5.10 (m, 2H, $CH_2CH{=}CH_2$), 5.21 (d, J = 14.5Hz, 1H, CH_2PhOCH_3), 5.62−5.74 (m, 1H, $CH_2CH{=}CH_2$), 6.50 (s, 1H, NH), 6.80 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.10 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]).

*(1S,2R,5S)-6-Allyl-2-methoxy-8-(4-methoxybenzyl)-2-(trimethylsiloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (**20**)*

Under N_2 atmosphere a 1 M solution of lithium hexamethyldisilazane in THF (13.5 mL, 13.5 mmol) was added dropwise to a cooled solution (−78°C) of **14** (3.25 g, 9.02 mmol) in THF (130 mL). After stirring at −78°C for 40 min, a solution of chlorotrimethylsilane (4.1 mL, 32.5 mmol) in THF (10 mL) was added. The mixture was stirred at −78°C for 1 h and at room temperature for 2 h. Then a saturated solution of sodium hydrogen carbonate (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried (Na_2SO_4), the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (6 cm, petroleum ether/ethyl acetate 6:4, 30 mL, Rf = 0.27) to give a colorless solid, yield 3.4 g (88%), mp 93−94°C. $[\alpha]_{589}$ = +22.07, (c 0.995, CH_2Cl_2). $C_{22}H_{32}N_2O_5Si$ (432.6). Calcd. C 61.1, H 7.46, N 6.48, found C 60.6, H 7.30, N 6.38. MS (EI): *m/z* (%) = 432 (M, 33), 311 (M − CH_2PhOCH_3, 24), 121 (CH_2PhOCH_3, 100). IR (neat): ν [cm^1] = 2954 (w, $\nu_{C-Halip.}$), 1679 (s, $\nu_{C=Oamide}$), 1251 (s, ν_{COC}), 832 (s, p-disubst. ar.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.01 (s, 9H, $Si(CH_3)_3$), 1.61−1.69 (m, 1H, 4-H), 1.74−1.81 (m, 2H, 3-H), 1.87−1.95 (m, 1H, 4-H) 3.03 (s, 3H, OCH_3), 3.61 (s, 3H, $PhOCH_3$), 3.71 (dd, J = 5.5/2.4 Hz, 1H, 5-H), 3.72 (s, 1H, 1-H), 3.79 (d, J = 14.9 Hz, 1H, CH_2PhOCH_3), 3.80 (m, 2H, $NCH_2CH{=}CH_2$), 4.99 (d, J = 14.9 Hz, 1H, CH_2PhOCH_3), 5.03−5.07 (m, 2H, $NCH_2CH{=}CH_2$), 5.52−5.62 (m, 1H, $NCH_2CH{=}CH_2$), 6.68 (d, J= 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.96 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]). ^{13}C NMR ($CDCl_3$): δ (ppm) = 24.7 (1C, C-4), 33.3 (1C, C-3), 47.6 (1C, $NCH_2CH{=}CH_2$), 48.0 (1C, CH_2PhOCH_3), 49.0 (1C, OCH3), 55.2 (1C, $PhOCH_3$), 58.3 (1C, C-5), 65.8 (1C, C-1), 98.6 (1C, C-2), 114.2 (2C, C-3′ and C-5′[H_3COPh]), 119.0 (1C, $NCH_2CH{=}CH_2$), 127.9 (1C, C-1′[H_3COPh]), 129.4 (2C, C-2′ and C-6′ [H_3COPh]), 132.2 (1C, $NCH_2CH{=}CH_2$), 159.2 (1C, C-4′ [H_3COPh]), 165.8 (1C, C=O), 168.6 (1C, C=O).

*(1S,5S)-6-Allyl-8-(4-methoxybenzyl)-6,8-diazabicyclo[3.2.2]-nonane-2,7,9-trione (**17**)*

Under N_2 atmosphere a solution of **20** (1.12 g, 2.59 mmol) was stirred at room temperature in a degassed mixture of THF/2 N HCl (10:1, 50 mL) for 2 h. Subsequently, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Colorless solid, yield 0.85 g (100%), mp 195-196°C. $[\alpha]_{589}$ = +120.29 (*c* 0.49, CH_2Cl_2). $C_{18}H_{20}N_2O_4$ (328.4). Calcd. C 65.8, H 6.14, N 8.53, found C 65.6, H 5.95, N 8.25. MS (EI): *m/z* (%) = 329 (M, 100), 121 (CH_2PhOCH_3, 12). IR (neat): ν [cm^{-1}] = 3005 (w, $\nu_{C-Harom.}$), 2955 (w, $\nu_{C-Haliph.}$), 1724 (s, $\nu_{C=Oketone}$), 1670 (s, $\nu_{C=Oamide}$), 1243, (m, ν_{COC}), 828 (s, p-disubst. ar.).^{1}H NMR (CDCl3): δ (ppm) = 1.99−2.13 (m, 1H, 4-H), 2.21−2.32 (m, 1H, 3-H), 2.35−2.48 (m, 2H, 3−H, 4-H), 3.71 (s, 3H, $PhOCH_3$), 3.81 (ddt, J = 17.9/6.3/1.6 Hz, 1H, $NCH_2CH{=}CH_2$), 3.99 (dd, 1H, J = 6.3/1.6 Hz, 1H, 5-H), 4.11 (ddt, J = 17.9/6.3/1.6 Hz, 1H, $NCH_2CH{=}CH_2$), 4.20 (s, 1H, 1-H), 4.26 (d, J = 14.1 Hz, 1H, CH_2PhOCH_3), 4.76 (d, J = 14.1 Hz, 1H, CH_2PhOCH_3) 5.16−5.24 (m, 2H, $NCH_2CH{=}CH_2$), 5.61−5.73 (m, 1H, $NCH_2CH{=}CH_2$), 6.76 (d, J = 8.6 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 7.14 (d, J = 8.6 Hz, 2H, 2′-H and 6′-H [H_3COPh]). ^{13}C NMR ($CDCl_3$): δ (ppm) = 30.2 (1C, C-4), 36.9 (1C, C-3), 48.1 (1C, $NCH_2CH{=}CH_2$), 49.4 (1C, CH_2PhOCH_3), 55.8 (1C, OCH_3), 59.0 (1C, C-5), 72.1 (1C, C-1), 114.7 (2C, C-3′ and C-5′[H_3COPh]), 120.2 (1C, $NCH_2CH{=}CH_2$), 127.0 (1C, C-1′[H_3COPh]), 130.5 (2C, C-2′ and C-6′ [H_3COPh]), 131.6 (1C, $NCH_2CH{=}CH_2$), 159.7 (1C, C-4′[H_3COPh]), 163.2 (1C, C=O), 167.1 (1C, C=O), 200.2 (1C, C= Oketone).

*(1S,2S,5S)-6-Allyl-2-hydroxy-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo[3.2.2]- nonane-7,9-dione (**21**)*

Under N_2 atmosphere a solution of **17** (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 NH4Cl (200 mL). The mixture was extracted four times with CH_2Cl_2 (150 mL), the organic layer was dried, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (4 cm, petroleum ether/ethyl acetate 2:8, 20 mL, Rf = 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). MS (EI): *m/z* (%) = 406 (M, 25), 365 (M-allyl, 10), 285 (M-CH_2PhOCH_3), 121 (CH_2PhOCH_3, 100). IR (neat): ν [cm^{-1}] = 3400 (w, ν_{O-H}), 2935 (w, $\nu_{C-Haliph.}$),1664 (s, $\nu_{C=Oamide}$), 1244 (s, ν_{COC}), 809 (w, p-disubst. ar.), 753 (m, monosubst. ar), 701 (s, monosubst. ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.94−2.07 (m, 1H, 3-H), 2.13−2.21 (m, 2H, 4-H), 2.48−2.60 (m, 1H, 3−H), 2.82 (d, J = 14.7 Hz, 1H, CH_2PhOCH_3), 3.37 (s, 1H,

OH), 3.70 (s, 3H, OCH_3), 3.89 (dd, J = 15.3/6.1 Hz, 1H, $NCH_2CH=CH_2$), 3.94 (s, 1H, 1−H), 3.97(m, 1H, 5−H), 4.14 (dd, J = 15.3/6.1 Hz, 1H, $NCH_2CH=CH_2$), 4.86 (d, J = 14.7 Hz, 1H, CH_2PhOCH_3), 5.16−5.26 (m, 2H, $NCH_2CH=CH_2$), 5.68−5.83 (m, 1H, $NCH_2CH=CH_2$), 6.66 (d, J = 9.0 Hz, 2H, 3′-H and 5′-H [H_3COPh]), 6.73 (d, J = 9.0 Hz, 2H, 2′-H and 6′-H [H_3COPh]), 7.23−7.54 (m, 5H, aromat. H).

*(1S,5S)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo-[3.2.2]non-2-en-7,9-dione (**22**)*

Under N_2 atmosphere diphoshorpentoxide (3 g, 21 mmol) was added to a solution of **21** (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 flash column chromatography (3 cm, petroleum ether/ethyl acetate 3:7, 10 mL, Rf = 0.43) to give a colorless solid, yield 0.54 g (67%), mp 142−143 °C. $[\alpha]_{589}$ = +184.4, (*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. MS (EI): *m/z* (%) = 388 (M, 41), 226 (M-allyl-CH_2PhOCH_3, 22), 121 (CH_2PhOCH_3, 100). IR (neat): ν [cm^{-1}] = 3010 (w, $\nu_{C\text{-}Harom}$), 2937 (w, $\nu_{C\text{-}Haliph.}$), 1672 (s, $\nu_{C=Oamide}$), 1239, (w, ν_{COC}), 811 (w, p-disubst ar.), 753, 699 (m, monosubst. ar.). ^{1}H NMR($CDCl_3$): δ (ppm) = 2.67 (ddd, J = 19.5/4.3/2.7 Hz, 1H, 4-H), 2.79 (ddd, J = 19.5/4.3/2.7 Hz, 1H, 4-H), 3.72 (s, 3H, OCH_3), 4.02 (dddd, J = 15.2/6.3/1.56/1.2 Hz, 1H, $NCH_2CH=CH_2$,), 4.10 (ddd, J = 4.3/2.7/1.2 Hz, 1H, 5−H), 4.18 (dddd, J = 15.2/6.3/1.6/1.2 Hz, 1H, $NCH_2CH=CH_2$), 4.34 (d, 14.7 Hz, 1H, CH_2PhOCH_3), 4.47 (d, J =1.6 Hz, 1H, 1−H), 4.66 (d, 14.7 Hz, 1H, CH_2PhOCH_3), 5.24−5.30 (m, 2H, $NCH_2CH=CH_2$), 5.70−5.74 (m, 1H, 3−H), 5.76−5.86 (m, 1H, $NCH_2CH=CH_2$), 6.62 (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]), 7.01−7.23 (m, 5H, aromat. H).

*(1S,5S)-6-Allyl-8-(4-methoxybenzyl)-2-phenyl-6,8-diazabicyclo-[3.2.2]non-2-ene (**23**)*

Under N_2 atmosphere lithium aluminium hydride (0.464 g, 12.2 mmol) was added to an ice-cooled solution of **22** (0.95 g, 2.45 mmol) in THF (90 mL). The mixture was stirred with ice-cooling for 30 min and then refluxed for 6 h. Water (0.88 mL, 48.9 mmol) was added dropwise, and the mixture was stirred at 0−5 °C for 30 min and refluxed for 30 min. The mixture was filtered, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (3 cm, CH_2Cl_2/methanol 9.5:0.5, 10 mL, Rf = 0.15) to give a yellow oil, yield 0.23 g (26%). $[\alpha]_{589}$ = +42.8 (c 0.48, CH_2Cl_2). $C_{24}H_{28}N_2O$ (360.5). MS (EI): *m/z*(%) = 360 (M, 55), 239 (M−CH_2PhOCH_3, 100), 198 (M−CH_2PhOCH_3 − allyl, 45), 121 (CH_2PhOCH_3, 22). IR (neat): ν [cm^{-1}] = 3024 (w, $\nu_{C\text{-}Harom}$), 2930 (w, $\nu_{C\text{-}Haliph.}$), 1510 (m, $\nu_{C=C}$), 1244 (m, ν_{COC}), 830 (w, p-disubst. ar.), 758, 699 (m, monosubst. ar). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.26−2.38 (m, 1H, 4−H), 2.56−2.66 (m, 1H, 9−H), 2.74−2.88 (m, 1H, 4−H), 2.89−3.02 (m, 1H, 7−H), 3.08−3.20 (m, 1H, 5−H), 3.22−3.38 (m, 4H, 7−H, 8−H, $NCH_2CH=CH_2$), 3.46 (d, J = 12.9 Hz, 1H, CH_2PhOCH_3), 3.52 (d, J = 12.9 Hz, 1H, CH_2PhOCH_3), 3.60 (m, 1H, 1−H), 3.70 (s, 3H, OCH_3), 5.03−5.23 (m, 2H, $NCH_2CH=CH_2$), 5.85−6.01 (m, 2H, $NCH_2CH=CH_2$, 3−H), 6.67 (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]), 7.04−7.23 (m, 5H, aromat. H).

*(1S,5S)-6-Allyl-2-phenyl-6,8-diazabicyclo[3.2.2]non-2-ene (**24**)*

Under N_2 atmosphere a solution of **23** (0.145 g, 0.4 mmol) in TFA (40 mL) was refluxed for 48 h. Then, under ice-cooling 10 M KOH solution (50 mL) was added dropwise. The mixture was extracted with CH_2Cl_2 (5 × 100 mL), the organic layer was dried (Na_2SO_4), the solvent was removed *in vacuo* and the residue was purified by flash chromatography (2 cm, CH_2Cl_2/methanol 8.5 : 1.5, 5 mL, Rf = 0.27) to give a colorless oil, yield 0.074 g (77%). $C_{16}H_2ON_2$ (240.3). MS (ESI): *m/z* (%) = 241 (MH^+, 22). IR (neat): ν [cm^{-1}] = 3274 (w, $\nu_{N\text{-}H}$), 3025 (w, $\nu_{C\text{-}Harom}$), 2924 (w, $\nu_{C\text{-}alliph}$), 1506 (m, $\delta_{N\text{-}H}$). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.49−2.60 (m, 1H, 4−H), 2.85−2.98 (m, 1H, 4−H), 3.23−3.43 (m, 7H, $NCH_2CH=CH_2$, 5−H, 7−H, 9−H), 5.08−5.20 (m, 2H, $NCH_2CH=CH_2$), 5.79−5.92 (m, 2H, $NCH_2CH=CH_2$, 3-H), 7.07−7.31 (m, 5H, arom.H).

*4-[(1S,5S)-(8-Allyl-4-phenyl-6,8-diazabicyclo[3.2.2]non-3-en-6-ylmethyl]-N,N-diethylbenzamide (**9**)*

Under N_2 atmosphere potassium carbonate (39 mg, 0.28 mmol) and **25** [16] (0.47 mg, 0.21 mmol) were added to a solution of **24** (45 mg, 0.19 mmol) and tetrabutylammonium iodide (7.0 mg, 0.019 mmol) in acetonitrile (20 mL). The mixture was refluxed for 9 h, filtered and the solvent was removed *in vacuo*. 1 M HCl (10 mL) was added to the residue, the mixture was washed with ethyl acetate (2 × 10 mL), 2 M NaOH (10 mL) was added to the aqueous layer and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (1 cm, CH_2Cl_2/ methanol 9.5:0.5, 3 mL, Rf = 0.07) to give a colorless oil, yield 51 mg (63%). $[\alpha]_{589}$ = +70.1, (*c* 0.65, CH_2Cl_2). $C_{28}H_{35}N_3O$ (429.6). MS (ESI): *m/z* (%) = 430 (MH^+, 100). IR (neat): ν [cm^{-1}] = 3077 (w, $\nu_{C\text{-}Harom.}$), 2972, 2878 (w, $\nu_{C\text{-}Haliph.}$), 1631 (s, $\nu_{C=Oamide}$), 843 (w, p-disubst. ar.) 757, 699 (w, monosubst. ar.). ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.93−1.23 (m, 6H, $N(CH_2CH_3)_2$), 2.26 (dt, J = 18.8/4.3 Hz, 1H, 2−H), 2.51−2.61 (m, 1H, 7− H), 2.70−2.81 (m, 1H, 2−H), 2.83−2.91 (m, 1H, 9−H), 3.04−3.12 (m, 1H, 1−H), 3.12−3.19 (m, 2H, $N(CH_2CH_3)_2$), 3.21−3.27 (m, 2H, $NCH_2CH=CH_2$), 3.27−3.51 (m, 2H, 7−H, 9−H), 3.41−3.50 (m, 2H, $N(CH_2CH_3)_2$), 3.50 (d, J = 13.3 Hz, 1H, CH_2PhOCH_3), 3.53−3.56 (m, 1H, 5−H), 3.59 (d, J = 13.3 Hz, 1H, CH_2PhOCH_3), 5.03−5.18 (m, 2H, $NCH_2CH=CH_2$), 5.83−5.91 (m, 1H, $NCH_2CH=CH_2$), 5.91−5.96 (m, 1H, 3−H), 7.04−7.17 (m, 9H, arom. H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.4 (1C, $N(CH_2CH_3)_2$), 14.7 (1C, $N(CH_2CH_3)_2$), 34.9 (1C, C−2), 39.6 (1C, N ($CH_2CH_3)_2$), 43.8 (1C, $N(CH_2CH_3)_2$), 52.9 (1C, C-1), 54.4 (1C, C−7), 56.4 (1C, C−5), 57.5 (1C, C−9), 59.1 (1C, $NCH_2CH=CH_2$), 60.1 (1C, CH_2PhOCH_3), 117.5 (1C, $NCH_2CH=CH_2$), 126.1 (2C, arom. C), 126.2 (2C, arom. C) 126.7 (1C, arom. C), 127.8 (1C, C−3), 128.4 (2C, arom. C), 129.0 (2C, arom. C), 135.9 (1C, C−4), 136.5 (1C, $NCH_2CH=CH_2$), 140.2 (1C, C−1′[phenyl]), 142.5 (1C, C−1′[benzyl]), 143.7 (1C, C− 4′[benzyl]), 171.4 (1C, C=O).

The purity of **9** was determined by HPLC: Method a): Hibar® RT 250-4 Merck with LiChrospher® 100 RP-18 (5 μm), MeOH/H_2O = 70:30 + 0.1% NEt_3; detection UV, λ = 235 nm, t_R = 26 min, 98.9%. Method b): LiChroCART® 250-4 Merck with LiChrospher® 100 RP-8 endcapped (5 μm), CH_3CN/H_2O = 50:50 + 0.1%, NEt_3; detection UV λ = 254 nm, t_R = 17 min, 99.0%.

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