Rigid Scaffolds: Synthesis of 2,6-Bridged Piperazines with Functional Groups in all three Bridges

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The activity of pharmacologically active compounds can be increased by presenting a drug in a defined conformation, which fits exactly into the binding pocket of its target. Herein, the piperazine scaffold was conformationally restricted by substituted C_2- or C_3-bridges across the 2- and 6-position. At first, a three-step, one-pot procedure was developed to obtain reproducibly piperazine-2,6-diones with various substituents at the N-atoms in high yields. Three strategies for bridging of piperazine-2,6-diones were pursued: 1. The bicyclic mixed ketals 8-benzyl-6-ethoxy-3-(4-methoxybenzyl)-6-(trimethylsilyloxy)-3,8-diazabicyclo[3.2.1]octane-2,4-diones were prepared by Dieckmann analogous cyclization of 2-(3,5-dioxopiperazin-2-yl) acetates. 2. Stepwise allylation, hydroboration and oxidation of piperazine-2,6-diones led to 3-(3,5-dioxopiperazin-2-yl)propionaldehydes. Whereas reaction of such an aldehyde with base provided the bicyclic alcohol 9-benzyl-6-hydroxy-3-(4-methoxybenzyl)-3,9-diazabicyclo[3.3.1]nonane-2,4-dione in only 10% yield, the corresponding sulfinylimines reacted with base to give *N*-(2,4-dioxo-3,9-diazabicyclo[3.3.1]nonan-6-yl)-2-methylpropane-2-sulfinamides in >66% yield. 3. Transformation of a piperazine-2,6-dione with 1,4-dibromobut-2-ene and 3-halo-2-halomethylprop-1-enes provided 3,8-diazabicyclo[3.2.1]octane-2,4-dione and 3,9-diazabicyclo[3.3.1]nonane-2,4-dione with a vinyl group at the C_2- or a methylene group at the C_3-bridge, respectively. Since bridging via sulfinylimines and the one-pot bridging with 3-bromo-2-bromomethylprop-1-ene gave promising yields, these strategies will be exploited for the synthesis of novel receptor ligands bearing various substituents in a defined orientation at the carbon bridge

1. Introduction

The piperazine ring is a common structural element in various pharmacologically active compounds[1] such as the antidepressant trazodone (**1**)[2] and the histamine H_1 receptor antagonist cetirizine (**2**).[3,4] (Figure 1)

The piperazine ring can adopt two chair and several twist conformations. Introduction of a bridge into the piperazine scaffold would restrict the conformational flexibility. Presenting a drug in an optimal but fixed conformation would increase its free binding energy due to entropic reasons.[5] The natural product atropine (**3**) represents the most prominent example for an N-heterocycle bearing an additional two-carbon bridge. This bridge between 2- and 6-position holds the piperidine ring in a particular chair conformation and forces the O-acyl moiety to adopt an axial orientation.[6] The granatane derivative granisetron is an important 5-HT_3 receptor antagonist used for the treatment of strong emesis caused by chemotherapy and radiotherapy. In the granatane structure, the piperidine ring is bridged by a three-carbon bridge. As in atropine, this conformational restriction leads to an axial orientation of the acylamino moiety.[7,8] (Figure 2)

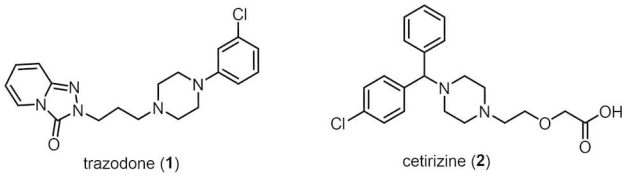

Figure 1. Pharmacologically active compounds containing a piperazine ring.

In general, we are interested in piperidine and piperazine rings with an additional bridge leading to conformational restriction of the ring system. We have reported the bicyclic KOR agonist **5** ($K_i = 73$ nM),[9] in which the 2- and 4-positions of the piperazine ring are connected by a three-carbon bridge substituted with an additional amino moiety (pyrrolidine ring). The same three-carbon bridge connects the 2- and 5-positions of the piperazine ring in the (1*S*,2*R*,5*R*)-configured KOR agonist **6** ($K_i = 1.0$ nM).[10] Although the bicyclic systems **5** and **6** contain the same three-carbon bridge, the piperazine rings adopt different defined conformations due to the different ring positions, which are connected by the bridge (2,4-bridge in **5**, 2,5-bridge in **6**). The 6,8-diazabicyclo[3.2.2]nonane **7** with an OH moiety at the bridge shows very high affinity towards σ_1 receptors ($K_i = 6.5$ nM).[11] Embedding the σ_1 pharmacophoric

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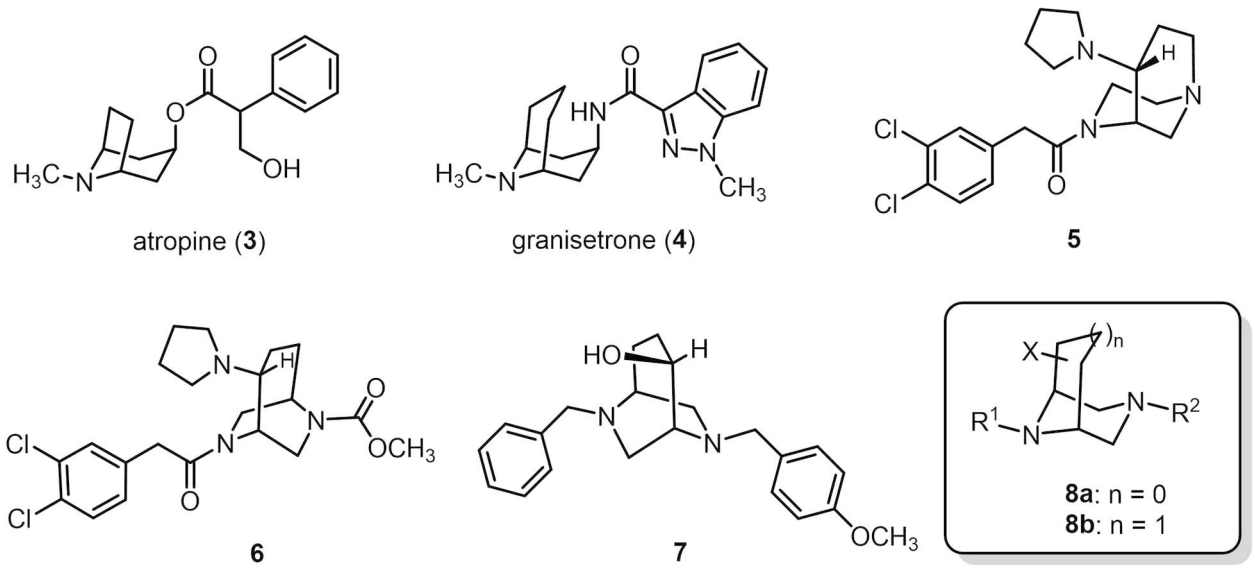


Figure 2. Potent drugs with a bridged piperidine ring (**3**,**4**) and piperazine ring (**5**–**7**) stimulating the design of the 2,6-bridged piperazines **8**.

structural elements (basic amino moiety, two lipophilic residues) into a bicyclic framework resulted in particular high σ_1 affinity. Compared to **6**, the σ_1 ligand **7** contains an enantiomeric scaffold, two benzyl moieties at the N-atoms and a hydroxy moiety instead of the pyrrolidine ring. (Figure 2)

In order to follow the concept of conformational restriction we became interested in piperazine derivatives bearing a two- or three-carbon bridge across the 2- and 6-positions (see compound **8** in Figure 2). On the one hand, 2,6-bridged piperazines **8** are regarded as aza-analogs of the tropane and granatane scaffolds of **3** and **4**, on the other hand, they are regarded as regioisomers of **5**–**7** bearing a 2,6-bridge instead of a 2,4- or 2,5-bridge across the piperazine ring.

Some methods for the synthesis of 3,8-diazabicyclo[3.2.1] octane (**8a**, n = 0) and 3,9-diazabicyclo[3.3.1]nonane derivatives (**8b**, n = 1) have been reported in literature. Compounds with the scaffold **8a** were prepared starting from adipic acid. A four-step reaction sequence provided pyrrolidine-2,5-dicarboxylate, which was transformed into the bicyclic imide upon reaction with NH_3 and Ac_2O. Final reduction of the imide functional group was performed with $LiAlH_4$.[12,13] Corresponding 3,9-diazabicyclo[3.3.1]nonane derivatives **8b** with an extended C_3-bridge were prepared by imide formation from piperidine-2,6-dicarboxylate and subsequnt $LiAlH_4$ reduction.[14] Another one-pot synthesis of the bicyclic system **8a** started with hexa-1,5-diene, which was reacted with trifluoromethanesulfonamide in the oxidation system t-BuOCl/NaI to introduce two N-atoms oxidatively at 1,6- and 2,5-position of the diene system in 37% yield.[15]

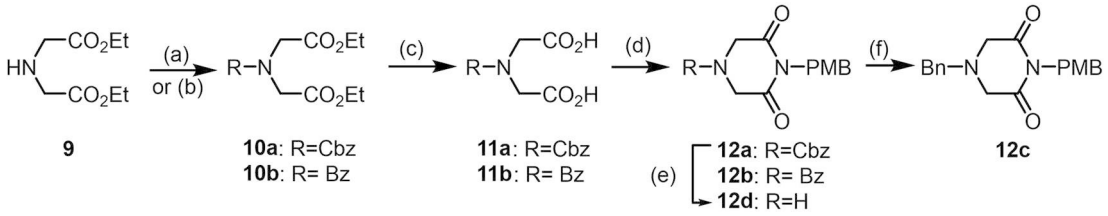
However, there are only few reports dealing with the synthesis of 3,8-diazabicyclo[3.2.1]octane (**8a**, n = 0) or 3,9-diazabicyclo[3.3.1]nonane derivatives (**8b**, n = 1) with additional substituents at the two- or three-carbon bridge.[16–18] Herein, we report various strategies to synthesize bicyclic compounds of type **8** with different length of the carbon bridge. The particular feature of type **8** compounds is the additional functional group at the two- or three-carbon bridge allowing introduction of various pharmacophoric elements in a defined 3D orientation.

2. Results and Discussion

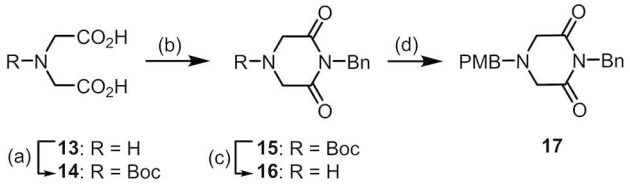
2.1. Synthesis

In order to establish the bridge providing the desired bicyclic compounds of type **8** key intermediate piperazine-2,6-diones (e.g. **12**, **17**) should react with various dielectrophiles stepwise or in a one-pot procedure. Piperazine-2,6-diones can be prepared either by alkylation of α-amino acid esters with bromoacetamide and subsequent cyclization[19,20] or by condensation of iminodiacetic acid derivatives with primary amines or NH_3.[21–24] As reported in literature, iminodiacetic acids **13** and **14** (structures see Scheme 2) were reacted with primary amines under microwave irradiation. However, instead of the desired imides only salts could be isolated.

Therefore, different strategies were pursued to synthesize key piperazine-2,6-diones with two orthogonal protective groups at the N-atoms. At first, piperazinediones **12a** (R = Cbz) and **12b** (R = Bz) were prepared in three steps from diethyl iminodiacetate **9**. Acylation of the secondary amine **9** with benzyl chloroformate or benzoyl chloride afforded protected diesters **10a** and **10b**, respectively, which were hydrolyzed by NaOH to give the diacids **11a** and **11b**. CDI coupling of the diacids **11a** and **11b** with *p*-methoxybenzylamine led to the imides **12a** and **12b** in 68% and 60% yield, respectively. The imide formation was conducted in three steps. At first, one equivalent CDI was added, which was supposed to form a cyclic anhydride. The anhydride was then opened by addition of *p*-methoxybenzylamine to afford an amido acid. Finally, the second acid was activated by another equivalent of CDI to form



Scheme 1. Preparation of piperazine-2,6-diones **12a**–**d**. Reagents and reaction conditions: (a) Cbz-Cl, NEt_3, CH_2Cl_2, 0 °C, 18 h, 70%. (b) Bz–Cl, NEt_3, CH_2Cl_2, r.t., 24 h, 90%. (c) NaOH, EtOH, H_2O, r.t., 18 h, 90% (**11a**), 90% (**11b**). (d) i. CDI (1.0 eq), CH_3CN, THF, reflux, 90 min; ii. PMB-NH_2, THF, reflux, 90 min; iii. CDI (2.0 eq), CH_3CN, THF, reflux, 60 h, 68% (**12a**), 60% (**12b**). (e) H_2, Pd/C, THF, r.t., 1 h, 95%. (f) **12d:** BnBr, CH_3CN, reflux, 18 h, 84%.



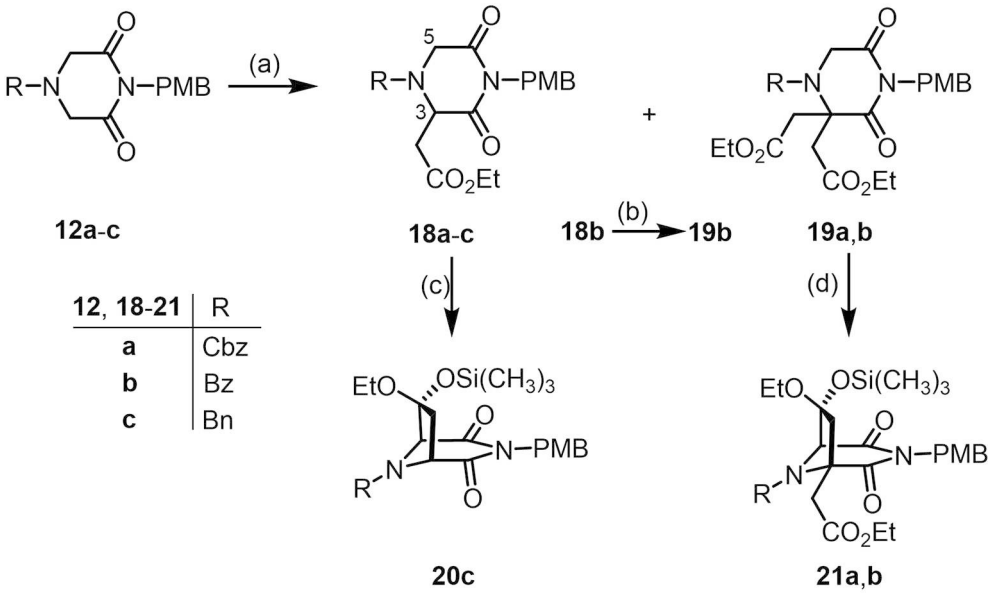
Scheme 2. Preparation of piperazine-2,6-dione **17**. Reagents and reaction conditions: (a) Boc_2O, $NaHCO_3$, THF, H_2O, r.t., 72 h, 74%. (b) i. CDI (1.0 eq), CH_3CN, THF, reflux, 60 min; ii. $BnNH_2$, THF, reflux, 60 min; iii. CDI (2.0 eq), CH_3CN, THF, reflux, 18 h, 62%. (c) TFA, CH_2Cl_2, r.t., 24 h, 99%. (d) PMB–Cl, DIPEA, CH_3CN, reflux, 18 h, 88%.

the imides **12a** and **12b**. The N-benzyl derivative **12c** was obtained by hydrogenolytic cleavage of the Cbz protective group of **12a** followed by alkylation of secondary amine **12d** with benzyl bromide. (Scheme 1)

In the second approach leading to piperazine-2,6-dione **17** bearing the benzyl and *p*-methoxybenzyl protective groups at opposite N-atoms compared to **12c**, iminodiacetic acid (**13**) was used as starting material. Reaction of the secondary amine **13** with Boc_2O afforded **14** in 74% yield. CDI coupling of diacid **14** with $BnNH_2$ provided the Boc-protected imide **15**. After removal of the Boc-protective group of **15** with trifluoroacetic acid, the resulting secondary amine **16** was alkylated with *p*-methoxybenzyl chloride to afford piperazinedione **17** with two orthogonal protective groups at the N-atoms. (Scheme 2)

In order to introduce a side chain with two C-atoms and a functional group for bridging, the piperazinediones **12a**–**c** were deprotonated with LiHMDS or KHMDS and treated with ethyl 2-bromoacetate. The monoalkylated piperazinediones **18a**–**c** were obtained in 79–84% yield. Additionally, small amounts of the dialkylated products **19a** and **19b** (4–6%) could be isolated from the reaction mixture. (Scheme 3)

The introduction of both substituents at the same position of the piperazinediones **12a** and **12b** was unexpected. Therefore, the monoalkylated piperazinedione **18b** was deprotonated with KHMDS at −78 °C and the resulting enolate was subsequently treated with ethyl bromoacetate. This reaction led exclusively to the dialkylated piperazinedione **19b** (73%) bearing both acetate moieties at the same C-atom. (Scheme 3) This experiment showed unequivocally that the CH-group (3-CH) of N-acylated piperazinedione **18b** reacted preferably with



Scheme 3. Synthesis of the 3,8-diazabicyclo[3.2.1]octane framework. Reagents and reaction conditions: (a) LiHMDS or KHMDS, THF, −78 °C, 1 h, then $BrCH_2CO_2Et$, THF, −78 °C–r.t., 18 h, 84% (**18a**), 79% (**18b**), 84% (**18c**). (b) KHMDS, THF, −78 °C, 1 h, then $BrCH_2CO_2Et$, THF, −78 °C, 3 h, 73%. (c) LiHMDS, THF, −78 °C, 15 min, then Me_3SiCl, THF, −78 °C, 1 h, then r.t., 12%. (d) LiHMDS, THF, −78 °C, 15 min, then Me_3SiCl, THF, −78 °C, 1 h, then r.t., 21% (**21a**), 10% (**21b**).

electrophiles compared to the 5-CH_2-moiety. Other electrophiles such as CH_3I also reacted at the 3-position of **18b**. (See Scheme SI1 in Supporting information)

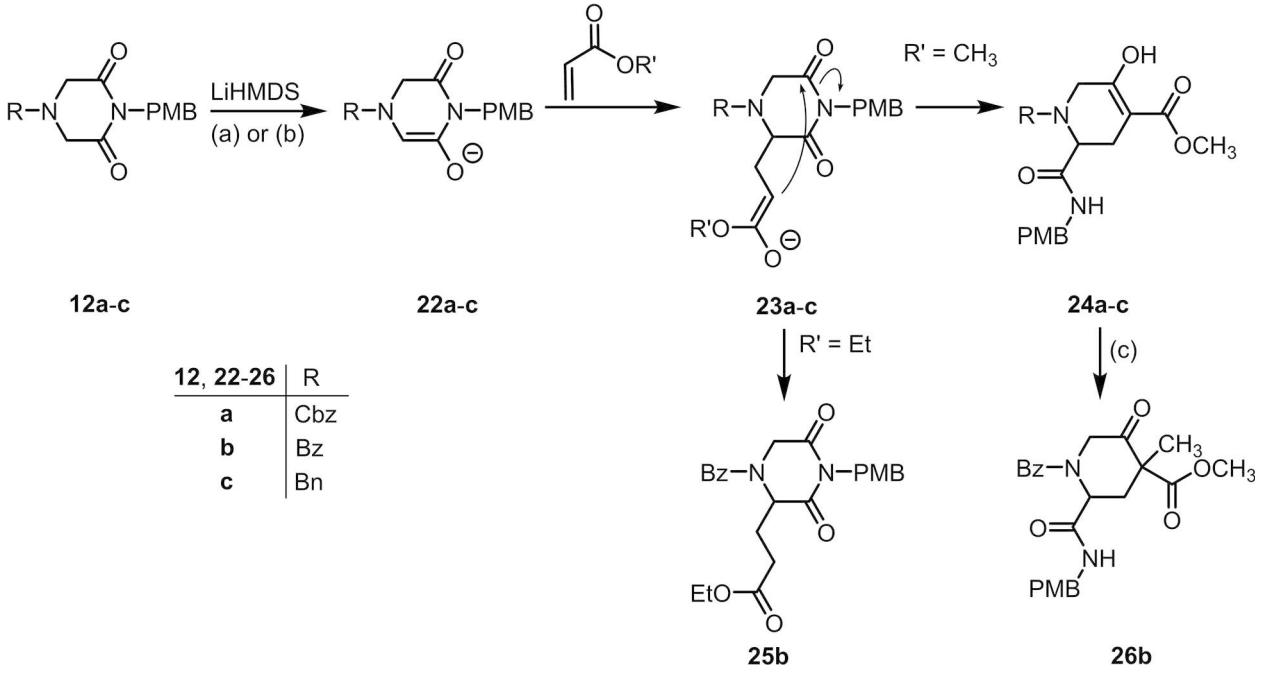
For the synthesis of bicyclic systems, a Dieckmann analogous cyclization making use of trapping the intermediate addition product (anion of an hemiketal) by Me_3SiCl proved itself well.[25–27] Therefore the piperazinediones **18a–c** with one acetate moiety were treated with LiHMDS at −78 °C and after 15 min Me_3SiCl was added to the mixture. Unexpectedly, only the benzylated piperazinedione **18c** provided the mixed ethyl silyl ketal **20c** in low yield (12%) and the corresponding mixed ethyl silyl ketals from the Cbz and Bz protected piperazinediones **18a** and **18b** could not be detected. This failure of the bridging reaction was attributed to the preferred deprotonation in 3-position of N-acylated piperazinediones **18a** and **18b**, which could not lead to the cyclization products. (Scheme 3)

Therefore, the 3,3-dialkylated piperazinediones **19a** and **19b**, which could no longer be deprotonated in 3-position were treated in the same manner with LiHMDS and Me_3SiCl. Although the yields were rather low, both compounds led to the mixed ethyl silyl ketals **21a** and **21b**. This observation supports the hypothesis of first deprotonation in 3-position of the acylated monoacetates **18a**,**b** as reason for the failure of the bridging reaction. (Scheme 3)

In addition to the preferred deprotonation in 3-position, the low yields of the ethano bridged piperazinediones **20** and **21** could be due to the short acetate (two C-atoms) side chain, which could not reach the enolate at the opposite side of the piperazine ring. In order to improve the accessibility of the enolate, a propionate side chain leading to propano bridged piperazinediones was envisaged. Therefore, the conjugate addition of piperazinediones **12a–c** at methyl acrylate was investigated. For this purpose, **12a–c** were deprotonated with LiHMDS or KHMDS at −78 °C and after 1 h, methyl acrylate was added. However, instead of the expected addition products **25**, the tetrahydropyridine derivatives **24** were isolated in 40–90% yields. Several experiments were performed to avoid this undesired reaction, including variation of the base (LiHMDS, KHMDS, NaHMDS, LDA, KDA), the electrophile (methyl acrylate, ethyl acrylate, ethyl 3-bromopropionate, ethyl 3-iodopropionate), the temperature and reaction time. Only, after deprotonation of **12b** with KDA or KHMDS and then reaction with ethyl acrylate or ethyl 3-iodopropionate provided a small amount (15% and 9%) of the propionate **25b**. (Scheme 4). It is assumed that the larger ethyl ester decreased the reactivity of the intermediate enolate **23** to attack intramolecularely the imide group.

Formation of the tetrahydropyridines **24** was explained by deprotonation of piperazinediones **12a–c** and subsequent addition of the enolates **22** at acrylate resulting in the new enolates **23**. Protonation of these enolates **23** can afford the desired propionates **25**. However, usually a fast attack of the enolates **23** at one of the imide carbonyl moieties occurred leading to cleavage of the imide and finally to the tetrahydropyridines **24a–c**. (Scheme 4)

The structure of the unexpected tetrahydropyridines **24a–c** was confirmed unequivocally by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. In the ^1H NMR spectrum of **24c** a singlet at 11.90 ppm typical for an enol proton of a vinylogous acid is observed. Moreover, the imide structure can no longer be identified due to the high field shift of the signals for the CH_2 group of the *p*-methoxybenzyl moiety. The doublets of



12, 22-26	R
a	Cbz
b	Bz
c	Bn

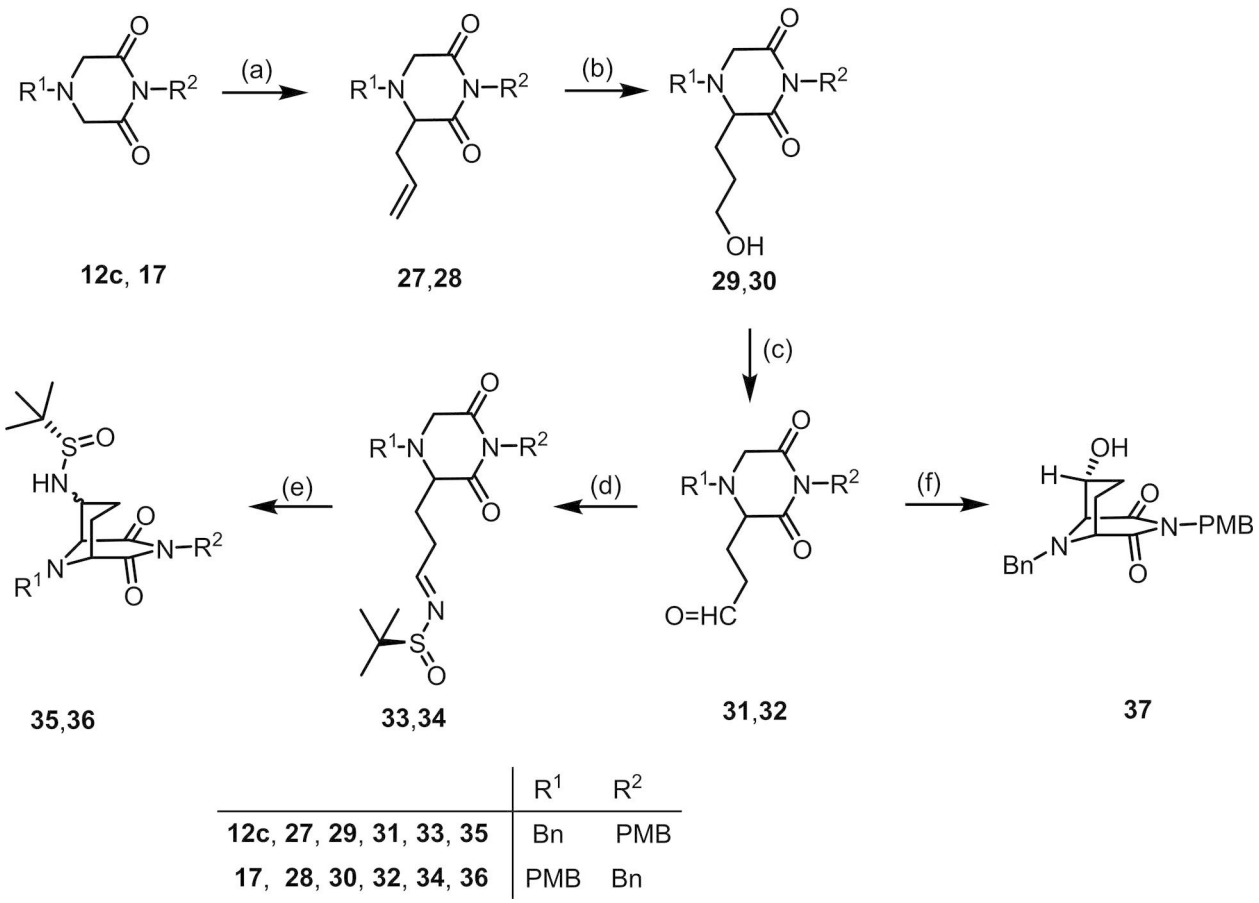
Scheme 4. Reaction of piperazinediones **12a-c** with acrylates. Reagents and reaction conditions: (a) LiHMDS or KHMDS, THF, −78 °C, 1–3 h, then methyl acrylate, −78 °C, 2 h, r.t. 16 h, 90% (**24a**), 34% (**24b**), 19% (**24c**). (b) KDA or KHMDS, THF, −78 °C, 30 min, then ethyl acrylate, −78 °C, 2 h, r.t. 14 h, 15% (**25b**). (c) KHMDS, THF, −78 °C, 90 min, then CH_3I, −78 °C, 2 h, r.t. 15 h, 33%.

doubles for these protons indicate an additional coupling with the NH-proton of the amide in **24c**. Deprotonation of the β-oxoester **24b** and subsequent methylation with CH_3I, afforded the methylated β-oxoester **26b** providing an additional proof for the tetrahydropyridine structure of **24a–c**.

Since the direct introduction of a propionate side chain was not successful, the stepwise introduction of a C_3-fragment with an electrophilic functional group at the end was envisaged. For this purpose, the piperazinediones **12c** and **17** were deprotonated and reacted with allyl bromide to afford racemic allyl substituted piperazinediones **27** and **28**, respectively. After hydroboration with 9-BBN and then oxidation with H_2O_2, the alcohols **29** and **30** were oxidized with Dess-Martin Periodinane (DMP) and the resulting aldehydes **31** and **32** were condensed with (*S*)-configured Ellman's sulfinamide *(S)*-2-methylpropane-2-sulfinamide in the presence of $Ti(OC_2H_5)_4$ to give the sulfinylimines **33** and **34** in 82% and 90% yield, respectively. Due to the high electrophilicity of the sulfinylimines **33** and **34**, the bridge could be established by deprotonation with LiHMDS. The resulting enolates were able to attack intramolecularly the electrophilic *C*-atom of the sulfinylimine group of **33** and **34** leading to the bicyclic sulfinamides **35** and **36**. Both transformations led to high yields of mixtures of diastereomeric bridged piperazinediones **35** (66%) and **36** (69%). The main isomer of the mixture of diastereomers could be isolated in 22% and 27% yields, respectively. (Scheme 5)

Since the sulfinylimines **33** and **34** provided the bridged systems **35** and **36** in high yields, the same reaction was tried with the corresponding aldehyde **31**. In fact, deprotonation of the aldehyde **31** with LiHMDS led to the *endo*-oriented bicyclic alcohol **37**. However, the yield of **37** did not exceed 10% even after careful optimization. (Scheme 5)

As the reaction of the enolates of piperazinediones **12c** and **17** with allyl bromide gave high yields of substitution products **27** and **28**, a dihalide presenting the allyl halide moiety twice should be reacted with the enolate of **17** to establish the bridge in only one reaction step. The linear dibromide **38** was frequently used in the literature to form systems with a vinyl moiety.[28] The branched dihalides **40** were employed to prepare compounds with large rings,[29–32] in particular, 1,5-diazacyclooctanes and tricyclic fused tetrazole derivatives. 3,7-Dimethylene-1,5-diazacyclooctanes were obtained by reaction of two equivalents of *p*-toluenesulfonamide or methanesulfonamide with two equivalents of dichloride **40a**.[31,32] Tricyclic fused tetrazole derivatives were achieved in two steps. At first, diazotizative allylation of 2-aminobenzonitrile derivatives with dibromide



	R^1	R^2
12c, **27**, **29**, **31**, **33**, **35**	Bn	PMB
17, **28**, **30**, **32**, **34**, **36**	PMB	Bn

Scheme 5. Synthesis of 3,9-diazabicyclo[3.2.1]nonanes. Reagents and reaction conditions: (a) LiHMDS, THF, −78 °C, 30 min, then $BrCH_2CH{=}CH_2$, THF, −78 °C, 2 h, r.t., 18 h, 61% (**27**), 67% (**28**). (b) i. 9-BBN, r.t. 16 h; ii. H_2O_2, NaOH, THF, −25 °C, 45 min, r.t., 60 min, 94% (**29**), 55% (**30**) (c) DMP, CH_2Cl_2, 3 h, r.t., 87% (**31**), 94% (**32**). (d) *(S)*-2-methylpropane-2-sulfinamide, $Ti(OC_2H_5)_4$, THF, r.t., 3 h, 82% (**33**), 90% (**34**). (e) LiHMDS, THF, −78 °C-r.t., 6 h, 66% (**35**), 69% (**36**). (f) LiHMDS, THF, −78 °C, 30 min, then r.t. 2.5 h, 10%.

40b was performed and then a tandem reaction comprised of a cycloaddition between the nitrile and $(TMS)N_3$ followed by an intramolecular N-allylation gave the desired products.[29]

For this purpose, piperazinedione **17** was deprotonated with 1.2 equivalents of LiHMDS. Subsequently, *trans*-1,4-dibromobut-2-ene (**38**) was added and after 16 h, another 1.2 equivalents of LiHMDS were added. Thus, the 2,6-bridged piperazinedione **39** was obtained by subsequent S_N2 and S_N2' reactions at 1,4-dibromobut-2-ene **38** in 22% yield. As for the alcohol **37**, only the *endo*-oriented vinyl derivative **39** was formed. The reaction of piperazinedione **17** with allylic dihalides **40** was performed in the same manner. Among the three allylic dihalides, the highest yield of 52% was obtained by reacting **17** with 3-bromo-2-(bromomethyl)prop-1-ene (**40b**). This one-step procedure will allow to prepare large amounts of **41** and exploit the additional double bond in the bridge to introduce further substituents as pharmacophoric elements. (Scheme 6)

3. Conclusions

Different strategies were investigated to obtain 2,6-bridged piperazine derivatives **8** with various functional groups in the third carbon bridge. For this purpose, at first a method was developed to prepare piperazine-2,6-diones **12** and **17** in high and reproducible yields. These piperazine-2,6-diones **12** and **17** contain different orthogonal protective groups at the N-atoms.

The first approach made use of a Dieckmann analogous cyclization of piperazinediones **18** and **19** with an acetate side chain leading to bicyclic ethyl silyl ketals **20** and **21**, although in low yields.

Cyclization of sulfinylimines **33** and **34** afforded the 3,9-diazabicyclo[3.3.1]nonanes **35** and **36** bearing a sulfinamido group in the C_3-bridge in 66% (**35**) and 69% (**36**) yields. Both compounds were obtained as mixtures of four diastereomers. It has to be noted that the sulfinylimino group is an ideal functional group to initiate this cyclization, since the intramolecular aldol reaction of aldehyde **31** led to the bicyclic alcohol **37** in only 10% yield.

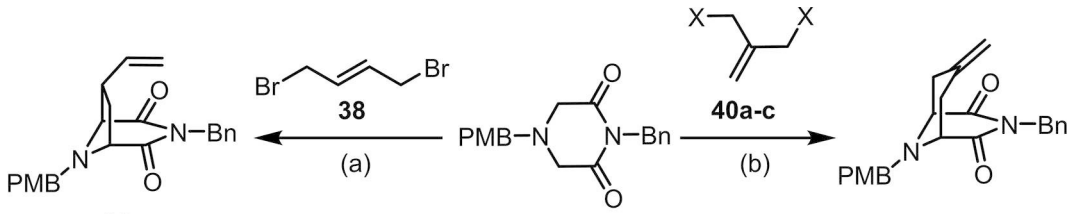
Two one-step syntheses of the bicyclic compounds **39** and **41** employed the linear and branched allylic dihalides **38** and **40**. The bicyclic system **39** with an additional vinyl group at the C_2-bridge and **41** with a methylene moiety at the C_3-bridge were obtained in 22% (**39**) and 52% (**41**) yield, respectively. The vinyl and methylene moiety at the carbon bridge will allow the introduction of various substituents and functional groups at the carbon bridge.

Altogether, bridged piperazines with a mixed ketal (**20**,**21**), an OH moiety (**37**) and a vinyl group (**39**) at the carbon bridge were obtained in low yields, whereas piperazines with a three-carbon bridge bearing a sulfinamido group (**35**,**36**) and a methylene moiety (**41**) were obtained in high yields. The 3,9-diazabicyclo[3.3.1]nonanes **35**, **36** and **41** will be exploited for synthesis of pharmacologically active compounds.

Experimental Section

Chemistry, General Methods

Oxygen and moisture sensitive reactions were carried out under nitrogen, dried with silica gel with moisture indicator (orange gel, VWR, Darmstadt, Germany) and in dry glassware (Schlenk flask or Schlenk tube). Temperature was controlled with dry ice/acetone (−78 °C/−25 °C), ice/water (0 °C), Cryostat (Julabo TC100E-F, Seelbach, Germany), magnetic stirrer MR 3001K (Heidolph, Schwalbach, Germany) or RCT CL (IKA, Staufen, Germany), together with temperature controller EKT HeiCon (Heidolph) or VT-5 (VWR) and PEG or silicone bath. All solvents were of analytical or technical grade quality. Demineralized water was used. CH_2Cl_2 was distilled from CaH_2; THF was distilled from sodium/benzophenone; MeOH was distilled from magnesium methanolate. Thin layer chromatography (tlc): tlc silica gel 60 F_{254} on aluminum sheets (VWR). Flash chromatography (fc): Silica gel 60, 40–63 μm (VWR); parentheses include: diameter of the column (∅), length of the stationary phase (l), fraction size (v) and eluent. Automated flash chromatography: Isolera™ Spektra One (Biotage®); parentheses include: cartridge size, flow rate, eluent, fractions size was always 20 mL. Melting point: Melting point system MP50 (Mettler Toledo, Gießen, Germany), open capillary, uncorrected. MS: MicroTOFQII mass spectrometer (Bruker Daltonics, Bremen, Germany); deviations of the found exact masses from the calculated exact masses were



40	X	yield 41
a	Cl	26 %
b	Br	52 %
c	I	35 %

Scheme 6. Reaction of piperazinedione **17** with dielectrophiles **38** and **40**. Reagents and reaction conditions: (a) i. LiHMDS, THF, −78 °C, 90 min; ii. *trans*-1,4-dibromobut-2-ene (**38**), THF, −78 °C; 90 min, then r.t., 16 h; iii. LiHMDS, THF, −78 °C, 2 h, r.t., 18 h, 22%. (b) i. LiHMDS, THF, −78 °C, 30 min; ii. 3-halo-2-(halomethyl)prop-1-enes **40a-c**, THF, −78 °C; 90 min; iii. LiHMDS, THF, −78 °C, 2 h, r.t., 18 h, 26–52%.

5 ppm or less; the data were analyzed with DataAnalysis® (Bruker Daltonics). NMR: NMR spectra were recorded in deuterated solvents on a AV300 (Bruker), DPX (Bruker), AV400 (Bruker), AS400 mercury plus NMR spectrometer (Varian), a 600 MHz unity plus NMR spectrometer (Varian), Agilent DD2 400 MHz and 600 MHz spectrometers (Agilent, Santa Clara CA, USA); chemical shifts (δ) are reported in parts per million (ppm) against the reference substance tetramethylsilane and calculated using the solvent residual peak of the undeuterated solvent; coupling constants are given with 0.5 Hz resolution; assignment of ^{1}H and ^{13}C NMR signals was supported by 2-D NMR techniques where necessary.IR: FT/IR IR Affinity®-1 spectrometer (Shimadzu, Düsseldorf, Germany) using ATR technique. Optical rotation: UniPol L1000 (Schmidt + Haensch); 1.0 dm tube; concentration c in g/100 mL; T = 20 °C; wavelength 589 nm (D-line of Na light); the unit of the specific rotation ($[\alpha]_D^T$ grad·mL dm^{-1} g^{-1}) is omitted for clarity.

HPLC

Equipment 1: Pump: L-7100, degasser: L-7614, autosampler: L-7200, UV detector: L-7400, interface: D-7000, data transfer: D-line, data acquisition: HSM-Software (all from Merck Hitachi, Darmstadt, Germany); Equipment 2: Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (equipment and software from Thermo Fisher Scientific, Lauenstadt, Germany); column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250–4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized water with 0.05 % (V/V) trifluoroacetic acid, B: CH_3CN with 0.05 % (V/V) trifluoroacetic acid; gradient elution (% A): 0–4 min: 90 %; 4–29 min: gradient from 90 % to 0 %; 29–31 min: 0 %; 31–31.5 min: gradient from 0 % to 90 %; 31.5–40 min: 90 %. Unless otherwise mentioned, the purity of all test compounds is greater than 95 %.

Synthetic Procedures

Diethyl 2,2′-(N-benzyloxycarbonylimino)diacetate (10a)

Under ice-cooling, benzyl chloroformate (10.8 mL, 75.68 mmol) was added slowly to a solution of diethyl iminodiacetate **9** (13.0 g, 68.80 mmol) and NEt_3 (10.6 mL, 75.68 mmol) in CH_2Cl_2. The mixture was warmed to rt and stirred for 18 h. Then the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane: ethyl acetate = 3:1, ∅ = 8.0 cm, l = 8.0 cm, V = 100 mL, R_f 0.17) to yield a colorless oil. Yield 15.6 g (70 %). $C_{16}H_{21}NO_6$ (323.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 4.10 (s, 2H, NCH_2CO_2), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.17 (s, 2H, NCH_2CO_2), 4.20 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.15 (s, 2H, $PhCH_2O$), 7.27–7.39 (m, 5H, $H_{arom.}$). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 14.2 (1C, OCH_2CH_3), 14.3 (1C, OCH_2CH_3), 49.3 (1C, NCH_2CO_2), 49.5 (1C, NCH_2CO_2), 61.4 (1C, OCH_2CH_3), 61.5 (1C, OCH_2CH_3), 68.0 (1C, OCH_2Ph), 127.9 (2C, C-2_{phenyl}, C-6_{phenyl}), 128.2 (1C, C-4_{phenyl}), 128.6 (2C, C-3_{phenyl}, C-5_{phenyl}), 136.2 (1C, C-1_{phenyl}), 156.1 (1C, OCO_2N), 169.5 (1C, NCH_2CO_2), 169.6 (1C, NCH_2CO_2). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2982 (m, v, C–H, alkyl), 1744 (s, v, C=O, ester), 1708 (s, v, C=O, carbamate), 737, 698 (m, δ, C–H, arom.). MS (APCI): calcd. for $C_{16}H_{21}NO_6H^+$ 324.1442, found 324.1377. HPLC: purity 98.4 %, t_R = 19.44 min.

Diethyl 2,2′-(N-benzoylimino)diacetate (10b)

Diethyl iminodiacetate **9** (1.0 g, 5.29 mmol) was dissolved in CH_2Cl_2 (30 mL) and NEt_3 (535 mg, 5.29 mmol) was added. Then benzoyl chloride (817 mg, 5.81 mmol) was added. The reaction mixture was stirred at rt for 24 h. The solution was washed with H_2O (4×), the combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The remaining residue was purified by fc (∅ = 4.5 cm, h = 23 cm, V = 20 mL, cyclohexane:ethyl acetate = 3:1, R_f 0.18) to obtain a pale yellow oil. Yield 1.39 g (90 %). $C_{15}H_{19}NO_5$ (293.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.31 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 4.11 (s, 2H, NCH_2CO_2), 4.21 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.26 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.32 (s, 2H, NCH_2CO_2), 7.37–7.47 (m, 5H, $H_{arom.}$). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 2983 (w, v, C–H, alkyl), 1739 (s, v, C=O, ester), 1650 (s, v, C=O, amide), 701 (m, δ, C–H, arom.). MS (ESI): 609 [$(2\times M + Na)^+$, 100], 587 [$(2\times M + H)^+$, 14].

2,2′-(N-Benzyloxycarbonylimino)diacetic acid (11a)

The diester **10a** (14.68 g, 45.46 mmol) was dissolved in a mixture of 2 M NaOH (200 mL) and EtOH (200 mL). The mixture was stirred for 18 h at rt. Then this mixture was extracted with Et_20 (300 mL) once. Conc. HCl was added to the aqueous layer until pH 1 and the aqueous layer was extracted with Et_20 (8×). The organic layers were dried (Na_2SO_4) and the solvent was removed in vacuum. The obtained oil was dried in high vacuum over night to yield a colorless viscous oil. Yield 10.97 g (90 %). $C_{12}H_{13}NO_6$ (267.0). ^{1}H NMR (300 MHz, DMSO): δ (ppm) = 3.99 (s, 2H, NCH_2CO_2), 4.02 (s, 2H, NCH_2CO_2), 5.08 (s, 2H, $PhCH_2O$), 7.27–7.41 (m, 5H, H_{phenyl}), 12.75 (s, 2H, CO_2H). ^{13}C NMR (300 MHz, DMSO): δ (ppm) = 49.2 (1C, NCH_2CO_2), 49.6 (1C, NCH_2CO_2), 66.6 (1C, OCH_2Ph), 127.2 (2C, C-2_{phenyl}, C-6_{phenyl}), 127.8 (1C, C-4_{phenyl}), 128.4 (2C, C-3_{phenyl}, C-5_{phenyl}), 136.7 (1C. C-1_{phenyl}), 155.6 (1C, OCO_2N), 170.9 (1C, NCH_2CO_2), 171.0 (1C, NCH_2CO_2). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3600–2300 (s, v, O–H, acid), 3037 (w, v, C–H, arom.), 2987 (m, v, C–H, alkyl), 1693 (s, v, C=O, acid), 737, 696 (m, δ, C–H, mono-substituted arom.). A signal for the C=O moiety of the carbamate cannot be detected. MS (APCI): calcd. for $C_{12}H_{13}NO_6H^+$ 268.0821, found 268.0847. HPLC: purity 99.1 %, t_R = 12.21 min.

2,2′-(N-Benzoylimino)diacetic acid (11b)

The diester **10b** (839 mg, 2.86 mmol) was dissolved in a mixture of 2 M NaOH (25 mL) and EtOH (25 mL). The mixture was stirred for 6 h at rt. Then this mixture was acidified with 1 M HCl until pH 1. The aqueous layer was extracted with Et_2O (6×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to obtain a colorless viscous oil. Yield 608 mg (90 %). $C_{15}H_{19}NO_5$ (237.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.97 (s, 2H, NCH_2CO_2), 4.13 (s, 2H, NCH_2CO_2), 7.29–7.33 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.43–7.50 (m, 3H, 2-H_{phenyl}, 4-H_{phenyl}, 6-H_{phenyl}). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3600–2300 (s, v, O–H, acid), 2925 (s, v, C–H, alkyl), 1719, (s, v, C=O, acid), 1596 (s, v, C=O, amide), 700 (m, δ, C–H, arom.). MS (ESI, negative mode): 473 [$(2\times M–H)^-$, 100], 236 [$(M–H)^-$, 89].

Benzyl 4-(4-methoxybenzyl)-3,5-dioxopiperazine-1-carboxylate (12a)

A solution of the diacid **11a** (11.06 g, 41.40 mmol) in THF (250 mL) was heated to reflux in a three-neck-flask (Two necks sealed with rubber septa.). Then a solution of carbonyldiimidazole (6.71 g, 41.40 mmol) in acetonitrile (20 mL) was added slowly over 30 min. The mixture was heated to reflux for 90 min. Subsequently a solution of p-methoxybenzylamine (5.37 mL, 41.40 mmol) in THF (20 mL) was added slowly over 30 min and the mixture was heated to reflux for 90 min. Subsequently a solution of carbonyldiimidazole (13.42 g, 82.80 mmol) in acetonitrile (50 mL) was added slowly to the reaction mixture over 30 min. The mixture was heated to reflux for 60 h. Then most of the solvent was removed in vacuum. The

residue was dissolved in Et_2O and 2 M HCl was added. The mixture was extracted with Et_2O (2×), then 5 M NaOH was added to the aqueous layer until pH 12. The aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 7:3, ∅ = 8.0 cm, l = 8.0 cm, V = 100 mL) to obtain a pale yellow solid. (R_f 0.48, cyclohexane:ethyl acetate = 1:1): Pale yellow solid, mp. 71 °C. Yield 10.37 g (68%). $C_{20}H_{20}N_2O_5$ (368.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.78 (s, 3H, OCH_3), 4.39 (s, 4H, 2-CH_2, 6-CH_2), 4.88 (s, 2H, NCH_2Ph), 5.15 (s, 2H, $PhCH_2O$), 6.82 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.31–7.41 (m, 5H, H_{phenyl}), 7.34 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 42.4 (1C, NCH_2Ar), 47.3 (2C, C-2, C-6), 55.4 (1C, OCH_3), 68.5 (1C, OCH_2Ph), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 128.4 (1C, C-1_{PMB}), 128.5 (2C, C-2_{phenyl}, C-6_{phenyl}), 128.8 (2C, C-3_{phenyl}, C-5_{phenyl}), 128.8 (1C, C-4_{phenyl}), 131.0 (2C, C-2_{PMB}, C-6_{PMB}), 135.5 (1C, C-1_{phenyl}), 154.0 (1C, OC(=O)N), 159.4 (1C, C-4_{PMB}), 167.8 (2C, CO_{imide}). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3067 (w, v, C–H, arom.), 2961 (w, v, C–H, alkyl), 1738 (w, v, C=O, imide), 1676 (s, v, C=O, imide), 820 (w, δ, C–H, para-substituted arom.), 747, 694 (m, δ, C–H, mono-substituted arom.). A signal for the C=O of the carbamate group cannot be detected. MS (APCI): calcd. for $C_{20}H_{20}N_2O_5$ 368.1372, found 368.1362. HPLC: purity 98.9%, t_R = 20.22 min.

4-Benzoyl-1-(4-methoxybenzyl)piperazine-2,6-dione (12b)

A solution of the diacid **11b** (2.75 g, 11.60 mmol) in THF (150 mL) was heated to reflux in a three-neck-flask (Two necks sealed with rubber septa.). Then a solution of carbonyldiimidazole (1.88 g, 11.60 mmol) in acetonitrile (30 mL) was added slowly over 30 min. The mixture was stirred for 60 min. Subsequently a solution of p-methoxybenzylamine (1.51 mL, 11.60 mmol) in THF (10 mL) was added slowly over 30 min and the mixture was stirred for 60 min. A solution of carbonyldiimidazole (3.76 g, 23.20 mmol) in acetonitrile (50 mL) was added slowly to the reaction mixture over 30 min. The mixture was refluxed for 18 h. Then most of the solvent was removed in vacuum. The remaining residue was dissolved in CH_2Cl_2 and 1 M HCl was added. The mixture was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 layers were alkalized with 2 M NaOH and washed with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 7:3, ∅ = 8.0 cm, l = 10.0 cm, V = 100 mL) to obtain a pale yellow oil. (R_f 0.35, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 2.36 g (60%). $C_{19}H_{18}N_2O_4$ (338.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.78 (s, 3H, OCH_3), 4.51 (s, broad, 4H, 2×NCH_2CO), 4.89 (s, 2H, NCH_2Ar), 6.83 (d, J = 8.7 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.34 (d, J = 8.6 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.37–7.41 (m, 2H, 3-$H_{benzoyl}$, 5-$H_{benzoyl}$), 7.41–7.53 (m, 3H, 2-$H_{benzoyl}$, 4-$H_{benzoyl}$, 6-$H_{benzoyl}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 42.6 (1C, NCH_2Ar), 48.7 (s, broad, 2C, NCH_2CO), 55.4 (1C, OCH_3), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 127.6 (2C, C-$2_{benzoyl}$, C-$6_{benzoyl}$), 128.4 (1C, C-1_{PMB}), 129.1 (2C, C-$3_{benzoyl}$, C-$5_{benzoyl}$), 130.9 (1C, C-$4_{benzoyl}$), 131.3 (2C, C-2_{PMB}, C-6_{PMB}), 133.1 (1C, C-$1_{benzoyl}$), 159.4 (1C, C-4_{PMB}), 167.5 (1C, NCH_2CO), 170.2 (1C, NCH_2CO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3060 (w, v, C–H, arom.), 2927 (m, v, C–H, alkyl), 1737 (m, v, C=O, imide), 1683 (s, v, C=O, imide), 810 (m, δ, C–H, para-substituted arom.), 721, 701 (m, δ, C–H, mono-substituted arom.). MS (EI): 338 [M^+, 100].

4-Benzyl-1-(4-methoxybenzyl)piperazine-2,6-dione (12c)

N-Ethyl-N,N-diisopropylamine (15.8 mL, 88.1 mmol) and benzyl bromide (1.58 mL, 13.2 mmol) were added to a solution of the secondary amine **12d** (2.58 g, 11.01 mmol) in acetonitrile (60 mL). The mixture was heated to reflux and stirred for 18 h. The solvent was removed in vacuum almost completely. The remaining solution was dissolved in CH_2Cl_2 and saturated $NaHCO_3$ solution and mixture was washed with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 1:1, ∅ = 5.0 cm, l = 8.5 cm, V = 30 mL) to obtain a pale yellow solid. (R_f 0.63, cyclohexane:ethyl acetate = 1:1): Yellow solid. Yield 2.99 g (84%). $C_{19}H_{20}N_2O_3$ (324.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.39 (s, 4H, NCH_2CO), 3.59 (s, 2H, NCH_2Ph), 3.78 (s, 3H, OCH_3), 4.86 (s, 2H, NCH_2Ar), 6.82 (d, J = 8.7 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.24 (dd, J = 6.1/4.4 Hz, 2H, 2-H_{benzyl}, 6-H_{benzyl}), 7.28–7.39 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-H_{benzyl}), 7.34 (d, J = 8.7 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 41.9 (1C, NCH_2Ar), 55.4 (2C, NCH_2CO), 56.5 (1C, OCH_3), 60.9 (1C, NCH_2Ph), 113.9 (2C, C-3_{PMB}, C-5_{PMB}), 128.2 (1C, C-1_{PMB}), 128.8 (2C, C-2_{benzyl}, C-6_{benzyl}), 129.0 (2C, C-3_{benzyl}, C-5_{benzyl}), 129.3 (1C, C-4_{benzyl}), 130.7 (2C, C-2_{PMB}, C-6_{PMB}), 135.4 (1C, C-1_{benzyl}), 159.2 (1C, C-4_{PMB}), 170.0 (2C, NCH_2CO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2958 (m, v, C–H, alkyl), 1736 (s, v, C=O, imide), 1679 (s, v, C=O, imide), 822 (m, δ, C–H, para-substituted arom.), 742, 700 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{19}H_{20}N_2O_3H^+$ 325.1547, found 325.1582. HPLC: purity 95.1%, t_R = 20.19 min.

1-(4-Methoxybenzyl)piperazine-2,6-dione (12d)

The imide **12a** (1.01 g, 2.73 mmol) was dissolved in THF (50 mL) and Pd/C (10%, 0.11 mg) was added. The mixture was stirred under H_2 atmosphere (1 atm) at rt for 1 h. The mixture was filtered through Celite® with THF and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 1:1→100% ethyl acetate, ∅ = 3.0 cm, l = 4.5 cm, V = 30 mL) to obtain a pale yellow solid. (R_f 0.01, cyclohexane:ethyl acetate = 1:1). mp: 131–132 °C. Yield 0.61 g (95%). $C_{12}H_{14}N_2O_3$ (234.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 4H, NCH_2CO), 3.78 (s, 3H, OCH_3), 4.88 (s, 2H, NCH_2Ar), 6.82 (d, J = 8.7 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.35 (d, J = 8.7 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 41.5 (1C, NCH_2Ar), 50.0 (2C, NCH_2CO), 55.4 (1C, OCH_3), 113.9 (2C, C-3_{PMB}, C-5_{PMB}), 129.2 (1C, C-1_{PMB}), 130.9 (2C, C-2_{PMB}, C-6_{PMB}), 159.2 (1C, C-4_{PMB}), 171.1 (2C, NCH_2CO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3335 (s, v, N–H, amine), 3075 (w, v, C–H, arom.), 2962 (m, v, C–H, alkyl), 1714 (s, v, C=O, imide), 1665 (s, v, C=O, imide), 832 (m, δ, C–H, para-substituted arom.). MS (APCI): calcd. for $C_{12}H_{14}N_2O_3H^+$ 235.1077, found 235.1103. HPLC: purity 99.7%, t_R = 11.52 min.

*N-(***tert***-Butoxycarbonyl)iminodiacetic acid (14)*

A mixture of iminodiacetic acid (11.0 g, 83 mmol, 1 eq) and $NaHCO_3$ (27.8 g, 331 mmol, 4 eq) were dissolved in H_2O (100 mL) of water. After bubbling finished, THF (100 mL) was added followed by Boc_2O (18.0 g, 83 mmol, 1 eq). The mixture was stirred at ambient temperature for 3 d. THF was removed in vacuo and the aqueous layer was washed with Et_2O (2×). The pH of the aqueous layer was then adjusted to pH 1 using 6 M HCl. The aqueous layer was extracted with ethyl acetate (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo to provide the product. Colorless solid, mp 127–131 °C, (decomposition), yield 14.2 g (74%). $C_9H_{15}NO_6$ (233.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.35 (s, 9H, $C(CH_3)_3$), 3.87 (s, 2H, NCH_2COOH), 3.91 (s, 2H, NCH_2COOH), 12.63 (s, 2H, 2×$COOH$). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 27.8 (3C, $C(CH_3)_3$), 49.1 (1C, NCH_2CO), 49.7 (1C, NCH_2CO), 79.5 (1C, $C(CH_3)_3$), 154.8 (1C, NCOO), 171.18 (1C, COOH), 171.21 (1C, COOH). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3113 (O–H), 2978 and 2943 (C-H_{aliph}), 1724 (C=O, acid), 1651 (C=O, carbamate). MS (APCI): m/z = 234.0966 (calcd. 234.0972 for $C_9H_{16}NO_6$ $[M+H]^+$).

tert-*Butyl 4-benzyl-3,5-dioxopiperazine-1-carboxylate (15)*

A solution of the diacid **14** (15.0 g, 64 mmol, 1 eq) in THF (250 mL) was heated to reflux in a three-necked-flask. Two necks were sealed with rubber septum. Then, a solution of carbonyldiimidazole (10.0 g, 64 mmol, 1 eq) in CH_3CN (60 mL) was added slowly over 30 min. The mixture was stirred for 60 min. Subsequently, a solution of benzylamine (7.03 mL, 64 mmol, 1 eq) in THF (20 mL) was added slowly over 30 min and the mixture was stirred for 60 min. A solution of carbonyldiimidazole (21.0 g, 129 mmol, 2 eq) in CH_3CN (100 mL) was added slowly to the reaction mixture over 30 min. The mixture was heated to reflux for 18 h. Then, most of the solvent was removed in vacuo. The remaining residue was dissolved in ethyl acetate and 1 M HCl was added. The mixture was extracted with ethyl acetate (3×). 2 M NaOH was added to the combined ethyl acetate layers and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane: ethyl acetate = 91:9→83:17, ø = 5 cm, l = 12 cm, V = 100 mL). (R_f 0.66, cyclohexane:ethyl acetate = 67:33). Colorless solid, mp 147–149 °C, yield 12.1 g (62 %). $C_{16}H_{20}N_2O_4$ (304.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 9H, C(CH_3)$_3$), 4.32 (s, 4H, NCH_2CO), 4.95 (s, 2H, NCH_2Ph), 7.25–7.32 (m, 3H, 3-CH_{benzyl}, 4-CH_{benzyl}, 5-CH_{benzyl}), 7.35–7.39 (m, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 28.3 (3C, C(CH_3)$_3$), 42.9 (1C, NCH_2Ph), 47.3 (2C, NCH_2CO), 82.4 (1C, C(CH_3)$_3$), 128.0 (1C, C-4$_{benzyl}$), 128.7 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.2 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 136.3(1C, C-1$_{benzyl}$), 153.2 (1C, NCOO), 168.2 (2C, NCOCH$_2$).IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2982 (C-H_{aliph}), 1678 (C=O), 856 (C-H_{arom}). MS (APCI): m/z = 305.1408 (calcd. 305.1496 for $C_{16}H_{21}N_2O_4$ $[M+H]^+$). Purity (HPLC): 99.8 % (t_R = 20.9 and 21.1 min).

1-Benzylpiperazine-2,6-dione (16)

A solution of **15** (70 mg, 0.23 mmol, 1 eq) in CH_2Cl_2 (5 mL) was cooled to 0 °C. CF_3COOH (2 mL) was added slowly to the mixture. The mixture was stirred overnight at rt. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and the mixture was washed with saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4×). The organic layers were combined and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by fc (cyclohexane:ethyl acetate: dimethylethylamine = 50:50:1→25:75:1, ø = 1 cm, l = 10 cm, V = 7 mL). (R_f 0.24, cyclohexane:ethyl acetate:dimethylethylamine = 20:80:1): Colorless solid, mp 149–151 °C, yield 12.1 g (99 %). $C_{11}H_{12}N_2O_2$ (204.2). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 3.59 (s, 4H, NCH_2CO), 4.82 (s, 2H, NCH_2Ph), 7.20–7.27 (m, 3H, 2-CH_{benzyl}, 4-CH_{benzyl}, 6-CH_{benzyl}), 7.27–7.33 (m, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 40.8 (1C, NCH_2Ph), 49.1 (2C, NCH_2CO), 126.9 (1C, C-4$_{benzyl}$), 127.4 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 128.2 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 137.2 (1C, C-1$_{benzyl}$), 172.1 (2C, C=O). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3321 (N–H), 2954, 2924 and 2854 (C-H_{aliph}), 1724 and 1662 (C=O), 840 (C-H_{arom}). MS (APCI): m/z = 205.0973 (calcd. 205.0972 for $C_{11}H_{13}N_2O_2$ $[M+H]^+$). Purity (HPLC): 95.9 % (t_R = 12.2 min).

1-Benzyl-4-(4-methoxybenzyl)piperazine-2,6-dione (17)

N-Ethyl-N,N-diisopropylamine (24.3 mL, 147 mmol, 3 eq) and 4-methoxybenzyl chloride (7.0 mL, 52 mmol, 1.05 eq) were added to a solution of the secondary amine **16** (10.0 g, 49 mmol, 1 eq) in CH_3CN (100 mL). The mixture was heated to reflux for 18 h. The solvent was removed in vacuo almost completely. The remaining residue was dissolved in CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ solution (100 mL). The mixture was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane: ethyl acetate = 91:9→75:25, ø = 6 cm, l = 18 cm, V = 65 mL). (R_f 0.38, cyclohexane:ethyl acetate = 75:25). Pale yellow solid, mp. 51–52 °C, yield 14.0 g (88 %). $C_{19}H_{20}N_2O_3$ (324.4). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 3.46 (s, 4H, NCH_2CO), 3.58 (s, 2H, NCH_2PhOMe), 3.74 (s, 3H, OCH_3), 4.80 (s, 2H, NCH_2Ph), 6.91 (d, J = 8.6 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.20 (d, J = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.21–7.23 (m, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}), 7.23–7.26 (m, 1H, 4-CH_{benzyl}), 7.28–7.34 (m, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 41.3 (1C, NCH_2Ph), 55.0 (1C, CH_3O), 55.1 (2C, NCH_2CO), 58.3 (1C, NCH_2PhOMe), 113.8 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 127.1 (1C, C-4$_{benzyl}$), 127.5 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 127.8 (1C, C-1$_{PMB}$), 128.4 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 130.4 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 136.9 (1C, C-1$_{benzyl}$), 158.7 (1C, C-4$_{PMB}$), 170.3 (2C, NCH$_2$CO). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2955 and 2931 (C-H_{aliph}), 1735 and 1682 (C=O), 821 (C-H_{arom}). MS (APCI): m/z = 325.1553 (calcd. 325.1547 for $C_{19}H_{21}N_2O_3$ $[M+H]^+$). Purity (HPLC): 97.2 % (t_R = 21.2 min).

Benzyl 2-(ethoxycarbonylmethyl)-4-(4-methoxybenzyl)-3,5-dioxopiperazine-1-carboxylate (18a) and diethyl 2,2′-[1-(benzyloxycarbonyl)-4-(4-methoxybenzyl)-3,5-dioxopiperazine-2,2-diyl]diacetate (19a)

A solution of the imide **12a** (1.02 g, 2.76 mmol) in THF (30 mL) was cooled to −78 °C. Then a 1 M solution of lithium hexamethyldisilazide (LiHMDS, 2.76 mL, 2.76 mmol) was added and the mixture was stirred for 1 h. Ethyl 2-bromoacetate (0.61 mL, 5.51 mmol) was added and the mixture was stirred at −78 °C for 2 h. The mixture was warmed to rt overnight. The solvent was removed in vacuum and the remaining residue was purified by fc (n-hexane:ethyl acetate = 8/2, ∅ = 4.0 cm, l = 8.5 cm, V = 30 mL) to obtain two pale yellow oils. **18a** (R_f 0.57, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 1.06 g (84 %). $C_{24}H_{26}N_2O_7$ (454.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.18 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 2.92 (s, broad, 1H, CHCH_2CO$_2$Et), 3.14 (dd, broad, J = 17.3/4.8 Hz, 1H, CHCH_2CO$_2$Et), 3.77 (s, 3H, OCH$_3$), 3.99–4.15 (m, 3H, OCH_2CH$_3$, 2-CH), 4.90 (d, J = 13.8 Hz, 1H, NCH$_2$Ph), 4.91 (s, broad, 2H, 6-CH$_2$), 4.97 (d, J = 13.8 Hz, 1H, NCH$_2$Ph), 5.15 (s, 2H, PhCH$_2$O), 6.81 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.29–7.41 (m, 5H, H_{phenyl}), 7.32 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3067 (w, v, C–H, arom.), 2962 (m, v, C–H, alkyl), 1726 (s, v, C=O, ester),1712 (s, v, C=O, carbamate), 1681 (s, v, C=O, imide), 815 (m, δ, C–H, para-substituted arom.), 735, 698 (m, δ, C–H, mono-substituted arom.). A second signal for the imide-C=O group cannot be detected. MS (APCI): calcd. for $C_{24}H_{26}N_2O_7H^+$ 455.1813, found 455.1969. HPLC: purity 82.6 %, t_R = 21.24 min. **19a** (R_f 0.65, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 0.06 g (4 %). $C_{28}H_{32}N_2O_9$ (540.2). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.09 (t, J = 7.1 Hz, 6H, OCH$_2$CH_3), 3.01 (d, J = 17.2 Hz, 2H, 2×CH$_2$CO$_2$), 3.76 (s, 3H, OCH$_3$), 3.82–4.10 (m, 6H, OCH_2CH$_3$, 2×CH$_2$CO$_2$), 4.45 (s, 2H, 6-$H_{dioxopiperazine}$), 4.97 (s, 2H, NCH$_2$Ph), 5.14 (s, 2H, PhCH$_2$O), 6.79 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.27–7.42 (m, 5H, H_{phenyl}), 7.32 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2958 (m, v, C–H, alkyl), 1728 (s, v, C=O, ester), 1706 (s, v, C=O, carbamate), 1675 (s, v, C=O, imide), 819 (m, δ, C–H, para-substituted arom.), 736, 698 (m, δ, C–H, mono-substituted arom.). A second signal for the imide-C=O group cannot be detected. MS (ESI, negative mode): m/z (%) = 1103 [(2×M + Na)$^-$, 97], 563 [(M + Na)$^-$, 100].

Ethyl 2-(1-benzoyl-4-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl) acetate (18b) and diethyl 2,2′-(1-benzoyl-4-(4-methoxybenzyl)-3,5-dioxopiperazine-2,2-diyl)diacetate (19b)

A solution of the imide **12b** (257 mg, 0.76 mmol) in THF (15 mL) was cooled to −78 °C and 0.5 M KHMDS-solution in THF (1.59 mL,

0.76 mmol) was added. After 30 min ethyl 2-bromoacetate (168 μL, 1.52 mmol) was added. The reaction mixture was stirred for 1.5 h at −78 °C and then warmed to rt. An excess of 1 M HCl solution was added and the mixture was concentrated in vacuum. The residue was dissolved in CH_2Cl_2 and washed with water (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by fc (cyclohexane:ethyl acetate = 8:2, ∅ = 3.0 cm, l = 12.0 cm, V = 20 mL) to obtain two pale yellow oils **18b** and **19b. 18b** (R_f 0.42, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 254 mg (79%). $C_{23}H_{24}N_2O_6$ (424.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.00 (d, broad, J = 16.9 Hz, 1H, CH_2CO_2Et), 3.20 (d, broad, J = 16.3 Hz, 1H, CH_2CO_2Et), 3.79 (s, 3H, OCH_3), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.38 (d, J = 16.3 Hz, 1H, NCH_2CO), 4.61 (s, broad, 1H, NCH_2CO), 4.94 (s, 2H, NCH_2Ar), 5.48 (s, broad, 1H, NCHCO), 6.83 (d, J = 8.7 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.32 (d, J = 8.6 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.36 (dd, J = 8.0/1.3 Hz, 2H, 3-$H_{benzoyl}$, 5-$H_{benzoyl}$), 7.40–7.53 (m, 3H, 2-$H_{benzoyl}$, 4-$H_{benzoyl}$, 6-$H_{benzoyl}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 14.2 (1C, OCH_2CH_3), 36.5 (1C, C-2), 42.9 (1C, NCH_2Ar), 51.1 (1C, NCH_2CO), 55.4 (1C, OCH_3), 60.5 (1C, NCHCO), 61.8 (1C, OCH_2CH_3), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 127.4 (2C, C-$2_{benzoyl}$, C-$6_{benzoyl}$), 128.4 (1C, C-1_{PMB}), 129.0 (2C, C-$3_{benzoyl}$, C-$5_{benzoyl}$), 130.5 (1C, C-$4_{benzoyl}$), 131.1 (2C, C-2_{PMB}, C-6_{PMB}), 133.6 (1C, C-$1_{benzoyl}$), 159.3 (1C, C-4_{PMB}), 167.4 (1C, $CO_{benzoyl}$), 167.4 (1C, NCH_2CO), 170.0 (1C, NCH_2CO), 171.3 (1C, CH_2CO_2Et). FT-IR: ṽ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2940 (w, v, C–H, alkyl), 1731 (m, v, C=O, imide), 1683 (s, v, C=O, imide), 1652 (s, v, C=O, amide), 811 (m, δ, C–H, para-substituted arom.), 722, 702 (m, δ, C–H, mono-substituted arom.). MS (EI): 424 [M^+, 100], 319 [$(M–C_6H_5CO)^+$, 70], 303 [$(M-H_3COC_6H_4CH_2)^+$, 98]. **19b** (R_f 0.52, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 22 mg (6%). $C_{27}H_{30}N_2O_8$ (510.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.17 (t, J = 7.1 Hz, 6H, 2×OCH_2CH_3), 3.09 (d, J = 17.4 Hz, 2H, 2× CH_2CO_2Et), 3.76 (s, 3H, OCH_3), 4.00 (q, J = 7.2 Hz, 4H, 2× OCH_2CH_3), 4.16 (d, J = 17.4 Hz, 2H, 2× CH_2CO_2Et), 4.36 (s, 2H, NCH_2CO), 4.94 (s, 2H, NCH_2Ar), 6.80 (d, J = 8.6 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.22–7.25 (m, 2H, 3-$H_{benzoyl}$, 5-$H_{benzoyl}$), 7.31 (d, J = 8.6 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.37–7.47 (m, 3H, 2-$H_{benzoyl}$, 4-$H_{benzoyl}$, 6-$H_{benzoyl}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 14.2 (2C, OCH_2CH_3), 31.1 (1C, CH_2CO_2Et), 41.1 (1C, CH_2CO_2Et), 43.8 (1C, NCH_2Ar), 51.7 (1C, NCH_2CO), 55.3 (1C, OCH_3), 60.6 (1C, NCCO), 61.2 (1C, OCH_2CH_3), 62.5 (1C, OCH_2CH_3), 113.7 (2C, C-3_{PMB}, C-5_{PMB}), 126.2 (2C, C-$2_{benzoyl}$, C-$6_{benzoyl}$), 128.3 (1C, C-1_{PMB}), 129.1 (2C, C-$3_{benzoyl}$, C-$5_{benzoyl}$), 130.3 (1C, C-$4_{benzoyl}$), 130.5 (2C, C-2_{PMB}, C-6_{PMB}), 136.2 (1C, C-$1_{benzoyl}$), 159.1 (1C, C-4_{PMB}), 166.4 (1C, $CO_{benzoyl}$), 170.5 (1C, NCH_2CO), 171.6 (1C, NCH_2CO), 172.9 (1C, CH_2CO_2). FT-IR: ṽ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2936 (w, v, C–H, alkyl), 1727 (s, v, C=O, imide), 1676 (s, v, C=O, imide), 1651 (s, v, C=O, amide), 818 (m, δ, C–H, para-substituted arom.), 728, 702 (m, δ, C–H, mono-substituted arom.). MS (EI): 510 [M^+, 100], 465 [$(M-OCH_2CH_3)^+$, 16], 405 [$(M–C_6H_5CO)^+$, 15].

Ethyl 2-(1-benzyl-4-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl) acetate (18c)

A solution of the imide **12c** (21 mg, 0.07 mmol) in THF (5 mL) was cooled to −78 °C. Then a 1 M solution of lithium hexamethyldisilazide (LiHMDS, 0.07 mL, 0.07 mmol) was added and the mixture was stirred for 1 h. Ethyl 2-bromoacetate (15 μL, 0.13 mmol) was added and the mixture was stirred at −78 °C for 1 h. The mixture was warmed to rt. The solvent was removed in vacuum and the remaining residue was purified by fc (n-hexane: ethyl acetate = 8/2, ∅ = 1.0 cm, l = 4.0 cm, V = 5 mL) to obtain a yellow oil. (R_f 0.62, cyclohexane:ethyl acetate = 1:1): Yellow oil. Method A: Yield 0.32 g (85%). Method B; Yield 24 mg (89%). $C_{23}H_{26}N_2O_5$ (410.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.87 (dd, J = 15.6/7.5 Hz, 1H, $CHCH_2CO_2Et$), 2.96 (dd, J = 15.6/5.7 Hz, 1H, $CHCH_2CO_2Et$), 3.40 (d, J = 17.6 Hz, 1H, 6-$H_{dioxoperazine}$), 3.62 (d, J = 12.9 Hz, 1H, NCH_2Ar), 3.67 (d, J = 17.6 Hz, 1H, 6-$H_{dioxopiperazine}$), 3.68 (d, J = 12.9 Hz, 1H, NCH_2Ar), 3.79 (s, 3H, OCH_3), 4.04 (t, J = 6.8 Hz, 1 H, 2-$H_{dioxopiperazine}$), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.84 (d, J = 13.8 Hz, 1H, NCH_2Ph), 4.90 (d, J = 13.8 Hz, 1H, NCH_2Ph), 6.83 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.27–7.38 (m, 5H, H_{benzyl}) 7.34 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 14.3 (1C, OCH_2CH_3), 34.9 (1C, CH_2CO_2Et), 42.2 (1C, NCH_2Ar), 52.4 (1C, NCH_2CO), 55.4 (1C, OCH_3), 57.7 (1C, NCHCO), 61.1 (1C, OCH_2CH_3), 61.3 (1C, $PhCH_2N$), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 128.3 (1C, C-1_{PMB}), 128.8 (1C, C-4_{benzyl}), 129.2 (2C, C-2_{benzyl}, C-6_{benzyl}), 129.7 (2C, C-3_{benzyl}, C-5_{benzyl}), 130.7 (2C, C-2_{PMB}, C-6_{PMB}), 135.7 (1C, C-1_{benzyl}), 159.2 (1C, C-4_{PMB}), 169.6 (1C, NCH_2CO), 170.3 (CO_{ester}), 171.1 (1C, NCHCO). FT-IR: ṽ (cm^{-1}) = 3062 (w, v, C–H, arom.), 2982 (m, v, C–H, alkyl), 1732 (s, v, C=O, ester), 1679 (s, v, C=O, imide), 819 (m, δ, C–H, para-substituted arom.), 744, 700 (m, δ, C–H, mono-substituted arom.). A second signal for the imide-C=O cannot be detected. MS (APCI): calcd. for $C_{23}H_{26}N_2O_5H^+$ 411.1914, found 411.1944. HPLC: purity 92.8%, t_R = 21.05 min.

(1RS,5SR,6RS)-8-Benzyl-6-ethoxy-3-(4-methoxybenzyl)-6-(trimethylsilyloxy)-3,8-diazabicyclo[3.2.1] octane-2,4-dione (20c)

A solution of the acetate **18c** (145 mg, 0.35 mmol) in THF (15 mL) was cooled to −78 °C and 1.0 M LiHMDS-solution (531 μL, 0.53 mmol) was added. After 15 min TMS–Cl (157 μL, 1.24 mmol) was added. The reaction mixture was stirred for 1.0 h at −78 °C and then warmed to rt. The solvent was removed in vacuum, the residue dissolved in CH_2Cl_2 was poured into CH_2Cl_2/saturated $NaHCO_3$ and extracted four time with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 9:1, ∅ = 2.0 cm, l = 8.5 cm, V = 20 mL) to obtain a pale yellow oil. (R_f 0.72, cyclohexane:ethyl acetate = 1:1). Yield 20 mg (12%). $C_{26}H_{34}N_2O_5Si$ (482.6). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.02 (s, 9H, $Si(CH_3)_3$), 1.16 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.56 (d, J = 11.0 Hz, 1H, 7-CH_2), 2.63 (d, J = 13.0 Hz, 1H, 7-CH_2), 3.41 (dq, J = 9.4/7.0 Hz, 1H, OCH_2CH_3), 3.49 (s, 1H, 5-CH), 3.57 (dq, J = 9.4/7.1 Hz, 1H, OCH_2CH_3), 3.62 (d, J = 12.9 Hz, 1H, NCH_2Ph), 3.70 (d, J = 13.0 Hz, 1H, NCH_2Ph), 3.78 (s, 3H, OCH_3), 3.80–3.84 (m, 1H, 1-CH), 4.79 (d, J = 13.6 Hz, 1H, NCH_2Ar), 4.85 (d, J = 13.7 Hz, 1H, NCH_2Ar), 6.84 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.14 (dd, J = 7.5/2.0 Hz, 2H, 2-H_{benzyl}, 6-H_{benzyl}), 7.27–7.34 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-H_{benzyl}), 7.41 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). FT-IR: ṽ (cm^{-1}) = 3067 (w, v, C–H, arom.), 2925 (m, v, C–H, alkyl), 1736 (m, v, C=O, imide), 1685 (s, v, C=O, imide), 843 (m, δ, C–H, para-substituted arom.), 739, 697 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{26}H_{34}N_2O_5SiH^+$ 483.2315, found 483.2386. HPLC: purity 83.1%, t_R = 23.87 min.

Benzyl (1RS,5RS,7SR)-6-ethoxy-1-(ethoxycarbonylmethyl)-3-(4-methoxybenzyl)-2,4-dioxo-6-(trimethylsilyloxy)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (21a)

A solution of the diacetate **19a** (158 mg, 0.29 mmol) in THF (15 mL) was cooled to −78 °C and 1.0 M LiHMDS-solution (438 μL, 0.44 mmol) was added. After 15 min TMS–Cl (129 μL, 1.02 mmol) was added. The reaction mixture was stirred for 1.0 h at −78 °C and then warmed to rt. The solvent was removed in vacuum, the remaining residue was purified by fc (cyclohexane:ethyl acetate = 8:2, ∅ = 3.0 cm, l = 8.0 cm, V = 20 mL) to obtain a pale yellow oil. (R_f 0.55, cyclohexane:ethyl acetate = 1:1). Pale yellow oil. Yield 38 mg (21%). $C_{31}H_{40}N_2O_9Si$ (612.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.01 (s, 9H, $Si(CH_3)_3$), 1.13 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.20 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.27 (d, J = 13.3 Hz, 1H, 7-CH_2), 2.75 (dd, J = 13.9/0.9 Hz, 1H, 7-CH_2), 3.31 (d, J = 16.9 Hz, 1H, CH_2CO_2Et), 3.44 (d,

J = 16.6 Hz, 1H, CH_2CO_2Et), 3.43–3-54 (m, 1H, OCH_2CH_3), 3.54–3.63 (m, 1H, OCH_2CH_3), 3.74 (s, 3H, OCH_3), 4.05–4.16 (m, 2H, $CO_2CH_2CH_3$), 4.68 (d, J = 13.9 Hz, 1H, NCH_2Ar), 4.81 (d, J = 13.9 Hz, 1H, NCH_2Ar), 4.96 (s, 1H, 5-CH), 4.96 (d, J = 12.2 Hz, 1H, $PhCH_2O$), 5.04 (d, J = 12.2 Hz, 1H, $PhCH_2O$), 6.77 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.19–7.25 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.28–7.38 (m, 5H, 2-H_{phenyl}, 4-H_{phenyl}, 6-H_{phenyl}, 2-H_{PMB}, 6-H_{PMB}).

Ethyl 2-[(1RS,5RS,6SR)-8-benzoyl-6-ethoxy-3-(4-methoxybenzyl)-2,4-dioxo-6-(trimethylsilyloxy)-3,8-diazabicyclo[3.2.1]octan-1-yl]acetate (21b)

A solution of the diacetate **19b** (42 mg, 0.08 mmol) in THF (10 mL) was cooled to −78 °C and 1.0 M LiHMDS-solution in THF (123 μL, 0.12 mmol) was added. After 15 min TMS–Cl (36 μL, 0.29 mmol) was added. The reaction mixture was stirred for 1.0 h at −78 °C and then warmed to rt. The solvent was removed in vacuum, the residue was purified by fc (cyclohexane:ethyl acetate = 8:2, ∅ = 1.5 cm, l = 8.0 cm, V = 20 mL) to obtain a pale yellow oil. Yield 5 mg (10 %). $C_{30}H_{38}N_2O_8Si$ (582.7). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.00 (s, 9H, $Si(CH_3)_3$), 1.19 (t, J = 7.1 Hz, 3H, $COCH_2CH_3$), 1.20 (t, J = 6.9 Hz, 3H, $CO_2CH_2CH_3$), 2.32 (d, J = 14.0 Hz, 1H, 7-CH_2), 2.87 (d, J = 14.1 Hz, 1H, 7-CH_2), 3.28 (dq, J = 8.8/6.8 Hz, 1H, OCH_2CH_3), 3.50 (d, J = 16.4 Hz, 1H, CH_2CO_2Et), 3.53–3.62 (m, 1H, OCH_2CH_3), 3.60 (d, J = 16.4 Hz, 1H, CH_2CO_2Et), 3.78 (s, 3H, OCH_3), 4.06–4.17 (m, 2H, $CO_2CH_2CH_3$), 4.61 (s, 1H, 5-CH), 4.73 (d, J = 14.0 Hz, 1H, NCH_2Ar), 4.90 (d, J = 13.9 Hz, 1H, NCH_2Ar), 6.83 (d, J = 8.6 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.31 (d, J = 8.6 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.35–7.51 (m, 5H, $H_{benzoyl}$).

1-Benzyl 4-methyl 5-hydroxy-2-[(4-methoxybenzyl)carbamoyl]-1,2,3,6-tetrahydro-pyridine-1,4-dicarboxylate (24a)

A solution of the imide **12a** (0.51 g, 1.38 mmol) in THF (20 mL) was cooled to −78 °C. Then a 1 M solution of lithium hexamethyldisilazide (LiHMDS, 1.38 mL, 1.38 mmol) was added and the mixture was stirred for −78 °C for 1 h. Methyl acrylate (0.37 mL, 4.13 mmol) was added and the reaction mixture was stirred at −78 °C for 2 h and then warmed to rt overnight. The reaction was stopped with a few drops of a solution of saturated $NaHCO_3$. The solvent was almost completely evaporated in vacuum and CH_2Cl_2 and water were added to the residue. The mixture was extracted with CH_2Cl_2 (4×) and the combined organic layers were dried (Na_2SO_4). The solvent was removed in vacuum and the residue was purified by fc (cyclohexane:ethyl acetate = 7:3→1:1→100 % ethyl acetate, ∅ = 3.0 cm, l = 8.5 cm, V = 30 mL) to obtain a pale yellow solid. (R_f: 0.34, cyclohexane:ethyl acetate = 1:1). Yield 0.56 g (90 %). $C_{24}H_{26}N_2O_7$ (454.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.26 (dd, broad, J = 15.6/5.9 Hz, 1H, 3-H), 3.09 (dd, broad, J = 27.8/15.9 Hz, 1H, 5-H), 3.78 (s, 3H, CO_2CH_3), 3.79 (s, 3H, $ArOCH_3$), 3.85 (d, broad, J = 22.0 Hz, 1H, 6-H), 4.24–4.48 (s, broad, 3H, $NHCH_2Ar$, 2-H), 4.96 (d, broad, J = 22.8 Hz, 1H, 6-H), 5.14 (d, J = 13.0 Hz, 1H, $PhCH_2O$), 5.19 (d, J = 13.0 Hz, 1H, $PhCH_2O$), 6.06 (d, broad, J = 32.9 Hz, 1H, NH), 6.83 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.12 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.27–7.41 (m, 5H, H_{phenyl}), 11.96 (s, 1H, OH). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 22.6 (1C, C-3), 43.2 (1C, C-6), 43.4 (1C, $NHCH_2Ar$), 52.0 (1C, CO_2CH_3), 52.8 (1C, C-2), 55.4 (1C, $ArOCH_3$), 68.4 (1C, $PhCH_2O$), 95.1 (1C, C-4), 110.1 (1C, C-5), 114.3 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 128.2 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 128.6 (1C, C-1$_{PMB}$), 128.7 (1C, C-4$_{phenyl}$), 128.8 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.0 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 135.8 (1C, C-1$_{phenyl}$), 159.2 (1C, C-4$_{PMB}$), 165.2 (1C, OCON), 169.7 (1C, CO_2CH_3), 171.7 (1C, CONH). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3331 (m, v, O–H), 3067 (w, v, C–H, arom.), 2954 (m, v, C–H, alkyl), 1747 (s, v, C=O, ester), 1704 (s, v, C=O, carbamate), 1665 (s, v, C=O, imide), 808 (m, δ, C–H, para-substituted arom.), 734, 698 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{24}H_{26}N_2O_7H^+$ 455.1813, found 455.1858.

Methyl 1-benzoyl-5-hydroxy-2-[N-(4-methoxybenzyl)carbamoyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (24b)

A solution of the imide **12b** (49 mg, 0.15 mmol) in THF (5 mL) was cooled to −78 °C and 0.5 M KHMDS-solution in THF (290 μL, 0.15 mmol) was added. After 180 min methyl acrylate (39 μL, 0.44 mmol) was added. The reaction mixture was stirred for 2.0 h at −78 °C and then at rt for 16 h. The solvent was removed in vacuum and the residue was purified by fc (cyclohexane:ethyl acetate = 7:3, ∅ = 1.5 cm, l = 7.5 cm, V = 10 mL) to obtain a colorless solid. (R_f 0.21, cyclohexane:ethyl acetate = 1:1): Colorless solid. Yield 21 mg (34 %). $C_{23}H_{24}N_2O_6$ (424.5). The ^{1}H NMR spectrum shows only broad signals. The structure of **24b** was identified by subsequent transformation. FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3316 (m, v, N–H, amide), 3059 (w, v, C–H, arom.), 2953 (m, v, C–H, alkyl), 1733 (s, v, C=O, ester), 1667 (s, v, C=O, amide), 810 (m, δ, C–H, para-substituted arom.), 730, 702 (m, δ, C–H, mono-substituted arom.). MS (EI): 424 [M^+, 15], 392 [(M-$HOCH_3$)$^+$, 50], 287 [(M-$H_3OC_6H_4CH_2NH_2$)$^+$, 100].

Methyl 1-benzyl-5-hydroxy-2-[(4-methoxybenzyl)carbamoyl]-1,2,3,6-tetrahydro-pyridine (24c)

A solution of the imide **12c** (210 mg, 0.65 mmol) in THF (30 mL) was cooled to −78 °C and 1.0 M LiHMDS-solution in THF (646 μL, 0.65 mmol) was added. After 180 min methyl acrylate (70 μL, 0.78 mmol) was added. The reaction mixture was stirred for 2.0 h at −78 °C and then at rt for 16 h. The solvent was removed in vacuum and the residue was purified by fc (cyclohexane:ethyl acetate = 19:1, ∅ = 2.0 cm, l = 9.0 cm, V = 10 mL) to obtain a colorless solid. (R_f: 0.38, cyclohexane:ethyl acetate = 1:1). Yield 50 mg (19 %). $C_{23}H_{26}N_2O_5$ (410.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.61 (dd, J = 16.5/6.0 Hz, 1H, 3-H), 2.85 (dd, J = 16.5/6.3 Hz, 1H, 3-H), 3.17 (d, J = 18.4 Hz, 1H, 6-H), 3.37 (d, J = 18.5 Hz, 1H, 6-H), 3.48 (t, J = 6.1 Hz, 1H, 2-H), 3.62 (d, J = 13.4 Hz, 1H, NCH_2Ph), 3.71 (d, J = 13.2 Hz, 1H, NCH_2Ph), 3.79 (s, 6H, $ArOCH_3$, CO_2CH_3), 4.36 (dd, J = 14.4/5.6 Hz, 1H, $NHCH_2Ar$), 4.45 (dd, J = 14.3/6.3 Hz, 1H, $NHCH_2Ar$), 6.84 (d, J = 8.7 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.07–7.23 (m, 4H, 2-H_{PMB}, 6-H_{PMB}, 2-H_{benzyl}, 6-H_{benzyl}) 7.27–7.39 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-H_{benzyl}), 11.90 (s, 1H, OH). A signal for the N–H of the amide cannot be detected. ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 19.1 (1C, C-3), 43.1 (1C, $NHCH_2Ar$), 50.0 (1C, C-6), 51.8 (1C, CO_2CH_3), 55.4 (1C, $ArOCH_3$), 57.0 (1C, C-2), 60.2 (1C, $PhCH_2N$), 95.2 (1C, C-4), 114.3 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 127.1 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 127.8 (1C, C-1$_{PMB}$), 128.75 (1C, C-4$_{phenyl}$), 128.76 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.3 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 137.5 (1C, C-1$_{phenyl}$), 159.2 (1C, C-4$_{PMB}$), 167.6 (1C, CO_2CH_3), 171.1 (1C, C-5), 172.1 (1C, CONH). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3378 (m, v, O–H), 3285 (m, v, N–H, amide), 3062 (w, v, C–H, arom.), 2952 (m, v, C–H, alkyl), 1732 (s, v, C=O, ester), 1666 (s, v, C=O, imide), 817 (m, δ, C–H, para-substituted arom.), 735, 699 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{23}H_{26}N_2O_5H^+$ 411.1914, found 411.1949.

Ethyl 3-(1-benzoyl-4-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl)propanoate (25b)

A solution of the imide **12b** (155 mg, 0.46 mmol) in THF (10 mL) was cooled to −78 °C and a freshly prepared potassium diisopropylamide solution (KDA, 1 M in THF, 0.46 mL, 0.46 mmol) was added. After 30 min ethyl acrylate (100 μL, 0.92 mmol) was added. The reaction mixture was stirred for 2 h at −78 °C, then warmed to rt and stirred for additional 14 h. Then an excess of 1 M HCl solution was added. The solvent of the mixture was removed in vacuum, the residue was dissolved in CH_2Cl_2 and washed with water (4×). The

combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by fc (cyclohexane: ethyl acetate = 3:1, ∅ = 2.5 cm, l = 12.0 cm, V = 20 mL) to obtain a pale yellow oil. (R_f 0.40, cyclohexane:ethyl acetate = 1:1). Yield 30 mg (15%). $C_{24}H_{26}N_2O_6$ (438.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.20 (s, broad, 2H, 3-CH_2), 2.47 (s, broad, 2H, 2-CH_2), 3.79 (s, 3H, OCH_3), 4.04–4.15 (m, 2H, OCH_2CH_3), 4.25 (s, broad, 1H, NCHCO), 4.86 (d, J = 13.7 Hz, 1H, NCH_2Ph), 4.91 (d, J = 13.8 Hz, 1H, NCH_2Ph), 6.83 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.31 (d, J = 8.8 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.35 (dd, J = 8.1/1.4 Hz, 2H, 3-$H_{benzoyl}$, 5-$H_{benzoyl}$), 7.40–7.52 (m, 3H, 2-$H_{benzoyl}$, 4-$H_{benzoyl}$, 6-$H_{benzoyl}$). The signals for the CH_2 protons of the piperazine ring appear as very broad signals and are therefore not given. ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 14.3 (1C, OCH_2CH_3), 29.9 (1C, C-1), 32.1 (1C, C-2), 42.6 (1C, NCH_2Ar), 52.8 (1C, NCH_2CO), 55.4 (1C, OCH_3), 60.6 (1C, NCHCO), 61.1 (1C, OCH_2CH_3), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 127.4 (2C, C-$2_{benzoyl}$, C-$6_{benzoyl}$), 128.5 (1C, C-1_{PMB}), 129.1 (2C, C-$3_{benzoyl}$, C-$5_{benzoyl}$), 130.6 (1C, C-$4_{benzoyl}$), 131.1 (2C, C-2_{PMB}, C-6_{PMB}), 133.4 (1C, C-$1_{benzoyl}$), 159.4 (1C, C-4_{PMB}), 166.5 (1C, $CO_{benzoyl}$), 167.4 (1C, NCH_2CO), 170.6 (1C, NCH_2CO), 177.4 (1C, CH_2CO_2). MS (EI): 438 [M^+, 20], 333 [$(M-C_6H_5CO)^+$, 64], 121 [$H_3COC_6H_4CH_2^+$, 100].

Methyl 1-benzoyl-2-(4-methoxybenzylcarbamoyl)-4-methyl-5-oxopiperidine-4-carboxylate (26b)

A solution of the amide **24b** (312 mg, 0.73 mmol) in THF (20 mL) was cooled to −78 °C and 0.5 M KHMDS-solution in THF (1.47 mL, 0.73 mmol) was added. After 60 min CH_3I (181 μL, 2.57 mmol) was added. The reaction mixture was stirred for 2 h at −78 °C and then warmed to rt over 15 h. The solvent was removed in vacuum and the residue was purified by fc (cyclohexane:ethyl acetate = 8:2, ∅ = 3.0 cm, l = 8.5 cm, V = 20 mL) to obtain a colorless oil. (R_f 0.48, cyclohexane:ethyl acetate = 3:7): Colorless oil. Yield 107 mg (33%). $C_{24}H_{26}N_2O_6$ (438.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 3H, CCH_3), 2.46 (dd, J = 14.7/10.3 Hz, 1H, 3-CH_2), 2.64 (dd, J = 14.7/8.6 Hz, 1H, 3-CH_2), 3.75 (s, 3H, CO_2CH_3), 3.80 (s, 3H, $ArOCH_3$), 4.00 (d, J = 19.0 Hz, 1H, 6-CH_2), 4.33 (d, J = 18.7 Hz, 1H, 6-CH_2), 4.36 (dd, 14.4/5.9 Hz, 1H, $NHCH_2Ar$), 4.44 (dd, J = 14.6/6.0 Hz, 1H, $NHCH_2Ar$), 5.24 (t, J = 9.4 Hz, 1H, 2-CH), 6.86 (d, J = 8.6 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 6.99 (s, broad, 1H, NH), 7.19 (d, J = 8.5 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 7.24–7.28 (m, 2H, 3-$H_{benzoyl}$, 5-$H_{benzoyl}$), 7.38–7.47 (m, 3H, 2-$H_{benzoyl}$, 4-$H_{benzoyl}$, 6-$H_{benzoyl}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 21.2 (1C, CCH_3), 31.2 (1C, C-3), 43.3 (1C, NCH_2Ar), 51.6 (1C, C-5), 53.1 (1C, CO_2CH_3), 53.5 (1C, C-4), 53.7 (1C, C-2), 55.5 (1C, $ArOCH_3$), 114.3 (2C, C-3_{PMB}, C-5_{PMB}), 127.1 (2C, C-$2_{benzoyl}$, C-$6_{benzoyl}$), 128.9 (1C, C-1_{PMB}), 129.0 (2C, C-$3_{benzoyl}$, C-$5_{benzoyl}$), 130.2 (1C, C-$4_{benzoyl}$), 130.8 (2C, C-2_{PMB}, C-6_{PMB}), 133.1 (1C, C-$1_{benzoyl}$), 159.2 (1C, C-4_{PMB}), 169.3 (1C, $CO_{benzoyl}$), 171.5 (1C, CO_2CH_3), 171.8 (1C, CONH), 202.3 (1C, CO_{ketone}). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3309 (m, v, N–H, amide), 3062 (w, v, C–H, arom.), 2936 (m, v, C–H, alkyl), 1726 (s, v, C=O, ester), 1644 (s, v, C=O, amide), 819 (m, δ, C–H, para-substituted arom.), 728, 701 (m, δ, C–H, mono-substituted arom.). MS (EI): 438 [M+, 12], 302 [$(M-H_3COC_6H_4CH_2NH)^+$, 100]. HPLC: purity 82.3%, t_R = 18.65 min.

3-Allyl-4-benzyl-1-(4-methoxybenzyl)piperazine-2,6-dione (27)

A solution of the imide **12c** (1.42 g, 4.38 mmol) in THF (30 mL) was cooled down to −78 °C and a 1 M LiHMDS-solution in THF (4.38 mL, 5.26 mmol) was added. After 30 min, allyl bromide (0.46 mL, 0.40 mmol) was added. The reaction mixture was stirred at −78 °C for 2 h and then warmed up to rt overnight. The reaction was stopped with an excess of saturated $NaHCO_3$ solution. The solvent was removed in vacuum and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 19:1, ∅ = 4.0 cm, l = 9.5 cm, V = 20 mL) to obtain two pale yellow oils. (R_f 0.58, cyclohexane:ethyl acetate = 1:1): Pale yellow oil. Yield 0.97 g (61%). $C_{22}H_{24}N_2O_3$ (364.4). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.62 (m, 2H, $CHCH_2CH=CH_2$), 3.38 (d, 17.9 Hz, 1H, 5-H), 3.54 (t, J = 6.9 Hz, 1H, 3-$H_{piperazine-2,6-dione}$), 3.63 (d, J = 13.1 Hz, 1H, NCH_2Ph), 3.72 (d, J = 13.5 Hz, 1H, NCH_2Ph), 3.72 (d, J = 17.8 Hz, 1H, 5-H), 3.79 (s, 3H, OCH_3), 4.83 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.91 (d, J = 13.7 Hz, 1H, NCH_2Ar), 5.08–5.12 (m, 2H, $CHCH_2CH=CH_2$), 5.70–5.87 (m, 1H, $CHCH_2CH=CH_2$), 6.83 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.18–7.25 (m, 2H, 2-H_{benzyl}, 6-H_{benzyl}), 7.27–7.36 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-H_{benzyl}), 7.33 (d, J = 8.7 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 33.2 (1C, $CHCH_2CH=CH_2$), 41.8 (1C, NCH_2Ar), 51.7 (1C, NCH_2CO), 55.4 (1C, OCH_3), 58.2 (1C, NCH_2Ph), 63.3 (1C, NCHCO), 113.9 (2C, C-3_{PMB}, C-5_{PMB}), 118.1 (1C, $CHCH_2CH=CH_2$), 128.1 (1C, C-1_{PMB}), 128.8 (2C, C-2_{benzyl}, C-6_{benzyl}), 129.1 (2C, C-3_{benzyl}, C-5_{benzyl}), 129.4 (1C, C-4_{benzyl}), 130.6 (2C, C-2_{PMB}, C-6_{PMB}), 133.5 (1C, $CHCH_2CH=CH_2$), 136.4 (1C, C-1_{benzyl}), 159.1 (1C, C-4_{PMB}), 170.1 (1C, NCH_2CO), 172.0 (1C, NCHCO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3064 (w, v, C–H, arom.), 2933 (w, v, C–H, alkyl), 1729 (m, v, C=O, imide), 1677 (s, v, C=O, imide), 821 (m, δ, C–H, para-substituted arom.), 737, 700 (m, δ, C–H, mono-substituted arom.). MS (EI): m/z = 365 [$(M+H)^+$, 100]. HPLC: purity 98.2%, t_R = 22.17 min.

3-Allyl-1-benzyl-4-(4-methoxybenzyl)piperazine-2,6-dione (28)

A solution of imide **17** (22.1 g, 68 mmol, 1 eq) in dry THF (500 mL) was cooled down to −78 °C and a 1 M LiHMDS-solution in THF (72 mL, 72 mmol, 1.05 eq) was added. After 1 h, allyl bromide (7.1 mL, 82 mmol, 1.2 eq) was added. The reaction mixture was stirred at −78 °C for 2 h and then warmed up to rt overnight. The reaction was stopped with an excess of saturated $NaHCO_3$ solution. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution (4×) and the organic solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane:ethyl acetate = 95:5→83:17). (R_f 0.62, cyclohexane:ethyl acetate = 2:1). Pale yellow solid, mp 58–60 °C, yield 16.62 g (67%). $C_{22}H_{24}N_2O_3$ (364.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.56–2.75 (m, 2H, $CHCH_2CH=CH_2$), 3.44 (d, *J* = 17.9 Hz, 1H, NCH_2CO), 3.59 (t, *J* = 6.9 Hz, 1H, $CHCH_2CH=CH_2$), 3.65 (d, *J* = 12.9 Hz, 1H, NCH_2PhOMe), 3.70 (d, *J* = 12.9 Hz, 1H, NCH_2PhOMe), 3.76 (d, *J* = 17.9 Hz, 1H, NCH_2CO), 3.80 (s, 3H, OCH_3), 4.91 (d, *J* = 13.9 Hz, 1H, NCH_2Ph), 4.96 (d, *J* = 13.9 Hz, 1H, NCH_2Ph), 5.09 (d, *J* = 11.5 Hz, 1H, $CHCH_2CH=CH_2$), 5.10 (d, *J* = 15.5 Hz, 1H, $CHCH_2CH=CH_2$), 5.70–5.85 (m, 1H, $CHCH_2CH=CH_2$), 6.85 (d, *J* = 8.6 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.14 (d, *J* = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.24–7.28 (m, 1H, 4-CH_{benzyl}), 7.28–7.33 (m, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}), 7.34–7.39 (m, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 33.1 (1C, $CHCH_2CH=CH_2$), 42.5 (1C, NCH_2Ph), 51.3 (1C, NCH_2CO), 55.5 (1C, OCH_3), 57.7 (1C, NCH_2PhOMe), 62.9 (1C, $CHCH_2CH=CH_2$), 114.3 (2C, C-3_{PMB}, C-5_{PMB}), 118.4 (1C, $CHCH_2CH=CH_2$), 127.2 (1C, C-1_{PMB}), 127.8 (1C, C-4_{benzyl}), 128.6 (2C, C-3_{benzyl}, C-5_{benzyl}), 129.0 (2C, C-2_{benzyl}, C-6_{benzyl}), 130.6 (2C, C-2_{PMB}, C-6_{PMB}), 133.1 (1C, $CHCH_2CH=CH_2$), 136.9 (1C, C-1_{benzyl}), 159.7 (1C, C-4_{PMB}), 169.4 (1C, NCH_2CO), 171.3 (1C, NCHCO). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3066 (C-H_{arom}), 2951 (C-H_{aliph}), 1732 and 1670 (C=O), 721 (C-H_{arom}). MS (APCI): m/z = 365.1882 (calcd. 365.1860 for $C_{22}H_{25}N_2O_3$ $[M+H]^+$). Purity (HPLC): 97.6% (t_R = 23.5 min).

4-Benzyl-3-(3-hydroxypropyl)-1-(4-methoxybenzyl) piperazine-2,6-dione (29)

The allyl compound **27** (0.89 g, 2.45 mmol) was dissolved in THF (100 mL). Under N_2 atmosphere, 9-borabicyclo[3.3.1]nonane (0.5 M

solution, 9.81 mL, 4.91 mmol) was slowly added. The solution was stirred overnight. On the next morning again 9-borabicyclo[3.3.1] nonane (0.5 M solution, 3.68 mL, 1.84 mmol) was slowly added to transform **27** completely. 90 min later the solution was cooled to −25 °C and then NaOH (2 M solution, 3.68 mL, 7.36 mmol) was added while vigorously stirring. After 15 min H_2O_2 (30 % solution, 2.79 mL, 24.5 mmol) was added. The mixture was stirred for further 45 min at −25 °C and subsequently for 60 min at rt. Then it was warmed to 40 °C to destroy the excess of H_2O_2. When the formation of gas while cooling to rt was finished, the solution was poured into H_2O/CH_2Cl_2 and extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 8:2→1:1, ∅ = 3.0 cm, l = 10.0 cm, V = 20 mL) to obtain a colorless oil. (R_f 0.16, cyclohexane:ethyl acetate = 1:1). Yield 0.88 g (94 %). $C_{22}H_{26}N_2O_4$ (382.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.72 (q, J = 13.1/6.6 Hz, 2H, $CH_2CH_2CH_2OH$), 1.91–1.99 (m, 2H, $CH_2CH_2CH_2OH$), 3.44 (d, J = 18.0 Hz, 1H, NCH_2Ph), 3.52 (t, J = 7.0 Hz, 1H, 3-$H_{piperazine\text{-}2,6\text{-}dione}$), 3.53–3.69 (m, 2H, CH_2OH), 3.69 (s, 2H, NCH_2CO_2), 3.75 (d, J = 18.0 Hz, 1H, NCH_2Ph), 3.79 (s, 3H, OCH_3), 4.85 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.90 (d, J = 13.7 Hz, 1H, NCH_2Ar), 6.84 (d, J = 8.8 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.20 (dd, J = 7.7/1.6 Hz, 2H, 2-H_{benzyl}, 6-H_{benzyl}), 7.28–7.36 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-H_{benzyl}), 7.33 (d, J = 8.7 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 26.0 (1C, $CH_2CH_2CH_2OH$), 29.4 (1C, $CH_2CH_2CH_2OH$), 41.7 (1C, NCH_2Ar), 50.9 (1C, NCH_2CO), 55.4 (1C, OCH_3), 58.7 (1C, NCH_2Ph), 62.4 (1C, NCHCO), 63.4 (1C, $CH_2CH_2CH_2OH$), 114.0 (2C, C-3_{PMB}, C-5_{PMB}), 128.2 (1C, C-1_{PMB}), 128.9 (2C, C-2_{benzyl}, C-6_{benzyl}), 129.3 (2C, C-3_{benzyl}, C-5_{benzyl}), 129.3 (1C, C-4_{benzyl}), 130.6 (2C, C-2_{PMB}, C-6_{PMB}), 136.0 (1C, C-1_{benzyl}), 159.2 (1C, C-4_{PMB}), 169.7 (1C, NCH_2CO), 172.7 (1C, NCHCO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3454 (m, v, O–H, alcohol), 3062 (w, v, C–H, arom.), 2931 (m, v, C–H, alkyl), 1727 (s, v, C=O, imide), 1674 (s, v, C=O, imide), 822 (m, δ, C–H, para-substituted arom.), 736, 700 (m, δ, C–H, mono-substituted arom.). MS (EI): m/z (%) = 382 [M^+, 40], 91 [$PhCH_2^+$, 100]. HPLC: purity 99.1 %, t_R = 19.19 min.

1-Benzyl-3-(3-hydroxypropyl)-4-(4-methoxybenzyl) piperazine-2,6-dione (30)

The allyl derivative **28** (9.1 g, 25 mmol, 1 eq) was dissolved in THF (400 mL). Under N_2 atmosphere, a 0.5 M solution of 9-borabicyclo [3,3,1]nonane in THF (0.5 M, 100 mL, 50 mmol) was slowly added. The solution was stirred overnight. After 20 h, again 9-BBN in THF (0.5 M, 38 mL, 19 mmol) was slowly added to transform **28** completely. 90 min later the solution was cooled to −25 °C and then 2 M NaOH (37 mL, 75 mmol) was added while vigorously stirring. After 15 min H_2O_2 (30 %, 26 mL, 250 mmol) was added. The mixture was stirred for further 45 min at −25 °C and subsequently for 60 min at rt. Then $Na_2S_2O_3$ was added to destroy the excess of H_2O_2. After the mixture was stirred for 30 min, most of the solvent was removed in vacuo. The residue was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane:ethyl acetate = 91:9→50:50, ∅ = 5 cm, l = 14 cm, V = 35 mL). (R_f 0.34, cyclohexane:ethyl acetate = 50:50): Colorless oil, yield 5.2 g (55 %). $_{22}H_{26}N_2O_4$ (382.5). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.40–1.60 (m, 2H, $CH_2CH_2CH_2OH$), 1.93–1.70 (m, 2H, $CH_2CH_2CH_2OH$), 3.37 (q, J = 6.1 Hz, 2H, $CH_2CH_2CH_2OH$), 3.43 (d, J = 18.0 Hz, 1H, NCH_2CO), 3.48 (dd, J = 8.9/6.0 Hz, 1H, NCHCO), 3.62 (d, J = 13.1 Hz, 1H, NCH_2PhOMe), 3.67 (d, J = 13.0 Hz, 1H, NCH_2PhOMe), 3.74 (s, 3H, OCH_3), 3.81 (d, J = 17.8 Hz, 1H, NCH_2CO), 4.40 (t, J = 5.2 Hz, 1H, $CH_2CH_2CH_2OH$), 4.80 (d, J = 15.1 Hz, 1H, NCH_2Ph), 4.81 (d, J = 15.1 Hz, 1H, NCH_2Ph), 6.90 (d, J = 8.7 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.15 (d, J = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.21–7.26 (m, 3H, 2-CH_{benzyl}, 4-CH_{benzyl}, 6-CH_{benzyl}), 7.32 (t, J = 7.2 Hz, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 24.6 (1C, $CH_2CH_2CH_2OH$), 28.7 (1C, $CH_2CH_2CH_2OH$), 41.3 (1C, NCH_2Ph), 50.4 (1C, NCH_2CO), 55.0 (1C, OCH_3), 56.5 (1C, NCH_2PhOMe), 60.01 (1C, $CH_2CH_2CH_2OH$), 61.9 (1C, NCHCO), 113.8 (2C, C-3_{PMB}, C-5_{PMB}), 127.1 (1C, C-4_{benzyl}), 127.3 (2C, C-2_{benzyl}, C-6_{benzyl}), 128.3 (2C, C-3_{benzyl}, C-5_{benzyl}), 128.9 (1C, C-1_{PMB}), 130.0 (2C, C-2_{PMB}, C-6_{PMB}), 137.2 (1C, C-1_{benzyl}), 158.7 (1C, C-4_{PMB}), 170.1(1C, NCH_2CO), 172.7 (1C, NCHCO). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3390 (OH), 2935 (C-H_{aliph}), 1728 and 1674 (C=O), 817 and 698 (C-H_{arom}). MS (APCI): m/z = 383.1957 (calcd. 365.1965 for $C_{22}H_{27}N_2O_4$ $[M+H]^+$). Purity (HPLC): 99.7 % (t_R = 19.8 min).

3-[1-Benzyl-4-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl] propanal (31)

The primary alcohol **29** (0.77 g, 2.0 mmol) was dissolved in CH_2Cl_2 (50 mL) and Dess-Martin-Periodinane (1.02 g, 2.4 mmol) was added. The mixture was stirred at rt for 2 h. Then NaOH (2 M solution, 30 mL) was added. When the mixture was clear again the mixture was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 9:1→8:2, ∅ = 3.0 cm, l = 9.5 cm, V = 20 mL) to obtain a colorless oil. (R_f 0.42, cyclohexane:ethyl acetate = 1:1). Yield 0.66 g (87 %). $C_{22}H_{24}N_2O_4$ (380.4). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.02–2.27 (m, 2H, CH_2CH_2CHO), 2.55 (t, J = 6.8 Hz, 2H, CH_2CH_2CHO), 3.38 (d, J = 17.6 Hz, 1H, NCH_2Ph), 3.41 (dd, J = 6.8/2.4 Hz, 1H, 2-H), 3.64 (s, 2H, 5-H), 3.71 (d, J = 18.0 Hz, 1H, NCH_2Ph), 3.79 (s, 3H, OCH_3), 4.84 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.90 (d, J = 13.8 Hz, 1H, NCH_2Ar), 6.84 (d, J = 8.6 Hz, 2H, 3-H_{PMB}, 5-H_{PMB}), 7.17 (d, J = 7.7 Hz, 2H, 2-H_{benzyl}, 6-H_{benzyl}), 7.27–7.37 (m, 3H, 3-H_{benzyl}, 4-H_{benzyl}, 5-$H_{benzyll}$), 7.32 (d, J = 8.7 Hz, 2H, 2-H_{PMB}, 6-H_{PMB}), 9.77 (s, 1H, CHO). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 21.6 (1C, CH_2CH_2CHO), 40.0 (1C, CH_2CH_2CHO), 41.7 (1C, NCH_2Ar), 50.9 (1C, NCH_2CO), 55.3 (1C, OCH_3), 58.8 (1C, NCH_2Ph), 62.4 (1C, NCHCO), 113.9 (2C, C-3_{PMB}, C-5_{PMB}), 128.1 (1C, C-1_{PMB}), 128.8 (2C, C-2_{benzyl}, C-6_{benzyl}), 129.1 (2C, C-$3_{benzyll}$, C-5_{benzyl}), 129.2 (1C, C-4_{benzyl}), 130.5 (2C, C-2_{PMB}, C-6_{PMB}), 136.2 (1C, C-1_{benzyl}), 159.1 (1C, C-4_{PMB}), 169.9 (1C, NCH_2CO), 172.1 (1C, NCHCO), 200.7 (1C, CHO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3067 (w, v, C–H, arom.), 2929 (m, v, C–H, alkyl), 1731 (s, v, C=O, aldehyde), 1677 (s, v, C=O, imide), 819 (m, δ, C–H, para-substituted arom.), 745, 701 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{22}H_{24}N_2O_4H^+$ 381.1809, found 381.1813. HPLC: purity 91.2 %, t_R = 19.87 min.

3-[4-Benzyl-1-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl] propanal (32)

The primary alcohol **30** (5.15 g, 13.5 mmol, 1 eq) was dissolved in CH_2Cl_2 (250 mL) and Dess Martin Periodinane (6.85 g, 16.2 mmol, 1.2 eq) was added. The mixture was stirred at rt for 3 h. Then 2 M NaOH (300 mL) was added. When the mixture became clear again, it was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane: ethyl acetate = 91:9→75:25, ∅ = 4 cm, l = 10 cm, V = 25 mL). (R_f 0.34, cyclohexane:ethyl acetate = 2:1): Colorless oil, yield 4.8 g (94 %). $C_{22}H_{24}N_2O_4$ (380.4). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.96–2.03 (m, 1H, $CHCH_2CH_2CHO$), 2.15–2.22 (m, 1H, $CHCH_2CH_2CHO$), 2.51 (t, J = 6.8 Hz, 2H, $CHCH_2CH_2CHO$), 3.39 (d, J = 17.8 Hz, 1H, NCH_2CO), 3.53 (dd, J = 9.8, 5.2 Hz, 1H, NCHCO), 3.62 (d, J = 13.1 Hz, 1H, NCH_2PhOMe), 3.66 (d, J = 13.1 Hz, 1H, NCH_2PhOMe), 3.74 (s, 3H, OCH_3), 3.84 (d, J = 17.8 Hz, 1H, NCH_2CO), 4.79 (s, 2H, NCH_2Ph), 6.89 (d, J = 8.6 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.13 (d, J = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.22 (d, J = 6.9 Hz, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}), 7.25 (t, J = 7.4 Hz, 1H, 4-CH_{benzyl}), 7.32 (t, J = 7.6 Hz, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}), 9.65–9.63 (t, J = 1.4 Hz, 1H, $CHCH_2CH_2CHO$). The

peak at 2.51 ppm is partly overlapping with the signal for DMSO. ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 21.2 (1C, CHCH$_2$CH$_2$CHO), 39.5 (1C, CHCH$_2$ CH$_2$CHO), 41.3 (1C, NCH$_2$Ph), 49.9 (1C, NCH$_2$CO), 55.0 (1C, OCH$_3$), 56.9(1C, NCH$_2$PhOMe), 61.6 (1C, NCHCO), 113.9 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 127.1 (1C, C-4$_{benzyl}$), 127.4 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 128.4 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 128.7 (1C, C-1$_{PMB}$), 130.1 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 137.1 (1C, C-1$_{benzyl}$), 158.7 (1C, C-4$_{PMB}$), 170.1 (1C, NCH$_2$CO), 172.2(1C, NCHCO), 202.4 (CH=O). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2835 (C-H$_{aliph}$), 1720 and 1674 (C=O), 821and 698 (C-H$_{arom}$). MS (APCI): m/z = 383.1768 (calcd. 381.1809 for $C_{22}H_{25}N_2O_4$ [M + H]$^+$). Purity (HPLC): 98.3 % (t$_R$ = 20.7 min).

(S)-N-{(E)-3-[(S)- and (R)-1-Benzyl-4-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl] propylidene}- 2-methylpropane-2-sulfinamide (33)

The aldehyde **31** (0.16 g, 0.42 mmol) was dissolved in THF (10 mL).(*S*)-2-methylpropane-2-sulfinamide (0.06 g, 0.49 mmol) and titanium(IV) ethanolate (0.20 mL) were added to this mixture, which was stirred for 3 h at rt. Then the mixture was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuum. The residue was purified by fc (cyclohexane: ethyl acetate = 8:2→1:1, ∅ = 3.0 cm, l = 9.5 cm, V = 20 mL) to obtain a colorless oil of both diastereomers. (R$_f$ 0.36, cyclohexane:ethyl acetate = 1 : 1). Yield 0.17 g (82 %). $C_{26}H_{33}N_3O_4S$ (483.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.166 (s, 9×0.5H, C(CH$_3$)$_3$), 1.169 (s, 9× 0.5H, C(CH$_3$)$_3$), 2.04–2.30 (m, 2H, CH$_2$CH$_2$CH=N), 2.50–2.75 (m, 2H, CH$_2$CH$_2$CH=N), 3.42 (d, J = 18.0 Hz, 1H, PhCH$_2$N), 3.50 (dd, J = 8.2/ 6.0 Hz, 0.5H, NCHCO), 3.57 (dd, J = 8.2/6.0 Hz, 0.5H, NCHCO), 3.65 (s, 2H, NCH$_2$CO), 3.72 (d, J = 17.9 Hz, 0.5 H, PhCH$_2$N), 3.73 (d, J = 18.0 Hz, 0.5H, PhCH$_2$N), 3.79 (s, 3H, OCH$_3$), 4.85 (d, J = 13.7 Hz, 0.5H, NCH$_2$Ar), 4.86 (d, J = 13.8 Hz, 0.5H, NCH$_2$Ar), 4.90 (d, J = 13.7 Hz, 1H, NCH$_2$Ar), 6.84 (d, J = 8.7 Hz, 2H, 3-H$_{PMB}$, 5-H$_{PMB}$), 7.15–7.24 (m, 2H, 2-H$_{benzyl}$, 6-H$_{benzyl}$), 7.27–7.35 (m, 5H, 3-H$_{benzyl}$, 4-H$_{benzyl}$, 5-H$_{benzyl}$, 2-H$_{PMB}$, 6-H$_{PMB}$), 8.07 (t, J = 3.8 Hz, 0.5H, NH), 8.10 (t, J = 3.8 Hz, 0.5H, NH). Ratio of diastereomers 1 : 1. ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 22.5 (0.5 C, CH$_2$CH$_2$CH=N), 22.4 (0.5 C, CH$_2$CH$_2$CH=N), 22.5 (9 C, C(CH$_3$)$_3$), 24.3 (0.5 C, CH$_2$CH$_2$CH=N), 24.5 (0.5 C, CH$_2$CH$_2$CH=N), 41.7 (1C, NCH$_2$Ar), 51.1 (0.5 C, NCH$_2$CO), 51.3 (0.5 C, NCH$_2$CO), 55.4 (1C, OCH$_3$), 56.78 (0.5 C, C(CH$_3$)$_3$), 56.82 (0.5 C, C(CH$_3$)$_3$), 58.7 (0.5 C, NCH$_2$Ph), 58.8 (0.5 C, NCH$_2$Ph), 62.4 (0.5 C, NCHCO), 62.6 (0.5 C, NCHCO), 114.0 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 128.2 (1C, C-1$_{PMB}$), 128.9 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 129.1 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.3 (1C, C-4$_{benzyl}$), 130.5 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 136.3 (1C, C-1$_{benzyl}$), 159.2 (1C, C-4$_{PMB}$), 168.1 (1C, C=N), 169.9 (1C, NCH$_2$CO), 172.2 (2C, NCHCO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3063 (w, v, C–H, arom.), 2928 (m, v, C–H, alkyl), 1724 (m, v, C=O, imide), 1678 (s, v, C=O, imide), 822 (m, δ, C–H, para-substituted arom.), 745, 702 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{26}H_{33}N_3O_4H^+$ 484.2265, found 484.2347. HPLC: purity 79.2 %, t$_R$ = 21.66 min.

(S)-N-{(E)-3-[(S)- and (R)-4-Benzyl-1-(4-methoxybenzyl)-3,5-dioxopiperazin-2-yl] propylidene}-2-methylpropane-2-sulfinamide (34)

The aldehyde **32** (3.13 g, 8.2 mmol, 1.0 eq) was dissolved in THF (200 mL). (*S*)-2-Methylpropane-2-sulfinamide (1.00 g, 8.2 mmol, 1.0 eq) and titanium(IV) ethanolate (4 mL) were added to this mixture, which was stirred for 4 h at rt. Then the mixture was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 for four times. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (cyclohexane:ethyl acetate = 90 : 10→67 : 33, ∅ = 4 cm, l = 16 cm, V = 35 mL). (R$_f$ 0.19, cyclohexane:ethyl acetate = 67 : 33). Colorless oil of both diastereomers, yield 3.6 g (90 %). $C_{26}H_{33}N_3O_4S$ (483.6). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.07 (s, 9×0.5H, (CH$_3$)$_3$C),1.08 (s, 9×0.5H, (CH$_3$)$_3$C), 2.01–2.10 (m, 1H, CHCH$_2$CH$_2$CH=N), 2.17–2.26 (m, 1H, CHCH$_2$CH$_2$CH=N), 2.58–2.65 (m, 2H, CHCH$_2$CH$_2$CH=N), 3.44 (d, J = 17.7 Hz, 1H, NCH$_2$CO), 3.55 (dd, J = 9.6/5.3 Hz, 0.5H, NCHCO), 3.60–3.65 (m, 1.5H, NCHCO (0.5H), NCH$_2$PhOMe (1H)), 3.68 (d, J = 13.0 Hz, 0.5H, NCH$_2$PhOMe), 3.69 (d, J = 13.1 Hz, 0.5H, NCH$_2$PhOMe), 3.735 (s, 3×0.5H, OCH$_3$), 3.737 (s, 3× 0.5H, OCH$_3$), 3.898 (d, J = 17.8 Hz, 0.5H, NCH$_2$CO), 3.901 (d, J = 17.8 Hz, 0.5H, NCH$_2$CO), 4.80 (s, 2H, NCH$_2$Ph), 6.88 (d, J = 8.7 Hz, 2× 0.5H, 3-CH$_{PMB}$, 5-CH$_{PMB}$), 6.89 (d, J = 8.7 Hz, 2×0.5H, 3-CH$_{PMB}$, 5-CH$_{PMB}$), 7.14 (d, J = 8.6 Hz, 2×0.5H, 2-CH$_{PMB}$, 6-CH$_{PMB}$), 7.15 (d, J = 8.5 Hz, 2×0.5H, 2-CH$_{PMB}$, 6-CH$_{PMB}$), 7.20–7.26 (m, 3H, 2-CH$_{benzyl}$, 4-CH$_{benzyl}$, 6-CH$_{benzyl}$), 7.32 (t, J = 7.4 Hz, 2H, 3-CH$_{benzyl}$, 5-CH$_{benzyl}$), 7.96 (t, J = 3.9 Hz, 0.5H, CHCH$_2$CH$_2$CH=N), 7.98 (t, J = 3.9 Hz, 0.5H, CHCH$_2$CH$_2$CH=N). Ratio of diastereomers 1 : 1. ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) = 21.8 (3C, (CH$_3$)$_3$C), 23.7/23.8 (1C, CHCH$_2$CH$_2$CH=N), 31.75/31.76 (1C, CHCH$_2$CH$_2$CH=N), 41.3 (1C, NCH$_2$Ph), 50.27/50.31 (1C, NCH$_2$CO), 55.0 (1C, OCH$_3$), 55.9/56.0 (1C, (CH$_3$)$_3$C), 56.8 /56.9 (1C, NCH$_2$PhOMe), 61.3/61.5 (1C, NCHCO), 113.8/ 113.9 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 127.1 (1C, C-4$_{benzyl}$), 127.33/127.35 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 128.4 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 128.7 (1C, C-1$_{PMB}$), 129.97/130.01 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 137.1 (1C, C-1$_{benzyl}$), 158.7 (1C, C-4$_{PMB}$), 169.10 /169.14 (1C, CHCH$_2$CH$_2$CH=N), 170.05/170.07 (1C, NCH$_2$CO), 172.28 /172.31 (1C, NCHCO). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2958 (C-H$_{aliph}$), 1728, 1674 and 1620 (C=O), 1342 (S=O), 817and 698 (C-H$_{arom}$). MS (APCI): m/z = 484.2347 (calcd. 484.2265 for $C_{26}H_{34}N_3O_4S$ [M + H]$^+$). Purity (HPLC): 83.2 % (t$_R$ = 22.9 min).

9-Benzyl-3-(4-methoxybenzyl)-2,4-dioxo-3,9-diazabicyclo[3.3.1] nonan- 6-yl]-2-methylpropane-2-sulfinamide (35)

A solution of (*S*)-sulfinylimine **33** (ratio of diastereomers 1 : 1, 589 mg, 1.22 mmol) in THF (30 mL) was cooled under N_2 atmosphere to −78 °C. Then LiHMDS (1 M solution in THF, 1.82 mL, 1.82 mmol) was added. After 3 h, the mixture was warmed to rt, poured into CH_2Cl_2/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 19:1→1:1→100 % ethyl acetate, ∅ = 3.0 cm, l = 9.5 cm, V = 20 mL) to obtain two pale oils of the main diastereomer of **35** and a mixture of the other three diastereomers of **35**. Total yield 386 mg (66 %). Main stereoisomer **35 a** (R$_f$ 0.32, cyclohexane:ethyl acetate = 1 : 1): Pale yellow oil. Yield 127 mg (22 %). $C_{26}H_{33}N_3O_4S$ (483.6). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.24 (s, 9H, C(CH$_3$)$_3$), 1.39–1.48 (m, 1H, 7-CH$_2$),1.63–1.68 (m, 1H, 7-CH$_2$), 1.70–1.78 (m, 1H, 8-CH$_2$), 1.89–1.99 (m, 1H, 8-CH$_2$), 3.52–3.54 (m, 1H, 1-CH), 3.53 (d, J = 13.0 Hz, 1H, NCH$_2$Ph), 3.69 (d, J = 13.1 Hz, 1H, NCH$_2$Ph), 3.71–3.75 (m, 1H, 6-CH), 3.79 (s, 3H, OCH$_3$), 3.93 (m, 1H, 5-CH), 4.44 (d, J = 9.1 Hz, 1H, NH), 4.88 (s, 2H, NCH$_2$Ar), 6.83 (d, J = 8.8 Hz, 2H, 3-H$_{PMB}$, 5-H$_{PMB}$), 7.13–7.20 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.27–7.34 (m, 3H, 3-H$_{phenyl}$, 4-H$_{phenyl}$, 5-H$_{phenyl}$), 7.36 (d, J = 8.7 Hz, 2H, 2-H$_{PMB}$, 6-H$_{PMB}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 22.7 (3C, C(CH$_3$)$_3$), 23.0 (1C, C-8), 25.3 (1C, C-7), 41.6 (1C, NCH$_2$Ar), 51.9 (1C, C-6), 55.4 (1C, OCH$_3$), 56.0 (1C, C(CH$_3$)$_3$), 58.3 (1C, C-1), 59.4 (1C, PhCH$_2$N), 65.9 (1C, C-5), 114.0 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 128.2 (1C, C-1$_{PMB}$), 128.9 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 129.2 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.3 (1C, C-4$_{benzyl}$), 130.8 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 136.2 (1C, C-1$_{benzyl}$), 159.2 (1C, C-4$_{PMB}$), 170.5 (1C, NCH$_2$CO), 172.1 (1C, NCHCO). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3267 (w, v, N–H, sulfinamide), 2932 (m, v, C–H, alkyl), 1728 (m, v, C=O, imide), 1674 (s, v, C=O, imide), 818 (m, δ, C–H, para-substituted arom.), 733, 698 (m, δ, C–H, mono-substituted arom.). MS (APCI): calcd. for $C_{26}H_{33}N_3O_4SH^+$ 484.2265, found 484.2282. HPLC: purity 97.9 %, t$_R$ = 21.74 min. specific rotation: $[\alpha]^{20}_D$ = +53.0 (c = 0.80; CH_2Cl_2).

N-*[-3-Benzyl-9-(4-methoxybenzyl)-2,4-dioxo-3,9-diazabicyclo [3.3.1]nonan-6-yl]-2-methylpropane-2-sulfinamide (36)*

A solution of the (*S*)-sulfinylimine **34** (ratio of diastereomers 1:1, 3.37 g, 7.0 mmol, 1 eq) in THF (150 mL) was cooled down to −78 °C under N_2 atmosphere. Then LiHMDS (1 M solution in THF, 10.4 mL, 10.4 mmol, 1.5 eq) was added dropwise. After 3 h, the mixture was warmed to rt. Saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by fc (cyclohexane : ethyl acetate = 90:10→50:50, ∅ = 4 cm, l = 15 cm, V = 35 mL) to obtain a pale yellow oil of the main diastereomer of **36** and a mixture of the other three diastereomers of **36**. Total yield 2.34 g (69%). Main stereoisomer **36a** (R_f 0.47, cyclohexane:ethyl acetate = 50:50): pale yellow oil, yield 0.91 g (27%). $C_{26}H_{33}N_3O_4S$ (483.6). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.14 (s, 9H, C(CH_3)$_3$), 1.47 (tt, *J* = 14.0/4.5 Hz, 1H, 7-CH_2), 1.57–1.71 (m, 2H, 7-CH_2, 8-CH_2), 2.07–2.20 (m, 1H, 8-CH_2), 3.50–3.57 (m, 2H, 1-CH, 6-CH), 3.62 (s, 2H, NCH_2PhOMe), 3.73 (s, 4H, 5-CH, OCH_3), 4.85 (s, 2H, NCH_2Ph), 5.12 (d, *J* = 7.6 Hz, 1H, NH), 6.87 (d, *J* = 8.6 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.13 (d, *J* = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.24–7.31 (m, 3H, 2-CH_{benzyl}, 4-CH_{benzyl}, 6-CH_{benzyl}), 7.38–7.32 (m, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) = 22.0 (1C, C-8), 22.4 (3C, C(*C*H_3)$_3$), 24.3 (1C, C-7), 41.6 (1C, NCH_2Ph), 49.7 (1C, C-6), 55.0 (1C, OCH_3), 55.3 (1C, *C*(CH$_3$)$_3$), 57.5 (1C, NCH_2PhOMe)„ 58.2 (1C, C-1), 64.3 (1C, C-5), 113.8 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 127.3 (1C, C-4$_{benzyl}$), 128.1 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 128.3 (1C, C-1$_{PMB}$), 128.4 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.8 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 137.1 (1C, C-1$_{benzyl}$), 158.7 (1C, C-4$_{PMB}$), 170.7 (1C, C-4), 171.9 (1C, C-2). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 3275 (N–H), 2951 (C-H$_{aliph}$), 1732 and 1678 (C=O), 1346 and 1330 (S=O), 806 and 698 (C-H$_{arom}$). MS (APCI): m/z = 484.2275 (calcd. 484.2265 for $C_{26}H_{34}N_3O_4S$ $[M+H]^+$). Purity (HPLC): 98.3% (t_R = 22.8 min). Specific rotation: $[\alpha]^{20}_D = +57.1$ (c = 0.18; CH_3CN).

*(1*RS*,5*SR*,6*RS*)-9-Benzyl-6-hydroxy-3-(4-methoxybenzyl)-3,9-diazabicyclo[3.3.1]no-nane-2,4-dione (37)*

A solution of the aldehyde **31** (100 mg, 0.26 mmol) in THF (10 mL) was cooled under N_2 atmosphere to −78 °C. Then LiHMDS (1 M solution in THF, 0.39 mL, 0.39 mmol) was added. After 30 min at −78 °C, the mixture was warmed to rt and stirred at rt for 3 h. The mixture was poured into CH_2Cl_2/saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was purified by fc (cyclohexane:ethyl acetate = 9:1, ∅ = 2.0 cm, l = 9.5 cm, V = 20 mL) to obtain a pale yellow oil. (R_f 0.26, cyclohexane: ethyl acetate = 1:1). Yield 10 mg (10%). $C_{22}H_{24}N_2O_4$ (380.4). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.07–1.22 (m, 1H, 8-CH_2), 1.92–1.99 (m, 2H, 7-CH_2), 2.00–2.08 (m, 1H, 8-CH_2), 3.53 (t, J = 2.8 Hz, 1H, 1-CH), 3.61 (d, J = 13.2 Hz, 1H, NCH_2Ph), 3.63–3.70 (m, 1H, 5-CH), 3.67 (d, J = 13.0 Hz, 1H, NCH_2Ph), 3.79 (s, 3H, OCH_3), 4.00 (dt, J = 14.2/4.0 Hz, 1H, 6-CH), 4.93 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.97 (d, J = 13.7 Hz, 1H, NCH_2Ar), 6.85 (d, J = 8.8 Hz, 2H, 3-H$_{PMB}$, 5-H$_{PMB}$), 7.13–7.17 (m, 2H, 2-H$_{benzyl}$, 6-H$_{benzyl}$), 7.27–7.35 (m, 3H, 3-H$_{benzyl}$, 4-H$_{benzyl}$, 5-H$_{benzyl}$), 7.38 (d, J = 8.7 Hz, 2H, 2-H$_{PMB}$, 6-H$_{PMB}$). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 26.9 (1C, C-8), 27.8 (1C, C-7), 41.6 (1C, NCH_2Ar), 55.4 (1C, OCH_3), 59.0 (1C, C-1), 59.1 (1C, PhCH_2N), 64.6 (1C, C-5), 68.1 (1C, 6-C), 114.0 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 128.1 (1C, C-1$_{PMB}$), 128.8 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 128.9 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.5 (1C, C-4$_{benzyl}$), 130.8 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 136.2 (1C, C-1$_{benzyl}$), 159.2 (1C, C-4$_{PMB}$), 171.1 (1C, NCH_2CO), 172.5 (1C, NCH*C*O). FT-IR: $\tilde{\nu}$ (cm^{-1}) = 3434 (m, v, O–H, alcohol), 3062 (w, v, C–H, arom.), 2932 (m, v, C–H, alkyl), 1726 (m, v, C=O, imide), 1671 (s, v, C=O, imide), 823 (m, δ, C–H, para-substituted arom.), 730, 698 (m, δ, C–H, mono-substituted arom.). MS (EI): 380 [M^+, 7], 121 [$H_3COC_6H_4CH_2^+$, 88], 91 [$C_6H_5CH_2^+$, 100].

*(1*RS*,5*SR*,6*SR*)-3-Benzyl-8-(4-methoxybenzyl)-6-vinyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (39)*

A solution of **17** (120 mg, 0.37 mmol) in dry THF (4 mL) was cooled down to −78 °C and LiHMDS (0.44 mL, 0.44 mmol) was added slowly. After 90 min, *trans*-1,4-dibromobut-2-ene (**38**, 95 mg, 0.44 mmol) was added. The reaction was stirred at −78 °C for 90 min and then warmed up to rt for 16 h. Another portion of LiHMDS (0.44 mL, 0.44 mmol) was added at −78 °C and the mixture was stirred for another 2 h and then warmed up to room temperature overnight. Saturated $NaHCO_3$ solution was added to the reaction mixture, which was then extracted with CH_2Cl_2 (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (cyclohexane: ethyl acetate = 98:2→94:6, ∅ = 1.5 cm, l = 20 cm, V = 10 mL). R_f 0.24, cyclohexane:ethyl acetate = 80:20. Pale yellow oil, yield 30 mg (22%). $C_{23}H_{24}N_2O_3$ (376.5). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.73 (dd, *J* = 13.7/5.5 Hz, 1H, 7-CH_2), 2.64 (ddd, *J* = 13.7/10.6/7.8 Hz, 1H, 7-CH_2), 3.30–3.39 (m, 1H, 6-CH), 3.63 (d, *J* = 12.7 Hz, 1H, NCH_2PhOMe), 3.66 (d, J = 12.1 Hz, 1H, NCH_2PhOMe), 3.79 (s, 3H, OCH_3), 3.82 (d, *J* = 6.9 Hz, 1H, 5-CH), 3.85 (d, *J* = 7.7 Hz, 1H, 1-CH), 4.91 (s, 2H, NCH_2Ph), 5.02 (dt, *J* = 10.4/1.3 Hz, 1H, CH=CH_2), 5.05 (dt, *J* = 16.9/1.2 Hz, 1H, CH=CH_2), 5.41 (ddd, J = 17.1/10.3/7.7 Hz, 1H, C*H*=CH$_2$), 6.83 (d, *J* = 8.7 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.06 (d, *J* = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.26–7.29 (m, 1H, 4-CH_{benzyl}), 7.32 (t, J = 7.3 Hz, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}), 7.44 (d, J = 6.9 Hz, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 31.9 (1C, C-7), 41.8 (1C, NCH_2Ph), 43.2 (1C, C-6), 52.8 (1C, NCH_2PhOMe), 55.4 (1C, OCH_3), 63.7 (1C, C-1), 68.1 (1C, C-5), 114.2 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 118.4 (1C, CH=CH_2), 127.6 (1C, C-1$_{PMB}$), 128.0 (1C, C-4$_{benzyl}$), 128.6 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.6 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 130.4 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 134.3 (1C, *C*H=CH$_2$), 136.9 (1C, C-1$_{benzyl}$), 159.6 (1C, C-4$_{PMB}$), 170.4 (1C, C-4), 172.9 (1C, C-2). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2959 (C-H$_{aliph}$), 1732 and 1678 (C=O), 822 and 698 (C-H$_{arom}$). MS (APCI): m/z = 377.1869 (calcd. 377.1860 for $C_{23}H_{25}N_2O_3$ $[M+H]^+$). Purity (HPLC): 98.7% (t_R = 23.3 min).

3-Benzyl-9-(4-methoxybenzyl)-7-methylene-3,9-diazabicyclo [3.3.1]nonane-2,4-dione (41)

A solution of **17** (214 mg, 0.66 mmol) in dry THF (5 mL) was cooled down to −78 °C and LiHMDS (0.73 mL, 0.73 mmol) was added slowly. After 30 min, 3-bromo-2-bromomethylprop-1-ene (**40b**, 0.83 µL, 0.73 mmol) was added. The reaction was stirred at −78 °C for 90 min and then LiHMDS (0.73 mL, 0.73 mmol) was added again. The mixture was stirred at −78 °C for another 2 h and then warmed up to room temperature overnight. Saturated $NaHCO_3$ solution was added and THF was removed almost completely in vacuo. The residue was extracted with ethyl acetate (4×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (cyclohexane: ethyl acetate = 20:1, ∅ = 1 cm, l = 12 cm, V = 8 mL). R_f 0.62, cyclohexane:ethyl acetate = 2:1. Pale yellow solid, mp 58–60 °C, yield 129 mg (52%). $C_{23}H_{24}N_2O_3$ (376.5). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.48 (dm, *J* = 13.8 Hz, 2H, 6-CH_2, 8-CH_2), 2.69 (dm, *J* = 12.0 Hz, 2H, 6-CH_2, 8-CH_2), 3.65 (s, 2H, NCH_2PhOMe), 3.68–3.71 (m, 2H, 1-CH, 5-CH), 3.80 (s, 3H, OCH_3), 4.70 (t, *J* = 2.0 Hz, 2H, C=CH_2), 4.93 (s, 2H, NCH_2Ph), 6.84 (d, *J* = 8.6 Hz, 2H, 3-CH_{PMB}, 5-CH_{PMB}), 7.11 (d, *J* = 8.6 Hz, 2H, 2-CH_{PMB}, 6-CH_{PMB}), 7.24 (t, *J* = 7.3 Hz, 1H, 4-CH_{benzyl}), 7.29 (t, J = 7.3 Hz, 2H, 3-CH_{benzyl}, 5-CH_{benzyl}), 7.37 (d, J = 6.9 Hz, 2H, 2-CH_{benzyl}, 6-CH_{benzyl}). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 36.7 (2C, C-6, C-8), 42.1 (1C, NCH_2Ph), 55.4 (1C, OCH_3), 58.3 (1C, NCH_2PhOMe), 60.3 (2C, C-1, C-5), 114.2 (2C, C-3$_{PMB}$, C-5$_{PMB}$), 114.6 (1C, C=CH_2), 127.7 (2C, C-1$_{PMB}$, C-4$_{benzyl}$), 128.4 (2C, C-3$_{benzyl}$, C-5$_{benzyl}$), 129.2 (2C, C-2$_{benzyl}$, C-6$_{benzyl}$), 130.4 (2C, C-2$_{PMB}$, C-6$_{PMB}$), 137.1 (1C, C-1$_{benzyl}$), 137.7 (1C, *C*=CH$_2$), 159.6 (1C, C-4$_{PMB}$), 172.2 (2C, 2×

C=O). IR (neat): $\tilde{\nu}$ (cm^{-1}) = 2959 and 2936 (C-H_{aliph}), 1670 (C=O), 733 and 694 (C-H_{arom}). MS (APCI): m/z = 377.1852 (calcd. 377.1860 for $C_{23}H_{25}N_2O_3$ $[M+H]^+$). Purity (HPLC): 97.9% (t_R = 22.4 min).

Supporting Information

Supporting Information contains the methylation of monoalkylated piperazinedione **18b** and all ^1H and ^{13}C NMR spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: bridged piperazines · rigid scaffolds · Dieckmann cyclization · aldol reactions · medicinal chemistry

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