Application of the 'Direct Amide Cyclization' to Peptides Containing an Anthranilic Acid Residue

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

The 2,2-disubstituted 2*H*-azirin-3-amines **7a**–**7c** were used as amino acid synthons to prepare linear peptides derived from anthranilic acid. These linear peptides, which contain α,α-disubstituted α-amino acids, were synthesized by using the 'azirine/oxazolone method' (*Schemes 2–5*) and were subjected to the acid-catalyzed 'direct amide cyclization'. Unfortunately, all attempts to isolate the ten-membered cyclotripeptides, by starting with different precursors, failed. Instead of the expected cyclotripeptides, the corresponding 1,3a,7-triazabenz[*e*]azulene-3,6-diones **12** and **17** (*Schemes 2* and *3*) were obtained in up to 44% yield. Most likely, these products were formed by a transannular ring contraction of the desired products, followed by dehydration. In the case of the linear precursor **24**, the 20-membered cyclodimer **25** was formed in 50% yield, together with traces of the 1,3a,7-triazabenz[*e*]azulene-3,6-dione **27** and the completely unexpected quinazolinone **26** (*Scheme 5*). In the cases of the linear precursors **30** and **34**, no ring closure was observed under the conditions of the 'direct amide cyclization', which indicates the limitations of this method.

Introduction. – Non-proteinogenic amino acids and their peptides are of significant interest with respect to their biological activity. For example, α,α-disubstituted α-amino acids considerably restrict the conformational freedom of peptides because of the presence of the tetrasubstituted C(α)-atom. Therefore, the incorporation of one or several α,α-disubstituted α-amino acids is a common method for introducing rigidity into the peptide backbone. One procedure for the introduction of such amino acids into peptides is the so-called 'azirine/oxazolone method', in which 2,2-disubstituted 2*H*-azirin-3-amines are used as amino acid synthons [1]. This strategy has been employed widely in the synthesis of linear oligopeptides [2–9], peptaibols [10–13], and endothiopeptides [14][15]. A further application is the synthesis of conformationally restricted cyclic depsipeptides [16–20] and cyclic peptides [17][21–24] by using a combination of the 'azirine/oxazolone method' and the so-called 'direct amide cyclization'. The concept of this cyclization method is outlined in *Scheme 1:* condensation of a carboxylic acid, bearing a nucleophilic group, with a 2*H*-azirin-3-amine **1** leads to the corresponding diamide of type **2**, which, on treatment with dry HCl gas, affords the corresponding 1,3-oxazol-5(4*H*)-one **3**. Under the acidic conditions, this intermediate can be attacked by an external nucleophile to produce **4** *via* ring opening. In the absence of an external nucleophile, suitable substrates are able to undergo an intramolecular nucleophilic attack and yield the ring-enlarged product of type **5** [17].

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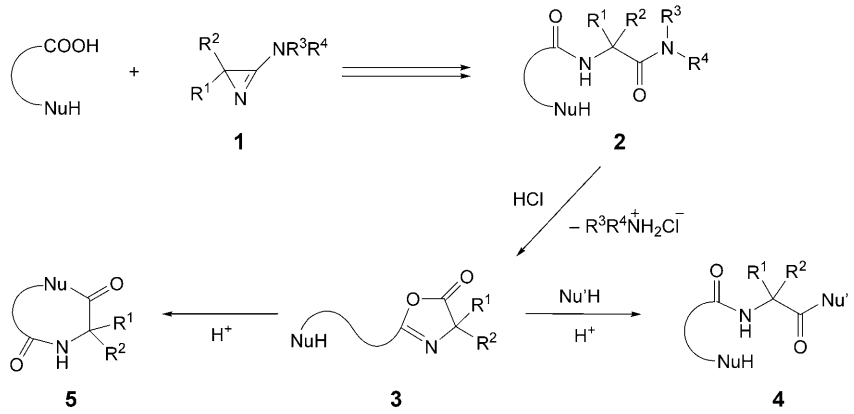
Scheme 1



Natural cyclic peptides have been studied extensively in recent years, and the synthesis of cyclopeptide analogues continues to be of great interest [25][26]. Stabilization of specific backbone conformations in such peptides by the incorporation of fragments with restricted molecular freedom has become a focus of increasing attention [27]. Conformationally restricted structures can be obtained by using nonpeptidal fragments of low conformational flexibility [28]. For example, the presence of an *ortho*-aminobenzoyl (anthraniloyl) moiety should decrease the molecular flexibility as a result of the rigid aromatic skeleton. A few examples of cyclic peptides with an anthranilic acid (Ant) residue are known [29][30]. Two such peptides, which contain 5-methylanthranilic acid (MeAnt), *i.e.*, *cyclo*(Phe-MeAnt-Gly_n) ($n=4$ and 6, resp.) have been synthesized to study their hydrolysis with α-chymotrypsin [30]. With the aim of investigating the influence of the nonpeptidal amino acids, two cyclic peptides, *cyclo*(Ant-$Gly)_2$ and *cyclo*(Ant-$Gly)_3$, have been prepared [29]. The synthesis and conformation of ten-membered cyclotripeptides containing a β-amino acid have also been studied extensively [31–35]. They have been obtained by incorporating the β-amino acid residue into a diketopiperazine *via* ring enlargement [35][36] or by cyclization of the linear precursor *via* the 'active ester method' [31][34][37]. β-Alanine and anthranilic acid derivatives have been used as the N-terminal residue, since they represent two extreme cases of high and low conformational flexibility. Natural peptides containing an anthranilic acid, the so-called 'cycloaspeptides', are very rare, although some, such as actinomycin D from *Streptomyces* sp. [38], viridic acid from *Penicillium viridicatum* [39], and cycloaspeptides A–C from the fungus *Aspergillus* sp. NE-45 [40] were reported some years ago. Two new linear peptides with a C-terminal anthranilic acid residue, dictyonamides A and B, have been isolated from a marine-derived fungus recently [41].

As part of our continuing investigation of the synthesis and the conformation of cyclic peptides and depsipeptides with conformationally restricted amino or hydroxy acids [19–24], we started to examine such peptides containing anthranilic acid and its derivatives [18][42]. As the combination of the 'azirine/oxazolone method' with the 'direct amide cyclization' proved to be an excellent preparative route to cyclic

depsipeptides and peptides, these methods should be used for the synthesis of analogues of 'cycloaspeptides'. Here, we present the results concerning the 'direct amide cyclization' of linear peptide precursors containing a N-terminal anthranilic acid.

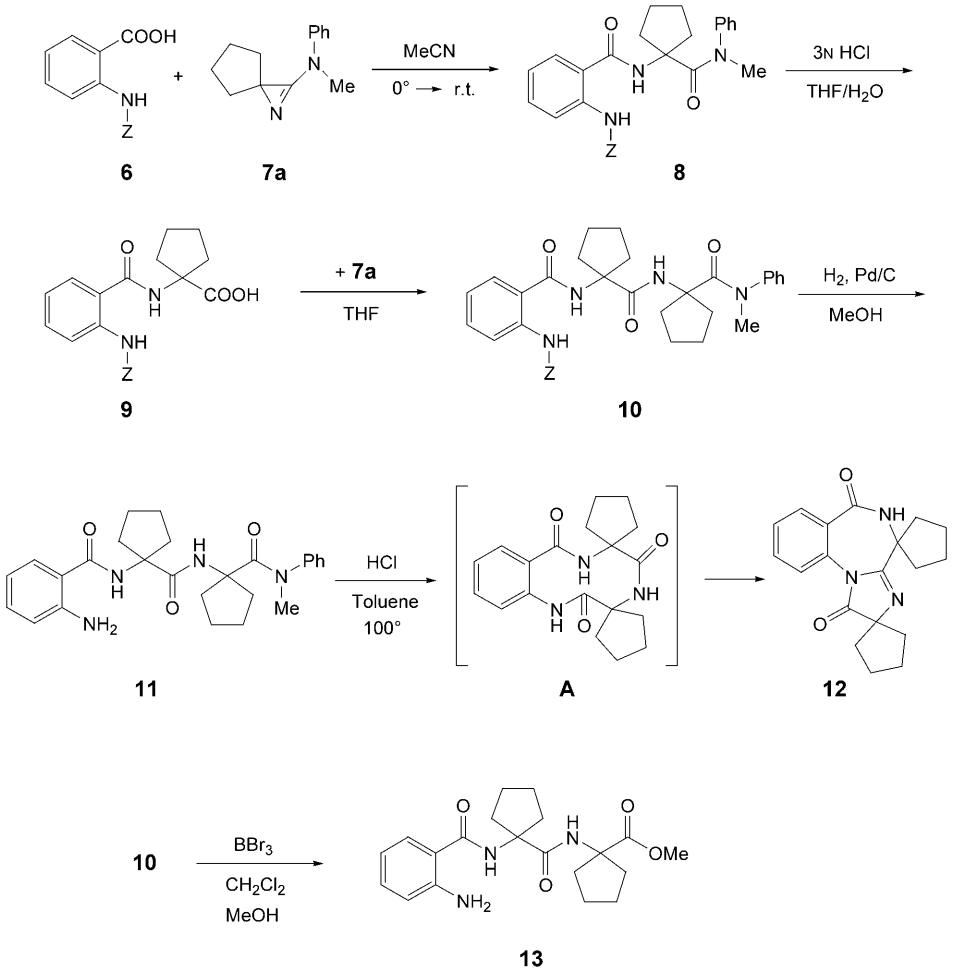
Results and Discussion. – The linear peptide precursors were designed with 2-aminobenzoic acid (anthranilic acid, Ant) as the N-terminus of the chain. The peptides were prepared *via* the so-called 'azirine/oxazolone method' [1] by using the 2*H*-azirin-3-amines **7a**–**c**. In contrast to the classical methods for the synthesis of peptides containing α,α-disubstituted α-amino acids [43][44], the 'azirine/oxazolone method' does not require additional reagents, and the coupling reaction is performed under mild conditions, where no side-products are formed. This simplifies the purification of the products considerably.

The linear tripeptide **11** was prepared straightforwardly by the standard procedure according to *Scheme 2*. The reaction of Z-protected anthranilic acid (**6**) [18] with **7a** in dry MeCN at room temperature led to the corresponding diamide **8** in 87% yield. The selective hydrolysis of the C-terminal amide group was performed under standard conditions with 3N HCl/THF 1:1 at room temperature [3] and yielded the corresponding carboxylic acid **9** in nearly quantitative yield. The latter compound was coupled with another unit of **7a** to give the N-protected tripeptide **10** in 74% yield. Deprotection of the amino group by hydrogenolysis (Pd/C in MeOH) led to compound **11**, which was subjected to the reaction conditions of the 'direct amide cyclization': a weak stream of dry HCl gas was bubbled through a suspension of the linear peptide **11** in toluene at 100°. Toluene was chosen as the solvent because of the low solubility of **11**, which assured a low concentration of the oxazolone intermediate **3** formed in the course of the reaction (*Scheme 1*). This high dilution of the reactive intermediate provides the optimum condition for the intramolecular ring closure, *i.e.*, the formation of the cyclic monomer is favored over the formation of oligomers [19]. The reaction of **11** with dry HCl gas was complete within 10 min and provided the heterobicyclic compound **12**, but not the desired 10-membered cyclopeptide **A** (*Scheme 2*). After chromatographic purification, **12** was isolated in 44% yield. Its formation obviously proceeds *via* the desired **A** as an intermediate, followed by a transannular ring contraction and the elimination of H_2O. Analogous transannular cyclizations of anthranilic acid derivatives have been observed previously [18][31][43]. The formation of **12** confirms the tendency of peptides, which contain the rigid anthranilic acid residue, to undergo transannular reactions. In the ten-membered rings, this contraction is favored due to the flattening effect of the fused benzene ring. Compound **12** was isolated as a colorless solid and its structure was established by NMR, IR, and mass spectra, and, finally, single crystals of **12** were grown successfully from CH_2Cl_2/Et_2O, and its structure was established by X-ray crystallography (*Fig. 1*).

The NH group of molecule **12** forms an intermolecular H-bond with the amide O(3)-atom of a neighboring molecule. This interaction links the molecules into dimeric units, which are situated about a center of inversion and have a graph-set motif [46] of $R_2^2(8)$.

With the aim of exploiting a different pathway for the preparation of the ten-membered cyclopeptide **A**, we synthesized the tripeptide ester **13** by treatment of **10** with BBr_3 in CH_2Cl_2 and addition of MeOH [47] (*Scheme 2*). Then, **13** was heated in

Scheme 2



toluene according to the cyclization conditions reported by *Aguilar* and *Meyers* [48], but even after heating the solution under reflux for 2 days, only the starting material was recovered.

As a second example, we prepared the linear tripeptide **16** as a precursor of a ten-membered cyclic peptide containing the α,α-disubstituted α-amino acid 1-amino-cyclopentane carboxylic acid (cPent) and glycine (*Scheme 3*). The presence of the latter should increase the flexibility of the peptide chain. The coupling of **6** with commercially available methyl glycinate hydrochloride was performed by using the coupling reagent *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) in MeCN in the presence of 1-hydroxybenzotriazole (HOBt) and EtN(i-Pr)$_2$. After chromatographic workup, the dipeptide **14** was obtained in 88% yield. The deprotection of both the carboxy and amino group in a one-pot reaction was carried out

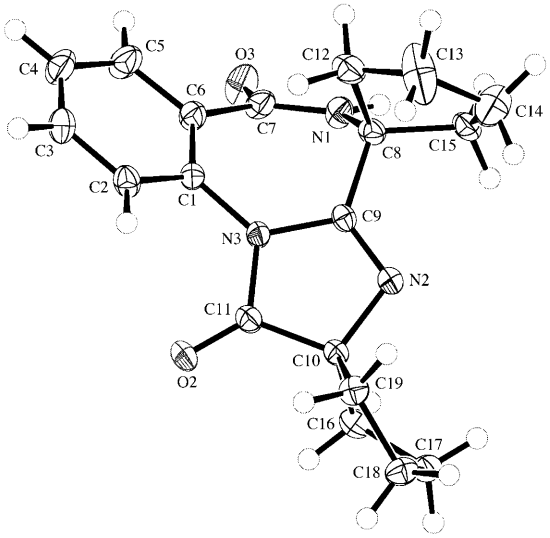
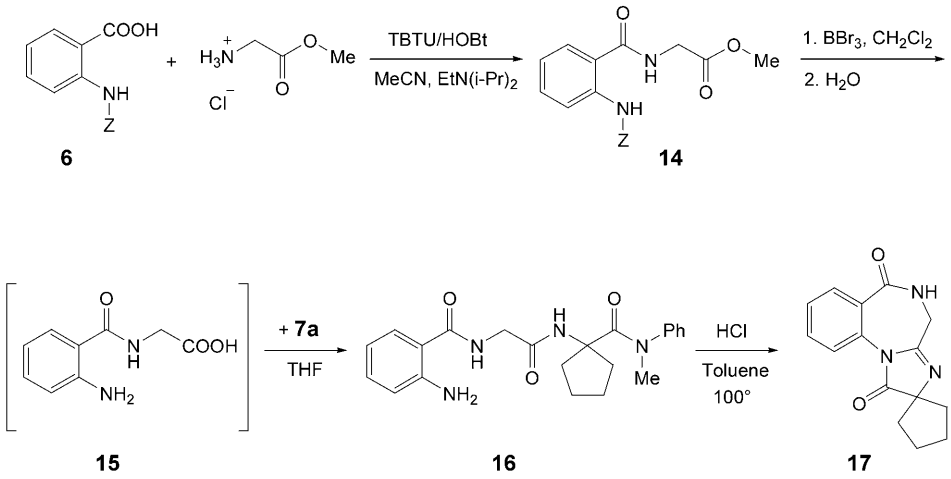


Fig. 1. *ORTEP Plot* [45] *of the molecular structure of* **12** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability)

with BBr_3 (1M solution in CH_2Cl_2) [47]. The crude dipeptide **15** was used for the next step without purification: the reaction with **7a** in THF yielded the tripeptide **16**. When the latter was subjected to the cyclization conditions reported above, only the heterobicyclic compound **17** could be isolated after chromatographic workup. The structure of **17** was established by spectroscopic methods, and after crystallization from CH_2Cl_2/Et_2O, it was confirmed by X-ray crystallography (*Fig. 2*).

Scheme 3



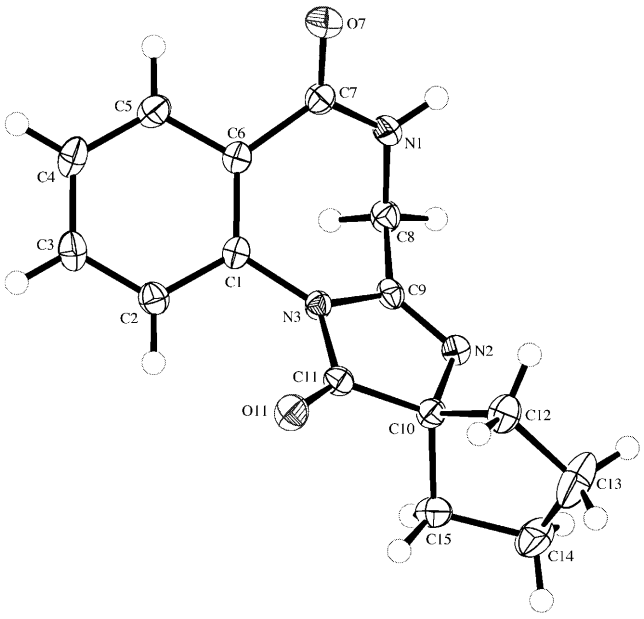
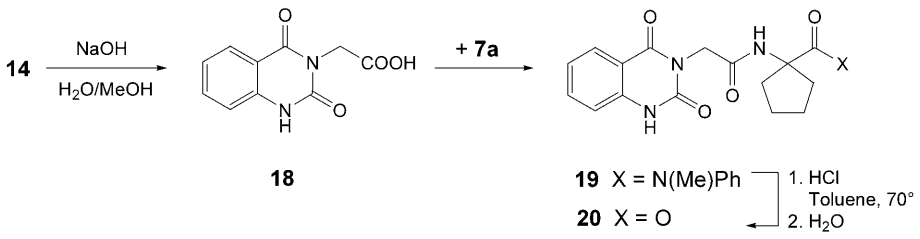


Fig. 2. *ORTEP Plot* [45] *of the molecular structure of* **17** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability)

The H-bonding pattern of **17** is quite different to that of **12**. The NH group forms an intermolecular H-bond with N(2) of the heterocyclic five-membered ring of a neighboring molecule. This latter molecule is related to the original one by a center of inversion, so that centrosymmetric dimeric units with a graph-set motif of $R_2^2(10)$ are formed.

The attempt to transform **14** into the corresponding N-protected carboxylic acid by saponification (1N NaOH/MeOH 9:4, 70 h) led to 2,4-dioxoquinazoline-3-acetic acid (**18**) in quantitative yield (*Scheme 4*). After a shorter reaction time (30 min) and treatment with a 0.3:2 mixture of 1N NaOH/MeOH, the corresponding methyl 2,4-dioxoquinazoline-3-acetate was obtained in 79% yield. The reaction of **18** with **7a** gave the quinazoline dipeptide amide **19** (78% yield), which, on treatment of its suspension in toluene with HCl gas and aqueous workup, yielded the dipeptide acid **20** (72%). After crystallization from $MeOH/Et_2O/CH_2Cl_2$, the structure of the latter was again established by X-ray crystallography (*Fig. 3*).

Scheme 4



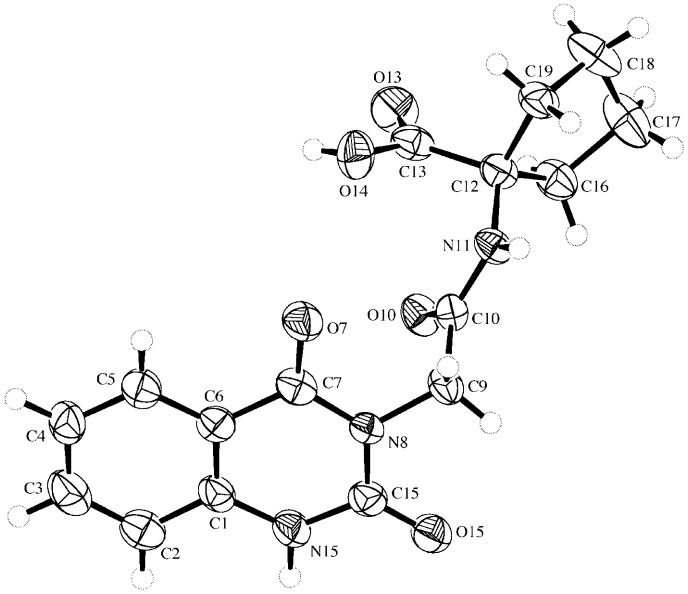
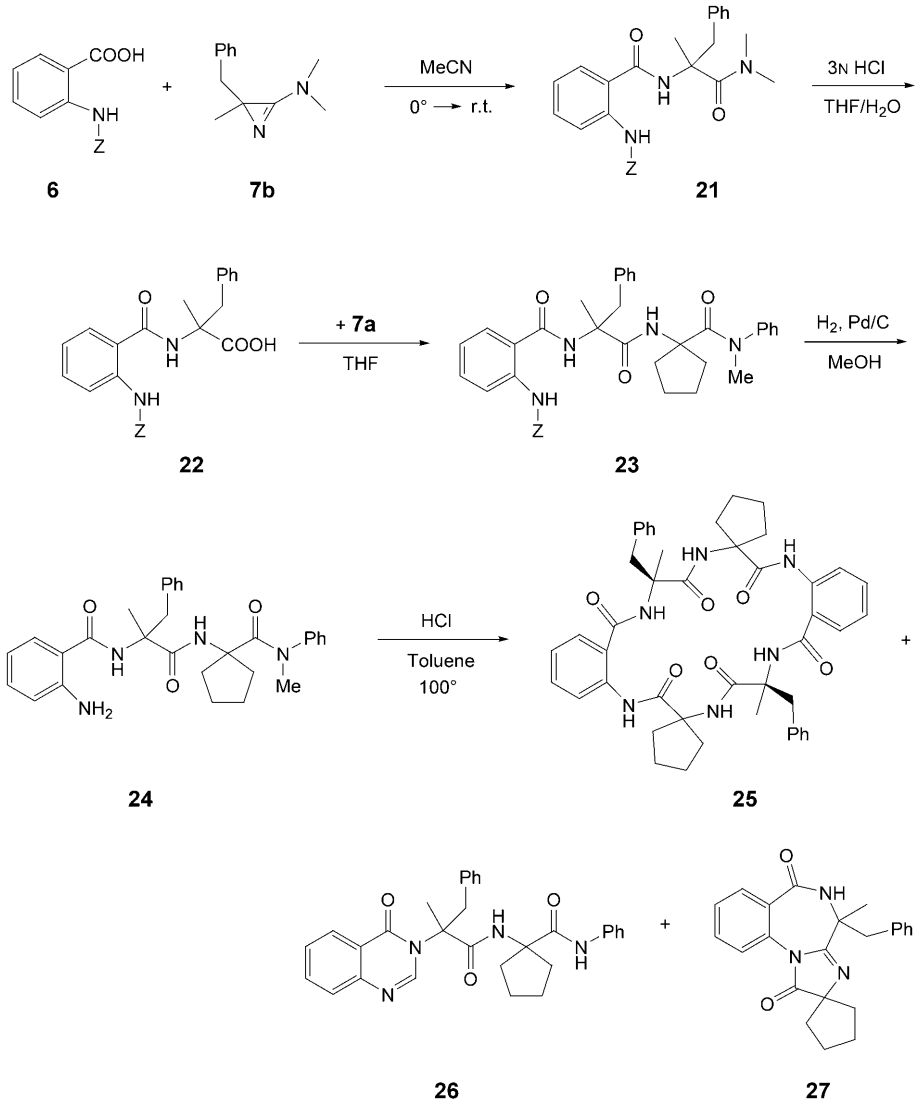


Fig. 3. *ORTEP Plot* [45] *of the molecular structure of one of the two symmetry-independent molecules of* **20** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability; the solvent molecule is not shown)

The asymmetric unit contains two symmetry-independent molecules of **20** plus one MeOH molecule. The independent molecules of **20** differ significantly in their conformations as a result of a twist of *ca.* 30° about the C(9)–C(10) bond. The OH group in molecule A forms an intermolecular H-bond with the O(15)-atom of molecule B. Instead of the OH group in molecule B forming a similar intermolecular H-bond with the corresponding O-atom in a different molecule A, this interaction actually involves a route *via* the O-atom of the MeOH molecule, which accepts one H-bond and then donates another H-bond to complete the link. The combination of these interactions links the molecules into extended chains composed of the sequence $\cdots A \cdots B \cdots MeOH \cdots A' \cdots B' \cdots MeOH' \cdots$. These chains run parallel to the [100] direction and have a ternary graph-set motif [46] of $C_3^3(22)$. The chain amide H-atom in molecule A forms an intermolecular H-bond with the O-atom of the corresponding amide group in molecule B, and this amide group in molecule B forms a similar H-bond with a different molecule A, thus building extended chains composed of the sequence $\cdots A \cdots B \cdots A' \cdots B' \cdots$, and which run parallel to the [100] direction and have a binary graph set motif of $C_2^2(8)$. The ring amide H-atom in molecule A forms an intermolecular H-bond to the ring carbonyl O-atom that is adjacent to the aromatic ring of molecule B, while molecule B has a similar interaction with a different molecule A. These interactions form extended chains composed of the sequence $\cdots A \cdots B \cdots A'' \cdots B'' \cdots$, and which run parallel to the [010] direction and have a binary graph-set motif of $C_2^2(12)$. The combination of all the interactions links all moieties in the structure into two-dimensional networks which lie parallel to the (110) plane.

Similar to the synthesis of **8**, the reaction of **6** with aminoazirine **7b** in dry MeCN led to the corresponding diamide **21** (*Scheme 5*). Acidic hydrolysis gave the corresponding carboxylic acid **22**, which was further coupled with **7a** to yield the tripeptide **23**. Removal of the protecting group by hydrogenolysis gave the linear precursor **24**, which was subjected to the conditions of the 'direct amide cyclization' (HCl gas in toluene at 100°). The results were quite different from our expectations and somewhat surprising. The desired cyclic peptide of type **A** could not be obtained, but three products have been isolated instead, *i.e.*, the dimer **25** of the desired ten-

Scheme 5



membered cyclic peptide (50% yield), an unexpected product recognized as the quinazolinone **26** (32%), and traces of the transannular-ring-contraction product **27**.

The formation of the cyclodimer **25** is obviously a result of an intermolecular reaction of the oxazolone intermediate of type **3** (see, *e.g.*, [19][20]), which is probably influenced by the concentration and the conformational flexibility of the peptide backbone, which may vary considerably in different peptides. The structure of **25** was deduced on the basis of 1D- and 2D-NMR spectra: the assignment of the ^{1}H and ^{13}C signals was achieved using HSQC and HMBC techniques. To determine the molecular mass of the cyclic peptide, the soft-ionization technique ESI-MS was employed and indicated the base peak at m/z 783 ($[M+Na]^{+}$), which corresponds to the 20-membered cyclodimer **25**. Finally, the structure of **25** was established by X-ray crystallography (*Fig. 4*). As only one very poor-quality crystal of **25** could be isolated, the crystallographic data do not permit precise bond lengths and angles to be determined. However, the data were good enough for the structure of the dimer to be recognized. It is worth mentioning that the two benzyl groups are *cis* oriented. The corresponding *trans* isomer could not be detected despite of the fact that racemic **7b** was used for the synthesis.

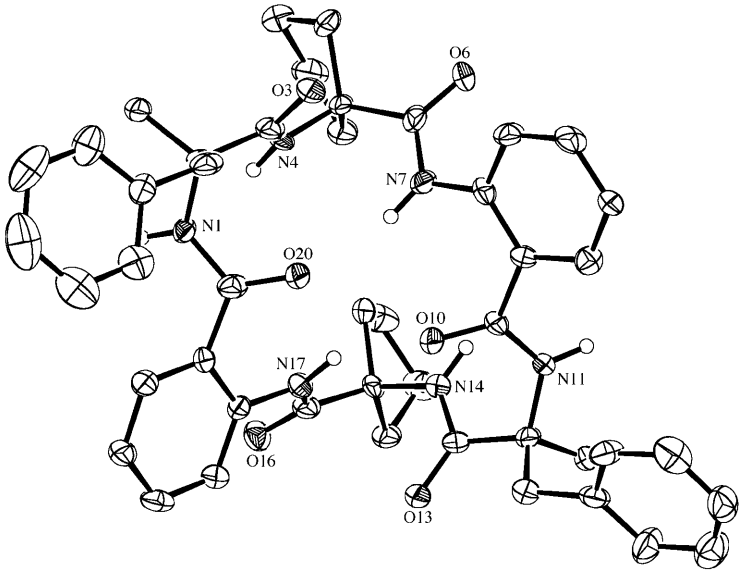


Fig. 4. *ORTEP Plot* [45] *of the molecular structure of* **25** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability; H-atoms, except amide H-atoms, omitted for clarity)

The amide N(7)–H and N(17)–H form intramolecular H-bonds with the amide O(20)- and O(10)-atoms, respectively, that are on the other side of the macrocycle, two peptide units further around. Each of these interactions has the graph-set motif of S(10). N(1)–H and N(11)–H form intermolecular H-bonds with amide O(16′)- and O(6″)-atoms, respectively, from two different neighboring molecules. Each of these interactions independently links the molecules into extended chains, which run parallel to the [001] direction and have a graph-set motif of C(8). In this way, two H-bonds

bridge adjacent peptide molecules, with the sense of the N(1)–H···O and N(11)–H···O progression being in opposite directions. No reasonable H-bond acceptor could be located for N(4)–H and N(17)–H, but the acceptors may be part of the omitted solvent molecules (see *Exper. Part*).

The formation of compound **26** is very surprising, and we are not able to give a reasonable explanation at this time. The structure of **26** was elucidated by means of its NMR and IR spectra and confirmed by X-ray crystallography (*Fig. 5*). Compound **26** crystallized in a polar, non-centrosymmetric space group, but one, which dictates that the crystals are racemic. There are two symmetry-independent molecules of **26** plus one CH_2Cl_2 molecule in the asymmetric unit. Both molecules of **26** have similar conformations. The most-significant difference is in the orientation of the benzyl substituent, which, in molecule B, is pivoted about the C(42)–C(58) bond by *ca.* 30° with respect to the orientation of the corresponding group in molecule A. The five-membered ring of molecule A is disordered with one atom of the ring occupying two positions. The terminal NH group of each molecule forms an intramolecular H-bond with the O-atom of the bicyclic ring system. This creates a ten-membered loop with a graph-set motif [46] of S(10) and corresponds with the normal intramolecular interactions seen for peptides with β-turns. The NH group in the center of molecule A

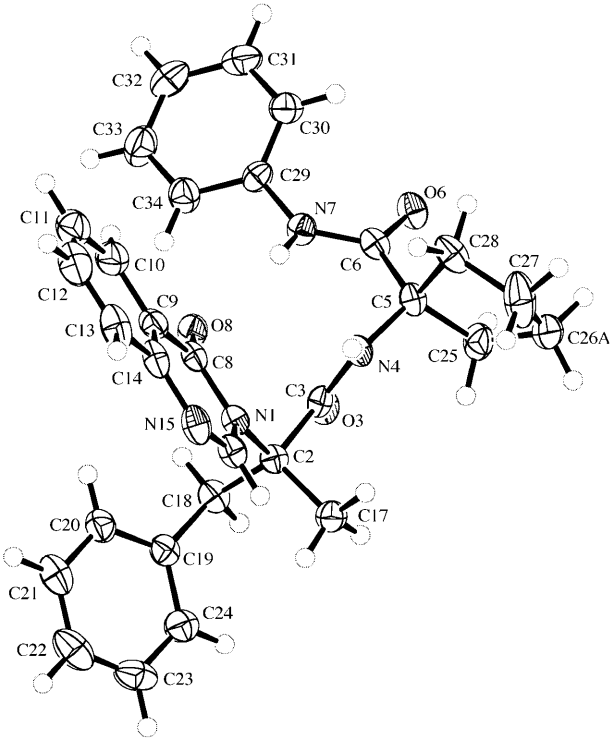


Fig. 5. *ORTEP Plot* [45] *of the molecular structure of* **26** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability)

forms an intermolecular H-bond with the amide O-atom at the Ph end of a neighboring molecule B. The latter molecule, in turn, has an identical intermolecular interaction with another molecule A. These interactions link the peptide molecules into extended $\cdots A \cdots B \cdots A \cdots B \cdots$ chains, which run parallel to the [−110] direction and have a binary graph set motif of $C_2^2(10)$.

Finally, the traces of compound **27** were successfully crystallized from CH_2Cl_2/Et_2O/hexane and its structure, which is analogous to that of **12** and **17**, was established by X-ray crystallography (*Fig. 6*).

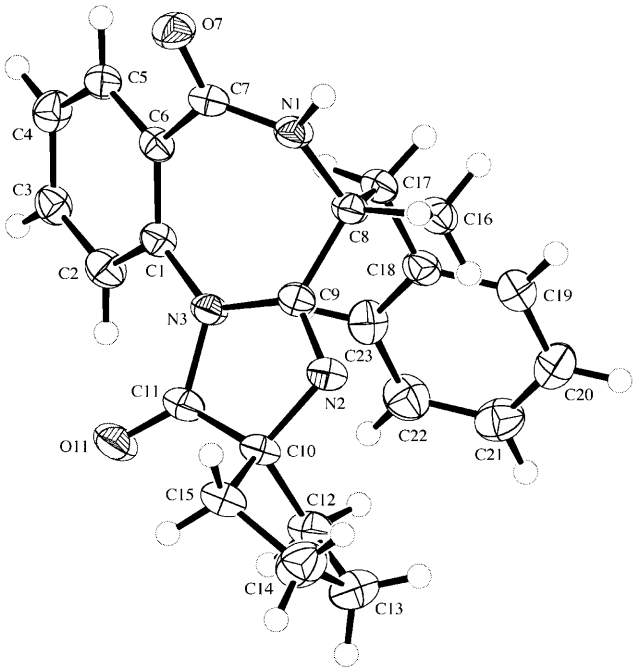
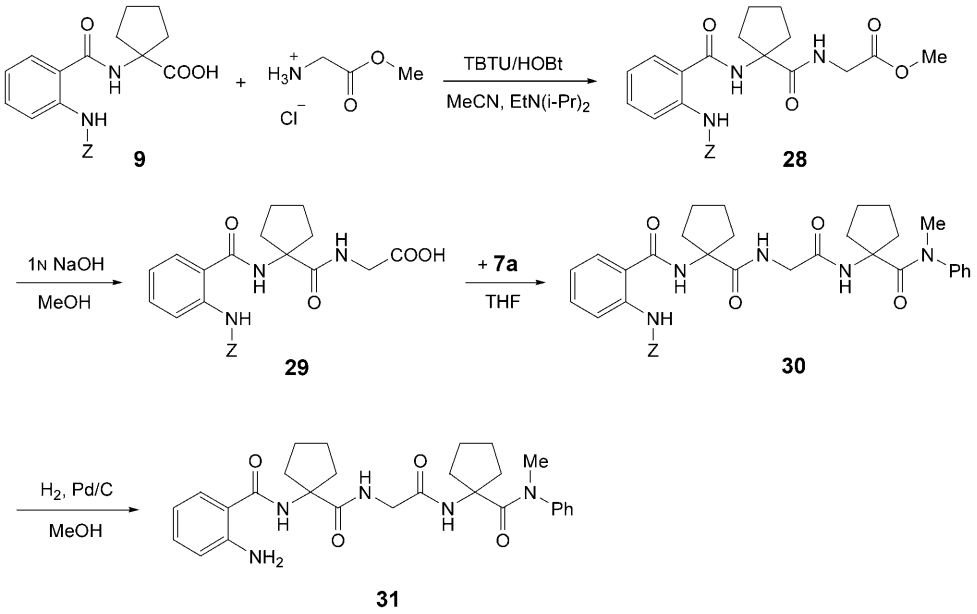


Fig. 6. *ORTEP Plot* [45] *of the molecular structure of* **27** (arbitrary numbering of the atoms; displacement ellipsoids with 50% probability)

As a result of the described reactions, the conditions of the 'direct amide cyclization' proved not to be suitable for the formation of ten-membered 'cycloaspeptides'. Therefore, it was of interest to test the application of this method to a corresponding tetrapeptide precursor, which should lead to the 13-membered cyclopeptide. Tetrapeptide **31** was synthesized according to *Scheme 6:* the coupling reaction of carboxylic acid **9** with methyl glycinate hydrochloride in the presence of TBTU, HOBt, and $EtN(i\text{-}Pr)_2$ gave the tripeptide methyl ester **28** in 98% yield, which was then hydrolyzed with 1N NaOH in MeOH to yield the corresponding carboxylic acid **29**. The coupling of the latter with another unit of **7a** afforded the tetrapeptide amide **30** in 93% yield, which, after deprotection of the amino group by hydrogenolysis, gave **31**. All attempts to cyclize this tetrapeptide by treatment of its suspension with HCl gas failed. Only a mixture of inseparable decomposition products was obtained. This result

parallels the observation of a similar decomposition of tetrapeptide derivatives under these conditions [18].

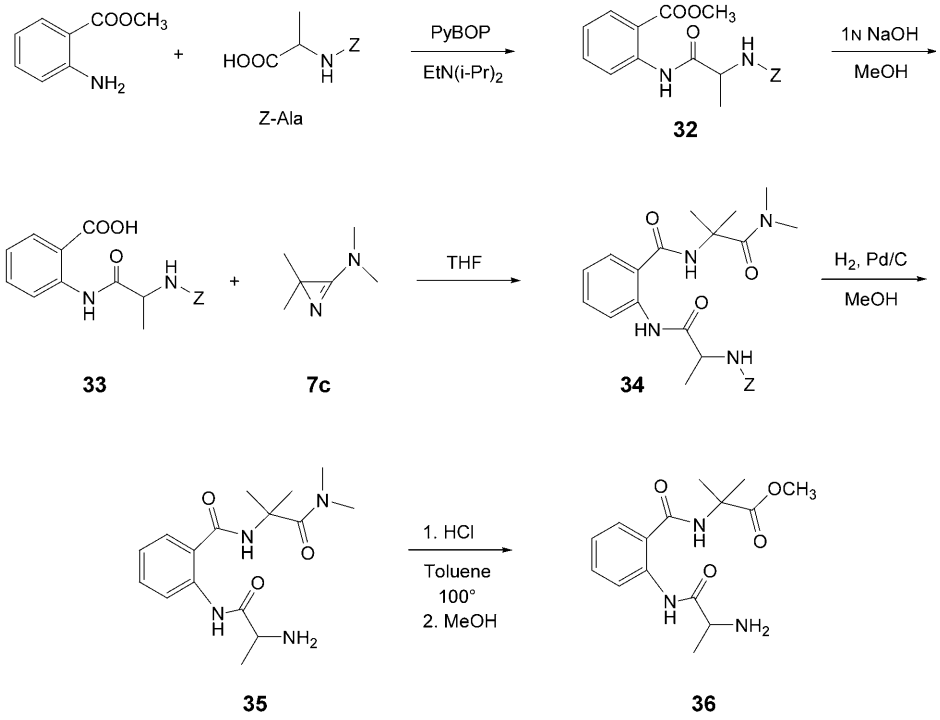
Scheme 6



Finally, a tripeptide derivative of type **36** was prepared (*Scheme 7*). Condensation of Z-protected alanine with methyl anthranilate under standard conditions with [(1*H*-benzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP) and $EtN(i\text{-}Pr)_2$ led to the corresponding amide **32**, and saponification of the ester group with 1N NaOH in MeOH yielded the acid **33** [49]. The latter compound was coupled with 2*H*-azirin-3-amine **7c** to give the N-protected tripeptide **34**. Deprotection of the amino group by hydrogenolysis led to the compound **35**, which was subjected to the cyclization conditions. Unfortunately the 'direct amide cyclization', as depicted in *Scheme 1*, failed to give the desired cyclopeptide. This is most likely due to a complete protonation of the primary amino group of **35** under the acidic conditions needed for this cyclization. Hydrolytic ring opening of the initially formed 1,3-oxazol-5(4*H*)-one intermediate with MeOH during workup explains the formation of the isolated methyl ester **36**. With this ester in hand, we were able to try the cyclization in refluxing toluene according to [48], but even after heating for several days, only the starting material was recovered.

Conclusions. – We have shown that the 'azirine/oxazolone method' is a convenient preparative route for the synthesis of peptides containing α,α-disubstituted α-amino acids and anthranilic acid. Unfortunately, attempts to prepare the corresponding ten-membered cyclic peptide by the 'direct amide cyclization' have so far been unsuccessful. In the case of peptides **11** and **16**, the tricyclic products **12** and **17** were

Scheme 7



obtained as major products. Obviously, the initially formed cyclic peptides, under acidic conditions, undergo a transannular ring closure, which is followed by elimination of H_2O. On the other hand, the 'direct amide cyclization' of **24** gave the cyclodimer **25**, *i.e.*, a 20-membered cyclohexapeptide. In all cases, the expected formation of the 1,3-oxazol-5(4*H*)-one intermediate of type **3** takes place, and the aniline NH_2 group acts as a nucleophile. Finally, in the case of **35**, oxazolone formation is proven by the isolation of the ester **36**. The NH_2 group of alanine, in contrast, undergoes neither an intra- nor an intermolecular nucleophilic addition, as it is completely protonated under the chosen conditions.

As a conclusion, the 'direct amide cyclization', which has been shown to be a superior method for the preparation of cyclodepsipeptides containing α,α-disubstituted α-amino acids, is not suitable for the synthesis of ten-membered 'cycloaspeptides'.

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Experimental Part

1. *General.* Solvents were purified by standard procedures. Thin layer chromatography (TLC): aluminium sheets coated with silica gel *Merck 60* F_{254}. Column chromatography (CC): silica gel (0.040–0.063 mm, *Merck 60*). M.p.: *Büchi B-540* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1600 Series* FT-IR spectrometer; in

KBr; absorptions in cm^{-1}. NMR Spectra: *Bruker ARX-300* spectrometer (^1H: 300 MHz, ^{13}C: 75.5 MHz); in $CDCl_3$; chemical shifts δ [ppm] refer to residual $CHCl_3$ (7.27 ppm, ^1H) and to $CDCl_3$ (77.0 ppm, ^{13}C); coupling constants *J* in Hz; the multiplicity of the ^{13}C signals was deduced from DEPT spectra. MS: *Finnigan MAT-SSQ-700* (CI) and *Finnigan MAT-TSQ-700* (ESI) spectrometer; *m/z* (rel.%). The following 2*H*-azirin-3-amines were used: *N*-methyl-*N*-phenyl-1-azaspiro[2.4]hept-1-en-2-amine (**7a**) [50], 2-benzyl-*N*,*N*,2-trimethyl-2*H*-azirin-3-amine (**7b**) [51], and *N*,*N*,2,2-tetramethyl-2*H*-azirin-3-amine (**7c**) [52].

General Procedure 1 (*GP 1*): *Azirine Coupling.* To a soln. of an N-protected amino acid or peptide acid in the given solvent, the 2*H*-azirin-3-amine (**7**) was added at 0°, and the mixture was stirred under N_2 at r.t. After completion of the reaction (TLC), the soln. was concentrated *in vacuo*, and the residue was purified by CC (SiO_2).

General Procedure 2 (*GP 2*): *Selective Hydrolysis of the Terminal Amide Group.* The C- and N-protected peptide was dissolved in THF/6N HCl 1:1 (*v*/*v*, *ca.* 5 ml/mmol) at 0°, and the soln. was stirred at r.t. until completion of the reaction (TLC). Then, the solvent was evaporated, CH_2Cl_2 and H_2O were added, and the layers were separated. The aq. layer was washed with Et_2O, and the combined org. layer was dried ($MgSO_4$) and concentrated. The product was pure enough (> 90%) to be used in the next step without further purification.

General Procedure 3 (*GP 3*): *Hydrolysis of the Methyl Ester.* To a soln. of the C- and N-protected peptide in MeOH, 1N NaOH was added. The mixture was stirred until completion of the reaction (TLC). Then, 1N HCl was added to the mixture to adjust pH to 2–3. The solvent was evaporated, CH_2Cl_2 and H_2O were added, and the layers were separated. The aq. layer was washed with Et_2O, and the combined org. layer was dried ($MgSO_4$) and concentrated *in vacuo*.

General Procedure 4 (*GP 4*): *Hydrogenolysis of the Z-Protecting Group.* To a soln. of the C- and N-protected peptide in MeOH, 10% Pd/C was added at 0°, and the mixture was stirred at r.t. under H_2 until completion of the reaction (TLC). Then, the soln. was filtered over a *Celite* pad, the solvent was evaporated, and the resulting residue was purified by CC (SiO_2).

General Procedure 5 (*GP 5*): *Peptide Coupling.* To a soln. of an N-protected amino acid, $EtN(i\text{-}Pr)_2$ (2 equiv.), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 1 equiv.), and 1-hydroxy-1*H*-benzotriazole (HOBt, 1 equiv.) in MeCN or CH_2Cl_2 was added 1.1 equiv. of the amino acid ester. The mixture was stirred at r.t. until the starting material was completely consumed (TLC). Then, the soln. was concentrated *in vacuo* and the crude product purified by CC (SiO_2).

General Procedure 6 (*GP 6*): *Direct Amide Cyclization.* A stirred suspension of the peptide in dry toluene was warmed to 100° under N_2. A stream of dry HCl gas was slowly passed through the suspension at this temp. for *ca.* 10 min, followed by a stream of N_2 for 30 min to remove the remaining HCl. The solvent was evaporated and the residue partitioned between H_2O and CH_2Cl_2. The org. layer was dried ($MgSO_4$) and evaporated. The crude product was purified by CC (SiO_2).

2. *Dispiro[cyclopentane-1,2′(4′H)-[1H]imidazo[1,2-a][1,4]benzodiazepine-4′,1″-cyclopentane]-1′,6′(5′H)-dione* (**12**). 2.1. *Benzyl (2-{[(1-{[(Methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]carbonyl}phenyl)carbamate* (**8**). According to *GP 1*, with Z-protected anthranilic acid (**6**) (0.400 g, 1.470 mmol) in MeCN (4 ml), **7a** (0.353 g, 1.760 mmol) in MeCN (2 ml); reaction time 22 h. The obtained precipitate was collected by filtration, washed with hexane, and dried *in vacuo:* 0.665 g of crude **8**. Recrystallization from EtOH gave 0.603 g (87%) of **8**. Colorless microcrystals. M.p. 202.3–202.8°. IR: 3320*m*, 3267*s*, 3060*w*, 2965*w*, 1733*s*, 1635*s*, 1594*s*, 1520*s*, 1445*s*, 1386*m*, 1320*m*, 1207*s*, 1041*m*, 764*m*. ^1H-NMR: 10.73 (br. *s*, NH); 8.35 (*d*, *J* = 8.4, 1 arom. H); 7.45–7.29 (*m*, 6 arom. H); 7.11–7.02 (*m*, 5 arom. H); 6.83–6.63 (*m*, 2 arom. H); 5.21 (*s*, PhCH_2); 3.24 (*s*, MeN); 2.64–2.55, 1.90–1.74, 1.68–1.56 (3*m*, $(CH_2)_4$). ^{13}C-NMR: 172.1, 167.9, 153.7 (3*s*, 3 CO); 144.6, 140.1, 136.3 (3*s*, 3 arom. C); 132.7, 129.4, 128.5, 128.3, 128.2, 127.3, 126.9, 126.4, 121.4, 120.0 (10*d*, 14 arom. CH); 119.0 (*s*, 1 arom. C); 67.7 (*s*, $(CH_2)_4C$); 66.8 (*t*, PhCH_2); 40.7 (*q*, MeN); 39.5, 24.7 (2*t*, $(CH_2)_4$). ESI-MS: 494 (95, $[M + Na]^+$), 472 (13, $[M + 1]^+$), 365 (100). Anal. calc. for $C_{28}H_{29}N_3O_4$ (471.56): C 71.32, H 6.20, N 8.91; found: C 71.06, H 6.25, N 8.93.

2.2. *1-[(2-{[(Benzyloxy)carbonyl]amino}benzoyl)amino]cyclopentanecarboxylic Acid* (**9**). According to *GP 2*, hydrolysis of **8** (0.300 g, 0.636 mmol) led to 0.237 g (98%) of **9**. Colorless powder. M.p. 195.6–196.4°. IR: 3326*m*, 2963*m*, 2875*w*, 1701*s*, 1642*s*, 1600*m*, 1588*s*, 1524*s*, 1447*s*, 1280*m*, 1244*s*, 1216*s*, 1039*s*, 976*w*, 918*m*, 754*m*. ^1H-NMR ((D_6)DMSO): 12.30 (br. *s*, COOH); 10.62, 8.80 (2*s*, 2 NH); 8.19 (*dd*, *J* = 8.4, 0.9, 1 arom. H); 7.76 (*dd*, *J* = 7.9, 1.4, 1 arom. H); 7.53–7.34 (*m*, 6 arom. H); 7.14–7.08 (*m*, 1 arom. H); 5.16 (*s*, PhCH_2); 2.51–2.48, 2.11–2.04 (2*m*, $(CH_2)_4$). ^{13}C-NMR ((D_6)DMSO): 175.0, 168.4, 152.6 (3*s*, 3 CO); 138.7, 136.2 (2*s*, 2 arom. C); 132.0, 128.7, 128.3, 127.9, 121.6 (5*d*, 8 arom. CH); 120.0 (*s*, 1 arom. C); 118.3 (*d*, 1 arom. CH); 66.0 (*t*, PhCH_2); 65.6 (*s*, $(CH_2)_4C$); 36.2, 24.1 (2*t*, $(CH_2)_4$). ESI-MS: 405 (100, $[M + Na]^+$).

2.3. *Benzyl (2-{[(1-{[(1-{[(Methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]carbonyl}cyclopentyl)amino]carbonyl}phenyl)carbamate* (**10**). According to *GP 1*, with **9** (0.480 g, 1.255 mmol) in THF (12 ml), **7a**

(0.276 g, 1.380 mmol) in THF (4 ml); reaction time 28 h. CC (CH_2Cl_2/MeOH 200:1 to 60:1) yielded 0.542 g (74%) of **10**. Colorless powder. M.p. 241.5–241.9°. IR: 3310*m*, 2954*m*, 2870*w*, 1739*s*, 1655*s*, 1632*s*, 1589*s*, 1525*s*, 1448*s*, 1383*m*, 1323*w*, 1280*w*, 1243*w*, 1211*s*, 1104*w*, 1044*m*, 1028*w*. ^{1}H-NMR ($CDCl_3$/CD_3OD): 10.00 (br. *s*, NH); 8.32 (*d*, *J* = 8.4, 1 arom. H); 7.53–7.31 (*m*, 8 arom. H); 7.08–7.01 (*m*, 5 arom. H); 5.20 (*s*, PhC*H*$_2$); 3.18 (*s*, MeN); 2.15–2.02, 1.97–1.89, 1.68–1.65, 1.54–1.51 (4*m*, 2 (CH_2)$_4$). ^{13}C-NMR ($CDCl_3$/CD_3OD): 172.6, 170.3, 153.6 (3*s*, 4 CO); 145.0, 139.7, 136.1 (3*s*, 3 arom. C); 133.2, 128.9, 128.7, 128.6, 127.4, 127.2, 122.3 (7*d*, 13 arom. CH); 120.6 (*s*, 1 arom. C); 120.4 (*d*, 1 arom. CH); 68.9, 67.5 (2*s*, 2 (CH_2)$_4$*C*); 67.2 (*t*, Ph*C*H$_2$); 41.0 (*q*, MeN); 38.5, 36.1, 23.9, 23.8 (4*t*, 2 (CH_2)$_4$). ESI-MS: 605 (100, $[M+Na]^+$). Anal. calc. for $C_{34}H_{38}N_4O_5$ (582.71): C 70.08, H 6.57, N 9.61; found: C 69.90, H 6.64, N 9.58.

2.4. *2-Amino*-N-*(1-{[(1-{[(methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]carbonyl}cyclopentyl)benzamide* (**11**). According to *GP 4*, hydrogenolysis of **10** (0.240 g, 0.412 mmol) in MeOH (30 ml); reaction time 3 h. Evaporation yielded 0.182 g (98%) of **11**. Colorless powder. M.p. 281.5–282.1°. IR: 3490*m*, 3333*s*, 2953*m*, 2870*m*, 1657*s*, 1632*s*, 1610*m*, 1583*s*, 1492*s*, 1451*s*, 1382*m*, 1299*m*, 1266*s*. ^{1}H-NMR ((D$_6$)DMSO): 7.83 (*s*, 1 NH); 7.56 (*d*, *J* = 6.6, 2 arom. H); 7.35–7.30 (*m*, 2 arom. H); 7.20–7.11 (*m*, 3 arom. H, NH); 6.67 (*dd*, *J* = 8.2, 0.8, 1 arom. H); 6.52 (*td*-like, *J* = 7.9, 7.0, 0.9, 1 arom. H); 6.20 (*s*, NH_2); 3.23 (*s*, MeN); 2.19–2.08, 2.92–1.88, 1.65–1.52 (3*m*, 2 (CH_2)$_4$). ^{13}C-NMR ((D$_6$)DMSO): 172.7, 172.3, 169.1 (3*s*, 3 CO); 149.3, 145.4 (2*s*, 2 arom. C); 131.6, 128.9, 128.4, 126.7, 125.7, 116.1 (6*d*, 8 arom. CH); 115.1 (*s*, 1 arom. C); 114.3 (*d*, 1 arom. CH); 66.5, 66.2 (2*s*, 2 (CH_2)$_4$*C*); 38.8 (*q*, MeN); 36.2, 35.7, 23.7 (3*t*, 2 (CH_2)$_4$). CI-MS: 449 (18, $[M+1]^+$), 342 (100).

2.5. *Compound* **12**. According to *GP 6*, with **11** (0.040 g, 0.089 mmol), in toluene (30 ml), at 100°; reaction time 10 min. CC (CH_2Cl_2/MeOH 180:1) yielded 0.012 g (44%) of **12**. Colorless crystals. M.p. 224.1–225.3°. IR: 3285*w*, 3178*s*, 3065*m*, 2961*s*, 2929*s*, 2878*m*, 1743*s*, 1661*s*, 1636*s*, 1600*s*, 1489*m*, 1460*s*, 1393*s*, 1358*s*, 1333*s*, 1271*m*, 1163*m*, 1062*m*, 1005*w*, 950*w*, 891*w*, 803*w*, 779*m*, 750*m*. ^{1}H-NMR: 7.92 (*dd*, *J* = 7.8, 1.5, 1 arom. H); 7.71 (*dd*, *J* = 8.2, 1.0, 1 arom. H); 7.59 (*td*-like, *J* = 8.2, 7.4, 1.1, 1 arom. H); 6.65 (*s*, NH); 2.11–1.65 (*m*, 2 (CH_2)$_4$). ^{13}C-NMR: 184.4 (*s*, CN_2); 168.7, 161.9 (2*s*, 2 CO); 132.5 (*d*, 1 arom. CH); 132.0 (*s*, 1 arom. C); 131.1 (*d*, 1 arom. CH); 127.8 (*s*, 1 arom. C); 126.9, 123.3 (2*d*, 2 arom. CH); 61.6 (*s*, 2 (CH_2)$_4$*C*); 38.1, 37.6, 37.2, 36.8, 26.2, 24.6, 23.2 (7*t*, 2 (CH_2)$_4$). ESI-MS: 324 (100, $[M+1]^+$).

Recrystallization from CH_2Cl_2/Et_2O yielded crystals of **12** suitable for X-ray crystal-structure determination.

3. *Methyl 1-[([1-[(2-Aminobenzoyl)amino]cyclopentyl]carbonyl)amino]cyclopentanecarboxylate* (**13**). *General Procedure 7* (*GP 7*): The soln. of **10** (0.150 g, 0.257 mmol) in CH_2Cl_2 (20 ml) was cooled to −10° and BBr_3 (4 ml, 1M in CH_2Cl_2, 4.0 mmol) was added dropwise while stirring. Stirring was continued at −10° for 1 h and at 25° for 2 h. The reaction was terminated by careful, dropwise addition of MeOH (20 ml). The solvents were evaporated, and the residue was partitioned between H_2O and CH_2Cl_2. The org. layer was dried ($MgSO_4$) and evaporated. The crude product was purified by CC (SiO_2, CH_2Cl_2/MeOH 60:1 to 30:1): 0.054 g (66%) of **13**. Colorless powder. M.p. 174.6–175.3°. IR: 3441*m*, 3377*s*, 3302*s*, 3030*w*, 2958*s*, 2874*m*, 1723*s*, 1654*s*, 1617*s*, 1596*s*, 1523*s*, 1452*m*, 1302*m*, 1252*m*, 1160*w*, 1133*w*, 1070*w*, 1029*w*. ^{1}H-NMR: 7.46 (br. *s*, 2 NH); 7.24–7.12 (*m*, 2 arom. H); 6.63–6.56 (*m*, 2 arom. H); 6.25 (*s*, NH_2); 3.61 (*s*, MeO); 2.37–2.30, 2.15–2.08, 2.01–1.86, 1.76–1.66 (4*m*, 2 (CH_2)$_4$). ^{13}C-NMR: 174.6, 173.2, 169.9 (3*s*, 3 CO); 148.6 (*s*, 1 arom. C); 132.6, 127.2, 117.4, 116.7 (4*d*, 4 arom. CH); 115.9 (*s*, 1 arom. C); 67.8, 65.8 (2*s*, 2 (CH_2)$_4$*C*); 52.2 (*q*, MeO); 37.0, 36.6, 24.4, 24.0 (4*t*, 2 (CH_2)$_4$). ESI-MS: 412 (100, $[M+K]^+$), 374 (71, $[M+1]^+$).

4. *4′,5′-Dihydrospiro[cyclopentane-1,2′(6′*H*)-[1*H*]imidazo[1,2-*a*][1,4]benzodiazepine]-1′,6′-dione* (**17**). 4.1. *Methyl [(2-{[(Benzyloxy)carbonyl]amino}benzoyl)amino]acetate* (**14**). According to *GP 5*, with **6** (0.200 g, 0.737 mmol), methyl glycinate hydrochloride (0.110 g, 0.737 mmol), HOBt (0.100 g, 0.737 mmol), TBTU (0.236 g, 0.737 mmol), EtN(i-Pr)$_2$ (0.26 ml, 1.474 mmol), and MeCN (8 ml); reaction time 4 h. CC (CH_2Cl_2/MeOH 250:1) gave 0.222 g (88%) of **14**. Colorless powder. M.p. 89.7–90.0°. IR: 3420*s*, 3157*m*, 3039*w*, 2953*m*, 1738*s*, 1641*s*, 1591*s*, 1537*s*, 1455*s*, 1407*s*, 1374*s*, 1331*m*, 1283*s*, 1207*s*, 1127*m*, 1084*w*, 1045*m*, 1028*w*, 1000*w*, 909*w*, 855*w*, 829*w*, 754*m*, 697*m*. ^{1}H-NMR: 10.42 (*s*, NH); 8.40 (*dd*, *J* = 8.4, 0.9, 1 arom. H); 7.54–7.31 (*m*, 7 arom. H); 7.04 (*td*-like, *J* = 8.6, 7.6, 1.1, 1 arom. H); 6.68 (*s*, NH); 5.20 (*s*, PhC*H*$_2$); 4.20 (*d*, *J* = 5.0, CH_2CO); 3.81 (*s*, MeO). ^{13}C-NMR: 170.1, 168.8, 153.5 (3*s*, 3 CO); 140.0, 136.2 (2*s*, 2 arom. C); 133.0, 128.5, 128.2, 128.1, 126.8, 121.9, 120.0 (7*d*, 9 arom. CH); 66.8 (*t*, Ph*C*H$_2$); 52.6 (*q*, MeO); 41.6 (*t*, *C*H$_2$CO). CI-MS: 360 (27, $[M+NH_4]^+$), 343 (100, $[M+1]^+$), 299 (15), 254 (52). Anal. calc. for $C_{18}H_{18}N_2O_5$ (342.36): C 63.15, H 5.30, N 8.18; found: C 63.08, H 5.30, N 8.16.

4.2. *2-Amino*-N-*{2-[(1-{[(methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]-2-oxoethyl}benzamide* (**16**). According to *GP 7*, with **14** (0.340 g, 0.993 mmol) in CH_2Cl_2 (15 ml), BBr_3 (12 ml, 1M in CH_2Cl_2, 12 mmol). The reaction was terminated by addition of H_2O (50 ml). The crude N-*(2-aminobenzoyl)glycine* (**15**) was used for the next step without further purification: according to *GP 1*, with **15** (0.072 g, 0.404 mmol) in THF

(10 ml), **7a** (0.121 g, 0.606 mmol) in THF (4 ml); reaction time 48 h. CC (CH_2Cl_2/MeOH 60:1) gave 0.090 g (57%) of **16**. Colorless powder. M.p. 206.7–207.9°. IR: 3480*m*, 3376*m*, 3317*m*, 3290*m*, 1683*s*, 1638*s*, 1611s, 1592*s*, 1518*s*, 1495*m*, 1444*w*, 1380*m*, 1315*w*, 1253*m*, 1155*w*, 1025*w*, 891*w*, 749*w*, 708*w*. ^{1}H-NMR ((D$_6$)DMSO): 8.20–8.10 (*m*, 1 NH); 7.65–7.55 (br. *s*, 1 NH); 7.51–6.90 (*m*, 7 arom. H); 6.72–6.69 (*d*-like, 1 arom. H); 6.55–6.48 (*t*-like, 1 arom. H); 6.35 (*s*, NH_2); 3.55 (*m*, CH_2CO); 3.13 (*s*, MeN); 2.30–2.15, 1.80–1.49 (2*m*, $(CH_2)_4$). ^{13}C-NMR ($CDCl_3$/CD_3DO): 176.1, 173.0, 171.5 (3*s*, 3 CO); 151.5, 148.3 (2*s*, 2 arom. C); 135.7, 132.4, 130.8, 130.6, 129.8, 120.4, 119.9 (7*d*, 9 arom. CH); 118.3 (*s*, 1 arom. C); 70.2 (*s*, $(CH_2)_4C$); 45.7 (*t*, CH_2CO); 43.6 (*q*, MeN); 41.7, 27.3 (2*t*, $(CH_2)_4$). ESI-MS: 417 (100, $[M+Na]^+$), 288 (23).

4.3. *Compound* **17**. According to *GP 6*, with **16** (0.075 g, 0.190 mmol), in toluene (60 ml), 100°; reaction time 10 min. CC (CH_2Cl_2/MeOH 150:1 to 50:1) yielded 0.010 g (20%) of **17**. Colorless crystals. M.p. 268.5–269.8°. IR: 3442*w*, 3190*s*, 3099*s*, 2960*m*, 2923*m*, 1729*s*, 1662*s*, 1599*s*, 1573*s*, 1484*m*, 1461*s*, 1430*m*, 1389*s*, 1333*s*, 1298*w*, 1270*m*, 1231*m*, 1158*m*, 1083*s*, 1058*m*, 1019*m*, 957*m*, 877*w*, 790*m*, 764*m*. ^{1}H-NMR ((D$_6$)DMSO): 9.03 (*t*, $J=5.7$, 1 NH); 8.07 (*td*, $J=7.6$, 1.0, 1 arom. H); 7.96–7.88 (*m*, 2 arom. H); 7.75–7.66 (*m*, 1 arom. H); 4.41–4.14 (*m*, CH_2NH); 2.15–2.04 (*m*, $(CH_2)_4$). ^{13}C-NMR ((D$_6$)DMSO): 182.8 (*s*, CN_2); 167.6, 158.6 (2*s*, 2 CO); 131.7, 130.9, 126.7, 123.0 (4*d*, 4 arom. CH); 131.0, 127.7 (2*s*, 2 arom. C); 77.5 (*s*, $(CH_2)_4C$); 39.2, 25.2 (2*t*, $(CH_2)_4$); 37.0 (*t*, CH_2NH). ESI-MS: 270 (100, $[M+1]^+$).

Recrystallization from CH_2Cl_2/Et_2O yielded crystals of **17** suitable for X-ray crystal-structure determination.

5. *Synthesis of 1-{[(1,4-Dihydro-2,4-dioxo-2*H*-quinazolin-3-yl)acetyl]amino}-*N*-methyl-*N*-phenylcyclopentanecarboxamide* (**19**). 5.1. *1,4-Dihydro-2,4-dioxoquinazoline-3(2*H*)-acetic Acid* (**18**). According to *GP 3*, with **14** (0.100 g, 0.290 mmol) in MeOH (2 ml) and 0.3 ml 1N NaOH; reaction time 30 min. CC (CH_2Cl_2/MeOH 300:1) gave 0.054 g (79%) of *methyl 1,4-dihydro-2,4-dioxoquinazoline-3(2*H*)-acetate*. ^{1}H-NMR ((D$_6$)DMSO): 11.61 (*s*, NH); 7.95 (*dd*, $J=7.7$, 1.4, 1 arom. H); 7.71 (*td*, $J=7.8$, 1.5, 1 arom. H); 7.30–7.15 (*m*, 2 arom. H); 4.67 (*s*, CH_2); 3.68 (*s*, MeO). ^{13}C-NMR ((D$_6$)DMSO): 168.6, 162.3, 150.5 (3*s*, 3 CO); 139.0 (*s*, 1 arom. C); 135.2, 127.9, 123.0, 115.0 (4*d*, 4 arom. CH); 113.7 (*s*, 1 arom. C); 52.2 (*q*, MeO); 41.3 (*t*, CH_2). ESI-MS: 257 (100, $[M+Na]^+$).

According to *GP 3*, **14** (0.115 g, 0.336 mmol) in MeOH (4 ml) was treated with 9 ml of 1N NaOH; reaction time 70 h: 0.073 g (99%) of **18**. ^{1}H-NMR ((D$_6$)DMSO): 13.0 (br. *s*, COOH); 11.56 (*s*, NH); 7.94 (*dd*, $J=8.3$, 1.4, 1 arom. H); 7.70 (*td*, $J=7.4$, 1.5, 1 arom. H); 7.27–7.21 (*m*, 2 arom. H); 4.56 (*s*, CH_2). ^{13}C-NMR: 169.2, 161.5, 149.8 (3*s*, 3 CO); 139.3 (*s*, 1 arom. C); 135.3, 127.3, 122.7, 115.2 (4*d*, 4 arom. CH); 113.3 (*s*, 1 arom. C); 41.3 (*t*, CH_2).

5.2. *Compound* **19**. According to *GP 1*, with **18** (0.073 g, 0.332 mmol) in THF (8 ml), **7a** (0.068 g, 0.341 mmol) in THF (2 ml); reaction time 98 h. CC (CH_2Cl_2/MeOH 100:1 to 50:1) gave 0.105 g (78%) of **19**. White powder. M.p. 263.7–264.3°. IR: 3340*s*, 3058*m*, 2934*m*, 2866*m*, 1721*s*, 1669*s*, 1635*s*, 1594*m*, 1537*m*, 1494*s*, 1455*s*, 1431*m*, 1367*m*, 1335*m*, 1278*m*, 1252*m*, 1139*m*, 977*w*, 723*w*. ^{1}H-NMR ((D$_6$)DMSO): 11.41 (*s*, NH); 7.94 (*dd*, $J=8.3$, 1.5, 1 arom. H); 7.85 (br. *s*, 1 NH); 7.68 (*td*, $J=8.2$, 1.5, 1 arom. H); 7.41–7.20 (*m*, 7 arom. H); 4.26 (*s*, CH_2CO); 3.13 (*s*, MeN); 2.25–2.09, 1.74–1.68, 1.60–1.58 (3*m*, $(CH_2)_4$). ^{13}C-NMR ((D$_6$)DMSO): 173.0, 166.3, 162.6, 150.6 (4*s*, 4 CO); 139.0 (*s*, 1 arom. C); 134.8, 129.0, 127.5, 127.0, 122.6, 114.7 (6*d*, 9 arom. CH); 113.7 (*s*, 1 arom. C); 66.8 (*s*, $(CH_2)_4C$); 42.2 (*t*, CH_2CO); 40.0 (*q*, MeN); 38.1, 23.9 (2*t*, $(CH_2)_4$); 1 arom. C not found. CI-MS: 421 (42, $[M+1]^+$), 314 (100). Anal. calc. for $C_{23}H_{24}N_4O_4$ (420.47): C 65.70, H 5.75, N 13.32; found: C 65.49, H 5.74, N 13.10.

5.3. *1-{[(1,4-Dihydro-2,4-dioxo-2*H*-quinazolin-3-yl)acetyl]amino}cyclopentanecarboxylate* (**20**). According to *GP 6*, with **19** (0.100 g, 0.238 mmol) in toluene (40 ml), 100°; reaction time 30 min: 0.057 g (72%) of **20**. White powder. M.p. 234.9–235.3°. IR: 3600*m*, 3359*m*, 3267*m*, 2962*m*, 1720*s*, 1700*s*, 1652*s*, 1537*s*, 1494*s*, 1449*s*, 1419*s*, 1406*m*, 1347*m*, 1324*m*, 1267*s*, 1184*w*, 1160*w*, 1135*m*, 1071*w*, 1031*w*, 983*m*, 785*m*, 761*m*, 749*m*, 689*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.1 (br. *s*, COOH); 11.41 (*s*, NH); 8.36 (*s*, NH); 7.92 (*d*-like, $J=7.2$, 1 arom. H); 7.67 (*t*-like, $J=8.2$, 1 arom. H); 7.21 (*t*-like, $J=7.7$, 2 arom. H); 4.49 (*s*, CH_2CO); 2.08–2.02, 1.99–1.82, 1.66–1.65 (3*m*, $(CH_2)_4$). ^{13}C-NMR ((D$_6$)DMSO): 174.9, 166.2, 161.2, 149.8 (4*s*, 4 CO); 139.3 (*s*, 1 arom. C); 134.9, 127.3, 122.4, 115.0 (4*d*, 4 arom. CH); 113.5 (*s*, 1 arom. C); 64.9 (*s*, $(CH_2)_4C$); 42.0 (*t*, CH_2CO); 36.2, 23.9 (2*t*, $(CH_2)_4$). CI-MS: 332 (67), 349 (100, $[M+NH_3]^+$).

Recrystallization from MeOH/Et_2O/CH_2Cl_2 yielded crystals of **20** suitable for X-ray crystal-structure determination.

6. *Cyclization of 2-[(2-Aminobenzoyl)amino]-2-methyl-*N*-(1-{[(methyl)(phenyl)amino]carbonyl}cyclopentyl)-3-phenyl-propanamide* (**24**). 6.1. *Benzyl [2-({[2-(Dimethylamino)-1-methyl-2-oxo-1-(phenylmethyl)-ethyl]amino}carbonyl)phenyl]carbamate* (**21**). According to *GP 1*, with **6** (0.500 g, 1.843 mmol) in MeCN (6 ml), **7b** (0.416 g, 2.110 mmol) in MeCN (4 ml); reaction time 48 h. The crude product was filtered, washed with cold hexane/Et_2O 1:1, and dried *in vacuo*: 0.695 g (82%) of **21**. Colorless powder. M.p. 211.5–212.4°. IR:

3281*m*, 3102*w*, 3066*w*, 3036*w*, 3098*w*, 2957*w*, 1733*s*, 1620*s*, 1587*s*, 1524*s*, 1450*s*, 1391*m*, 1374*m*, 1328*m*, 1306*w*, 1278*m*, 1221*s*, 1104*m*, 1090*s*, 1041*s*, 1029*m*, 895*m*, 849*w*, 768*m*, 758*m*, 739*w*, 706*w*. ^{1}H-NMR: 10.57 (*s*, NH); 8.36 (*dd*, *J* = 8.5; 1.0, 1 arom. H); 7.46 – 7.30 (*m*, 6 arom. H); 7.28 – 7.17 (*m*, 4 arom. H); 7.03 – 7.00 (*m*, 2 arom. H); 6.92 (*td*, *J* = 8.0, 1.2, 1 arom. H); 5.23, 5.18 (*AB*, *J* = 12.0, PhCH_2O); 3.73, 3.35 (*AB*, *J* = 14.1, PhCH_2C); 3.11 (*s*, Me_2N); 1.80 (*s*, MeC). ^{13}C-NMR: 171.9, 167.6, 153.7 (3*s*, 3 CO); 139.9, 136.4 (2*s*, 2 arom. C); 132.5, 129.9, 128.5, 128.4, 128.3 (5*d*, 10 arom. CH); 128.2 (*s*, 1 arom. C); 127.1, 126.7, 122.0 (3*d*, 3 arom. CH); 120.4 (*s*, 1 arom. C); 120.0 (*d*, 1 arom. CH); 66.7 (*t*, PhCH_2O); 61.1 (*s*, Me*C*); 40.1 (*t*, PhCH_2); 38.5 (*q*, Me_2N); 22.7 (*q*, Me). CI-MS: 460 (3, $[M+1]^+$), 415 (33), 308 (20), 307 (100). Anal. calc. for $C_{27}H_{29}N_3O_4$ (459.55): C 70.57, H 6.36, N, 9.14; found: C 70.06, H 6.43, N 9.04.

6.2. *2-[(2-[[(Benzyloxy)carbonyl]amino}benzoyl)amino]-2-methyl-3-phenylpropanoic Acid* (**22**). According to *GP 2*, hydrolysis of **21** (0.580 g, 1.260 mmol) led to 0.506 g (93%) of **22**. Colorless powder. M.p. 101.5 – 101.9°. IR: 3283*w*, 3064*m*, 3032*m*, 2943*w*, 1736*s*, 1648*s*, 1589*s*, 1524*s*, 1449*s*, 1375*w*, 1318*w*, 1280*w*, 1216*m*, 1109*w*, 1093*w*, 1043*m*, 1029*w*, 884*w*, 847*w*, 754*m*, 700*m*. ^{1}H-NMR: 10.34 (*s*, NH); 8.35 (*d*, *J* = 8.4, 1 arom. H); 7.46 – 7.10 (*m*, 12 arom. H); 6.94 (*td*, *J* = 8.4, 1.1, 1 arom. H); 6.69 (*s*, NH); 5.21 (*s*, PhCH_2O); 3.57, 3.37 (*AB*, *J* = 13.6, PhCH_2C); 1.76 (*s*, Me). ^{13}C-NMR: 178.6, 168.6, 153.8 (3*s*, 3 CO); 139.7, 136.3, 135.7 (3*s*, 3 arom. C); 132.8, 130.0, 128.6, 128.5, 128.3, 128.2, 127.3, 126.8, 122.1, 120.2 (10*d*, 14 arom. CH); 66.9 (*t*, Ph*C*H$_2$O); 61.3 (*s*, PhCH$_2$*C*); 41.0 (*t*, Ph*C*H$_2$C); 23.3 (*q*, Me); 1 arom. C could not be detected. CI-MS: 450 (10, $[M+NH_4]^+$), 434 (28), 433 (100, $[M+1]^+$), 415 (26), 281 (48).

6.3. *Benzyl {2-[({1-Methyl-2-[(1-{[(methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]-2-oxo-1-(phenylethyl)ethyl}amino)carbonyl]phenyl}carbamate* (**23**). According to *GP 1*, with **22** (0.470 g, 1.087 mmol) in THF (10 ml), **7a** (0.240 g, 1.196 mmol) in THF (5 ml); reaction time 72 h. The crude product was filtered, washed with cold hexane/Et_2O 1 : 1, and dried *in vacuo:* 0.544 g (79%) of **23**. Colorless powder. M.p. 205.4 – 206.8°. IR: 3316*s*, 3063*m*, 3031*m*, 2954*m*, 2872*m*, 1733*s*, 1660*s*, 1632*s*, 1589*s*, 1525*s*, 1449*s*, 1375*s*, 1323*s*, 1279*s*, 1214*s*, 1135*m*, 1105*m*, 1093*m*, 1042*s*, 1029*m*, 986*m*, 885*w*, 851*w*, 756*s*, 702*s*. ^{1}H-NMR: 10.03 (*s*, NH); 8.36 (*d*, *J* = 8.3, 1 arom. H); 7.54 – 7.19 (*m*, 12 arom. H); 7.08 – 6.97 (*m*, 2 arom. H); 6.86 – 6.85 (*m*, 4 arom. H); 6.57, 5.94 (2*s*, 2 NH); 5.22 (*s*, PhCH_2O); 3.66, 2.86 (*AB*, *J* = 13.8, PhCH_2C); 3.18 (*s*, MeN); 2.36 – 2.26, 1.79 – 1.72, 1.66 – 1.63 (3*m*, $(CH_2)_4$); 1.47 (*s*, Me). ^{13}C-NMR: 172.2, 172.0, 169.9, 153.4 (4*s*, 4 CO); 144.9, 139.8, 136.1, 135.6 (4*s*, 4 arom. C); 133.2, 130.8, 128.7, 128.65, 128.6, 128.5, 127.4, 127.3, 126.9, 126.7, 122.1, 120.4 (12*d*, 19 arom. CH); 120.5 (*s*, 1 arom. C); 67.7 (*s*, PhCH$_2$*C*); 67.0 (*t*, PhCH_2O); 62.3 (*s*, $(CH_2)_4$*C*); 41.5 (*t*, PhCH_2C); 40.9 (*q*, MeN); 38.8, 38.5, 24.1, 24.0 (4*t*, $(CH_2)_4$); 23.6 (*q*, Me). ESI-MS: 655 (100, $[M+Na]^+$). Anal. calc. for $C_{38}H_{40}N_4O_5$ (632.77): C 72.13, H 6.37, N 8.85; found: C 72.46, H 6.43, N 8.68.

6.4. *Compound* **24**. According to *GP 4*, hydrogenolysis of **23** (0.250 g, 0.395 mmol) in MeOH (30 ml) yielded 0.190 g (96%) of **24**. Colorless powder. M.p. 218.1 – 218.5°. IR: 3468*m*, 3348*s*, 3058*w*, 3026*w*, 2959*m*, 2870*w*, 1659*s*, 1635*s*, 1593*w*, 1577*m*, 1523*s*, 1493*s*, 1452*m*, 1371*m*, 1327*w*, 1263*m*, 1234*w*, 1160*w*, 1095*m*, 1026*w*, 985*w*, 799*w*, 745*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 7.88, 7.56 (2*s*, 2 NH); 7.38 – 7.32, 7.24 – 7.11 (2*m*, 12 arom. H); 6.70 (*dd*, *J* = 8.2, 0.7, 1 arom. H); 6.48 (*td*, *J* = 7.9, 0.9, 1 arom. H); 6.21 (*s*, NH_2); 3.61, 3.08 (*AB*, *J* = 13.5, PhCH_2); 3.28 (*s*, MeN); 2.34 – 2.28, 2.16 – 2.09, 2.05 – 1.95, 1.61 – 1.54 (4*m*, $(CH_2)_4$); 1.35 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 173.1, 172.4, 168.7 (3*s*, 3 CO); 149.2, 145.6, 137.4 (3*s*, 3 arom. C); 131.5, 130.4, 128.5, 127.6, 126.7, 126.0, 125.7, 116.0 (8*d*, 13 arom. CH); 115.5 (*s*, 1 arom. C); 114.4 (*d*, 1 arom. CH); 66.4 (*s*, PhCH$_2$*C*); 59.2 (*s*, $(CH_2)_4$*C*); 38.9 (*q*, MeN); 38.7 (*t*, PhCH_2); 36.3, 36.1, 24.2, 23.9 (4*t*, $(CH_2)_4$); 21.1 (*q*, Me). ESI-MS: 521 (100, $[M+Na]^+$), 391 (40).

6.5. cis-*10′,22′-Dibenzyl-10′,22′-dimethyl-10′,11′,22′,23′-tetrahydro-6′*H,*8′*H-*dispiro[cyclopentane-1,7′-dibenzo[*h,r*]*[1,4,7,11,14,17]hexaazacycloicosine-19′,1′′-cyclopentane]-6′,9′,12′,18′,21′,24′(5′*H,*17′*H,*20′*H*)-hexone* (**25**), *1-[[2-Methyl-1-oxo-2-(4-oxoquinazolin-3(4*H*)-yl)-3-phenylpropyl]amino]-*N*-phenylcyclopentanecarboxamide* (**26**), *and 4′-Benzyl-4′,5′-dihydro-4′-methylspiro[cyclopentane-1,2′(6′*H*)-[1*H*]imidazo[1,2-*a*][1,4]benzodiazepine]-1′,6′-dione* (**27**). According to *GP 6*, with **24** (0.193 g, 0.388 mmol), in toluene (120 ml), 100°; reaction time 3 min. CC (CH_2Cl_2/MeOH 150 : 1 to 50 : 1) yielded 0.075 g (50%) of **25**, 0.065 g (32%) of **26**, and traces of **27**.

Data of **25**: Colorless microcrystals. M.p. 270° (decomp.). IR: 3364*m*, 3031*w*, 2940*m*, 2926*s*, 2855*m*, 1681*s*, 1651*s*, 1603*m*, 1583*m*, 1523*s*, 1444*s*, 1371*w*, 1268*s*, 1170*w*, 1127*w*, 905*w*, 749*m*, 708*w*. ^{1}H-NMR ((D$_6$)DMSO, 360 K): 9.80 (*s*, 2 NH); 7.91 (*d*, *J* = 8.1, 2 arom. H); 7.72 (*s*, 2 NH); 7.64 (*s*, 2 NH); 7.46 – 7.37 (*m*, 4 arom. H); 7.25 – 7.10 (*m*, 12 arom. H); 3.82, 3.12 (*AB*, *J* = 13.3, 2 PhCH_2); 2.26 – 2.21, 2.09 – 2.01, 1.72 – 1.63 (3*m*, 2 $(CH_2)_4$); 1.32 (*s*, 2 Me). ^{13}C-NMR ((D$_6$)DMSO): 173.6, 173.5, 167.3 (3*s*, 6 CO); 137.0, 136.1 (2*s*, 6 arom. C); 130.6, 130.0, 127.8, 126.3, 124.0 (5*d*, 18 arom. CH); 67.4 (*s*, 2 $(CH_2)_4$*C*); 60.0 (*s*, 2 PhCH$_2$*C*); 38.7 (*t*, 2 PhCH_2); 35.9, 23.8 (2*t*, 2 $(CH_2)_4$); 22.6 (*q*, 2 Me). ESI-MS: 783 (100, $[M+Na]^+$), 511 (33), 419 (17), 392 (29).

Recrystallization from THF/toluene/MeOH/CH_2Cl_2 yielded crystals of **25** suitable for X-ray crystal-structure determination.

Data of **26**: Colorless crystals. M.p. 280° (decomp.). IR: 3448*w*, 3296*m*, 2950*w*, 1683*s*, 1665*s*, 1651*s*, 1603*w*, 1583*m*, 1520*s*, 1446*m*, 1363*w*, 1272*m*, 1167*w*, 1128*w*, 748*m*, 705*m*. ^{1}H-NMR: 9.17 (*s*, PhN*H*CO); 8.30–8.27 (*m*, 1 arom. H); 7.86–7.80 (*m*, 2 arom. H); 7.78–7.73 (*m*, 2 arom. H); 7.65–7.62 (*m*, 1 arom. H); 7.53–7.47 (*m*, 1 arom. H); 7.45 (*s*, NH); 7.31–7.21 (*m*, 1 arom. H); 7.16–6.99 (*m*, 4 arom. H); 6.76–6.72 (*m*, 2 arom. H); 5.77 (*s*, N=CH); 3.88, 3.17 (*AB*, J = 13.5, PhCH_2); 2.52–2.45, 2.31–2.22, 2.03–1.95, 1.85–1.75 (4*m*, $(CH_2)_4$); 1.70 (*s*, Me). ^{13}C-NMR: 171.9, 171.3, 162.4 (3*s*, 3 CO); 147.6 (*s*, 1 arom. C); 142.9 (*d*, N=CH); 138.9 (*s*, 1 arom. C); 135.2 (*d*, 1 arom. CH); 134.2 (*s*, 1 arom. C); 130.3, 128.6, 127.9, 127.7, 127.6, 127.0, 123.8 (7*d*, 12 arom. CH); 121.7 (*s*, 1 arom. C); 120.5 (*d*, 1 arom. CH); 68.4 (*s*, $(CH_2)_4C$); 66.2 (*s*, PhCH_2C); 38.7 (*t*, PhCH_2); 38.4, 37.5, 24.7, 24.6 (4*t*, $(CH_2)_4$); 23.0 (*q*, Me).

Recrystallization from Et_2O/CH_2Cl_2 yielded crystals of **26** suitable for X-ray crystal-structure determination.

Data of **27**. Recrystallization from CH_2Cl_2/Et_2O/hexane yielded a crystal of **27** suitable for X-ray crystal-structure determination.

7. *Synthesis of 2-Amino*-N-*{1-[({2-[(1-{[(methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]-2-oxoethyl}-amino)carbonyl]cyclopentyl}benzamide* (**31**). 7.1. *Methyl [({1-[(2-{[(Benzyloxy)carbonyl]amino}benzoyl)amino]cyclopentyl}carbonyl)amino]acetate* (**28**). According to *GP 5*, with **9** (0.160 g, 0.418 mmol), methyl glycinate hydrochloride (0.063 g, 0.502 mmol), TBTU (0.134 g, 0.418 mmol), HOBt (0.057 g, 0.418 mmol), EtN(i-Pr)$_2$ (0.14 ml, 0.837 mmol), and CH_2Cl_2 (10 ml); reaction time 2 h. CC (CH_2Cl_2/MeOH 300:1) gave 0.186 g (98%) of **28**. Colorless powder. M.p. 176.7–177.4°. IR: 3366*s*, 3313*s*, 3275*s*, 3066*m*, 2955*s*, 2874*w*, 1754*s*, 1738*s*, 1666*s*, 1627*s*, 1600*s*, 1586*s*, 1538*s*, 1511*s*, 1449*s*, 1300*m*, 1206*s*, 1179*m*, 1046*s*, 1057*m*, 771*w*, 700*w*. ^{1}H-NMR: 10.42 (*s*, NH); 8.35 (*dd*, J = 8.7, 0.7, 1 arom. H); 7.46–7.31 (*m*, 7 arom. H); 7.08 (*t*, J = 5.1, NH); 7.03–6.98 (*m*, 1 arom. H); 6.66 (*s*, NH); 5.18 (*s*, PhCH_2); 4.00 (*d*, J = 5.3, CH_2CO); 3.66 (*s*, MeO); 2.44–2.35, 2.12–2.03, 1.88–1.69 (3*m*, $(CH_2)_4$). ^{13}C-NMR: 173.8, 170.3, 169.3, 153.6 (4*s*, 4 CO); 139.9, 136.2 (2*s*, 2 arom. C); 132.9, 128.5, 128.2, 126.8, 122.0, 120.0 (6*d*, 9 arom. CH); 119.8 (*s*, 1 arom. C); 67.9 (*s*, $(CH_2)_4C$); 66.8 (*t*, PhCH_2); 52.2 (*q*, MeO); 41.5 (*t*, CH_2CO); 36.9, 24.2 (2*t*, $(CH_2)_4$). ESI-MS: 476 (100, $[M+Na]^+$). Anal. calc. for $C_{24}H_{27}N_3O_6$ (453.48): C 63.57, H 6.00, N 9.26; found: C 63.78, H 5.91, N 9.18.

7.2. *[({1-[(2-{[(Benzyloxy)carbonyl]amino}benzoyl)amino]cyclopentyl}carbonyl)amino]acetic Acid* (**29**). According to *GP 3*, with **28** (0.186 g, 0.410 mmol) in MeOH (10 ml) and 1N NaOH (2.05 ml, 2.05 mmol); reaction time 90 h: 0.134 g (74%) of **26**. Colorless powder. M.p. 203.2–203.8°. IR: 3300*s*, 3035*w*, 2961*m*, 2874*m*, 1736*s*, 1657*s*, 1628*s*, 1588*s*, 1521*s*, 1449*s*, 1304*w*, 1281*w*, 1244*s*, 1214*s*, 1108*w*, 1038*m*, 914*w*, 765*w*, 754*w*, 699*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.36 (br. *s*, OH); 10.55, 8.61 (2*s*, 2 NH); 8.09 (*dd*, J = 8.3, 0.9, 1 arom. H); 7.88–7.83 (*m*, 2 arom. H); 7.51–7.32 (*m*, 5 arom. H, NH); 7.14–7.09 (*m*, 1 arom. H); 5.15 (*s*, PhCH_2); 3.71 (*d*, J = 4.4, CH_2CO); 2.21–2.17, 2.04–1.99, 1.66–1.50 (3*m*, $(CH_2)_4$). ^{13}C-NMR ((D$_6$)DMSO): 177.2, 176.7, 171.0, 155.8 (4*s*, 4 CO); 138.0, 137.2 (2*s*, 2 arom. C); 133.4, 129.7, 129.5, 129.1 (4*d*, 7 arom. CH); 125.2 (*s*, 1 arom. C); 125.1, 122.7 (2*d*, 2 arom. CH); 68.9 (*s*, $(CH_2)_4C$); 68.2 (*t*, PhCH_2); 45.1 (*t*, CH_2CO); 37.9, 25.5 (2*t*, $(CH_2)_4$). ESI-MS: 462 (100, $[M+Na]^+$).

7.3. *Benzyl {2-[({1-[({2-[(1-{[(Methyl)(phenyl)amino]carbonyl}cyclopentyl)amino]-2-oxoethyl}amino)-carbonyl]cyclopentyl}amino)carbonyl]phenyl}carbamate* (**30**). According to *GP 1*, with **29** (0.127 g, 0.289 mmol) in THF (8 ml), **7a** (0.06 g, 0.300 mmol) in THF (2 ml); reaction time 90 h. CC (CH_2Cl_2/MeOH 200:1 to 20:1) gave 0.172 g (93%) of **30**. Colorless powder. M.p. 214.5–215.3°. IR: 3392*m*, 3335*s*, 3035*w*, 2952*m*, 2875*w*, 1728*s*, 1678*s*, 1655*s*, 1633*s*, 1594*s*, 1533*s*, 1453*s*, 1374*m*, 1328*m*, 1281*m*, 1244*m*, 1219*s*, 1106*m*, 1044*m*, 1028*w*, 985*w*, 954*w*, 849*w*. ^{1}H-NMR: 10.34 (*s*, 1 NH); 8.41 (*d*, J = 8.4, 1 arom. H); 7.66 (*d*, J = 7.9, 1 arom. H); 7.52 (*td*, J = 8.5, 1.2, 1 arom. H); 7.42–7.30 (*m*, 6 arom. H); 7.18–6.87 (*m*, 5 arom. H, NH); 6.41 (br. *s*, NH); 5.20 (*s*, PhCH_2); 3.51–3.43 (*m*, CH_2CO); 3.10 (*s*, MeN); 2.26–2.04, 1.97–1.85, 1.81–1.69, 1.62–1.52 (4*m*, 2 $(CH_2)_4$). ^{13}C-NMR: 173.6, 172.6, 169.7, 168.3, 153.5 (5*s*, 5 CO); 144.8, 139.9, 135.8 (3*s*, 3 arom. C); 132.2, 129.0, 128.5, 128.4, 127.5, 126.9, 126.7, 122.0, 119.8 (9*d*, 14 arom. CH); 118.9 (*s*, 1 arom. C); 67.4, 67.2 (2*s*, 2 $(CH_2)_4C$); 67.0 (*t*, PhCH_2); 43.5 (*t*, CH_2CO); 40.4 (*q*, MeN); 38.4, 37.1, 24.2, 24.0 (3*t*, 2 $(CH_2)_4$). ESI-MS: 662 (100, $[M+Na]^+$).

7.4. *Compound* **31**. According to *GP 4*, hydrogenolysis of **30** (0.163 g, 0.255 mmol) in MeOH (10 ml); reaction time 24 h. CC (AcOEt/hexane 2:1) yielded 0.091 g (71%) of **31**. Colorless powder. M.p. 158.2–159.5°. IR: 3448*m*, 3332*s*, 2956*s*, 2873*m*, 1636*s*, 1592*s*, 1525*s*, 1495*s*, 1450*m*, 1372*m*, 1260*m*, 750*m*, 703*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.33 (*s*, 1 NH); 7.65 (*dd*, J = 7.9, 1.2, 1 arom. H); 7.27–7.06 (*m*, 6 arom. H, NH); 6.71–6.69 (*m*, 1 arom. H); 6.59–6.54 (*m*, 1 arom. H); 6.21 (*s*, NH_2); 3.40–3.37 (*m*, CH_2CO); 3.07 (*s*, MeN); 2.21–2.12, 1.83–1.79, 1.65–1.63, 1.54–1.53 (4*m*, 2 $(CH_2)_4$). ^{13}C-NMR ((D$_6$)DMSO): 175.3, 173.5, 170.8, 169.2 (4*s*, 4 CO); 148.9, 144.9 (2*s*, 2 arom. C); 133.1, 129.5, 128.3, 127.4, 126.9, 117.6, 117.0 (7*d*, 9 arom. CH); 116.0 (*s*, 1 arom. C); 67.6, 67.3 (2*s*, 2 $(CH_2)_4C$); 43.3 (*t*, CH_2CO); 40.6 (*q*, MeN); 38.6, 37.4, 24.7, 24.5 (4*t*, 2 $(CH_2)_4$). ESI-MS: 528 (100, $[M+Na]^+$).

All attempts to cyclize **31** under the conditions of the 'direct amide cyclization' failed, and only decomposition was observed.

8. *Synthesis of Methyl 2-[({2-[(2-Amino-1-oxopropyl)amino]phenyl}carbonyl)amino]-2-methylpropanoate* (**36**). 8.1. *Methyl 2-[(1-Oxo-2-{[(benzyloxy)carbonyl]amino}propyl)amino]benzoate* (**32**). Methyl anthranilate (0.300 g, 1.98 mmol), Z-alanine (0.4386 g, 2.18 mmol), and [(1*H*-benzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP) (1.13 g, 2.18 mmol) were dissolved in CH_2Cl_2 (20 ml). At r.t., $EtN(i\text{-}Pr)_2$ (0.75 ml, 4.35 mmol) was added, and the mixture was stirred for 24 h. Then, the solvent was evaporated *in vacuo*, and the product was purified by CC (CH_2Cl_2/MeOH 500:1 to 250:1): 0.433 g (61%) of **32**. ^{1}H-NMR: 11.50 (*s*, NH); 8.69 (*dd*, J = 8.5, 1.5, 1 arom. H); 8.03 (*dd*, J = 8.0, 1.6, 1 arom. H); 7.57–7.52 (*m*, 1 arom. H); 7.37–7.26 (*m*, 5 arom. H); 7.10 (*td*, J = 8.2, 1.2, 1 arom. H); 5.47 (br. *s*, NH); 5.16 (*s*, Ph*C*H_2); 4.47–4.43 (*m*, Me*C*H); 3.89 (*s*, MeO); 1.53 (*d*, J = 7.1, *Me*CH). ^{13}C-NMR: 171.2, 171.0, 168.4 (3*s*, 3 CO); 140.9 (*s*, 1 arom. C); 134.5, 130.8, 128.4, 128.0 (4*d*, 7 arom. CH); 126.9 (*s*, 1 arom. C); 122.8, 120.3 (2*d*, 2 arom. CH); 115.3 (*s*, 1 arom. C); 67.0 (*t*, Ph*C*H_2); 52.2 (*q*, MeO); 51.8 (*d*, Me*C*H); 18.9 (*q*, *Me*CH).

8.2. *2-[(1-Oxo-2-{[(benzyloxy)carbonyl]amino}propyl)amino]benzoic Acid* (**33**). According to *GP 3*, with **32** (0.359 g, 1.008 mmol) in MeOH (12 ml) and 1N NaOH (2 ml, 2 mmol); reaction time 24 h: 0.233 g (68%) of **33**. ^{1}H-NMR ((D_6)DMSO): 11.70 (*s*, NH); 8.61 (*d*, J = 8.4, 1 arom. H); 8.03–7.94 (*m*, 2 arom. H); 7.63–7.58 (*m*, 1 arom. H); 7.39–7.21 (*m*, 4 arom. H); 7.17 (*td*, J = 8.3, 1.2, 1 arom. H); 5.12, 5.03 (*AB*, J = 12.7, Ph*C*H_2); 4.18–4.09 (*m*, Me*C*H); 1.36 (*d*, J = 7.3, *Me*CH). ^{13}C-NMR ((D_6)DMSO): 171.7, 169.2, 156.0 (3*s*, 3 CO); 140.6, 136.8 (2*s*, 2 arom. C); 134.0, 131.0, 128.2, 127.6, 127.5, 122.6, 119.4 (7*d*, 9 arom. CH); 116.1 (*s*, 1 arom. C); 65.6 (*t*, Ph*C*H_2); 51.9 (*d*, Me*C*H); 17.2 (*q*, *Me*CH).

8.3. *Benzyl* N-*(2-{[2-({[2-(Dimethylamino)-1,1-dimethyl-2-oxoethyl]amino}carbonyl)phenyl]amino}-1-methyl-2-oxoethyl)carbamate* (**34**). According to *GP 1*, with **33** (0.250 g, 0.730 mmol) in THF (15 ml), **7c** (0.080 g, 0.730 mmol) in THF (5 ml); reaction time 48 h. CC (CH_2Cl_2/MeOH 200:1 to 150:1) gave 0.195 g (59%) of **34**. Colorless powder. M.p. 165.8–166.5°. IR: 3299*m*, 3064*w*, 2936*w*, 1723*s*, 1710*s*, 1665*s*, 1649*s*, 1622*s*, 1587*m*, 1515*s*, 1447*s*, 1406*m*, 1389*m*, 1326*w*, 1298*m*, 1245*s*, 1174*w*, 1119*m*, 1069*m*, 915*w*, 909*w*, 756*m*, 701*w*. ^{1}H-NMR: 11.60 (*s*, 1 NH); 8.54 (*dd*, J = 8.5, 0.9, 1 arom. H); 7.96 (*s*, 1 NH); 7.54 (*dd*, J = 7.9, 1.4, 1 arom. H); 7.43 (*td*, J = 8.5, 1.4, 1 arom. H); 7.36–7.31 (*m*, 5 arom. H); 7.07 (*td*, J = 8.5, 1.1, 1 arom. H); 5.59–5.57 (*m*, 1 NH); 5.17, 5.09 (*AB*, J = 6.7, Ph*C*H_2); 4.41 (*t*, J = 6.7, Me*C*H); 3.08 (*s*, Me_2N); 1.78, 1.76 (2*s*, Me_2C); 1.49 (*d*, J = 7.0, *Me*CH). ^{13}C-NMR: 173.1, 171.1, 167.2, 155.7 (4*s*, 4 CO); 139.2, 136.4 (2*s*, 2 arom. C); 132.4, 128.4, 128.0, 126.8, 123.1, 121.4 (6*d*, 9 arom. CH); 121.0 (*s*, 1 arom. C); 66.8 (*t*, Ph*C*H_2); 57.4 (*s*, Me_2C); 51.7 (*d*, Me*C*H); 38.3 (*q*, Me_2N); 24.0, 23.9 (2*q*, Me_2C); 19.3 (*q*, *Me*CH). ESI-MS: 477 (21, $[M+Na]^+$), 455 (100, $[M+1]^+$), 410 (78), 348 (30), 281 (19).

8.4. *2-[(2-Amino-1-oxopropyl)amino]*-N-*[2-(dimethylamino)-1,1-dimethyl-2-oxoethyl]benzamide* (**35**). According to *GP 4*, hydrogenolysis of **34** (0.190 g, 0.418 mmol) in MeOH (15 ml); reaction time 2 h: 0.110 g (82%) of **35**. Colorless powder. M.p. 205.1–206.4°. IR: 3276*s*, 2985*m*, 2932*m*, 1627*s*, 1583*s*, 1513*s*, 1446*s*, 1393*s*, 1363*m*, 1320*m*, 1289*m*, 1206*m*, 1119*s*, 1055*w*, 948*w*, 904*w*, 794*w*, 759*m*, 706*w*. ^{1}H-NMR: 11.60 (*s*, 1 NH); 8.58 (*d*, J = 8.2, 1 arom. H); 7.76 (*s*, 1 NH); 7.53–7.43 (*m*, 2 arom. H); 7.08 (*t*, J = 7.4, 1 arom. H); 3.65–3.63 (*m*, Me*C*H); 3.10 (*s*, Me_2N); 1.79 (*s*, Me_2C); 1.43 (*d*, J = 6.7, *Me*CH). ^{13}C-NMR: 175.2, 173.1, 167.6 (3*s*, 3 CO); 137.9 (*s*, 1 arom. C); 131.9, 127.1, 123.1 (3*d*, 3 arom. CH); 122.1 (*s*, 1 arom. C); 121.4 (*d*, 1 arom. CH); 57.0 (*s*, Me_2C); 51.3 (*d*, Me*C*H); 37.9 (*q*, Me_2N); 24.8 (*q*, Me_2C); 21.0 (*q*, *Me*CH). ESI-MS: 343 (100, $[M+Na]^+$), 321 (34, $[M+1]^+$), 276 (22).

8.5. *Compound* **36**. According to *GP 6*, with **35** (0.100 g, 0.312 mmol), in toluene (100 ml), 100°; reaction time 10 min. CC (CH_2Cl_2/MeOH 150:1) yielded 0.027 g (28%) of **36**. White powder. M.p. 154.9–156.0°. IR: 3402*w*, 3300*m*, 3062*w*, 2986*m*, 2933*w*, 1740*s*, 1660*s*, 1643*s*, 1598*m*, 1580*m*, 1507*s*, 1444*s*, 1387*m*, 1327*m*, 1292*m*, 1270*m*, 1221*w*, 1194*w*, 1152*s*, 1002*w*, 923*w*, 792*w*, 756*m*. ^{1}H-NMR: 11.36 (*s*, 1 NH); 8.55 (*d*, J = 8.1, 1 arom. H); 7.51–7.43 (*m*, 2 arom. H); 7.08 (*td*, J = 8.1, 1.0, 1 arom. H); 6.78 (*s*, 1 NH); 3.78 (*s*, MeO); 3.64–3.59 (*m*, Me*C*H); 1.67 (*s*, Me_2C); 1.41 (*d*, J = 6.96, Me*C*H). ^{13}C-NMR: 175.1, 174.9, 168.3 (3*s*, 3 CO); 138.5 (*s*, 1 arom. C); 132.2, 126.8, 122.9 (3*d*, 3 arom. CH); 122.4 (*s*, 1 arom. C); 121.7 (*d*, 1 arom. CH); 57.0 (*s*, Me_2C); 52.8 (*q*, MeO); 52.0 (*d*, Me*C*H); 24.7 (*q*, Me_2C); 21.7 (*q*, *Me*CH). CI-MS: 309 (18, $[M+2]^+$), 308 (100, $[M+1]^+$), 191 (5).

9. *X-Ray Crystal-Structure Determinations of Compounds* **12**, **17**, **20**, **25**, **26**, *and* **27** (see *Tables 1* and *2* and *Figs. 1–6*)[2]). All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer [53] by

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[2]) CCDC-265726–265731 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk)).

using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream-700* cooler. Data reduction was performed with *HKL Denzo* and *Scalepack* [54]. The intensities were corrected for *Lorentz* and polarization effects. In the case of **26**, an absorption correction based on the multi-scan method [55] was applied. The data collection and refinement parameters are given in *Tables 1* and *2*, and views of the molecules are shown in *Figs. 1–6*. Each structure was solved by direct methods using SIR92 [56], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically.

Table 1. *Crystallographic Data of Compounds* **12**, **17**, **20**, *and* **27**

		12	**17**	**20**	**27**
Crystallized from		CH_2Cl_2/Et_2O	CH_2Cl_2/Et_2O	$MeOH/Et_2O/CH_2Cl_2$	CH_2Cl_2/Et_2O/hexane
Empirical formula		$C_{19}H_{21}N_3O_2$	$C_{15}H_{15}N_3O_2$	$2C_{16}H_{17}N_3O_5 \cdot CH_3OH$	$C_{23}H_{23}N_3O_2$
Formula weight [g mol^{-1}]		323.39	269.30	694.69	373.45
Crystal color, habit		colorless, prism	colorless, prism	colorless, prism	colorless, plate
Crystal dimensions [mm]		$0.22 \times 0.25 \times 0.40$	$0.10 \times 0.15 \times 0.25$	$0.05 \times 0.12 \times 0.12$	$0.07 \times 0.20 \times 0.20$
Temperature [K]		160(1)	160(1)	160(1)	160(1)
Crystal system		triclinic	monoclinic	triclinic	monoclinic
Space group		$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Z		2	4	2	4
Reflections for cell determination		3800	4039	3973	3608
2θ range for cell determination [°]		2–60	4–60	4–44	4–50
Unit cell parameters	a [Å]	6.1782(1)	10.8624(2)	9.1119(3)	17.4548 (5)
	b [Å]	9.2220(2)	7.5537(1)	13.5302(6)	7.0316 (2)
	c [Å]	14.7542(3)	15.9813(3)	13.9245(7)	17.0160 (4)
	α [°]	102.685(1)	90	89.080(2)	90
	β [°]	91.494(1)	101.4916(9)	90.123(2)	116.345 (1)
	γ [°]	97.7754(9)	90	72.749(2)	90
	V [Å^3]	811.22(3)	1285.00(4)	1639.2(1)	1871.55 (9)
D_x [g cm^{-3}]		1.324	1.392	1.407	1.325
μ(MoK_α) [mm^{-1}]		0.0876	0.0951	0.107	0.0860
Scan type		ϕ and ω	ϕ and ω	ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]		55	60	44	50
Total reflections measured		13837	37521	29317	26714
Symmetry-independent reflections		3686	3773	3990	3324
Reflections with $I > 2\sigma(I)$		3248	2797	2935	2527
Reflections used in refinement		3248	2797	2935	2527
Parameters refined		218	186	460	258
Final $R(F)$		0.0490	0.0480	0.0775	0.0446
$wR(F)$		0.0665	0.0486	0.0783	0.0461
Weighting parameter [p][a])		0.010	0.007	0.013	0.005
Goodness-of-fit		3.266	2.635	2.910	2.475
Secondary extinction coefficient		0.000004(2)	0.0000018(5)	0.0000013(5)	0.0000015(3)
Final Δ_{max}/σ		0.0003	0.0006	0.0001	0.0004
$\Delta\rho$ (max; min) [e Å^{-3}]		0.38; −0.28	0.32; −0.29	0.24; −0.20	0.25; −0.21

[a]) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$.

In the case of **26**, the asymmetric unit contains two molecules of the peptide plus one molecule of CH_2Cl_2. The five-membered ring of one peptide molecule is disordered. Two equally occupied positions were defined for one CH_2 group of the ring. Bond-length restraints were applied to all bonds involving the disordered atoms.

Table 2. *Crystallographic Data of Compounds* **25** *and* **26**

		25	**26**
Crystallized from		THF/toluene/MeOH/CH_2Cl_2	Et_2O/CH_2Cl_2
Empirical formula		$C_{46}H_{50}N_6O_6 \cdot CH_3OH \cdot H_2O$	$2C_{30}H_{30}N_4O_3 \cdot CH_2Cl_2$
Formula weight [g mol^{-1}]		832.99	1074.1
Crystal color, habit		colorless, needle	colorless, prism
Crystal dimensions [mm]		$0.02 \times 0.07 \times 0.30$	$0.07 \times 0.17 \times 0.25$
Temperature [K]		160(1)	160(1)
Crystal system		triclinic	monoclinic
Space group		$P\bar{1}$	Cc
Z		2	4
Reflections for cell determination		7098	94939
2θ range for cell determination [°]		4 – 50	4 – 50
Unit-cell parameters	a [Å]	11.456(1)	17.7319(2)
	b [Å]	11.948(2)	15.3756(2)
	c [Å]	16.975(3)	21.5283(3)
	α [°]	76.962(8)	90
	β [°]	87.559(9)	109.7593(7)
	γ [°]	77.471(6)	90
	V [Å^3]	2209.6(5)	5523.9(1)
D_x [g cm^{-3}]		1.252	1.291
μ(Mo K_α) [mm^{-1}]		0.0862	0.177
Scan type		ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]		50	50
Transmission factors (min; max)		–	0.914; 0.991
Total reflections measured		27387	40211
Symmetry-independent reflections		7656	9586
Reflections with $I > 2\sigma(I)$		3339	8323
Reflections used in refinement		7656	9579
Parameters refined		526	705
Final	$R(F)$ ($I > 2\sigma(I)$ reflections)	0.137	0.0365
	$wR(F^2)$ (all indept. reflections)	0.378	0.0849
Weighting parameters [a; b][a])		0.1666; 3.34	0.0361; 1.8544
Goodness-of-fit		1.032	1.062
Secondary extinction coefficient		0.034(5)	–
Final Δ_{max}/σ		0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.44; −0.37	0.18; −0.37

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$.

The crystal of **20** was very weakly diffracting and the results are of low precision. The asymmetric unit contains two molecules of the peptide plus one molecule of MeOH.

In the case of **25**, only one very poor crystal could be isolated, which was weakly diffracting and gave broad reflection profiles. The structure unambiguously reveals the nature of the peptide molecule, but the geometric parameters are very imprecise. The asymmetric unit contains one molecule of the peptide plus a region, which is presumably occupied by solvent molecules. It was not possible to model the solvent, or even find sensible residual electron-density peaks representing the solvent atoms. Therefore, the contribution of the solvent molecules to the intensity data was removed by using the SQUEEZE [57] routine of the PLATON [58] program. Omission of the solvent molecules leaves one cavity of 323 Å^3 per unit cell. The number of electrons contributing to each void in the structure was calculated by the SQUEEZE routine to be *ca.* 52 e. Allowing for two MeOH and two H_2O molecules per cavity and unit cell yields 56 e and this was used in the subsequent calculation of the empirical formula, formula weight, density, linear absorption coefficient and $F(000)$. The

nature of the solvent is purely an assumption used to approximate the correct values for the parameters just described, but would be consistent with the solvent from which the crystals were obtained and the positions of the residual electron-density peaks observed in the void.

The amide H-atoms in **17** and **27**, as well as the OH and MeO H-atoms in **20**, were placed in the positions indicated by difference electron-density maps and, except for the OH H-atom of one peptide molecule of **20**, their positions were allowed to refine together with individual isotropic displacement parameters. All of the remaining H-atoms in the structures were placed in geometrically calculated positions and refined using a riding model, where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent atom (1.5 U_{eq} for the Me groups in **25** and **26**).

For **12**, **17**, **20**, and **27**, each structure was refined on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. The refinement of the structures of **25** and **26** was carried out on F^2 by minimizing the corresponding function based on F^2. Corrections for secondary extinction were applied, except for **26**. Compound **26** has crystallized in a polar, non-centrosymmetric space group, but one which dictates that the crystals are racemic. The absolute structure was confirmed by refinement of the absolute-structure parameter [59], which yielded a value of $-0.03(4)$. Neutral-atom-scattering factors for non-H-atoms were taken from [60a], and the scattering factors for H-atoms were taken from [61]. Anomalous dispersion effects were included in F_c [62]; the values for f' and f'' were those of [60b]. The values of the mass-attenuation coefficients are those of [60c]. The calculations for **25** and **26** were performed by using the SHELXL97 program [63], while those for the remaining structures were carried out by using the teXsan crystallographic software package [64].

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