DOI: 10.1002/ejoc.200500996

Synthesis and Evaluation of the β-Turn Properties of 4-Amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones and of Their Spirocyclic Derivative

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Keywords: Lactams / Asymmetric synthesis / Conformation analysis / Molecular modeling

A series of 4-amino-tetrahydro-2-benzazepin-3-one derivatives (Ac–Aba–Xxx–NHMe) were prepared as tetrapeptide mimetics. Considering the structural resemblance with the so-called Freidinger lactams, their propensity to adopt a β-turn conformation was investigated by NMR spectroscopy (solvent and temperature dependence) and molecular modeling. Interestingly, most of these lactams adopt extended conformations, only the spiro-benzazepinone **9** has a strong preference for the formation of a β-turn.

Introduction

The three-dimensional structure of a protein is characterized by an arrangement of α-helices, β-sheets, tight turns, bulges, and random coil structures. Tight turns, which cause the polypeptide chain to reverse its overall direction, play a key role in diverse aspects of the protein: without them the protein is not capable of adopting a compact globular structure, and their location on the surface of the protein allows them to function as molecular recognition elements.[1] They are involved in interactions between peptides and their receptors, antibodies and antigens, and regulatory enzymes and their corresponding substrates.[2] Tight turns provide important information allowing the design of new potent and selective drugs, pesticides and antigens,[1] and consequently much effort has been done to prepare small mimetics of turn structures.[2–6]

β-Turns belong, together with δ-, γ-, α- and π-turns, to the collection of tight turns.[1] In a β-turn, the reversal of the peptide backbone occurs over four amino acid residues in such a way that the carbonyl oxygen atom of the first residue (*i*) and the amide NH proton of the fourth residue (*i* + 3) come close in space, and in most cases are involved in an intramolecular hydrogen bridge forming a pseudo-ten-membered ring.[7]

β-Turn mimetics can be categorized in two distinct classes: internal and external mimetics. Internal mimetics are constructed upon frameworks within the pseudo-ten-membered ring, preserving the amino acid side-chain orientations. In external mimetics, the central dipeptide unit of the β-turn is replaced by a dipeptide isosteric skeleton. In this way, the conformational flexibility of the peptide is reduced by a rigidified skeleton lying outside the pseudo-ten-membered ring, orienting the surrounding peptide chain in a turn conformation.[2]

Examples of external β-turn mimetics are the Freidinger lactams. In the 1980's, a five-membered γ-lactam (**1**) was incorporated in luteinizing hormone-releasing hormone, fixing residues five to eight in a type II′ β-turn (Figure 1).[8] This analog was more active than the parent hormone. The six- and seven-membered δ- and ε- Freidinger lactams **2** and **3**[9] were reported to stabilize type II β-turns. Dehydro-Freidinger lactams **4** were also claimed in literature to be β-turn mimics.[10;11]

The 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba) skeleton has been applied successfully to constrain a Phe or Tyr side chain in biologically active peptides.[12–20] Considering their structural resemblance with dehydro-Freidinger lactams **4**, we have investigated their potential for adopting turn conformations.

N-acetyl dipeptide *N*′-methylamides **5**, **6**, **7**, **8** and **9** were prepared as mimics for the tetrapeptides[21] and their conformational properties were examined by NMR and molecular modeling to evaluate their β-turn mimicry. Analogs containing Gly as the *i* + 2 residue (**7**), *N*-methylated Aba **8**, heterochiral (**5**) and homochiral sequences (**6**) were studied.

Several spirolactams have been reported to be very efficient β-turn inducers.[22–25] We now also report the preparation of the spiro derivative **9**, and its conformational analysis.

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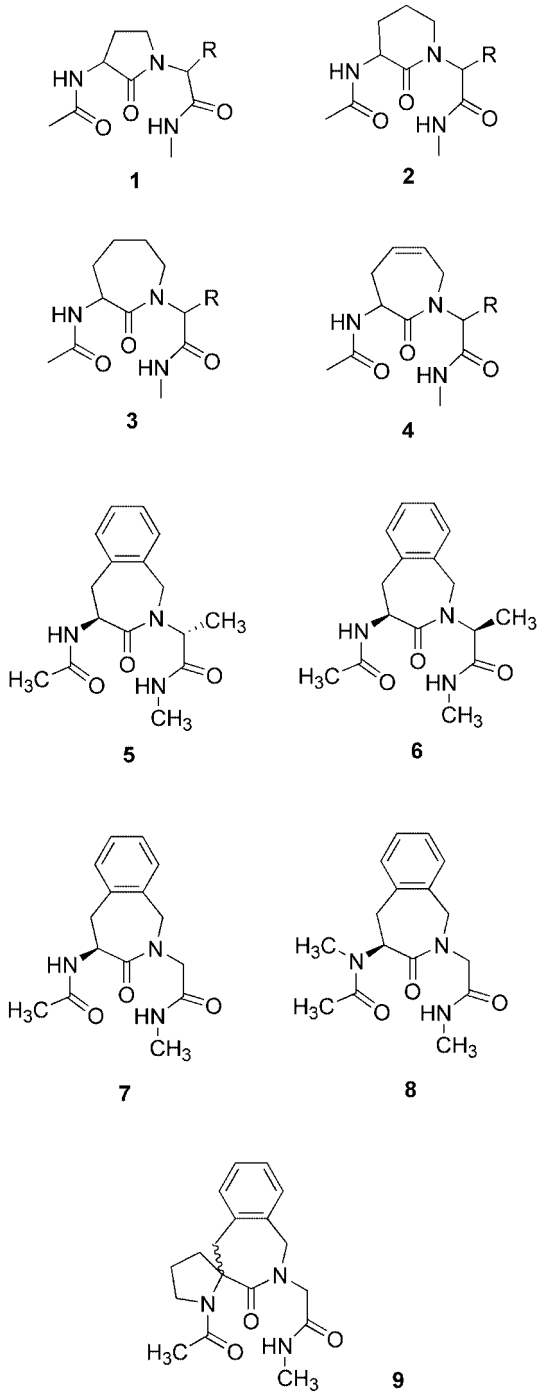

Figure 1. Freidinger lactams and benzazepinones as β-turn mimetics.

Results and Discussion

Synthesis of Tetrapeptide Mimetics

The starting material for Ac–(*S*)–Aba–(*R*)–Ala–NHMe (**5**), (*S*)-*o*-CN–Phe·HCl (**14**), was prepared through an asymmetric phase-transfer-catalysed alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate (**10**)[26] with *o*-cyanobenzyl bromide (**11**) using the commercially available and inexpensive catalyst *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide, resulting in the alkylated compound **12** (Figure 2). Hydrolysis of the benzophenone imine **12** using aqueous citric acid provides (*S*)-*o*-CN–Phe–O*t*Bu (**13**).

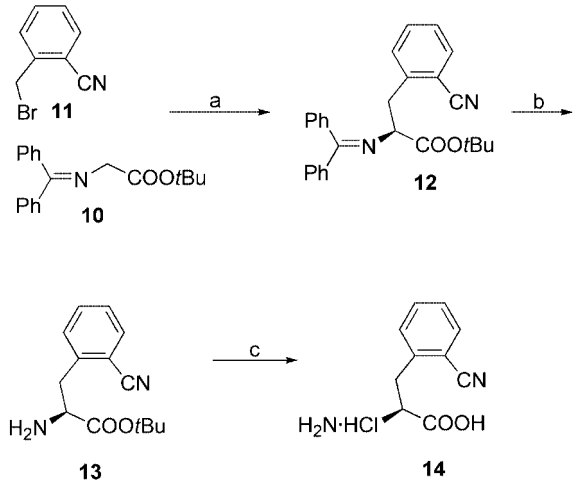

Figure 2. Synthesis of (*S*)-*o*-cyano–Phe. a) CsOH.H_2O, CH_2Cl_2, *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide, –78 °C, 27 h; b) 15% citric acid, THF, o.n., room temp., 90% yield (a+b); c) 6 N HCl, CH_2Cl_2, room temp., o.n., 97%.

At first a liquid/liquid phase-transfer alkylation of **10** (50% aq. KOH/toluene) at room temperature was examined,[27] which resulted in a low stereoinduction (62% *ee*). Excellent results were, however, obtained with solid/liquid PTC (CsOH·H_2O, CH_2Cl_2) at –78 °C:[28] 96% enantiomeric excess and 90% yield were achieved. In order to prevent the decomposition of the catalyst,[29] the base was suspended in CH_2Cl_2, the mixture was cooled, and then the catalyst and the Gly derivative were added.

A homogeneous alkylation of **10** using the phosphazene base BEMP was also evaluated,[30] but this resulted in lower yields and *ee* values (83% yield, 86% *ee*).

The *tert*-butyl ester of **13** was removed by acidolysis with 6 N HCl/CH_2Cl_2, 1:1 resulting in (*S*)-*o*-CN–Phe·HCl (**14**).[31] Other acidolytic conditions (TFA/H_2O, 9:1[32] and TFA/anisole, 3:1[33]) provided insufficient scavenging of the *t*Bu cation and caused *tert*-butylation of the aromatic ring of *o*-CN–Phe.

The stereoinduction of the alkylation reaction was determined by HPLC analysis of the FDAA derivative of **14**,[34] as the FDAA derivative of *tert*-butyl ester **13** and its optical antipode eluted at the same retention time.

(*S*)-*o*-CN–Phe·HCl **14** was phthaloyl-protected by means of methyl 2-[(succinimidooxy)carbonyl]benzoate (MSB)[35] and reduction of the nitrile **15** with H_2/Raney-Ni provided the aldehyde **16** (Figure 3).[36] This aldehyde was used in a reductive amination with (*R*)-Ala–OBn·*p*TosOH followed by ring closure, according to a procedure reported earlier.[37] Hydrogenolysis of Phth–(*S*)-Aba–(*R*)-Ala–OBn (**17**) provided the carboxylic acid **18**. Phthaloyl deprotection by hydrazinolysis led to (*S*)-Aba–(*R*)-Ala–OH (**19**).[18] Acetylation with acetic anhydride in water provided compound **20**,[38] which was used in a coupling reaction with methylamine using TBTU activation. During this coupling 30%

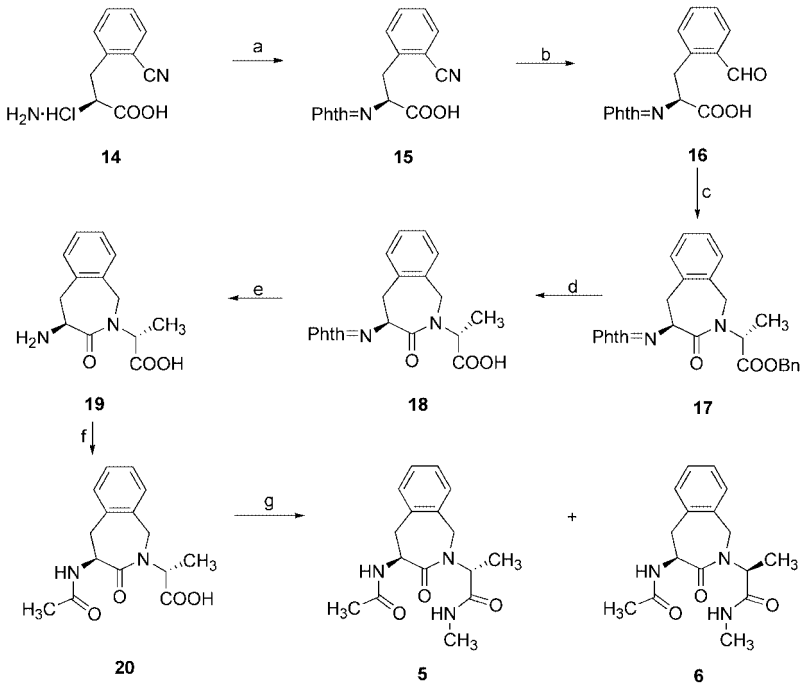

Figure 3. a) MSB, CH_3CN, H_2O, Na_2CO_3, 81%; b) Raney-Ni, H_2 (50 psi), H_2O/AcOH/Py, 1:1:1, 50 °C, 38 h, 78%; c) 1) (*R*)-Ala-OBn·*p*TosOH, $NaCNBH_3$, CH_2Cl_2, $MgSO_4$, NMM, 2) DCC, Py, AcN, 39% (2 steps); d) H_2 (50 psi), 10% Pd/C, dioxane/H_2O 3:2; e) NH_2NH_2, EtOH, reflux, 1.5 h, 84%; f) Ac_2O, NEt_3, water, 60%; g) CH_3NH_2·HCl, TBTU, NEt_3, CH_2Cl_2, room temp., o.n.

racemisation occurred, resulting in Ac–(*S*)-Aba–(*S*)-Ala–NHMe (**6**), beside the correct compound Ac–(*S*)-Aba–(*R*)-Ala–NHMe (**5**). Both compounds were isolated by preparative HPLC and were studied separately by NMR spectroscopy.

Likewise, (*S*)-Aba–Gly–OH[18] (**21**) was acetylated and converted into tetrapeptide mimic Ac–(*S*)-Aba–Gly–NHMe (**7**) (Figure 4).

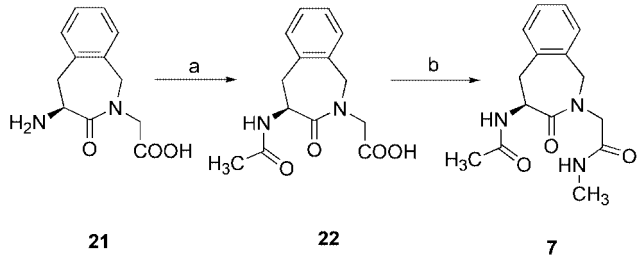

Figure 4. a) Ac_2O, NEt_3, water, 45%; b) CH_3NH_2·HCl, TBTU, NEt_3, CH_2Cl_2, room temp., 2 h, 55%.

N-Methylation of Boc–(*S*)-Aba–Gly–OH[18] (**23**) with sodium hydride and iodomethane[39] followed by Boc-deprotection, acetylation and coupling with methylamine provided the *N*-methylated tetrapeptide analog *N*-Ac,*N*-Me-(*S*)-Aba–Gly–NHMe (**8**) (Figure 5).

For the spiro derivative **9**, (*R*,*S*)-Boc-α-(*o*-cyanobenzyl)-proline (**27**) was reduced to the corresponding aldehyde **28** with H_2/Raney-Ni in aqueous pyridinium acetate (Figure 6).[36] After a few hours the reduction stopped, and repetitive addition of the catalyst was required to obtain complete conversion of the starting material. A problem associ-

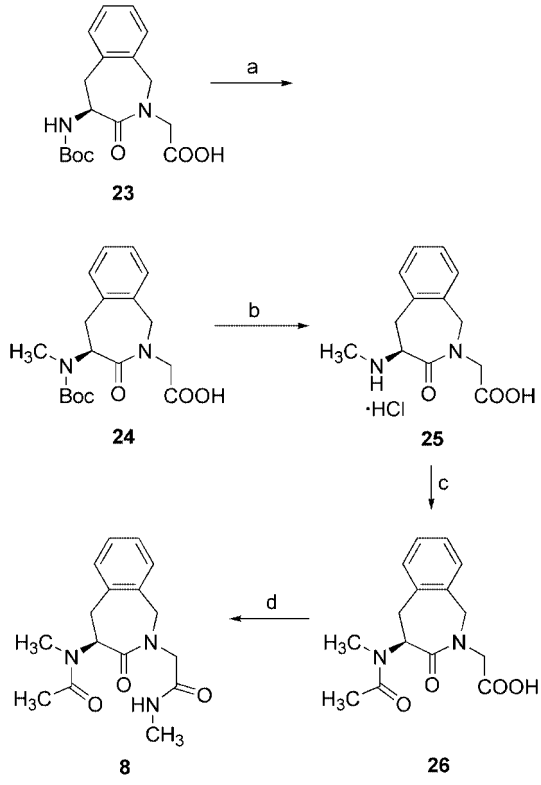

Figure 5. a) NaH, MeI, THF, 24 h, room temp., 79%; b) 6 N HCl/CH_2Cl_2, 1:1, room temp., o.n., 57%; c) Ac_2O, Et_3N, water, 45%; d) CH_3NH_2·HCl, TBTU, NEt_3, CH_2Cl_2, room temp., 2 h, 47%.

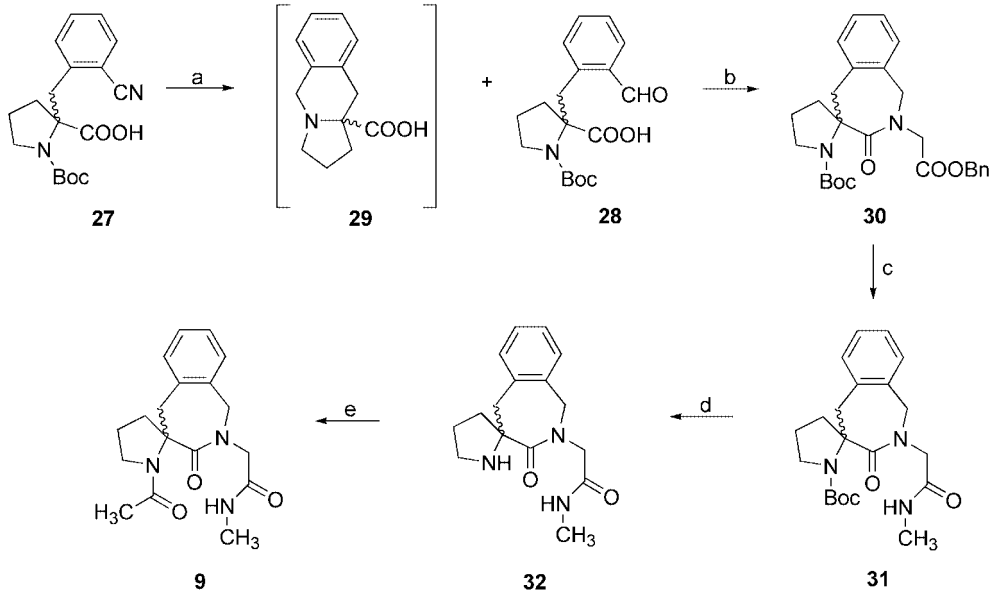

Figure 6. a) Raney-Ni, H_2 (50 psi), H_2O/AcOH/Py, 1:1:1, 50 °C, 56 h, 32%; b) 1) Gly-OBn·*p*TosOH, $NaCNBH_3$, CH_2Cl_2, $MgSO_4$, NMM, 2) DCC, Py, AcN, 21% (2 steps); c) CH_3NH_2, MeOH, o.n., room temp., 93%; d) TFA, CH_2Cl_2, 0 °C, 2 h, 92%; e) Ac_2O, NEt_3, room temp., 2 h, 91%.

ated with this reaction that took 48 h, was the formation of side product, which was identified as 2,3,5,10-tetrahydro-1*H*-pyrrolo[1,2-*b*]isoquinoline-10a-carboxylic acid (**29**). This compound is obtained by in situ removal of the Boc group and intramolecular reductive amination. A similar side reaction has been reported before for the reduction of Boc–*o*-CN–Phe and bis-Boc–*o*-CN–Phe resulting in Boc–Tic.[37]

The aldehyde **28** was used in a reductive amination with Gly–OBn·*p*TosOH. Ring closure provided Boc-spiro-(*R*,*S*)-Aba–Gly–OBn (**30**) (21% yield). Aminolysis of the benzyl ester **30** with a methanolic solution of methylamine followed by Boc deprotection and acetylation provided a fifth tetrapeptide analog **9** in racemic form.

In order to avoid the side reaction during the reduction of nitrile **27**, the Moc-protecting group was studied as an alternative nitrogen protection for α-(*o*-cyanobenzyl)proline (Figure 7). As for the Boc-protected compound, repetitive addition of catalyst was required in order to achieve complete conversion of the starting material **33** into the aldehyde **34**. In this case the side product **29** was not observed, and a much higher yield (69%) was obtained compared to the Boc derivative (32%). The crude (*R*,*S*)-Moc-α-(*o*-formylbenzyl)proline (**34**) was used to prepare a benzazepinone **35** with glycine benzyl ester (32% yield). Clearly, the Moc protection is more suitable for this synthetic strategy than the Boc protection.

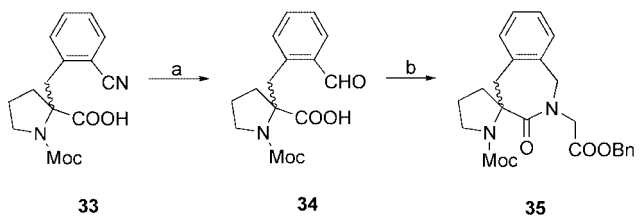

Figure 7. a) Raney-Ni, H_2 (50 psi), H_2O/AcOH/Py, 1:1:1, 50 °C, 35 h, 69%; b) 1) Gly-OBn·*p*TosOH, $NaCNBH_3$, CH_2Cl_2, $MgSO_4$, NMM, 2) DCC, Py, AcN, 32% (2 steps).

Molecular Modeling Results

In order to evaluate the intrinsic β-turn-inducing potency of this class of lactams, conformational searches were performed on Ac–(*S*)-Aba–Gly–NHMe (**7**), Ac–(*S*)-Aba–(*R and S*)-Ala–NHMe **5** and **6** and Ac–(*S*)-spiro-Aba–Gly–NHMe (**9**) using Macromodel 5.0.[40] Briefly, the procedure consisted of a MM3*[41] low-mode search[42] on the formyl–Xxx–NMe rings (Xxx = Aba, spiro-Aba) in vacuo (Figure 8).

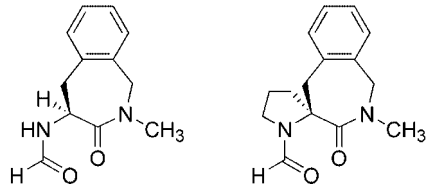

Figure 8. Formyl–Xxx–NMe (Xxx = Aba, spiro-Aba) structures.

Subsequently, the exocyclic functions were added to obtain the desired tetrapeptide mimics. Then, the peptide backbone was submitted to a systematic unbounded multiple minimum search (SUMM)[43] in water, using the GB/SA solvation model.[44] All conformations within 50 kJ/mol of the global minimum were clustered into families based on geometrical similarity.

The β-turn mimicry of the different tetrapeptide mimetics was evaluated by means of different criteria (Figure 9):

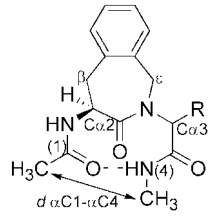

Figure 9. Criteria used to evaluate β-turn mimicry.

(1) The distance between the *N*-acetyl carbonyl oxygen atom and the methyl carboxamide proton should be smaller than 2.5 Å and the associated NH–O angle larger than 120°. This criterion reflects the presence of a hydrogen bond in type I and II β-turns.[45]

(2) The $C_\alpha1$–$C_\alpha4$ interatomic distance should be less than 7 Å.

(3) The virtual torsion angle β, defined by C1, $C_\alpha2$, $C_\alpha3$ and N4 of the tetrapeptide model[46] should lie between specified limits (Table 1).

Table 1. Virtual torsion angle β defining β-turn classes.

Type of β-turn	Virtual torsion angle β
I	$10 < \beta < 80$
I′	$-79 < \beta < -10$
	$20 < \beta < 40$
II	$-69 < \beta < -60$
	$-49 < \beta < -40$
	$-29 < \beta < 40$
II′	$-59 < \beta < -50$
	$-29 < \beta < 30$

(4) The φ- and ψ angles of the central residues of the β-turn, which are characteristic for the turn type.[1]

In Table 2 and Figure 10, the lowest-energy conformers are given, together with the values for the different criteria. The lowest-energy conformer of Ac–(*S*)-Aba–Gly–NHMe (**7**) is not a β-turn, and the lowest-energy conformation that does adopt a turn is 14.85 kJ/mol above the minimum. Similar results were obtained for Ac–(*S*)-Aba–(*R*)-Ala–NHMe (**5**) and Ac–(*S*)-Aba–(*S*)-Ala–NHMe (**6**): none of the low-energy structures has a turn character.

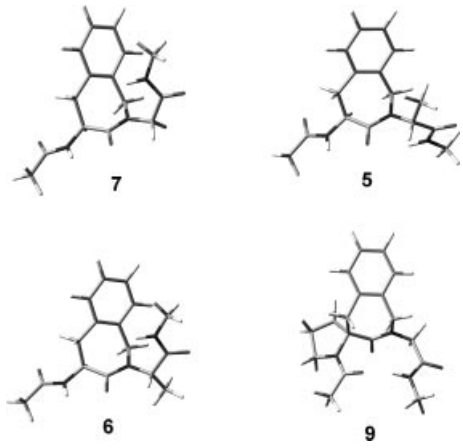

Figure 10. 3D representation of the lowest-energy conformers.

In contrast, the lowest-energy conformer of Ac–(*S*)-spiro-Aba–Gly–NHMe (**9**) displays a β-turn of type II′, indicating that spiro-Aba has β-turn inducing properties. Moreover, within the 16.74 kJ/mol range, several more turn structures were found.

Interestingly, when the ring conformation of the tetrapeptide mimetic adopts a *trans* 1 conformation, which is boat-like, a β-turn of type II′ can be induced. In contrast, none of the chair-like *trans* 2 ring conformations have β-turn properties.

NMR Analysis

The constitutional structure of all synthesized compounds was evidenced by ^{1}H and ^{13}C NMR, the chemical shift assignments being supported by 2D ^{1}H homonuclear DQF COSY[47] and 2D heteronuclear ^{1}H-^{13}C HMQC[48] and HMBC[49] NMR spectroscopy. The conformation of the benzazepinone ring was investigated by 2D ^{1}H NOESY

Table 2. The lowest-energy conformers and values for the different criteria.

Structure	Ac–(*S*)-Aba–Gly–NHMe (**7**)	Ac–(*S*)-Aba–(*R*)-Ala–NHMe (**5**)	Ac–(*S*)-Aba–(*S*)-Ala–NHMe (**6**)	Ac–(*S*)-spiro-Aba–Gly–NHMe (**9**)
Ring conformation	*trans* 2[a]	*trans* 2[a]	*trans* 2[a]	*trans* 1[a]
Turn	/	/	/	II′
d (NH–CO) [Å]	6.5	6.0	6.7	2.0
NHO angle [°]	149	153	137	164
d (Cα1–Cα4) [Å]	9.3	8.7	9.7	5.4
β [°]	139	–61	149	–11
φ2 [°]	162	162	161	58
ψ2 [°]	–162	–163	–164	–123
φ3 [°]	105	–124	126	–98
ψ3 [°]	–26	34	–43	17
E of first turn (kJ/mol)	14.85	24.94	13.39	0
	g(+)1	g(+)1	g(+)1	
	type I	type I	type I	

[a] The ring conformations are primarily classified by the χ_1 torsion angle of the Aba amino acid, which can either be gauche(+) or *trans*.[18] However, for each of these possible orientations of χ_1, two ring conformations are possible (e.g. *trans* 1 and *trans* 2). In the *trans* 1 conformation, one of the Cβ-H is in close proximity with one of the Cε-H, whereas in the *trans* 2 conformation the $C\alpha_2$-H is in close proximity with one of the Cε-H. (see also Figure 10).

NMR.[50] In every compound, the benzazepinone ring was shown to adopt a *trans* χ_1 conformation around the C_α–C_β bond (Figure 10).[18] This was demonstrated by the presence of NOE cross peaks as well as by the value of coupling constants (Table 3). For **5**, the small coupling constant and a strong NOE between Hα and Hβ, and the opposite for Hα and Hβ′ demonstrates the presence of the *trans* rotamer (see Figure 11 for atom labeling). Further evidence is given by the NOE cross peaks between the β-hydrogen atoms and N*H*–Ac, and the strong one between only one β-hydrogen (Hβ) and the aromatic H^6. A similar reasoning based on the NOE's only for spiro derivative **9** also indicates a *trans* χ_1 conformation.

Table 3. NMR spectroscopic data determining the conformation of the benzazepinone core. Compound **5** is chosen as a representative example of compounds **5**, **6**, **7** and **8** (solvent [D_6]DMSO).

Compound **5**		Compound **9**	
^3J(Hα,Hβ)	4.1 Hz	–	
^3J(Hα,Hβ′)	13.1 Hz	–	
NOE Hα/Hβ	strong	NOE H_3/Hβ	strong
NOE Hα/Hβ′	weak	NOE H_3/Hβ′	absent
NOE NH_{Ac}/Hβ	strong		
NOE NH_{Ac}/Hβ′	strong		
NOE Hβ/H^6	strong	NOE Hβ/H^6	strong
NOE Hα/Hε	strong		
NOE Hβ′/Hε′	absent	NOE Hβ′/Hε′	strong
NOE Hε/H^9	absent	NOE Hε/H^9	strong
NOE Hε′/H^9	strong	NOE Hε′/H^9	absent

Interestingly, the CH_2 ε protons show a different pattern in **9**, compared to **5**, **6**, **7** and **8**. Indeed, in **5** a strong NOE is observed between Hα and Hε, and between Hε′ and H^9, which corresponds to the calculated *trans* 2 conformation. In **9**, a strong NOE between Hβ′ and Hε′, and between Hε and the aromatic H^9 indicates a preferred *trans* 1 conformation (Figure 10).

The intramolecular hydrogen bond between the carbonyl oxygen atom of the first residue and the amide NH proton of the fourth residue, which is present in most of the β-turns, was also studied by NMR spectroscopy. Indeed, unlike intermolecular hydrogen bonds, intramolecular hydrogen bonds are very little influenced by external factors such as temperature and solvent.

^{1}H NMR spectra of the benzazepine compounds were measured in $CDCl_3$ and [D_6]DMSO, to evaluate the effect of switching from a non-hydrogen bond-forming solvent to a strong hydrogen bond-forming solvent on the chemical shift of the N*H*–Me. In a second experiment, samples in [D_6]DMSO were heated, to examine the effect of the temperature increase on the chemical shift of N*H*–Me.

In compounds **5**, **6** and **7** (Table 4), the chemical shift in $CDCl_3$ of N*H*–Me is smaller than the chemical shift of Ac–N*H*. This is in contrast with the expectation for the benzazepinones in the β-turn conformation. In that case the N*H*–Me would be involved in an intramolecular hydrogen bond, meaning that the proton is deshielded and that it should appear at higher chemical shift than the Ac–N*H*.[51]

Switching from $CDCl_3$ to [D_6]DMSO resulted in a large increase in chemical shift for both Ac–N*H* and N*H*–Me in **5**, **6** and **7**. When samples of **5**, **6** and **7** were heated in [D_6]DMSO (temperature range between 298 K and 343 K, temperature increments of 5 K), both Ac–N*H* and N*H*–Me showed a large fluctuation of the chemical shift with the temperature. The resonances of the amide protons shifted linearly, resulting in temperature coefficients around –6 to –7 ppb/K. Only coefficients between 0 and –4 ppb/K are accepted for solvent-shielded amide protons involved in intramolecular hydrogen bonds.[21] These data indicate that **5**, **6**, **7** and **8** do not adopt a β-turn conformation. Furthermore, the expected NOE correlations for these compounds in a β-turn conformation were not observed.

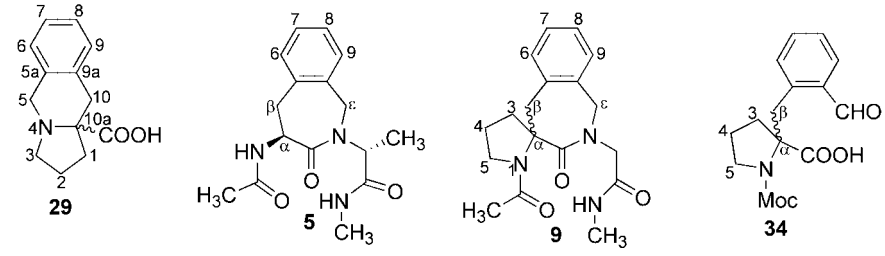

Figure 11. Atom labeling as used in the NMR interpretation.

Table 4. Solvent and temperature effect on amide protons in the benzazepinone compounds.

		δ $CDCl_3$	δ [D_6]DMSO	$\Delta\delta$ $CDCl_3 \rightarrow$ [D_6]DMSO	$\Delta\delta/\Delta T$
Ac–(*S*)-Aba–(*R*)-Ala–NHMe (**5**)	Ac–N*H*	6.99	8.08	1.09	–6.6
	N*H*–Me	6.41	7.86	1.45	–5.7
Ac–(*S*)-Aba–(*S*)-Ala–NHMe (**6**)	Ac–N*H*	6.92	8.12	1.20	–6.2
	N*H*–Me	5.45	7.55	2.10	–6.9
Ac–(*S*)-Aba–Gly–NHMe (**7**)	Ac–N*H*	6.93	8.12	1.19	–6.9
	N*H*–Me	6.57	7.87	1.30	–6.6
N-Ac,*N*-Me–Aba-Gly-NHMe (**8**)	N*H*–Me	7.51	7.83	0.32	–5.8
Ac-(*R*,*S*)-spiro-Aba-Gly-NHMe (**9**)	N*H*–Me	7.81	7.71	–0.10	–4.3

For the spiro derivative **9**, however, the amide resonance is only very weakly influenced by switching from $CDCl_3$ to [D_6]DMSO. Moreover, the temperature coefficient is approximately –4 ppb/K, indicating the presence of an intramolecular hydrogen bridge for this compound. Further evidence of the intramolecular hydrogen bond was given by the NOE correlations within the molecule, indicating a rigid conformation for all the backbone atoms, which are involved in the pseudo-ten-membered ring. A strong NOE cross peak between the resonances of the acetyl methyl protons and the hydrogen atoms at C-5 of the spiro ring (see Figure 11 for atom labeling), combined with the presence of only one set of signals in the ^{1}H NMR spectrum, indicates the presence of exclusively the *trans* rotamer for the acetyl-spiro amide bond. Additionally, the existence of an NOE effect between Hε (not Hε′) and only one of the α-hydrogen atoms of Gly indicates that there is no rotational freedom around the N^2–$C\alpha_{Gly}$ bond. The NMR spectroscopic data are therefore in complete agreement with the lowest energy conformer (Figure 10), which was obtained in the molecular modeling.

Conclusions

Although structurally similar seven-membered dehydro-Freidinger lactams were reported in literature as β-turn mimics, this finding could not be extended to the 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones **5**, **6**, **7** and **8**, as we have demonstrated by NMR analysis and molecular modeling.

In contrast, these NMR and molecular modeling data for the spiro derivative **9** are consistent with a β-turn conformation. It was also observed that the conformation of the seven-membered lactam ring was different in the spirolactam **9** and in benzazepinones **5**, **6**, **7** and **8**, suggesting that this may contribute to the β-turn mimicry of **9**.

Experimental Section

Molecular Modeling: The calculations were carried out using Macromodel 5.0[40] with Maestro 8.0 as a graphic interface. The MM3* force field[41] was used in vacuo for the energy minimizations on the formyl–Xxx–NMe rings (Xxx = Aba, spiro-Aba). The conformational analyses of the rings were carried out with the Pure Low-Mode search.[42] 1000 Structures were generated and minimized by means of the Polak–Ribière conjugate gradient method as implemented in Macromodel, using a gradient convergence criterion of 0.02 kJ/mol·Å. For the tetrapeptide mimetics, the MM3* force field was used as well, but this time in combination with the GB/SA solvation model of Still et al.,[44] using Macromodel's default parameters for an aqueous medium. The conformational space was sampled by a systematic unbounded multiple mimimum search[43] in which 3 internal coordinates (φ_2, φ_3 and ψ_3) were varied. Here the generation of 2000 structures was conducted and the conformers were minimized to an energy convergence of 0.1 kJ/mol·Å by use of the Polak–Ribière conjugate gradient method. After this search the found conformations were again minimized to an energy convergence of 0.01 kJ/mol·Å. In both strategies, duplicate structures and those greater than 50 kJ/mol above the global minimum were discarded. The generated structures were clustered in families with Xcluster 1.7. A RMSD value of 0.2 Å was used.

General Methods: (*R*,*S*)-Boc-α-(*o*-cyanobenzyl)proline (**27**) and (*R*,*S*)-Moc-α-(*o*-cyanobenzyl)proline (**33**) were kindly provided by BioQuadrant Inc. RP-HPLC was performed using a RP C-18 column (Supelco Discovery®BIO Wide Pore C18, *l* = 25 cm, *d* = 0.45 cm, *PS* = 5 μm). The mobile phase (water/acetonitrile) contained 0.1% TFA. Products were eluted using the following gradient: *t* = 0 min, 3% CH_3CN, *t* = 30 min, 80% CH_3CN, *t* = 40 min, 100% CH_3CN. Flow rate: 1.0 mL min^{-1}, λ = 215 nm. Preparative HPLC was performed using a RP C-18 column (Supelco Discovery®BIO Wide Pore C18, *l* = 25 cm, *d* = 2.12 cm, *PS* = 10 μm). The above mentioned gradient was used with a flow rate of 20.0 mL min^{-1}. FDAA analysis was performed as described earlier.[37] TLC analysis was performed with a plastic sheet precoated with silica gel 60F_{254} (Merck). Silicagel 60 (0.040–0.063 mm) from Merck was used for flash column chromatography (w/w, 60:1). Melting points were measured with a Büchi B 540 melting point apparatus, with a temperature increment of 1 °C·min^{-1}. Optical rotations were measured at room temperature using an optical activity type AA-5 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded at 250.13 and 62.90 MHz, respectively, with a Bruker Avance DRX250 spectrometer, or at 500.13 and 125.75 MHz with a Bruker AMX500 spectrometer, using TMS or the residual solvent signal as internal reference. For the advanced NMR analysis of **5**, **6**, **7**, **8** and **9**, samples were measured in $CDCl_3$ and [D_6]DMSO with the Bruker AMX500 spectrometer, using pulse sequences of the Bruker program library. The temperature study was performed in [D_6]DMSO, with a temperature increment of 5 K between 298 K and 343 K. For the atom labelling in the NMR spectra: see Figure 11. Mass spectra were recorded on a VG Quattro II spectrometer using electrospray ionisation (positive ion mode).

***tert*-Butyl (*S*)-*o*-Cyanophenylalaninate (13):** $CsOH·H_2O$ (34.10 g, 203 mmol) was put in a 250 mL flask and dried overnight at 130 °C under vacuum. After cooling to room temperature the system was put under Ar, and the CsOH was suspended in CH_2Cl_2 (analytical grade, 60 mL). The mixture was further cooled to –78 °C, and after 15 min stirring *tert*-butyl *N*-(diphenylmethylene)glycinate (**10**, 6.00 g, 20.3 mmol) and the phase-transfer catalyst *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (1.23 g, 2.03 mmol) were added. The mixture was stirred for 30 min, followed by the addition of *o*-cyanobenzyl bromide (**11**, 7.96 g, 40.6 mmol, addition in 4 portions with 3 min intervals). After a 27-h reaction time at –78 °C, the mixture was diluted with Et_2O (600 mL), washed with H_2O (3 × 150 mL) and brine (1 × 150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated and the so obtained crude *N*-(diphenylmethylene)-(*o*-cyanophenyl)alanine *tert*-butyl ester (**12**) was immediately hydrolysed in a mixture of THF/15% aqueous citric acid solution (2:1, 180 mL). After stirring overnight, the THF was evaporated and the residue was taken up in H_2O (400 mL). The aqueous layer was washed with Et_2O (3 × 150 mL), and the pH was adjusted with 20% K_2CO_3 until pH 10. The basic aqueous phase was extracted with EtOAc (4 × 120 mL). Drying ($MgSO_4$), filtration and evaporation of the organic layer afforded the crude (*S*)-*o*-cyanophenylalanine *tert*-butyl ester (**13**). The product was purified by flash column chromatography (EtOAc). A light brown paste was obtained. The enantiomeric purity was determined by FDAA analysis after removal of the *t*Bu ester [see (*S*)-*o*-cyanophenylalanine hydrochloride (**14**)], 96% *ee* was observed. Yield 4.51 g (90%). HPLC t_{ret} = 15.5 min; R_f = 0.49 (EtOAc/MeOH, 2:1). HRMS calcd. 247.1446, found 247.1453. $[\alpha]_D^{20}$ = +22.9 (*c* = 1.7, EtOAc). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.42 (s, 9 H, *t*Bu), 1.7 (br. s, 2 H, NH_2), 3.01 [dd, ^2J(Hβ,Hβ′) = 13.8 Hz, ^3J(Hα,Hβ) =

8.4 Hz, 1 H, Hβ], 3.26 [dd, ^2J(Hβ,Hβ′) = 13.9 Hz, ^3J(Hα,Hβ′) = 5.8 Hz, 1 H, Hβ′], 3.70 [dd, ^3J(Hα,Hβ) = 8.4 Hz, ^3J(Hα,Hβ′) = 5.8 Hz, 1 H, Hα], 7.28–7.65 (m, 4 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 28.36 (CH_3 *t*Bu), 40.17 (CH_2 β), 56.41 (CH α), 82.03 (C_q *t*Bu), 113.74 (C_q arom. next to C≡N), 118.48 (C≡N), 127.61, 130.93, 133.08, 133.28 (CH arom.), 142.53 (C_q arom. next to CH_2 β), 174.09 (C=O) ppm.

(*S*)-*o*-Cyanophenylalanine Hydrochloride (14): (*S*)-*o*-Cyanophenylalanine *tert*-butyl ester (**13**, 4.51 g, 18.3 mmol) was dissolved in CH_2Cl_2/6 N HCl (1:1, 520 mL). After stirring overnight, the solvent was removed in vacuo. A white powder was obtained after re-dissolving the residue in CH_3CN/H_2O (1:1) and lyophilisation. Yield 4.03 g (97%). M.p. (dec.) 225 °C; HPLC t_{ret} = 9.6 min; R_f = 0.61 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 191.0820, found 191.0829. $[\alpha]_D^{20}$ = +11.2 (*c* = 1, H_2O). ^{1}H NMR (D_2O, 250 MHz): δ = 3.26 [dd, ^2J(Hβ,Hβ′) = 14.6 Hz, ^3J(Hα,Hβ) = 7.7 Hz, 1 H, Hβ], 3.41 [dd, ^2J(Hβ,Hβ′) = 14.6 Hz, ^3J(Hα,Hβ′) = 7.2 Hz, 1 H, Hβ′], 4.17 [pseudo t, ^3J(Hα,Hβ) ≈ ^3J(Hα,Hβ′) = 7.4 Hz, 1 H, Hα], 7.34–7.69 (m, 4 H, H arom.) ppm. ^{13}C NMR (20 wt.-% DCl in D_2O, 63 MHz): δ = 32.24 (CH_2 β), 51.19 (CH α), 109.88 (C_q arom. next to C≡N), 116.11 (C≡N), 126.79, 128.70, 131.89, 132.23 (CH arom.), 135.50 (C_q arom. next to CH_2 β), 167.91 (C=O) ppm.

(*S*)-*N*,*N*-Phthaloyl-*o*-cyanophenylalanine (15): (*S*)-*o*-Cyanophenylalanine hydrochloride (**14**, 1.19 g, 5.25 mmol) was dissolved in CH_3CN/H_2O (65:40, 105 mL), to which $Na_2CO_3 \cdot H_2O$ (3.26 g, 26.3 mmol) was added, as well as methyl 2-[(succinimidooxy)carbonyl]benzoate (MSB) (1.46 g, 5.26 mmol). After stirring at room temperature for 8 h complete conversion was obtained, and the reaction mixture was acidified to pH 2 (2 N HCl). The mixture was diluted with EtOAc (200 mL), and the organic layer was washed with 1 N HCl (2×100 mL) and water (2×100 mL). A light yellow solid was obtained after drying ($MgSO_4$), filtration and evaporation. The product was used without further purification. Yield 1.36 g (81%). M.p. 198.8–200.7 °C; HPLC t_{ret} = 19.9 min; R_f = 0.46 (EtOAc/BuOH/AcOH/H_2O, 16:1:1:1). HRMS calcd. 321.0875, found 321.0869. $[\alpha]_D^{20}$ = –302.9 (*c* = 1.24, AcN/H_2O, 14:1). ^{1}H NMR (CD_3OD, 250 MHz): δ = 3.65 [dd, ^2J(Hβ,Hβ′) = 14.4 Hz, ^3J(Hα,Hβ) = 11.4 Hz, 1 H, Hβ], 3.81 [dd, ^2J(Hβ,Hβ′) = 14.4 Hz, ^3J(Hα,Hβ′) = 4.6 Hz, 1 H, Hβ′], 5.20 [dd, ^3J(Hα,Hβ) = 11.4 Hz, ^3J(Hα,Hβ′) = 4.6 Hz, 1 H, Hα], 7.28–7.62 (m, 4 H, H arom.), 7.73–7.85 (m, 4 H, H arom. Phth) ppm. ^{13}C NMR (CD_3OD, 63 MHz): δ = 34.60 (CH_2 β), 53.37 (CH α), 113.82 (C_q arom. next to C≡N), 118.49 (C≡N), 124.42 (2 CH Phth), 128.86, 131.64, 134.10 and 134.25 (CH arom.), 135.75 (2 CH Phth), 132.72 (C_q arom. Phth), 142.55 (C_q arom. next to CH_2 β), 168.72, 171.24 (C=O) ppm.

(*S*)-*N*,*N*-Phthaloyl-*o*-formylphenylalanine (16): Wet Raney-Ni (1.5 g, 50 µpore, Aldrich) was washed with milliQ water (15×10 mL) and suspended with (*S*)-Phth–*o*-cyano–Phe (**15**, 350 mg, 1.09 mmol, 1 equiv.) in Py/AcOH/H_2O (1:1:1, 30 mL). The suspension was hydrogenated in a Parr apparatus (50 psi, 50 °C, 38 h). The mixture was filtered through dicalite and rinsed with water. After evaporation of the solvent, the residue was redissolved in EtOAc (100 mL) and washed with 1 M HCl (3×50 mL). The organic layer was dried ($MgSO_4$), filtered and the solvents evaporated. A white sticky foam was obtained. Yield 275 g (78%). HPLC t_{ret} = 19.7 min; R_f = 0.42 (EtOAc/BuOH/AcOH/H_2O, 16:1:1:1). HRMS calcd. 324.0872, found 324.0877. $[\alpha]_D^{20}$ = –253 (*c* = 0.664, EtOAc). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.65 [dd, ^2J(Hβ,Hβ′) = 13.6 Hz, ^3J(Hα,Hβ) = 11.3 Hz, 1 H, Hβ], 4.24 [dd, ^2J(Hβ,Hβ′) = 13.6 Hz, ^3J(Hα,Hβ′) = 4.7 Hz, 1 H, Hβ′], 5.43 [dd, ^3J(Hα,Hβ) = 11.1 Hz, ^3J(Hα,Hβ′) = 4.7 Hz, 1 H, Hα], 7.01–8.07 (m, 8 H, H arom.), 10.15 (s, 1 H, H aldehyde) ppm. ^{13}C NMR ($CDCl_3$ 63 MHz): δ = 32.58 (CH_2 β), 51.75 (CH α), 123.50 (2 CH Phth), 127.77, 132.08, 133.66, 135.27 (CH arom.), 134.13 (2 CH Phth), 131.42, 138.55 (C_q arom.), 167.33, 173.66 (C=O), 193.44 (C=O aldehyde) ppm.

Benzyl (2*R*)-[(4*S*)-4-(Phthalimido)-3-oxo-1,3,4,5-tetrahydro-benz[*c*]-azepin-2-yl]propionate (17) [Phth-(*S*)-Aba-(*R*)-Ala-OBn]: To a solution of the aldehyde **16** (983 mg, 3.04 mmol) in CH_2Cl_2 (analytical grade, 60 mL) (*R*)-Ala–OBn·*p*TosOH (1.12 g, 3.19 mmol) was added. The pH was adjusted to 6 with *N*-methylmorpholine, followed by the addition of $MgSO_4$ (197 mg, 20 wt.-%) and $NaCNBH_3$ (478 mg, 7.60 mmol). When the reaction was complete (after 2 hours) the solvent was removed under reduced pressure. The residue was redissolved in acetonitrile (200 mL), and pyridine (492 µL, 6.08 mmol) was added. The mixture was cooled in an ice bath for 10 minutes, and DCC (690 mg, 3.34 mmol) was added. After 1 hour stirring at 0 °C the reaction was continued overnight at room temperature. Oxalic acid (5 M solution in DMF, 6.4 mL) was added and after 30 minutes stirring the abundant precipitate was filtered. The filtrate was evaporated and redissolved in EtOAc (400 mL). After washing with 1 N HCl and saturated aqueous $NaHCO_3$ (3×100 mL), the organic layer was dried ($MgSO_4$), filtered and the solvents evaporated. The small particles of DCU in the obtained paste could be removed by filtration after dissolving the paste in toluene. The product was further purified by flash column chromatography (eluent EtOAc/hexane, 12:20), a colourless paste was obtained. Yield 552 mg (39%). HPLC t_{ret} = 26.5 min; R_f = 0.36 (EtOAc/hexane, 1:1). HRMS calcd. 469.1763, found 469.1771. $[\alpha]_D^{20}$ = +47.8 (*c* = 0.993, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.43 (d, ^3J = 7.3 Hz, 3 H, CH_3 Ala), 3.17 [dd, ^2J(Hβ,Hβ′) = 16.2 Hz, ^3J(Hα,Hβ) = 4.2 Hz, 1 H, Hβ], 4.26 [dd, ^2J(Hβ,Hβ′) = 16.1 Hz, ^3J(Hα,Hβ′) = 13.3 Hz, 1 H, Hβ′], 4.37 [d, ^2J(Hε,Hε′) = 16.4 Hz, 1 H, Hε], 4.81 [d, ^2J(Hε,Hε′) = 16.4 Hz, 1 H, Hε′], 5.14 (s, 2 H, CH_2 Bn ester), 5.40 (q, ^3J = 7.3 Hz, 1 H, Hα Ala), 5.58 [dd, ^3J(Hα,Hβ) = 4.4 Hz, ^3J(Hα,Hβ′) = 13.2 Hz, 1 H, Hα benzazepine], 7.11–7.33 (m, 9 H, H arom. benzazepine, Bn ester), 7.71–7.89 (m, 4 H, Phth) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.68 (CH_3 Ala), 34.50 (CH_2 β), 48.65 (CH_2 ε), 51.96 (CH α benzazepine), 53.96 (CH α Ala), 67.92 (CH_2 Bn ester), 123.91, 127.36, 128.48, 128.70, 128.76, 128.99, 130.50, 134.50 (CH arom.), 132.42, 135.20, 135.84, 136.42 (C_q arom.), 168.35, 169.84, 171.90 (C=O) ppm.

(2*R*)-[(4*S*)-4-(Phthalimido)-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]propionic Acid (18) [Phth–(*S*)-Aba–(*R*)-Ala–OH]: Phth–(*S*)-Aba–(*R*)-Ala–OBn (**17**, 284 mg, 0.606 mmol) was dissolved in dioxane/H_2O (3:2, 30 mL). After the addition of 10% Pd/C (20 wt.-%, 60 mg) the suspension was hydrogenated during 5 h (50 psi) in a Parr hydrogenation apparatus. The mixture was filtered through dicalite, and a white solid was obtained after evaporation of the filtrate followed by lyophilisation from CH_3CN/H_2O. Yield 225 mg (98%). M.p. 170.0–179.2 °C; HPLC t_{ret} = 19.1 min; R_f = 0.48 (EtOAc/MeOH, 2:1). HRMS calcd. 379.1294, found 379.1285. $[\alpha]_D^{20}$ = +28.6 (*c* = 0.46, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.34 (m, 3 H, CH_3 Ala), 3.15 [dd, ^2J(Hβ,Hβ′) = 16.2 Hz, ^3J(Hα,Hβ) = 3.1 Hz, 1 H, Hβ], 4.17–4.35 (m, 2 H, Hβ′, Hε), 4.87 [d, ^2J(Hε,Hε′) = 16.3 Hz, 1 H, Hε′], 5.11 (m, 1 H, Hα Ala), 5.60 (m, 1 H, Hα benzazepine), 7.10–7.29 (4 H, H arom. benzazepine), 7.63–7.79 (m, 4 H, Phth) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.78 (CH_3 Ala), 34.27 (CH_2 β), 48.92 (CH_2 ε), 51.97 (CH α benzazepine, CH α Ala), 123.88 (2 CH Phth), 127.26, 128.47, 128.94, 130.39 (CH arom.), 134.46 (2 CH Phth), 132.27, 135.20, 136.02 (C_q arom.), 168.54, 170.30, 176.69 (C=O) ppm.

(2*R*)-[(4*S*)-4-Amino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]propionic Acid (19) [(*S*)-Aba–(*R*)-Ala–OH]: Phth–(*S*)-Aba–(*R*)-Ala–OH (**18**, 169 mg, 0.448 mmol) was dissolved in EtOH (5 mL). After the addition of $NH_2NH_2 \cdot H_2O$ (130 μL, 2.68 mmol) the mixture was refluxed for 1.5 h. The solvent was then removed under reduced pressure and the residue was suspended in H_2O (2.5 mL). The pH was adjusted with AcOH until pH 5. After 1 h stirring at room temperature the precipitate was filtered. The filtrate was evaporated and the product was further purified by preparative HPLC. A white powder that rapidly became a transparent paste was obtained. Yield 93 mg (84%). HPLC t_{ret} = 11.4 min; R_f = 0.65 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 249.1239, found 249.1243. $[\alpha]_D^{20}$ = +40.7 (*c* = 0.786, dioxane/H_2O, 9:1). ^{1}H NMR (CD_3OD, 250 MHz): δ = 1.35 (d, ^3J = 7.4 Hz, 3 H, CH_3 Ala), 3.18–3.44 (m, 2 H, 2 Hβ), 4.24 [d, ^2J(Hε,Hε′) = 17.5 Hz, 1 H, Hε], 5.07–5.23 (m, 3 H, Hε′, Hα Ala, Hα benzazepine), 7.17–7.32 (m, 4 H, H arom.) ppm. ^{13}C NMR (CD_3OD, 63 MHz): δ = 20.11 (CH_3 Ala), 39.26 (CH_2 β), 53.35 (CH_2 ε), 55.29 (CH α benzazepine, CH α Ala), 132.54, 132.65, 134.27, 135.99 (CH arom.), 138.84, 139.88 (C_q arom.), 174.91, 178.87 (C=O) ppm.

(2*R*)-[(4*S*)-4-Acetylamino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]propionic Acid (20) [Ac–(*S*)-Aba–(*R*)-Ala–OH]: (*S*)-Aba–(*R*)-Ala–OH (**19**, 70 mg, 0.282 mmol) was dissolved in water (3 mL). The pH was adjusted to 6 with NEt_3, and Ac_2O (133 μL, 1.41 mmol) was added in three portions. Meanwhile the pH was kept at 6 with NEt_3. After 2 h stirring at room temperature HPLC analysis demonstrated completion of the reaction. The reaction mixture was evaporated, and the product was further purified by preparative HPLC. A white powder that rapidly became a transparent paste was obtained. Yield 49 mg (60%). HPLC t_{ret} = 13.8 min; R_f = 0.24 (EtOAc/MeOH, 2:1). HRMS calcd. 291.1345, found 291.1348. $[\alpha]_D^{20}$ = +65.4 (*c* = 1, MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.34 (d, ^3J = 7.4 Hz, 3 H, CH_3 Ala), 2.14 (s, 3 H, CH_3 Ac), 2.96 [dd, ^2J(Hβ,Hβ′) = 16.8 Hz, ^3J(Hα,Hβ) = 12.8 Hz, 1 H, Hβ], 3.49 [dd, ^2J(Hβ,Hβ′) = 16.9 Hz, ^3J(Hα,Hβ′) = 4.0 Hz, 1 H, Hβ′], 4.00 [d, ^2J(Hε,Hε′) = 17.3 Hz, 1 H, Hε], 5.13 [d, ^2J(Hε,Hε′) = 17.1 Hz, 1 H, Hε′], 5.30 (q, ^3J = 7.3 Hz, 1 H, Hα Ala), 5.52 (m, 1 H, Hα benzazepine), 5.80 (br. s, 1 H, NH amide), 7.04–7.30 (m, 4 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.73 (CH_3 Ala), 23.26 (CH_3 Ac), 36.58 (CH_2 β), 49.29 (CH_2 ε), 53.32 (CH α benzazepine, CH α Ala), 127.05, 128.60, 128.66, 131.33 (CH arom.), 133.76, 135.45 (C_q arom.), 171.71, 172.44, 174.93 (C=O) ppm.

(2*R*)-[(4*S*)-4-Acetylamino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]-*N*-methylpropionamide (5) [Ac–(*S*)-Aba–(*R*)-Ala–NHMe]: Ac–(*S*)-Aba–(*R*)-Ala–OH (**20**, 104 mg, 0.358 mmol) was dissolved in CH_2Cl_2 (6.5 mL). NEt_3 (50 μL, 0.358 mmol) and TBTU (138 mg, 0.430 mmol) were added, and the reaction mixture was stirred for 5 min, followed by the addition of $CH_3NH_2 \cdot HCl$ (26.6 mg, 0.394 mmol) and NEt_3 (150 μL, 1.07 mmol). The coupling was continued overnight. HPLC analysis indicated that the starting material had been completely consumed. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1 N HCl (1 × 25 mL) in order to remove most of the HOBt. The product was dried ($MgSO_4$), filtered and the solvents evaporated. LC/MS demonstrated that 30% racemisation had occurred with formation of Ac–(*S*)-Aba–(*S*)-Ala–NHMe (**6**). The product was further purified by preparative HPLC (both diastereomers were collected) until sufficient material for the NMR study was obtained (21 mg of **5**, 9 mg of **6**).

Characterisation of 5: HPLC t_{ret} = 12.9 min; R_f = 0.64 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 304.1661, found 304.1667. $[\alpha]_D^{20}$ = +32.5 (*c* = 0.6, EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): δ = 1.26 (d, ^3J = 7.1 Hz, 3 H, CH_3 Ala), 2.10 (s, 3 H, CH_3 Ac), 2.83 (d, ^3J = 4.8 Hz, 3 H, NH–CH_3), 2.95 [dd, ^2J(Hβ,Hβ′) = 16.9 Hz, ^3J(Hα,Hβ′) = 13.0 Hz, 1 H, Hβ′], 3.45 [dd, ^2J(Hβ,Hβ′) = 16.9 Hz, ^3J(Hα,Hβ) = 4.2 Hz, 1 H, Hβ], 4.18 [d′, ^2J(Hε,Hε′) = 17.2 Hz, 1 H, Hε], 4.97 [d, ^2J(Hε,Hε′) = 17.2 Hz, 1 H, Hε], 5.16 (q, ^3J = 7.1 Hz, 1 H, Hα Ala), 5.45 (m, 1 H, Hα benzazepine), 6.41 (q, ^3J = 4.8 Hz, 1 H, *NH*–CH_3), 6.99 (d, ^3J = 6.3 Hz, 1 H, *NH*–Ac), 7.08–7.22 (m, 4 H, H arom.) ppm. ^{1}H NMR ([D$_6$]DMSO, 500 MHz, 298 K): δ = 1.10 (d, ^3J = 7.4 Hz, 3 H, CH_3 Ala), 1.94 (s, 3 H, CH_3 Ac), 2.61 (d, ^3J = 4.5 Hz, 3 H, NH–CH_3), 2.85 [dd, ^2J(Hβ,Hβ′) = 17.3 Hz, ^3J(Hα,Hβ′) = 13.1 Hz, 1 H, Hβ′], 3.17 [dd, ^2J(Hβ,Hβ′) = 17.3 Hz, ^3J(Hα,Hβ) = 4.1 Hz, 1 H, Hβ], 4.16 [d, ^2J(Hε,Hε′) = 17.5 Hz, 1 H, Hε′], 5.02 (q, ^3J = 7.4 Hz, 1 H, Hα Ala), 5.06 [d, ^2J(Hε,Hε′) = 17.5 Hz, 1 H, Hε], 5.40 (m, 1 H, Hα benzazepine), 7.12–7.27 (m, 4 H, H arom.), 7.86 (q, ^3J = 4.5 Hz, 1 H, *NH*–CH_3), 8.09 (d, ^3J = 7.0 Hz, 1 H, *NH*–Ac) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz, 298 K): δ = 14.4 (CH_3 Ala), 22.8 (CH_3 Ac), 26.3 (NH–CH_3), 36.1 (CH_2 β), 47.5 (CH_2 ε), 48.6 (CH α benzazepine), 52.7 (CH α Ala), 126.4, 127.9, 128.2, 130.6 (CH arom.), 133.2, 134.7 (C_q arom.), 170.1 (C=O Ac), 170.9 (C=O benzazepine), 172.0 (C=O Ala) ppm. ^{13}C NMR ([D$_6$]DMSO, 126 MHz, 298 K): δ = 15.7 (CH_3 Ala), 22.5 (CH_3 Ac), 25.8 (NH–CH_3), 36.1 (CH_2 β), 47.0 (CH_2 ε), 47.9 (CH α benzazepine), 52.3 (CH α Ala), 126.1, 127.3, 128.4, 130.4 (CH arom.), 135.1, 135.4 (C_q arom.), 168.5 (C=O Ac), 170.7 (C=O Ala), 171.6 (C=O benzazepine) ppm.

Characterisation of 6: HPLC t_{ret} = 12.0 min; R_f = 0.70 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 304.1661, found 304.1656. ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): δ = 1.41 (d, ^3J = 7.0 Hz, 3 H, CH_3 Ala), 2.09 (s, 3 H, CH_3 Ac), 2.33 (d, ^3J = 5.0 Hz, 3 H, NH–CH_3), 2.93 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ′) = 12.7 Hz, 1 H, Hβ′], 3.56 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ) = 5.0 Hz, 1 H, Hβ], 4.12 [d′, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε], 4.92 [d, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε], 5.16 (q, ^3J = 7.0 Hz, 1 H, Hα Ala), 5.40 (m, 1 H, Hα benzazepine), 5.45 (q, ^3J = 5.0 Hz, 1 H, *NH*–CH_3), 6.92 (d, ^3J = 6.4 Hz, 1 H, *NH*–Ac), 7.05–7.21 (m, 4 H, H arom.) ppm. ^{1}H NMR ([D$_6$]DMSO, 500 MHz, 298 K): δ = 1.20 (d, ^3J = 7.0 Hz, 3 H, CH_3 Ala), 1.92 (s, 3 H, CH_3 Ac), 2.29 (d, ^3J = 4.5 Hz, 3 H, NH–CH_3), 2.99 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ′) = 13.2 Hz, 1 H, Hβ′], 3.11 [dd, ^2J(Hβ,Hβ′) = 17.3 Hz, ^3J(Hα,Hβ) = 4.3 Hz, 1 H, Hβ], 4.18 [d, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε′], 4.80 (q, ^3J = 7.0 Hz, 1 H, Hα Ala), 4.95 [d, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε], 5.19 (m, 1 H, Hα benzazepine), 7.05–7.18 (m, 4 H, H arom.), 7.55 (q, ^3J = 4.5 Hz, 1 H, *NH*–CH_3), 8.12 (d, ^3J = 7.0 Hz, 1 H, *NH*–Ac) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz, 298 K): δ = 13.7 (CH_3 Ala), 23.0 (CH_3 Ac), 25.7 (NH-CH_3), 36.1 (CH_2 β), 47.0 (CH_2 ε), 48.8 (CH α benzazepine), 52.4 (CH α Ala), 126.1, 127.9, 128.9, 130.4 (CH arom.), 132.7, 134.4 (C_q arom.), 169.5 (C=O Ac), 170.0 (C=O Ala), 171.7 (C=O benzazepine) ppm. ^{13}C NMR ([D$_6$]DMSO, 126 MHz, 298 K): δ = 14.8 (CH_3 Ala), 22.6 (CH_3 Ac), 25.5 (NH-CH_3), 35.8 (CH_2 β), 47.4 (CH_2 ε), 48.4 (CH α benzazepine), 53.3 (CH α Ala), 125.6, 127.2, 128.7, 130.2 (CH arom.), 134.7, 135.6 (C_q arom.), 168.8 (C=O Ac), 170.1 (C=O Ala), 171.0 (C=O benzazepine) ppm.

[(4*S*)-4-Acetylamino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]-acetic Acid (22) [Ac–(*S*)-Aba–Gly–OH]: (*S*)-Aba–Gly–OH (**21**, 300 mg, 1.11 mmol) was dissolved in water (15 mL). The pH was adjusted to 6 with NEt_3, and Ac_2O (1.1 mL, 11.5 mmol) was added. Meanwhile the pH was kept at 6 with NEt_3. After overnight stirring at room temperature HPLC analysis demonstrated completion of the reaction. The reaction mixture was acidified with 1 N HCl to pH 2 and extracted with EtOAc (4 × 10 mL). The organic

layer was dried ($MgSO_4$), filtered and evaporated, and the product was further purified by preparative HPLC. A white solid was obtained. Yield 198 mg (65%). M.p. 287–289 °C; HPLC t_{ret} = 10.4 min; R_f = 0.53 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 277.1188, found 277.1195. $[\alpha]_D^{20}$ = 123.1 (c = 1, DMF). ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 1.92 (s, 3 H, CH_3 Ac), 2.90 [dd, ^2J(Hβ,Hβ′) = 16.8 Hz, ^3J(Hα,Hβ) = 13.0 Hz, 1 H, Hβ], 3.16 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ′) = 4.0 Hz, 1 H, Hβ′], 3.94 [d, ^2J(Hα,Hα′) = 17.3 Hz, 1 H, Hα Gly], 4.16 [d, ^2J(Hε,Hε′) = 17.0 Hz, 1 H, Hε], 4.25 [d, ^2J(Hα,Hα′) = 17.3 Hz, 1 H, Hα′ Gly], 5.21 [d′, ^2J(Hε,Hε′) = 16.9 Hz, 1 H, Hε], 5.37 (m, 1 H, Hα benzazepine), 7.10–7.24 (m, 4 H, H arom.), 8.12 [d, ^3J(NH–Hα) = 7.5 Hz, 1 H, NH amide] ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 22.9 (CH_3 Ac), 36.3 (CH_2 β), 48.0 (CH_2 ε), 49.5 (CH_2 Gly), 52.3 (CH α benzazepine), 126.2, 127.8, 129.2, 130.7 (CH arom.), 134.5, 135.9 (C_q arom.), 169.1, 170.8, 172.2 (C=O) ppm.

2-[(4*S*)-4-Acetylamino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]-*N*-methylacetamide (7) [Ac–(*S*)-Aba–Gly–NHMe]: Ac–(*S*)-Aba–Gly–OH (**22**, 60 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (12 mL). Et_3N (30 μL, 0.22 mmol) and TBTU (85 mg, 0.264 mmol) were added, and the reaction mixture was stirred for 5 min, followed by the addition of CH_3NH_2·HCl (16.3 mg, 0.242 mmol) and Et_3N (90 μL, 0.66 mmol). After a reaction time of 2 h complete conversion to **7** was observed by HPLC analysis. The solvent was removed from the reaction mixture, and the crude product was purified by preparative HPLC. Yield 35 mg (55%); HPLC t_{ret} = 10.55 min; R_f = 0.65 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS 290.1504, found 290.1508. $[\alpha]_D^{20}$ = +163 (c = 0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.06 (s, 3 H, CH_3 Ac), 2.74 [d ^3J(CH_3–NH) = 4.7 Hz, 3 H, NH–*CH*$_3$], 2.91 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ) = 13.5 Hz, 1 H, Hβ], 3.48 [dd, ^2J(Hβ,Hβ′) = 17.0 Hz, ^3J(Hα,Hβ′) = 4.7 Hz, 1 H, Hβ′], 3.77 [d, ^2J(Hα,Hα′) = 16.1 Hz, 1 H, Hα Gly], 3.98 [d, ^2J(Hε,Hε′) = 16.8 Hz, 1 H, Hε], 4.44 [d, ^2J(Hα,Hα′) = 16.1 Hz, 1 H, Hα′ Gly], 5.22 [d, ^2J(Hε,Hε′) = 16.8 Hz, 1 H, Hε′], 5.43 (m, 1 H, Hα benzazepine), 7.10–7.23 (m, 4 H, H arom.), 6.57 (br. s, 1 H, *NH*–CH_3), 6.93 [d, ^3J(NH–Hα) = 6.3 Hz, 1 H, *NH*–Ac] ppm. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 1.92 (s, 3 H, CH_3 Ac), 2.59 [d, ^3J(CH_3–NH) = 4.5 Hz, 3 H, NH–*CH*$_3$], 2.85 [dd, ^2J(Hβ,Hβ′) = 17.1 Hz, ^3J(Hα,Hβ) = 13.1 Hz, 1 H, Hβ], 3.18 [dd, ^2J(Hβ,Hβ′) = 17.1 Hz, ^3J(Hα,Hβ′) = 4.8 Hz, 1 H, Hβ′], 3.61 [d, ^2J(Hα,Hα′) = 16.4 Hz, 1 H, Hα Gly], 4.07 [d, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε], 4.23 [d, ^2J(Hα,Hα′) = 16.4 Hz, 1 H, Hα′ Gly], 5.19 [d, ^2J(Hε,Hε′) = 16.7 Hz, 1 H, Hε′], 5.37 (m, 1 H, Hα benzazepine), 7.12–7.21 (m, 4 H, H arom.), 7.87 [q, ^3J(NH–CH_3) = 4.5 Hz, 1 H, *NH*–CH_3], 8.12 [d, ^3J(NH–Hα) = 7.1 Hz, 1 H, *NH*–Ac] ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 22.9 (CH_3 Ac), 26.1 (NH–*CH*$_3$), 36.1 (CH_2 β), 48.6 (CH α benzazepine), 51.5 (CH_2 Gly), 53.0 (CH_2 ε), 126.4, 128.3, 128.8, 130.7 (CH arom.), 132.1, 134.8 (C_q arom.), 168.8 (C=O Gly), 170.1 (C=O Ac), 172.1 (C=O benzazepine) ppm. ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ = 22.3 (CH_3 Ac), 25.2 (NH–*CH*$_3$), 35.7 (CH_2 β), 47.6 (CH α benzazepine), 49.9 (CH_2 Gly), 51.5 (CH_2 ε), 125.6, 127.2, 128.6, 130.1 (CH arom.), 133.7, 135.2 (C_q arom.), 167.5 (C=O Gly), 168.1 (C=O Ac), 172.15 (C=O benzazepine) ppm.

[(4*S*)-4-[*tert*-Butoxycarbonyl(methyl)amino]-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]acetic Acid (24) [*N*-Boc,*N*-Me–(*S*)-Aba–Gly–OH]: Boc–(*S*)-Aba–Gly–OH (**23**, 1.00 g, 3.0 mmol) was dissolved in THF (20 mL), followed by the addition of CH_3I (1.5 mL, 24 mmol). The reaction mixture was cooled for 20 min in an ice bath, after which NaH (55–65% dispersion in oil, 393 mg, 9 mmol) was added. After removal of the ice bath the mixture was stirred for 24 h at room temperature. EtOAc (25 mL) was added, followed by the dropwise addition of water (10 mL). The solvent was evaporated and the residue was divided between water (20 mL) and ether (10 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL), and the combined organic layer was extracted with saturated aqueous $NaHCO_3$ (15 mL). The combined aqueous layer was acidified with 10% $KHSO_4$ until pH 3, followed by extraction with EtOAc (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvents evaporated. Yield 825 mg (79%). M.p. 110–127 °C. HPLC t_{ret} = 20.5 min; R_f = 0.53 (EtOAc/MeOH, 2:1). HRMS calcd. 349.1763, found 349.1760. $[\alpha]_D^{20}$ = –1.8 (c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.43 (s, 9 H, *t*Bu), 2.97 (br. s, 4 H, N–Me, Hβ), 3.43 (m, 1 H, Hβ′), 4.26 (m, 3 H, Hα Gly, 2 Hε), 4.83 (m, 1 H, Hα′ Gly), 5.15 (m, 1 H, Hα), 7.10–7.41 (m, 4 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 28.37 (CH_3 Boc), 31.75 (N–Me), 34.35 (CH_2 β), 44.68 (CH_2 ε), 53.33 (CH_2 Gly), 55.64 (CH α), 80.38 (C_q Boc), 126.64, 128.13, 128.66, 130.13 (CH arom.), 134.55, 135.68 (C_q arom.), 156.46 (C=O Boc), 172.92 (2 C=O) ppm.

[(4*S*)-4-Methylamino-3-oxo-1,3,4,5-tetrahydro-benz[*c*]azepin-2-yl]-acetic Acid Hydrochloride (25) [*N*-Me–(*S*)-Aba–Gly–OH·HCl]: *N*-Boc,*N*-Me–(*S*)-Aba–Gly–OH (**24**, 0.5 g, 1.45 mmol) was dissolved in a 6 N HCl/CH_2Cl_2 mixture (1:1, 20 mL) and stirred at room temperature overnight after which the solvent was removed in vacuo. Purification was performed by flash column chromatography (MeOH/CH_2Cl_2, 1:9). The desired product **25** was obtained as a white solid. Yield 233 mg (57%). M.p. 128–130 °C. HPLC t_{ret} = 8.4 min; R_f = 0.47 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 249.1239, found 249.1244. $[\alpha]_D^{20}$ = +0.46 (c = 1, MeOH). ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 2.67 (s, 3 H, NMe), 3.04 [dd, ^2J(Hβ,Hβ′) = 16.3 Hz, ^3J(Hα,Hβ) = 13.2 Hz, 1 H, Hβ], 3.48 [dd, ^2J(Hβ,Hβ′) = 16.3 Hz, ^3J(Hα,Hβ′) = 4.0 Hz, 1 H, Hβ′], 4.05 [d, ^2J(Hε,Hε′) = 17.4 Hz, 1 H, Hε], 4.25 (m, 2 H, 2 Hα Gly), 5.20 (m, 2 H, Hε′, Hα Aba), 7.14–7.30 (m, 4 H, H arom.), 9.14 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 31.6 (CH_3N), 49.6 (CH_2 β), 51.9 (CH_2 ε), 52.3 (CH_2 α Gly), 56.4 (CH α benzazepine), 126.8, 128.2, 129.4, 130.9 (CH arom.), 133.7, 133.9 (C_q arom.), 169.3, 170.2 (C=O) ppm.

{(4*S*)-4-[Acetyl(methyl)amino]-3-oxo-1,3,4,5-tetrahydro-benz[*c*]-azepin-2-yl}acetic Acid (26) [*N*-Ac,*N*-Me–(*S*)-Aba–Gly–OH]: *N*-Me–(*S*)-Aba–Gly–OH·HCl (**25**, 200 mg, 0.69 mmol) was dissolved in water (10 mL). The pH was adjusted to 6 with NEt_3, and Ac_2O (0.8 mL, 6.4 mmol) was added. Meanwhile the pH was kept at 6 with NEt_3. After 2 h stirring at room temperature HPLC analysis demonstrated completion of the reaction. The solvent was removed in vacuo, and the product was further purified by preparative HPLC. A white solid was obtained. Yield 90 mg (45%). M.p. 86–88 °C. HPLC t_{ret} = 12.1 min; R_f = 0.66 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS 291.1345, found 291.1340. $[\alpha]_D^{20}$ = +1.2 (c = 1, DMF). ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 2.02 and 2.05 (2s, 3 H, CH_3 Ac), 2.84 and 2.99 (2s, 3 H, CH_3N), 2.95 and 3.19 [dd, ^2J(Hβ,Hβ′) = 16.2 Hz, ^3J(Hα,Hβ) = 3.9 Hz, 1 H, Hβ], 3.41 and 3.46 (m, 1 H, Hβ′), 4.04 [d, ^2J(Hα,Hα′) = 17.6 Hz, 1 H, Hα Gly], 4.15 [d, ^2J(Hα,Hα′) = 17.6 Hz, 1 H, Hα′ Gly] 4.43 and 4.47 [2d, ^2J(Hε,Hε′) = 16.3 Hz, 1 H, Hε], 4.84 and 5.01 [2d, ^2J(Hε,Hε′) = 16.5 Hz, 1 H, Hε′], 5.21 and 5.61 [2 dd, ^3J(Hα,Hβ′) = 12.0 Hz, ^3J(Hα,Hβ) = 3.9 Hz, 1 H, Hα Aba], 7.10–7.30 (m, 4 H, H arom.) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 22.1 (CH_3 Ac), 29.2 and 32. 9 (CH_3N), 33.6 and 34.3 (CH_2 β), 50.5 and 52.3 (CH_2 ε), 53.6 (CH_2 Gly), 57.3 (CH α benzazepine), 126.7, 128.2, 128.9, 130.2 (CH arom.), 135.6 and 135.7 (C_q arom.), 136.2 and 136.6 (C_q arom.), 170.5 (C=O Gly), 170.9 (C=O Ac), 171.6 and 171.9 (C=O benzazepine) ppm.

2-[(4*S*)-4-[Acetyl(methyl)amino]-3-oxo-1,3,4,5-tetrahydro-benz[*c*]-azepin-2-yl]-*N*-methylacetamide (8) [*N*-Ac,*N*-Me–(*S*)-Aba–Gly–

NHMe]: *N*-Ac,*N*-Me–(*S*)-Aba–Gly–OH (**26**, 40 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (8 mL). Et_3N (20 μL, 0.15 mmol) and TBTU (54 mg, 0.168 mmol) were added and the reaction mixture was stirred for 5 minutes, followed by the addition of CH_3NH_2·HCl (10 mg, 0.154 mmol) and Et_3N (60 μL, 0.45 mmol). After a reaction time of 2 h complete conversion to **8** was observed by HPLC analysis. The solvent was removed from the reaction mixture and the crude product was purified by preparative HPLC. Yield 20 mg (47%); M.p. 170–172 °C. HPLC t_{ret} = 11.0 min; R_f = 0.54 (EtOAc/BuOH/AcOH/H_2O, 1:1:1:1). HRMS calcd. 304.1661, found 304.1668. $[\alpha]_D^{20}$ = +1.2 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.16 (s, 3 H, CH_3 Ac), 2.82 [d, $^3J(CH_3–NH)$ = 4.6 Hz, 3 H, NH–*CH*$_3$], 3.27 (s, 3 H, CH_3N), 2.89 [dd, ^2J(Hβ,Hβ′) = 14.3 Hz, ^3J(Hα,Hβ) = 5.3 Hz, 1 H, Hβ], 3.62 [dd, ^2J(Hβ,Hβ′) = 14.3 Hz, ^3J(Hα,Hβ′) = 13.0 Hz, 1 H, Hβ′], 3.72 [1 H, broadened d, Hα Gly, ^2J(Hα,Hα′) = 16.4 Hz], 4.07 [1 H, broadened d, Hε, ^2J(Hε,Hε′) = 15.1 Hz], 4.73 [d, ^2J(Hα,Hα′) = 16.6 Hz, 1 H, Hα′ Gly], 5.05 [d,′, ^2J(Hε,Hε′) = 15.1 Hz 1 H, Hε], 4.24 (dd, 1 H, Hα benzazepine, partially hidden by Hα Gly), 7.21–7.30 (m, 4 H, H arom.), 7.51 (br. s, 1 H, *NH*–CH_3) ppm. ^{1}H NMR ([D_6]DMSO, 500 MHz): δ = 2.05 (s, 3 H, CH_3 Ac), 2.59 [d, $^3J(CH_3–NH)$ = 4.5 Hz, 3 H, NH–*CH*$_3$], 2.85 and 3.05 (s, 3 H, CH_3N), 2.96 and 3.19 [dd, ^2J(Hβ,Hβ′) = 15.3 Hz, ^3J(Hα,Hβ) = 4.7 Hz, 1 H, Hβ], 3.41 and 3.45 [dd, ^2J(Hβ,Hβ′) = 14.8 Hz, ^3J(Hα,Hβ′) = 12.9 Hz, 1 H, Hβ′], 3.82 and 3.95 [d, ^2J(Hα,Hα′) = 16.2 Hz, 1 H, Hα Gly], 4.01 and 4.17 [d, ^2J(Hα,Hα′) = 16.4 Hz, 1 H, Hα′ Gly] 4.54 and 4.30 [2d, ^2J(Hε,Hε′) = 16.1 Hz, 1 H, Hε], 4.66 and 5.00 [2d, ^2J(Hε,Hε′,1 H, Hε′) = 16.2 Hz], 5.14 and 5.23 [2dd, ^3J(Hα,Hβ′) = 12.4 Hz, ^3J(Hα,Hβ) = 4.4 Hz, 1 H, Hα benzazepine], 7.20–7.30 (m, 4 H, H arom.), 7.75 and 7.83 [q, $^3J(NH–CH_3)$ = 4.5 Hz, 1 H, *NH*–CH_3] ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 21.9 (CH_3 Ac), 26.4 (*CH*$_3$NH), 28.2 (*CH*$_3$N), 33.2 (CH_2 β), 51.8 (CH_2 ε), 52.3 (CH α benzazepine), 53.4 (CH_2 Gly), 127.7, 128.2, 128.6, 129.5 (CH arom.), 136.3, 136.5 (C_q arom.), 169.9 (C=O Gly), 170.2 (C=O Ac), 171.8 (C=O Aba) ppm. ^{13}C NMR ([D_6]DMSO, 126 MHz): δ = 21.7 (CH_3 Ac), 25.4 (*CH*$_3$NH) 28.8 and 34.3 (*CH*$_3$N), 33.0 and 34.00 (CH_2 β), 51.4 and 52.1 (CH_2 ε), 51.2 and 51.6 (CH_2 Gly), 55.9 and 56.8 (CH α benzazepine), 127.6, 128.0, 128.8, 129.3 (CH arom.), 135.3, 135.4 (C_q arom.), 168.3 (C=O Gly), 170.2 (C=O Ac), 170.5 (C=O Aba) ppm.

(*R*,*S*)-1-(*tert*-Butoxycarbonyl)-2-(2-formylbenzyl)pyrrolidine-2-carboxylic Acid (28): Wet Raney-Ni (50 μpore, Aldrich 2800, 1.00 g) was washed with milliQ water (15 × 4 mL) and suspended with the nitrile **27** (1.00 g, 3.03 mmol) in Py/AcOH/H_2O (1:1:1, 50 mL). The suspension was hydrogenated in a Parr apparatus (50 psi, 50 °C). After 4 h, 8 h, 24 h, 32 h and 48 h fresh catalyst (1 g) was added. After a total reaction time of 56 h the mixture was filtered through dicalite and rinsed with water. After evaporation of the solvent, the residue was redissolved in EtOAc (200 mL) and washed with 1 M HCl (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvents evaporated. A brown oil was obtained (320 mg, 32%); HPLC t_{ret} = 16.0 min, HRMS calcd. 334.1654, found 334.1661. The side product 2,3,5,10-tetrahydro-1*H*-pyrrolo[1,2-*b*]-isoquinoline-10a-carboxylic acid (**29**) could be isolated as follows: The aqueous washing phase described above was evaporated and the residue was redissolved in water (500 mL). The pH was adjusted to 8 with an ammonia solution. The Ni^{II} salts were precipitated by the addition of a saturated ethanolic solution of dimethylglyoxime to the warmed solution. The red precipitate was removed by filtration, and the filtrate was evaporated. The residue was further purified by preparative HPLC. HPLC t_{ret} = 8.7 min, HRMS calcd. 218.1181, found 218.1172. ^{1}H NMR ([D_6]DMSO, 250 MHz): δ = 1.75 (m, 1 H, H^2), 1.99 (m, 2 H, $H^{2'}$ and H^1), 2.42 (m, 1 H, $H^{1'}$), 3.07 (m, 1 H, H^3), 3.22 [d, $^2J(H^{10},H^{10'})$ = 15.4 Hz, 1 H, H^{10}], 3.40 [d, $^2J(H^{10},H^{10'})$ = 15.4 Hz, 1 H, $H^{10'}$], 3.78 (m, 1 H, $H^{3'}$), 4.28 [d, $^2J(H^5,H^{5'})$ = 14.0 Hz, 1 H, H^5], 4.52 [d′, $^2J(H^5,H^{5'})$ = 14.0 Hz, 1 H, H^5], 7.35 (m, 4 H, H arom.) ppm. ^{13}C NMR ([D_6]-DMSO, 63 MHz): δ = 22.8 (CH_2 2), 34.6 (CH_2 10), 35.6 (CH_2 1), 51.4 (CH_2 5), 55.7 (CH_2 3), 73.7 (C_q 10a), 127.7, 127.8, 128.3, 129.2 (CH arom.), 130.2, 133.7 (C_q arom.), 172.4 (C=O) ppm.

[Boc-spiro-(*R*,*S*)-Aba–Gly–OBn] (30): To a solution of aldehyde **28** (700 mg, 2.1 mmol) in CH_2Cl_2 (analytical grade, 35 mL) Gly–OBn·*p*TosOH (742 mg, 2.2 mmol) was added. The pH was adjusted to 6 with *N*-methylmorpholine, followed by the addition of $MgSO_4$ (140 mg, 20 wt.-%) and $NaCNBH_3$ (331 mg, 5.25 mmol). After 18 h stirring at room temperature the solvent was removed under reduced pressure. The residue was redissolved in acetonitrile (130 mL) and pyridine (336 μL, 4.2 mmol) was added. The mixture was cooled in an ice bath for 10 minutes and DCC (474 mg, 2.3 mmol) was added. After 1 hour stirring at 0 °C the reaction was continued overnight at room temperature. Oxalic acid (5 M solution in DMF, 5 mL) was added, and after 30 minutes stirring the abundant precipitate was filtered. The filtrate was evaporated and the residue was redissolved in EtOAc (200 mL). After washing with 1 N HCl and satd. aq. $NaHCO_3$ (3 × 50 mL), the organic layer was dried ($MgSO_4$), filtered and the solvents evaporated. The small particles of DCU in the obtained paste could be removed by filtration after dissolving the paste in toluene. The product was further purified by flash column chromatography (EtOAc/petroleum ether, 1:3). Yield 200 mg (21%). HPLC t_{ret} = 26.4 min; R_f = 0.53 (EtOAc/petroleum ether, 1:2); R_f = 0.60 (EtOAc/*c*Hex, 1:1). HRMS calcd. 465.2389, found 465.2381. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.46 and 1.51 (2s, 9 H, *t*Bu), 1.91 (m, 4 H, CH_2 3 and CH_2 4), 2.56 and 2.64 [2d, ^2J(Hβ,Hβ′) = 14.2 Hz, 1 H, Hβ], 3.55 and 3.72 (2m, 2 H, CH_2 5), 3.89 and 3.94 [2d, ^2J(Hε,Hε′) = 14.6 Hz, 1 H, Hε], 3.99 and 4.11 [2d, ^2J(Hα,Hα′) = 17.0 Hz, 1 H, Hα Gly], 4.09 and 4.23 [2d, ^2J(Hβ,Hβ′) = 14.2 Hz, 1 H, Hβ′], 4.55 and 4.72 [2d, ^2J(Hα,Hα′) = 17.0 Hz, 1 H, Hα′ Gly], 5.09 and 5.14 (2s, 2 H, CH_2 Bn ester), 5.09 and 5.31 [2d, ^2J(Hε,Hε′) = 14.6 Hz, 1 H, Hε′], 7.27 (m, 9 H, H arom. benzazepine, Bn ester) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 22.3 and 23.2 (CH_2 4), 28.5 (CH_3 *t*Bu), 37.9 and 39.7 (CH_2 3), 39.9 and 40.9 (CH_2 β), 48.6 and 48.7 (CH_2 5), 52.9 and 53.2, 53.4 and 53.5 (CH_2 ε, CH_2 α Gly), 66.8 and 66.9 (CH_2 Bn ester), 69.0 and 69.3 (C_q α benzazepine), 80.0 and 81.1 (C_q *t*Bu), 127.2, 127.4, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 129.8, 130.0 (CH arom.), 136.6, 137.2, 137.6 (C_q arom.), 154.0 and 154.4 (C=O Boc), 169.0 and 169.1 (C=O Gly), 175.4 and 175.7 (C=O benzazepine) ppm.

[Boc-spiro-(*R*,*S*)-Aba–Gly–NHMe] (31): Benzyl ester **30** (96 mg, 0.20 mmol) was dissolved in a 33% solution of methylamine in methanol (25 mL, 200 mmol), and the reaction mixture was stirred overnight at room temperature The solvent was evaporated and the residue was redissolved in abs. EtOH. After evaporation of the solvent, the process of dissolving in EtOH and evaporation was repeated twice. The crude product was purified by preparative HPLC. Yield 74 mg (93%). HPLC t_{ret} = 22.3 min; R_f = 0.83 (CH_3CN/MeOH/H_2O, 4:1:2); R_f = 0.30 (EtOAc/*c*Hex, 2:1). HRMS calcd. 388.2236, found 388.2246. ^{1}H NMR ([D_6]DMSO, 250 MHz): δ = 1.40 and 1.44 (2s, 9 H, *t*Bu), 1.86 (m, 4 H, CH_2 3 and CH_2 4), 2.58 and 2.66 [2d, $^3J(CH_3–NH)$ = 4.5 Hz, 3 H, NH–*CH*$_3$], 2.69 [d, ^2J(Hβ,Hβ′) = 13.9 Hz, 1 H, Hβ], 3.46 (m, 2 H, CH_2 5), 3.69 [d, ^2J(Hα,Hα′) = 16.6 Hz, 1 H, Hα Gly], 3.84 and 3.93 [2d, ^2J(Hβ,Hβ′) = 13.9 H,1 H, Hβ′z], 4.15 and 4.18 [2d, ^2J(Hε,Hε′) = 14.5 Hz, 1 H, Hε], 4.46 [d ^2J(Hα,Hα′) = 16.6 Hz, 1 H, Hα′ Gly,], 4.89 and 5.04 [2d, ^2J(Hε,Hε′) = 14.5 Hz, 1 H, Hε′], 7.32 (m, 4 H, H arom.), 7.51 and 7.72 (2q, ^3J = 4.5 Hz, 1 H, *NH*–CH_3) ppm. ^{13}C

NMR ([D$_6$]DMSO, 63 MHz): δ = 22.2 and 23.1 (CH_2 4), 25.7 and 26.0 (NH–CH_3), 28.4 and 28.5 (CH_3 *t*Bu), 378.0 (CH_2 3), 38.8 (CH_2 β), 48.5 and 48.8 (CH_2 5), 51.3 and 52.4 (CH_2 ε), 53.6 and 54.5 (CH_2 α Gly), 68.7 and 69.3 (C_q α benzazepine), 79.5 and 80.2 (C_q *t*Bu), 127.1 and 127.4, 128.2 and 128.4, 128.5 and 128.7, 130.0 and 130.2 (CH arom.), 137.3 and 138.0, 138.3 and 138.4 (C_q arom.), 154.8 (C=O Boc), 168.7 and 169.0 (C=O Gly), 174.0 and 174.5 (C=O benzazepine) ppm.

[Spiro-(*R*,*S*)-Aba–Gly–NHMe] (32): Boc-spiro-Aba–Gly–NHMe (**31**, 45 mg, 0.116 mmol) was dissolved in cold CH_2Cl_2 (5 mL, 0 °C). To this solution cold TFA was added (10 mL, 0 °C). After 2 h stirring at 0 °C, the solvent was removed in vacuo. The crude product was purified by preparative HPLC. Yield 43 mg TFA salt (92%). HPLC t_{ret} = 9.7 min; R_f = 0.50 (CH_3CN/MeOH/H_2O, 4:1:1). HRMS 288.1712, found 288.1718. ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 2.03 (m, 4 H, CH_2 3 and CH_2 4), 2.62 [d, ^3J(CH_3–NH) = 4.5 Hz, 3 H, NH–*CH*$_3$], 3.24 [d, ^2J(Hβ,Hβ′) = 15.2 Hz, 1 H, Hβ], 3.40 (br. s, 2 H, CH_2 5), 3.56 [d, ^2J(Hβ,Hβ′) = 15.2 Hz, 1 H, Hβ′], 4.08 [d, ^2J(Hα,Hα′) = 16.1 Hz, 1 H, Hα Gly], 4.17 [d, ^2J(Hα,Hα′) = 16.1 Hz, 1 H, Hα′ Gly], 4.66 (s, 2 H, 2 Hε), 7.30 (m, 4 H, H arom.), 7.96 (q, ^3J = 4.5 Hz, 1 H, *NH*–CH_3), 8.94 and 9.47 (2s, 1 H, NH Pro) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 23.6 (CH_2 4), 25.8 (NH–CH_3), 35.6 (CH_2 3), 37.1 (CH_2 β), 45.5 (CH_2 5), 52.8 (CH_2 ε), 53.7 (CH_2 α Gly), 71.1 (C_q α benzazepine), 127.7, 128.6, 129.0, 130.6 (CH arom.), 135.0 and 136.2 (C_q arom.), 168.2 (C=O Gly), 171.3 (C=O benzazepine) ppm.

[Ac-spiro-(*R*,*S*)-Aba–Gly–NHMe] (9): Spiro-Aba–Gly–NHMe·TFA (**31**, 43 mg, 0.107 mmol) was dissolved in a mixture of Ac_2O and NEt_3 (5:1, 12 mL). After 2 h stirring at room temperature, the solvent was evaporated and the crude product was purified by preparative HPLC. Yield 32 mg (91%). HPLC t_{ret} = 22.2 min; R_f = 0.65 (CH_3CN/MeOH/H_2O, 4:1:1). HRMS calcd. 330.1817, found 330.1827. ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): δ = 1.86–2.16 (m, 4 H, CH_2 3 and CH_2 4), 2.13 (s, 3 H, CH_3 Ac), 2.56 [d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ], 2.86 (d, ^3J = 4.5 Hz, 3 H, NH–*CH*$_3$), 3.55 [d, ^2J(Hα,Hα′) = 16.8 Hz, 1 H, Hα Gly], 3.74 (m, 2 H, CH_2 5), 3.88 [d, ^2J(Hε,Hε′) = 14.5 Hz, 1 H, Hε], 4.04 [d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ′], 5.00 [d, ^2J(Hα,Hα′) = 16.8 Hz, 1 H, Hα′ Gly], 5.28 [d, ^2J(Hε,Hε′) = 14.5 Hz, 1 H, Hε′], 7.23–7.33 (m, 4 H, H arom.), 7.81 [q, ^3J(NH–CH_3) = 4.5 Hz, 1 H, *NH*–CH_3] ppm. ^{1}H NMR ([D$_6$]DMSO, 500 MHz, 298 K): δ = 1.80 (m, 2 H, CH_2 3), 2.04 (s, 3 H, CH_3 Ac), 2.09 (m, 2 H, CH_2 4), 2.64 [d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ], 2.64 (d, ^3J = 4.5 Hz, NH–*CH*$_3$, 3 H), 3.66 (m, 2 H, CH_2 5), 3.67 [d, ^2J(Hα,Hα′) = 16.5 Hz, 1 H, Hα Gly], 3.88 [d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ′], 4.14 [d, ^2J(Hε,Hε′) = 14.3 Hz, 1 H, Hε], 4.41 [d, ^2J(Hα,Hα′) = 16.5 Hz, 1 H, Hα′ Gly], 5.09 [d, ^2J(Hε,Hε′) = 14.3 Hz, 1 H, Hε′], 7.25–7.42 (m, 4 H, H arom.), 7.71 [q, ^3J(NH–CH_3) = 4.5 Hz, 1 H, *NH*–CH_3] ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 23.2 (CH_3 Ac), 23.9 (CH_2 4), 26.5 (NH–*CH*$_3$), 36.4 (CH_2 3), 38.6 (CH_2 β), 49.7 (CH_2 5), 52.3 (CH_2 ε), 54.8 (CH_2 Gly), 70.3 (C_q α benzazepine), 127.7, 127.8, 128.9, 130.0 (CH arom.), 136.5, 137.6 (C_q arom.), 170.0 (C=O Gly), 170.4 (C=O Ac), 173.8 (C=O benzazepine) ppm. ^{13}C NMR ([D$_6$] DMSO, 126 MHz): δ = 22.7 (CH_3 Ac), 23.1 (CH_2 4), 25.4 (NH–*CH*$_3$), 35.9 (CH_2 3), 37.3 (CH_2 β), 48.7 (CH_2 5), 50.7 (CH_2 ε), 53.9 (CH_2 Gly), 69.2 (C_q α benzazepine), 126.8, 127.6, 128.0, 129.6 (CH arom.), 136.7, 138.0 (C_q arom.), 168.0 (C=O Gly), 168.8 (C=O Ac), 172.7 (C=O benzazepine) ppm.

(*R*,*S*)-2-(2-Formylbenzyl)-1-(methoxycarbonyl)pyrrolidine-2-carboxylic Acid (34): See (*R*,*S*)-Boc–α-(*o*-formylbenzyl)proline (**28**) for experimental procedure. The nitrile **33** (3.00 g, 10.42 mmol) was dissolved in Py/AcOH/H_2O (1:1:1, 75 mL) and Raney-Ni was added in 11 portions of 1.00 g over 35 h. After work-up a brown oil was obtained. Yield 2.10 g (69%); HPLC t_{ret} = 17.6 min (gradient 16% CH_3CN → 40% CH_3CN + 0.1% TFA in 30 min); R_f = 0.65 (CH_2Cl_2/MeOH/AcOH, 90:8:2). HRMS calcd. 292.1185, found 292.1180. ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 0.64 (m, 1 H, H^4), 1.54 (m, 1 H, H$^{4'}$), 2.02 (m, 2 H, CH_2 3), 2.85 (m, 1 H, H^5), 3.29 (m, 1 H, H$^{5'}$), 3.55 and 3.65 (2s, 3 H, CH_3 Moc), 3.72 [d, ^2J(Hβ,Hβ′) = 13.9 Hz, 1 H, Hβ], 3.85 [d, ^2J(Hβ,Hβ′) = 13.9 Hz, 1 H, Hβ′], 7.35–7.83 (m, 4 H, H arom.), 10.13 and 10.15 (2s, 1 H, CHO) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 22.2 and 22.8 (CH_2 4), 33.1 and 34.5 (CH_2 β), 35.1 and 36.8 (CH_2 3), 48.0 and 48.9 (CH_2 5), 52.3 and 52.6 (CH_3 Moc), 68.6 and 69.0 (C_q α), 129.6, 130.0, 127.7, 133.5, 133.6, 133.7 (CH arom.), 135.9 and 136.0, 136.0 and 140.0 (C_q arom.), 154.9 and 155.1 (C=O Moc), 175.1 and 175.4 (C=O COOH), 192.6 and 192.8 (C=O ald.) ppm.

[Moc-spiro-(*R*,*S*)-Aba-Gly-OBn] (35): See compound **30** for the procedure. Yield 980 mg, 32% (starting from 2.10 g **34**); HPLC t_{ret} = 24.6 min; R_f = 0.35 (EtOAc/*c*Hex, 1:1). HRMS calcd. 423.1920, found 423.1925. ^{1}H NMR ([D$_6$]DMSO, 250 MHz): δ = 1.65 (m, 2 H, CH_2 3), 1.88 (m, 1 H, CH_2 4), 2.63 and 2.73 [2d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ], 3.49 (m, 2 H, CH_2 5), 3.56 and 3.59 (2s, 3 H, CH_3 Moc), 3.88 and 4.05 [2d, ^2J(Hβ,Hβ′) = 14.0 Hz, 1 H, Hβ′], 4.14 [d, ^2J(Hα,Hα′) = 16.8 Hz, 1 H, Hα Gly], 4.33 [d, ^2J(Hε,Hε′) = 14.7 Hz, 1 H, Hε], 4.45 [d, ^2J(Hα,Hα′) = 16.8 Hz, 1 H, Hα′ Gly], 5.05 [d, ^2J(Hε,Hε′) = 14.7 Hz, 1 H, Hε′], 5.06 and 5.14 (2s, 2 H, CH_2 Bn), 7.19–7.37 (m, 9 H, H arom.) ppm. ^{13}C NMR ([D$_6$]-DMSO, 63 MHz): δ = 22.4 and 23.1 (CH_2 4), 37.8 and 39.0 (CH_2 3), 39.2 and 40.3 (CH_2 β), 48.2 and 48.8 (CH_2 5), 51.8–52.8 (CH_2 ε, CH_2 α Gly, CH_3 Moc), 65.9 and 66.2 (CH_2 Bn), 69.0 and 69.4 (C_q α), 127.2–130.2 (CH arom.), 136.2, 137.8, 138.4 (C_q arom.), 154.5 and 154.6 (C=O Moc), 169.3 and 169.5 (C=O Gly), 174.4 and 177.7 (C=O benzazepine) ppm.

Acknowledgments

We are grateful to the Institution for the Promotion of Innovation by Science and Technology in Flanders (IWT) and the Fund for Scientific Research-Flanders (Belgium) for financial support (grant no G.0036.04).

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Received: December 21, 2005
Published Online: April 19, 2006

