

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

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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  $\beta$ -turn conformation was investigated by NMR spectroscopy (solvent and temperature dependence) and molecular model-

ing. Interestingly, most of these lactams adopt extended conformations, only the spiro-benzazepinone **9** has a strong preference for the formation of a  $\beta$ -turn.

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## Introduction

The three-dimensional structure of a protein is characterized by an arrangement of  $\alpha$ -helices,  $\beta$ -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.<sup>[1]</sup> They are involved in interactions between peptides and their receptors, antibodies and antigens, and regulatory enzymes and their corresponding substrates.<sup>[2]</sup> Tight turns provide important information allowing the design of new potent and selective drugs, pesticides and antigens,<sup>[1]</sup> and consequently much effort has been done to prepare small mimetics of turn structures.<sup>[2–6]</sup>

$\beta$ -Turns belong, together with  $\delta$ -,  $\gamma$ -,  $\alpha$ - and  $\pi$ -turns, to the collection of tight turns.<sup>[1]</sup> In a  $\beta$ -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.<sup>[7]</sup>

$\beta$ -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  $\beta$ -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.<sup>[2]</sup>

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

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.<sup>[12–20]</sup> 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<sup>[21]</sup> and their conformational properties were examined by NMR and molecular modeling to evaluate their  $\beta$ -turn mimicry. Analogs containing Gly as the *i* + 2 residue (**7**), *N*-methylated Aba **8**, heterochiral (**5**) and homochiral sequences (**6**) were studied.

Several spiro-lactams have been reported to be very efficient  $\beta$ -turn inducers.<sup>[22–25]</sup> We now also report the preparation of the spiro derivative **9**, and its conformational analysis.

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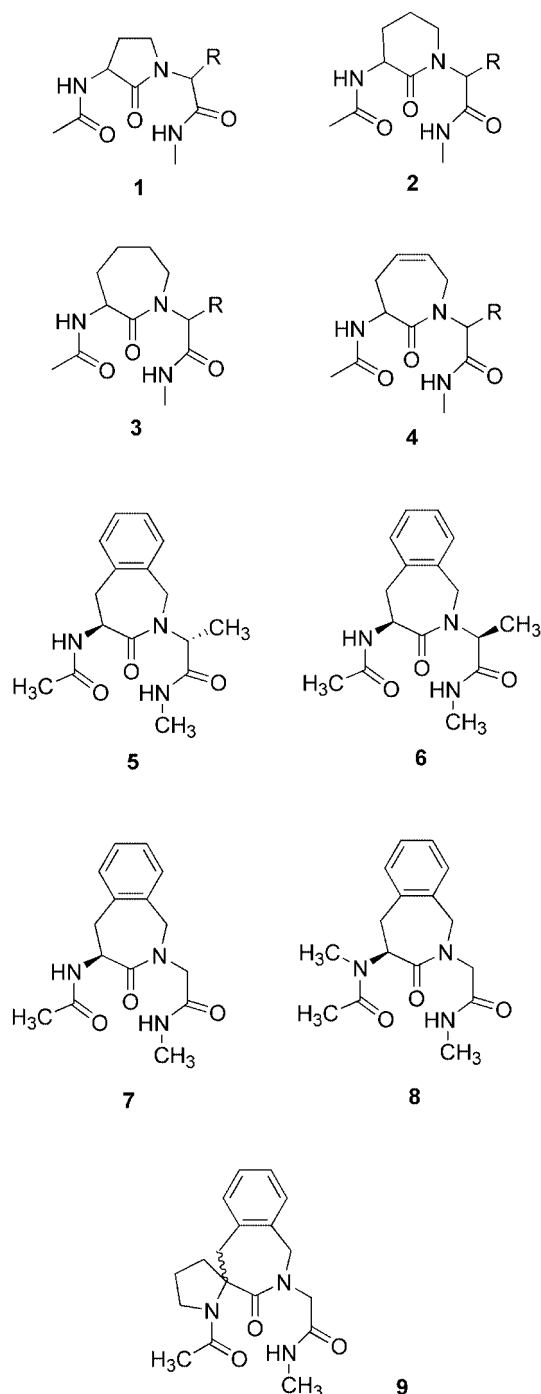


Figure 1. Freidinger lactams and benzazepinones as  $\beta$ -turn mimetics.

## 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**)<sup>[26]</sup> with *o*-cyanobenzyl bromide (**11**) using the commercially available and inexpensive catalyst *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidin-

ium bromide, resulting in the alkylated compound **12** (Figure 2). Hydrolysis of the benzophenone imine **12** using aqueous citric acid provides (*S*)-*o*-CN-Phe-*Or*Bu (**13**).

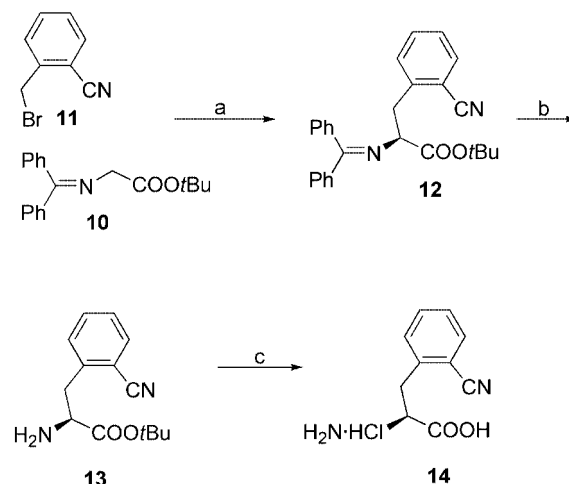


Figure 2. Synthesis of (*S*)-*o*-cyano-Phe. a) CsOH·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide,  $-78^{\circ}\text{C}$ , 27 h; b) 15% citric acid, THF, o.n., room temp., 90% yield (a+b); c) 6 N HCl, CH<sub>2</sub>Cl<sub>2</sub>, room temp., o.n., 97%.

At first a liquid/liquid phase-transfer alkylation of **10** (50% aq. KOH/toluene) at room temperature was examined,<sup>[27]</sup> which resulted in a low stereoselection (62% *ee*). Excellent results were, however, obtained with solid/liquid PTC (CsOH·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>) at  $-78^{\circ}\text{C}$ :<sup>[28]</sup> 96% enantiomeric excess and 90% yield were achieved. In order to prevent the decomposition of the catalyst,<sup>[29]</sup> the base was suspended in CH<sub>2</sub>Cl<sub>2</sub>, 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,<sup>[30]</sup> 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<sub>2</sub>Cl<sub>2</sub>, 1:1 resulting in (*S*)-*o*-CN-Phe·HCl (**14**).<sup>[31]</sup> Other acidolytic conditions (TFA/H<sub>2</sub>O, 9:1<sup>[32]</sup> and TFA/anisole, 3:1<sup>[33]</sup>) provided insufficient scavenging of the *t*Bu cation and caused *tert*-butylation of the aromatic ring of *o*-CN-Phe.

The stereoselection of the alkylation reaction was determined by HPLC analysis of the FDAA derivative of **14**,<sup>[34]</sup> 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)<sup>[35]</sup> and reduction of the nitrile **15** with H<sub>2</sub>/Raney-Ni provided the aldehyde **16** (Figure 3).<sup>[36]</sup> This aldehyde was used in a reductive amination with (*R*)-Ala-*OBn*·*p*TosOH followed by ring closure, according to a procedure reported earlier.<sup>[37]</sup> 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**).<sup>[18]</sup> Acetylation with acetic anhydride in water provided compound **20**,<sup>[38]</sup> which was used in a coupling reaction with methylamine using TBTU activation. During this coupling 30%

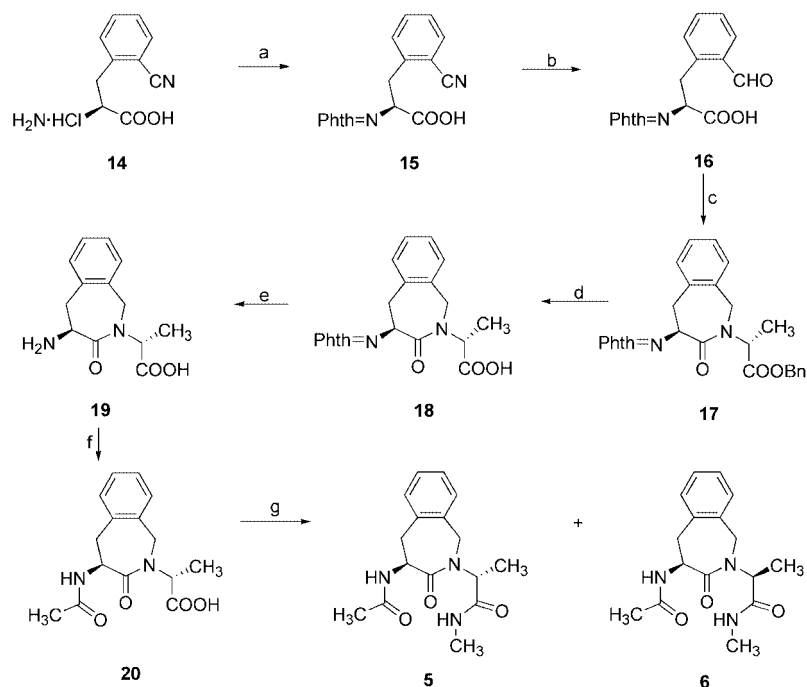
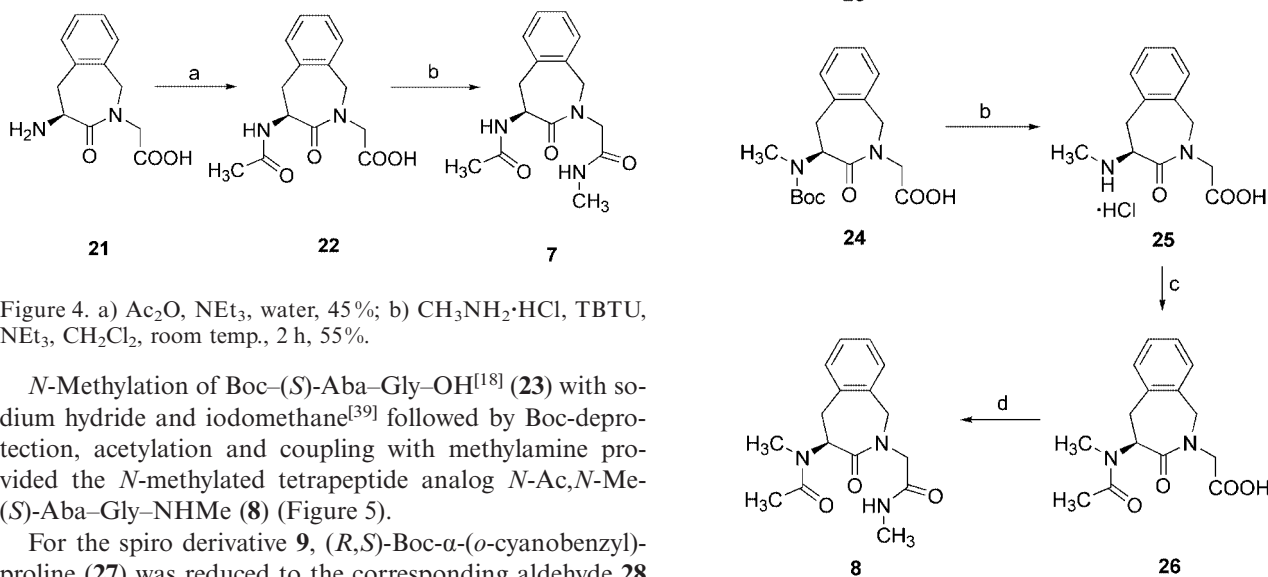


Figure 3. a) MSB, CH<sub>3</sub>CN, H<sub>2</sub>O, Na<sub>2</sub>CO<sub>3</sub>, 81%; b) Raney-Ni, H<sub>2</sub> (50 psi), H<sub>2</sub>O/AcOH/Py, 1:1:1, 50 °C, 38 h, 78%; c) 1) (R)-Ala-OBn-pTosOH, NaCNBH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MgSO<sub>4</sub>, NMM, 2) DCC, Py, AcN, 39% (2 steps); d) H<sub>2</sub> (50 psi), 10% Pd/C, dioxane/H<sub>2</sub>O 3:2; e) NH<sub>2</sub>NH<sub>2</sub>, EtOH, reflux, 1.5 h, 84%; f) Ac<sub>2</sub>O, NEt<sub>3</sub>, water, 60%; g) CH<sub>3</sub>NH<sub>2</sub>·HCl, TBTU, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>[18]</sup> (21) was acetylated and converted into tetrapeptide mimic Ac-(S)-Aba-Gly-NHMe (7) (Figure 4).



N-Methylation of Boc-(S)-Aba-Gly-OH<sup>[18]</sup> (23) with sodium hydride and iodomethane<sup>[39]</sup> 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<sub>2</sub>/Raney-Ni in aqueous pyridinium acetate (Figure 6).<sup>[36]</sup> 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<sub>2</sub>Cl<sub>2</sub>, 1:1, room temp., o.n., 57%; c) Ac<sub>2</sub>O, Et<sub>3</sub>N, water, 45%; d) CH<sub>3</sub>NH<sub>2</sub>·HCl, TBTU, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 2 h, 47%.

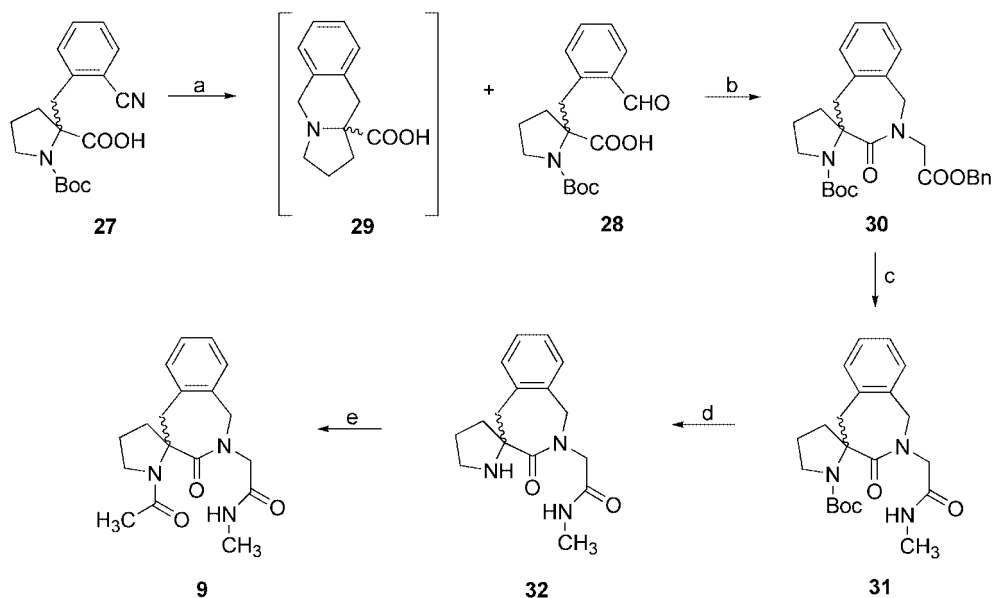


Figure 6. a) Raney-Ni, H<sub>2</sub> (50 psi), H<sub>2</sub>O/AcOH/Py, 1:1:1, 50 °C, 56 h, 32%; b) 1) Gly-OBn-*p*TosOH, NaCNBH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MgSO<sub>4</sub>, NMM, 2) DCC, Py, AcN, 21% (2 steps); c) CH<sub>3</sub>NH<sub>2</sub>, MeOH, o.n., room temp., 93%; d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 92%; e) Ac<sub>2</sub>O, NEt<sub>3</sub>, 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.<sup>[37]</sup>

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  $\alpha$ -(*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- $\alpha$ -(*o*-for-

mylbenzyl)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.

### Molecular Modeling Results

In order to evaluate the intrinsic  $\beta$ -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.<sup>[40]</sup> Briefly, the procedure consisted of a MM3\*<sup>[41]</sup> low-mode search<sup>[42]</sup> on the formyl-Xxx-NMe rings (Xxx = Aba, spiro-Aba) in vacuo (Figure 8).

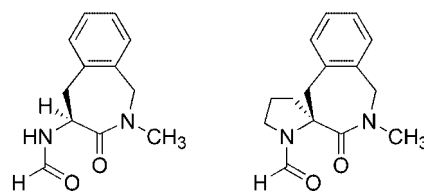


Figure 8. Formyl-Xxx-NMe (Xxx = Aba, spiro-Aba) structures.

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)<sup>[43]</sup> in water, using the GB/SA solvation model.<sup>[44]</sup> All conformations within 50 kJ/mol of the global minimum were clustered into families based on geometrical similarity.

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

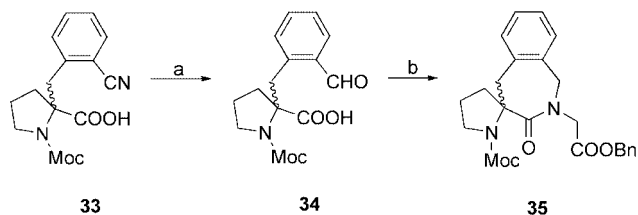
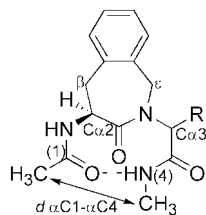


Figure 7. a) Raney-Ni, H<sub>2</sub> (50 psi), H<sub>2</sub>O/AcOH/Py, 1:1:1, 50 °C, 35 h, 69%; b) 1) Gly-OBn-*p*TosOH, NaCNBH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MgSO<sub>4</sub>, NMM, 2) DCC, Py, AcN, 32% (2 steps).

Figure 9. Criteria used to evaluate  $\beta$ -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  $\beta$ -turns.<sup>[45]</sup>

(2) The  $C_{\alpha}1$ – $C_{\alpha}4$  interatomic distance should be less than 7 Å.

(3) The virtual torsion angle  $\beta$ , defined by C1,  $C_{\alpha}2$ ,  $C_{\alpha}3$  and N4 of the tetrapeptide model<sup>[46]</sup> should lie between specified limits (Table 1).

Table 1. Virtual torsion angle  $\beta$  defining  $\beta$ -turn classes.

| Type of $\beta$ -turn | Virtual torsion angle $\beta$ |
|-----------------------|-------------------------------|
| 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  $\varphi$ - and  $\psi$  angles of the central residues of the  $\beta$ -turn, which are characteristic for the turn type.<sup>[1]</sup>

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  $\beta$ -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.

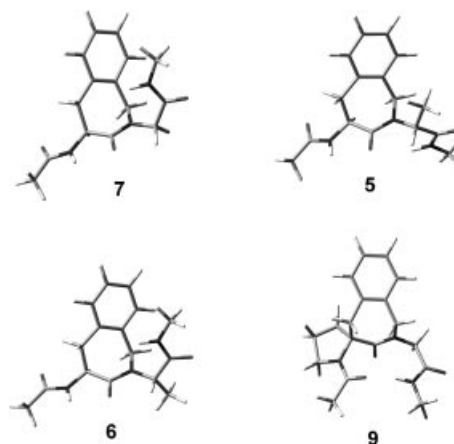


Figure 10. 3D representation of the lowest-energy conformers.

In contrast, the lowest-energy conformer of Ac-(*S*)-spiro-Aba-Gly-NHMe (9) displays a  $\beta$ -turn of type II', indicating that spiro-Aba has  $\beta$ -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  $\beta$ -turn of type II' can be induced. In contrast, none of the chair-like *trans* 2 ring conformations have  $\beta$ -turn properties.

## NMR Analysis

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

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

| Structure                  | Ac-( <i>S</i> )-Aba-Gly-NHMe (7) | Ac-( <i>S</i> )-Aba-( <i>R</i> )-Ala-NHMe (5) | Ac-( <i>S</i> )-Aba-( <i>S</i> )-Ala-NHMe (6) | Ac-( <i>S</i> )-spiro-Aba-Gly-NHMe (9) |
|----------------------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------|
| Ring conformation          | <i>trans</i> 2 <sup>[a]</sup>    | <i>trans</i> 2 <sup>[a]</sup>                 | <i>trans</i> 2 <sup>[a]</sup>                 | <i>trans</i> 1 <sup>[a]</sup>          |
| Turn                       | /                                | /                                             | /                                             | II'                                    |
| $d(\text{NH-CO})$ [Å]      | 6.5                              | 6.0                                           | 6.7                                           | 2.0                                    |
| NHO angle [°]              | 149                              | 153                                           | 137                                           | 164                                    |
| $d(\text{Ca1-Ca4})$ [Å]    | 9.3                              | 8.7                                           | 9.7                                           | 5.4                                    |
| $\beta$ [°]                | 139                              | -61                                           | 149                                           | -11                                    |
| $\varphi 2$ [°]            | 162                              | 162                                           | 161                                           | 58                                     |
| $\psi 2$ [°]               | -162                             | -163                                          | -164                                          | -123                                   |
| $\varphi 3$ [°]            | 105                              | -124                                          | 126                                           | -98                                    |
| $\psi 3$ [°]               | -26                              | 34                                            | -43                                           | 17                                     |
| $E$ of first turn (kJ/mol) | 14.85                            | 24.94                                         | 13.39                                         | 0                                      |
|                            | g(+) <sup>1</sup>                | g(+) <sup>1</sup>                             | g(+) <sup>1</sup>                             |                                        |
|                            | type I                           | type I                                        | type I                                        |                                        |

[a] The ring conformations are primarily classified by the  $\chi_1$  torsion angle of the Aba amino acid, which can either be gauche(+) or *trans*.<sup>[18]</sup> However, for each of these possible orientations of  $\chi_1$ , two ring conformations are possible (e.g. *trans* 1 and *trans* 2). In the *trans* 1 conformation, one of the C $\beta$ -H is in close proximity with one of the C $\epsilon$ -H, whereas in the *trans* 2 conformation the C $\alpha_2$ -H is in close proximity with one of the C $\epsilon$ -H. (see also Figure 10).

NMR.<sup>[50]</sup> In every compound, the benzazepinone ring was shown to adopt a *trans*  $\chi_1$  conformation around the C $_{\alpha}$ –C $_{\beta}$  bond (Figure 10).<sup>[18]</sup> 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 H $_{\alpha}$  and H $_{\beta}$ , and the opposite for H $_{\alpha}$  and H $_{\beta}'$  demonstrates the presence of the *trans* rotamer (see Figure 11 for atom labeling). Further evidence is given by the NOE cross peaks between the  $\beta$ -hydrogen atoms and NH–Ac, and the strong one between only one  $\beta$ -hydrogen (H $_{\beta}$ ) and the aromatic H $^6$ . A similar reasoning based on the NOE's only for spiro derivative **9** also indicates a *trans*  $\chi_1$  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 <b>5</b>                           |         | Compound <b>9</b>                   |        |
|---------------------------------------------|---------|-------------------------------------|--------|
| $^3J(\text{H}_{\alpha}, \text{H}_{\beta})$  | 4.1 Hz  | –                                   |        |
| $^3J(\text{H}_{\alpha}, \text{H}_{\beta}')$ | 13.1 Hz | –                                   |        |
| NOE H $_{\alpha}$ /H $_{\beta}$             | strong  | NOE H $_3$ /H $_{\beta}$            | strong |
| NOE H $_{\alpha}$ /H $_{\beta}'$            | weak    | NOE H $_3$ /H $_{\beta}'$           | absent |
| NOE NH $_{\text{Ac}}$ /H $_{\beta}$         | strong  |                                     |        |
| NOE NH $_{\text{Ac}}$ /H $_{\beta}'$        | strong  |                                     |        |
| NOE H $_{\beta}$ /H $^6$                    | strong  | NOE H $_{\beta}$ /H $^6$            | strong |
| NOE H $_{\alpha}$ /H $_{\epsilon}$          | strong  |                                     |        |
| NOE H $_{\beta}'$ /H $_{\epsilon}'$         | absent  | NOE H $_{\beta}'$ /H $_{\epsilon}'$ | strong |
| NOE H $_{\epsilon}$ /H $^9$                 | absent  | NOE H $_{\epsilon}$ /H $^9$         | strong |
| NOE H $_{\epsilon}'$ /H $^9$                | strong  | NOE H $_{\epsilon}'$ /H $^9$        | absent |

Interestingly, the CH $_2$   $\epsilon$  protons show a different pattern in **9**, compared to **5**, **6**, **7** and **8**. Indeed, in **5** a strong NOE is observed between H $_{\alpha}$  and H $_{\epsilon}$ , and between H $_{\epsilon}'$  and H $^9$ , which corresponds to the calculated *trans* 2 conformation. In **9**, a strong NOE between H $_{\beta}'$  and H $_{\epsilon}'$ , and between H $_{\epsilon}$  and the aromatic H $^9$  indicates a preferred *trans* 1 conformation (Figure 10).

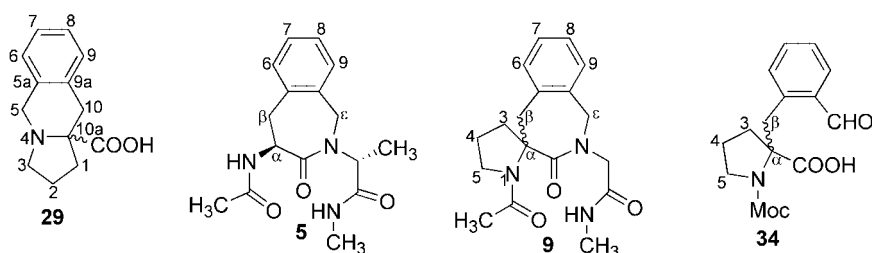


Figure 11. Atom labeling as used in the NMR interpretation.

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

|                                          |       | $\delta$<br>CDCl $_3$ | $\delta$<br>[D $_6$ ]DMSO | $\Delta\delta$<br>CDCl $_3 \rightarrow$ [D $_6$ ]DMSO | $\Delta\delta/\Delta T$ |
|------------------------------------------|-------|-----------------------|---------------------------|-------------------------------------------------------|-------------------------|
| Ac-(S)-Aba-(R)-Ala-NHMe ( <b>5</b> )     | Ac–NH | 6.99                  | 8.08                      | 1.09                                                  | –6.6                    |
|                                          | NH–Me | 6.41                  | 7.86                      | 1.45                                                  | –5.7                    |
| Ac-(S)-Aba-(S)-Ala-NHMe ( <b>6</b> )     | Ac–NH | 6.92                  | 8.12                      | 1.20                                                  | –6.2                    |
|                                          | NH–Me | 5.45                  | 7.55                      | 2.10                                                  | –6.9                    |
| Ac-(S)-Aba-Gly-NHMe ( <b>7</b> )         | Ac–NH | 6.93                  | 8.12                      | 1.19                                                  | –6.9                    |
|                                          | NH–Me | 6.57                  | 7.87                      | 1.30                                                  | –6.6                    |
| N-Ac,N-Me-Aba-Gly-NHMe ( <b>8</b> )      | NH–Me | 7.51                  | 7.83                      | 0.32                                                  | –5.8                    |
| Ac-(R,S)-spiro-Aba-Gly-NHMe ( <b>9</b> ) | NH–Me | 7.81                  | 7.71                      | –0.10                                                 | –4.3                    |

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  $\beta$ -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.

$^1\text{H}$  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 NH–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 NH–Me.

In compounds **5**, **6** and **7** (Table 4), the chemical shift in CDCl $_3$  of NH–Me is smaller than the chemical shift of Ac–NH. This is in contrast with the expectation for the benzazepinones in the  $\beta$ -turn conformation. In that case the NH–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–NH.<sup>[51]</sup>

Switching from CDCl $_3$  to [D $_6$ ]DMSO resulted in a large increase in chemical shift for both Ac–NH and NH–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–NH and NH–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.<sup>[21]</sup> These data indicate that **5**, **6**, **7** and **8** do not adopt a  $\beta$ -turn conformation. Furthermore, the expected NOE correlations for these compounds in a  $\beta$ -turn conformation were not observed.

For the spiro derivative **9**, however, the amide resonance is only very weakly influenced by switching from  $\text{CDCl}_3$  to  $[\text{D}_6]\text{DMSO}$ . 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  $^1\text{H}$  NMR spectrum, indicates the presence of exclusively the *trans* rotamer for the acetyl-spiro amide bond. Additionally, the existence of an NOE effect between  $\text{H}_\epsilon$  (not  $\text{H}_{\epsilon'}$ ) and only one of the  $\alpha$ -hydrogen atoms of Gly indicates that there is no rotational freedom around the  $\text{N}^2\text{--C}\alpha_{\text{Gly}}$  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  $\beta$ -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  $\beta$ -turn conformation. It was also observed that the conformation of the seven-membered lactam ring was different in the spiro-lactam **9** and in benzazepinones **5**, **6**, **7** and **8**, suggesting that this may contribute to the  $\beta$ -turn mimicry of **9**.

## Experimental Section

**Molecular Modeling:** The calculations were carried out using MacroModel 5.0<sup>[40]</sup> with Maestro 8.0 as a graphic interface. The MM3\* force field<sup>[41]</sup> 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.<sup>[42]</sup> 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  $0.02 \text{ kJ/mol}\cdot\text{\AA}$ . 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.,<sup>[44]</sup> using MacroModel's default parameters for an aqueous medium. The conformational space was sampled by a systematic unbounded multiple minimum search<sup>[43]</sup> in which 3 internal coordinates ( $\varphi_2$ ,  $\varphi_3$  and  $\psi_3$ ) were varied. Here the generation of 2000 structures was conducted and the conformers were minimized to an energy convergence of  $0.1 \text{ kJ/mol}\cdot\text{\AA}$  by use of the Polak–Ribière conjugate gradient method. After this search the found conformations were again minimized to an energy convergence of  $0.01 \text{ kJ/mol}\cdot\text{\AA}$ . In both strategies, duplicate structures and those greater than  $50 \text{ kJ/mol}$  above the global mini-

mum were discarded. The generated structures were clustered in families with Xcluster 1.7. A RMSD value of  $0.2 \text{ \AA}$  was used.

**General Methods:** (*R,S*)-Boc- $\alpha$ -(*o*-cyanobenzyl)proline (**27**) and (*R,S*)-Moc- $\alpha$ -(*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,  $l = 25 \text{ cm}$ ,  $d = 0.45 \text{ cm}$ ,  $PS = 5 \mu\text{m}$ ). The mobile phase (water/acetonitrile) contained  $0.1\%$  TFA. Products were eluted using the following gradient:  $t = 0 \text{ min}$ ,  $3\%$   $\text{CH}_3\text{CN}$ ,  $t = 30 \text{ min}$ ,  $80\%$   $\text{CH}_3\text{CN}$ ,  $t = 40 \text{ min}$ ,  $100\%$   $\text{CH}_3\text{CN}$ . Flow rate:  $1.0 \text{ mL min}^{-1}$ ,  $\lambda = 215 \text{ nm}$ . Preparative HPLC was performed using a RP C-18 column (Supelco Discovery®BIO Wide Pore C18,  $l = 25 \text{ cm}$ ,  $d = 2.12 \text{ cm}$ ,  $PS = 10 \mu\text{m}$ ). The above mentioned gradient was used with a flow rate of  $20.0 \text{ mL min}^{-1}$ . FDAA analysis was performed as described earlier.<sup>[37]</sup> TLC analysis was performed with a plastic sheet precoated with silica gel 60F<sub>254</sub> (Merck). Silicagel 60 ( $0.040\text{--}0.063 \text{ mm}$ ) 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  $1^\circ \text{C}\cdot\text{min}^{-1}$ . Optical rotations were measured at room temperature using an optical activity type AA-5 polarimeter.  $^1\text{H}$  and  $^{13}\text{C}$  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  $\text{CDCl}_3$  and  $[\text{D}_6]\text{DMSO}$  with the Bruker AMX500 spectrometer, using pulse sequences of the Bruker program library. The temperature study was performed in  $[\text{D}_6]\text{DMSO}$ , with a temperature increment of  $5 \text{ K}$  between  $298 \text{ K}$  and  $343 \text{ K}$ . 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<sub>2</sub>O ( $34.10 \text{ g}$ ,  $203 \text{ mmol}$ ) was put in a  $250 \text{ mL}$  flask and dried overnight at  $130^\circ \text{C}$  under vacuum. After cooling to room temperature the system was put under Ar, and the CsOH was suspended in  $\text{CH}_2\text{Cl}_2$  (analytical grade,  $60 \text{ mL}$ ). The mixture was further cooled to  $-78^\circ \text{C}$ , and after  $15 \text{ min}$  stirring *tert*-butyl *N*-(diphenylmethylene)glycinate (**10**,  $6.00 \text{ g}$ ,  $20.3 \text{ mmol}$ ) and the phase-transfer catalyst *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide ( $1.23 \text{ g}$ ,  $2.03 \text{ mmol}$ ) were added. The mixture was stirred for  $30 \text{ min}$ , followed by the addition of *o*-cyanobenzyl bromide (**11**,  $7.96 \text{ g}$ ,  $40.6 \text{ mmol}$ , addition in 4 portions with  $3 \text{ min}$  intervals). After a  $27\text{-h}$  reaction time at  $-78^\circ \text{C}$ , the mixture was diluted with  $\text{Et}_2\text{O}$  ( $600 \text{ mL}$ ), washed with  $\text{H}_2\text{O}$  ( $3 \times 150 \text{ mL}$ ) and brine ( $1 \times 150 \text{ mL}$ ). The organic layer was dried ( $\text{MgSO}_4$ ), 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 ( $2:1$ ,  $180 \text{ mL}$ ). After stirring overnight, the THF was evaporated and the residue was taken up in  $\text{H}_2\text{O}$  ( $400 \text{ mL}$ ). The aqueous layer was washed with  $\text{Et}_2\text{O}$  ( $3 \times 150 \text{ mL}$ ), and the pH was adjusted with  $20\%$   $\text{K}_2\text{CO}_3$  until pH 10. The basic aqueous phase was extracted with  $\text{EtOAc}$  ( $4 \times 120 \text{ mL}$ ). Drying ( $\text{MgSO}_4$ ), 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 ( $\text{EtOAc}$ ). 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  $4.51 \text{ g}$  ( $90\%$ ). HPLC  $t_{\text{ret}} = 15.5 \text{ min}$ ;  $R_f = 0.49$  ( $\text{EtOAc/MeOH}$ ,  $2:1$ ). HRMS calcd.  $247.1446$ , found  $247.1453$ .  $[\alpha]_D^{20} = +22.9$  ( $c = 1.7$ ,  $\text{EtOAc}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $250 \text{ MHz}$ ):  $\delta = 1.42$  (s, 9 H, *t*Bu),  $1.7$  (br. s, 2 H,  $\text{NH}_2$ ),  $3.01$  [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 13.8 \text{ Hz}$ ,  $^3J(\text{H}\alpha, \text{H}\beta) =$

8.4 Hz, 1 H, H $\beta$ ], 3.26 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 13.9$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 5.8$  Hz, 1 H, H $\beta$ ], 3.70 [dd,  $^3J(\text{H}\alpha, \text{H}\beta) = 8.4$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 5.8$  Hz, 1 H, H $\alpha$ ], 7.28–7.65 (m, 4 H, H arom.) ppm.  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta = 28.36$  (CH<sub>3</sub> *t*Bu), 40.17 (CH<sub>2</sub>  $\beta$ ), 56.41 (CH  $\alpha$ ), 82.03 (C<sub>q</sub> *t*Bu), 113.74 (C<sub>q</sub> arom. next to C $\equiv$ N), 118.48 (C $\equiv$ N), 127.61, 130.93, 133.08, 133.28 (CH arom.), 142.53 (C<sub>q</sub> arom. next to CH<sub>2</sub>  $\beta$ ), 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<sub>2</sub>Cl<sub>2</sub>/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<sub>3</sub>CN/H<sub>2</sub>O (1:1) and lyophilisation. Yield 4.03 g (97%). M.p. (dec.) 225 °C; HPLC  $t_{\text{ret}} = 9.6$  min;  $R_f = 0.61$  (EtOAc/BuOH/AcOH/H<sub>2</sub>O, 1:1:1:1). HRMS calcd. 191.0820, found 191.0829.  $[\alpha]_D^{20} = +11.2$  ( $c = 1$ , H<sub>2</sub>O).  $^1\text{H}$  NMR (D<sub>2</sub>O, 250 MHz):  $\delta = 3.26$  [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 14.6$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 7.7$  Hz, 1 H, H $\beta$ ], 3.41 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 14.6$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 7.2$  Hz, 1 H, H $\beta'$ ], 4.17 [pseudo t,  $^3J(\text{H}\alpha, \text{H}\beta) \approx ^3J(\text{H}\alpha, \text{H}\beta') = 7.4$  Hz, 1 H, H $\alpha$ ], 7.34–7.69 (m, 4 H, H arom.) ppm.  $^{13}\text{C}$  NMR (20 wt.-% DCl in D<sub>2</sub>O, 63 MHz):  $\delta = 32.24$  (CH<sub>2</sub>  $\beta$ ), 51.19 (CH  $\alpha$ ), 109.88 (C<sub>q</sub> arom. next to C $\equiv$ N), 116.11 (C $\equiv$ N), 126.79, 128.70, 131.89, 132.23 (CH arom.), 135.50 (C<sub>q</sub> arom. next to CH<sub>2</sub>  $\beta$ ), 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<sub>3</sub>CN/H<sub>2</sub>O (65:40, 105 mL), to which Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O (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  $\times$  100 mL) and water (2  $\times$  100 mL). A light yellow solid was obtained after drying (MgSO<sub>4</sub>), filtration and evaporation. The product was used without further purification. Yield 1.36 g (81%). M.p. 198.8–200.7 °C; HPLC  $t_{\text{ret}} = 19.9$  min;  $R_f = 0.46$  (EtOAc/BuOH/AcOH/H<sub>2</sub>O, 16:1:1:1). HRMS calcd. 321.0875, found 321.0869.  $[\alpha]_D^{20} = -302.9$  ( $c = 1.24$ , AcN/H<sub>2</sub>O, 14:1).  $^1\text{H}$  NMR (CD<sub>3</sub>OD, 250 MHz):  $\delta = 3.65$  [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 14.4$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 11.4$  Hz, 1 H, H $\beta$ ], 3.81 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 14.4$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 4.6$  Hz, 1 H, H $\beta'$ ], 5.20 [dd,  $^3J(\text{H}\alpha, \text{H}\beta) = 11.4$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 4.6$  Hz, 1 H, H $\alpha$ ], 7.28–7.62 (m, 4 H, H arom.), 7.73–7.85 (m, 4 H, H arom. Phth) ppm.  $^{13}\text{C}$  NMR (CD<sub>3</sub>OD, 63 MHz):  $\delta = 34.60$  (CH<sub>2</sub>  $\beta$ ), 53.37 (CH  $\alpha$ ), 113.82 (C<sub>q</sub> arom. next to C $\equiv$ N), 118.49 (C $\equiv$ 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<sub>q</sub> arom. Phth), 142.55 (C<sub>q</sub> arom. next to CH<sub>2</sub>  $\beta$ ), 168.72, 171.24 (C=O) ppm.

**(S)-N,N-Phthaloyl-o-formylphenylalanine (16):** Wet Raney-Ni (1.5 g, 50  $\mu$ pore, Aldrich) was washed with milliQ water (15  $\times$  10 mL) and suspended with (S)-Phth-o-cyano-Phe (**15**, 350 mg, 1.09 mmol, 1 equiv.) in Py/AcOH/H<sub>2</sub>O (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  $\times$  50 mL). The organic layer was dried (MgSO<sub>4</sub>), filtered and the solvents evaporated. A white sticky foam was obtained. Yield 275 g (78%). HPLC  $t_{\text{ret}} = 19.7$  min;  $R_f = 0.42$  (EtOAc/BuOH/AcOH/H<sub>2</sub>O, 16:1:1:1). HRMS calcd. 324.0872, found 324.0877.  $[\alpha]_D^{20} = -253$  ( $c = 0.664$ , EtOAc).  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta = 3.65$  [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 13.6$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 11.3$  Hz, 1 H, H $\beta$ ], 4.24 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 13.6$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 4.7$  Hz, 1 H, H $\beta'$ ], 5.43 [dd,  $^3J(\text{H}\alpha, \text{H}\beta) = 11.1$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 4.7$  Hz, 1 H, H $\alpha$ ], 7.01–8.07 (m, 8 H, H

arom.), 10.15 (s, 1 H, H aldehyde) ppm.  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta = 32.58$  (CH<sub>2</sub>  $\beta$ ), 51.75 (CH  $\alpha$ ), 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<sub>q</sub> arom.), 167.33, 173.66 (C=O), 193.44 (C=O aldehyde) ppm.

**Benzyl (2R)-[(4S)-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<sub>2</sub>Cl<sub>2</sub> (analytical grade, 60 mL) (R)-Ala-OBn·pTosOH (1.12 g, 3.19 mmol) was added. The pH was adjusted to 6 with *N*-methylmorpholine, followed by the addition of MgSO<sub>4</sub> (197 mg, 20 wt.-%) and NaCNBH<sub>3</sub> (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  $\mu$ L, 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<sub>3</sub> (3  $\times$  100 mL), the organic layer was dried (MgSO<sub>4</sub>), 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  $t_{\text{ret}} = 26.5$  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<sub>3</sub>).  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta = 1.43$  (d,  $^3J = 7.3$  Hz, 3 H, CH<sub>3</sub> Ala), 3.17 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.2$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 4.2$  Hz, 1 H, H $\beta$ ], 4.26 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.1$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 13.3$  Hz, 1 H, H $\beta'$ ], 4.37 [d,  $^2J(\text{H}\epsilon, \text{H}\epsilon') = 16.4$  Hz, 1 H, H $\epsilon$ ], 4.81 [d,  $^2J(\text{H}\epsilon, \text{H}\epsilon') = 16.4$  Hz, 1 H, H $\epsilon'$ ], 5.14 (s, 2 H, CH<sub>2</sub> Bn ester), 5.40 (q,  $^3J = 7.3$  Hz, 1 H, H $\alpha$  Ala), 5.58 [dd,  $^3J(\text{H}\alpha, \text{H}\beta) = 4.4$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 13.2$  Hz, 1 H, H $\alpha$  benzazepine], 7.11–7.33 (m, 9 H, H arom. benzazepine, Bn ester), 7.71–7.89 (m, 4 H, Phth) ppm.  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta = 15.68$  (CH<sub>3</sub> Ala), 34.50 (CH<sub>2</sub>  $\beta$ ), 48.65 (CH<sub>2</sub>  $\epsilon$ ), 51.96 (CH  $\alpha$  benzazepine), 53.96 (CH  $\alpha$  Ala), 67.92 (CH<sub>2</sub> 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<sub>q</sub> arom.), 168.35, 169.84, 171.90 (C=O) ppm.

**(2R)-[(4S)-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<sub>2</sub>O (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<sub>3</sub>CN/H<sub>2</sub>O. Yield 225 mg (98%). M.p. 170.0–179.2 °C; HPLC  $t_{\text{ret}} = 19.1$  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<sub>2</sub>Cl<sub>2</sub>).  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta = 1.34$  (m, 3 H, CH<sub>3</sub> Ala), 3.15 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.2$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 3.1$  Hz, 1 H, H $\beta$ ], 4.17–4.35 (m, 2 H, H $\beta'$ , H $\epsilon$ ), 4.87 [d,  $^2J(\text{H}\epsilon, \text{H}\epsilon') = 16.3$  Hz, 1 H, H $\epsilon'$ ], 5.11 (m, 1 H, H $\alpha$  Ala), 5.60 (m, 1 H, H $\alpha$  benzazepine), 7.10–7.29 (4 H, H arom. benzazepine), 7.63–7.79 (m, 4 H, Phth) ppm.  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta = 15.78$  (CH<sub>3</sub> Ala), 34.27 (CH<sub>2</sub>  $\beta$ ), 48.92 (CH<sub>2</sub>  $\epsilon$ ), 51.97 (CH  $\alpha$  benzazepine, CH  $\alpha$  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<sub>q</sub> arom.), 168.54, 170.30, 176.69 (C=O) ppm.

**(2R)-[(4S)-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  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  (130  $\mu\text{L}$ , 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  $\text{H}_2\text{O}$  (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  $t_{\text{ret}} = 11.4$  min;  $R_f = 0.65$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS calcd. 249.1239, found 249.1243.  $[\alpha]_{\text{D}}^{20} = +40.7$  ( $c = 0.786$ , dioxane/ $\text{H}_2\text{O}$ , 9:1).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 250 MHz):  $\delta = 1.35$  (d,  $^3J = 7.4$  Hz, 3 H,  $\text{CH}_3$  Ala), 3.18–3.44 (m, 2 H, 2 H $\beta$ ), 4.24 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.5$  Hz, 1 H, H $\text{E}$ ], 5.07–5.23 (m, 3 H, H $\text{E}'$ , H $\alpha$  Ala, H $\alpha$  benzazepine), 7.17–7.32 (m, 4 H, H arom.) ppm.  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 63 MHz):  $\delta = 20.11$  ( $\text{CH}_3$  Ala), 39.26 ( $\text{CH}_2 \beta$ ), 53.35 ( $\text{CH}_2 \epsilon$ ), 55.29 (CH  $\alpha$  benzazepine, CH  $\alpha$  Ala), 132.54, 132.65, 134.27, 135.99 (CH arom.), 138.84, 139.88 ( $\text{C}_q$  arom.), 174.91, 178.87 (C=O) ppm.

**(2R)-[(4S)-4-Acetylmino-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  $\text{NEt}_3$ , and  $\text{Ac}_2\text{O}$  (133  $\mu\text{L}$ , 1.41 mmol) was added in three portions. Meanwhile the pH was kept at 6 with  $\text{NEt}_3$ . 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  $t_{\text{ret}} = 13.8$  min;  $R_f = 0.24$  (EtOAc/MeOH, 2:1). HRMS calcd. 291.1345, found 291.1348.  $[\alpha]_{\text{D}}^{20} = +65.4$  ( $c = 1$ , MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta = 1.34$  (d,  $^3J = 7.4$  Hz, 3 H,  $\text{CH}_3$  Ala), 2.14 (s, 3 H,  $\text{CH}_3$  Ac), 2.96 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.8$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 12.8$  Hz, 1 H, H $\beta$ ], 3.49 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.9$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 4.0$  Hz, 1 H, H $\beta'$ ], 4.00 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.3$  Hz, 1 H, H $\text{E}$ ], 5.13 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.1$  Hz, 1 H, H $\text{E}'$ ], 5.30 (q,  $^3J = 7.3$  Hz, 1 H, H $\alpha$  Ala), 5.52 (m, 1 H, H $\alpha$  benzazepine), 5.80 (br. s, 1 H, NH amide), 7.04–7.30 (m, 4 H, H arom.) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 63 MHz):  $\delta = 15.73$  ( $\text{CH}_3$  Ala), 23.26 ( $\text{CH}_3$  Ac), 36.58 ( $\text{CH}_2 \beta$ ), 49.29 ( $\text{CH}_2 \epsilon$ ), 53.32 (CH  $\alpha$  benzazepine, CH  $\alpha$  Ala), 127.05, 128.60, 128.66, 131.33 (CH arom.), 133.76, 135.45 ( $\text{C}_q$  arom.), 171.71, 172.44, 174.93 (C=O) ppm.

**(2R)-[(4S)-4-Acetylmino-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  $\text{CH}_2\text{Cl}_2$  (6.5 mL).  $\text{NEt}_3$  (50  $\mu\text{L}$ , 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  $\text{CH}_3\text{NH}_2 \cdot \text{HCl}$  (26.6 mg, 0.394 mmol) and  $\text{NEt}_3$  (150  $\mu\text{L}$ , 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  $\text{CH}_2\text{Cl}_2$  (50 mL) and washed with 1 N HCl (1  $\times$  25 mL) in order to remove most of the HOBt. The product was dried ( $\text{MgSO}_4$ ), 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  $t_{\text{ret}} = 12.9$  min;  $R_f = 0.64$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS calcd. 304.1661, found

304.1667.  $[\alpha]_{\text{D}}^{20} = +32.5$  ( $c = 0.6$ , EtOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz, 298 K):  $\delta = 1.26$  (d,  $^3J = 7.1$  Hz, 3 H,  $\text{CH}_3$  Ala), 2.10 (s, 3 H,  $\text{CH}_3$  Ac), 2.83 (d,  $^3J = 4.8$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ), 2.95 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.9$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 13.0$  Hz, 1 H, H $\beta'$ ], 3.45 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.9$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 4.2$  Hz, 1 H, H $\beta$ ], 4.18 [d',  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.2$  Hz, 1 H, H $\text{E}$ ], 4.97 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.2$  Hz, 1 H, H $\text{E}$ ], 5.16 (q,  $^3J = 7.1$  Hz, 1 H, H $\alpha$  Ala), 5.45 (m, 1 H, H $\alpha$  benzazepine), 6.41 (q,  $^3J = 4.8$  Hz, 1 H,  $\text{NH}-\text{CH}_3$ ), 6.99 (d,  $^3J = 6.3$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ), 7.08–7.22 (m, 4 H, H arom.) ppm.  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 500 MHz, 298 K):  $\delta = 1.10$  (d,  $^3J = 7.4$  Hz, 3 H,  $\text{CH}_3$  Ala), 1.94 (s, 3 H,  $\text{CH}_3$  Ac), 2.61 (d,  $^3J = 4.5$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ), 2.85 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.3$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 13.1$  Hz, 1 H, H $\beta'$ ], 3.17 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.3$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 4.1$  Hz, 1 H, H $\beta$ ], 4.16 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.5$  Hz, 1 H, H $\text{E}'$ ], 5.02 (q,  $^3J = 7.4$  Hz, 1 H, H $\alpha$  Ala), 5.06 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 17.5$  Hz, 1 H, H $\text{E}$ ], 5.40 (m, 1 H, H $\alpha$  benzazepine), 7.12–7.27 (m, 4 H, H arom.), 7.86 (q,  $^3J = 4.5$  Hz, 1 H,  $\text{NH}-\text{CH}_3$ ), 8.09 (d,  $^3J = 7.0$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz, 298 K):  $\delta = 14.4$  ( $\text{CH}_3$  Ala), 22.8 ( $\text{CH}_3$  Ac), 26.3 ( $\text{NH}-\text{CH}_3$ ), 36.1 ( $\text{CH}_2 \beta$ ), 47.5 ( $\text{CH}_2 \epsilon$ ), 48.6 (CH  $\alpha$  benzazepine), 52.7 (CH  $\alpha$  Ala), 126.4, 127.9, 128.2, 130.6 (CH arom.), 133.2, 134.7 ( $\text{C}_q$  arom.), 170.1 (C=O Ac), 170.9 (C=O benzazepine), 172.0 (C=O Ala) ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 126 MHz, 298 K):  $\delta = 15.7$  ( $\text{CH}_3$  Ala), 22.5 ( $\text{CH}_3$  Ac), 25.8 ( $\text{NH}-\text{CH}_3$ ), 36.1 ( $\text{CH}_2 \beta$ ), 47.0 ( $\text{CH}_2 \epsilon$ ), 47.9 (CH  $\alpha$  benzazepine), 52.3 (CH  $\alpha$  Ala), 126.1, 127.3, 128.4, 130.4 (CH arom.), 135.1, 135.4 ( $\text{C}_q$  arom.), 168.5 (C=O Ac), 170.7 (C=O Ala), 171.6 (C=O benzazepine) ppm.

**Characterisation of 6:** HPLC  $t_{\text{ret}} = 12.0$  min;  $R_f = 0.70$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS calcd. 304.1661, found 304.1656.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz, 298 K):  $\delta = 1.41$  (d,  $^3J = 7.0$  Hz, 3 H,  $\text{CH}_3$  Ala), 2.09 (s, 3 H,  $\text{CH}_3$  Ac), 2.33 (d,  $^3J = 5.0$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ), 2.93 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 12.7$  Hz, 1 H, H $\beta'$ ], 3.56 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 5.0$  Hz, 1 H, H $\beta$ ], 4.12 [d',  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 16.7$  Hz, 1 H, H $\text{E}$ ], 4.92 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 16.7$  Hz, 1 H, H $\text{E}$ ], 5.16 (q,  $^3J = 7.0$  Hz, 1 H, H $\alpha$  Ala), 5.40 (m, 1 H, H $\alpha$  benzazepine), 5.45 (q,  $^3J = 5.0$  Hz, 1 H,  $\text{NH}-\text{CH}_3$ ), 6.92 (d,  $^3J = 6.4$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ), 7.05–7.21 (m, 4 H, H arom.) ppm.  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 500 MHz, 298 K):  $\delta = 1.20$  (d,  $^3J = 7.0$  Hz, 3 H,  $\text{CH}_3$  Ala), 1.92 (s, 3 H,  $\text{CH}_3$  Ac), 2.29 ( $^3J = 4.5$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ), 2.99 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta') = 13.2$  Hz, 1 H, H $\beta'$ ], 3.11 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.3$  Hz,  $^3J(\text{H}\alpha, \text{H}\beta) = 4.3$  Hz, 1 H, H $\beta$ ], 4.18 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 16.7$  Hz, 1 H, H $\text{E}'$ ], 4.80 (q,  $^3J = 7.0$  Hz, 1 H, H $\alpha$  Ala), 4.95 [d,  $^2J(\text{H}_{\text{E}}, \text{H}_{\text{E}}') = 16.7$  Hz, 1 H, H $\text{E}$ ], 5.19 (m, 1 H, H $\alpha$  benzazepine), 7.05–7.18 (m, 4 H, H arom.), 7.55 (q,  $^3J = 4.5$  Hz, 1 H,  $\text{NH}-\text{CH}_3$ ), 8.12 (d,  $^3J = 7.0$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz, 298 K):  $\delta = 13.7$  ( $\text{CH}_3$  Ala), 23.0 ( $\text{CH}_3$  Ac), 25.7 ( $\text{NH}-\text{CH}_3$ ), 36.1 ( $\text{CH}_2 \beta$ ), 47.0 ( $\text{CH}_2 \epsilon$ ), 48.8 (CH  $\alpha$  benzazepine), 52.4 (CH  $\alpha$  Ala), 126.1, 127.9, 128.9, 130.4 (CH arom.), 132.7, 134.4 ( $\text{C}_q$  arom.), 169.5 (C=O Ac), 170.0 (C=O Ala), 171.7 (C=O benzazepine) ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 126 MHz, 298 K):  $\delta = 14.8$  ( $\text{CH}_3$  Ala), 22.6 ( $\text{CH}_3$  Ac), 25.5 ( $\text{NH}-\text{CH}_3$ ), 35.8 ( $\text{CH}_2 \beta$ ), 47.4 ( $\text{CH}_2 \epsilon$ ), 48.4 (CH  $\alpha$  benzazepine), 53.3 (CH  $\alpha$  Ala), 125.6, 127.2, 128.7, 130.2 (CH arom.), 134.7, 135.6 ( $\text{C}_q$  arom.), 168.8 (C=O Ac), 170.1 (C=O Ala), 171.0 (C=O benzazepine) ppm.

**[(4S)-4-Acetylmino-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  $\text{NEt}_3$ , and  $\text{Ac}_2\text{O}$  (1.1 mL, 11.5 mmol) was added. Meanwhile the pH was kept at 6 with  $\text{NEt}_3$ . 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  $\times$  10 mL). The organic

layer was dried ( $\text{MgSO}_4$ ), 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  $t_{\text{ret}} = 10.4$  min;  $R_f = 0.53$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS calcd. 277.1188, found 277.1195.  $[\alpha]_{\text{D}}^{20} = 123.1$  ( $c = 1$ , DMF).  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 250 MHz):  $\delta = 1.92$  (s, 3 H,  $\text{CH}_3$  Ac), 2.90 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.8$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 13.0$  Hz, 1 H,  $\text{H}\beta$ ], 3.16 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{Ha}, \text{H}\beta') = 4.0$  Hz, 1 H,  $\text{H}\beta'$ ], 3.94 [d,  $^2J(\text{Ha}, \text{Ha}') = 17.3$  Hz, 1 H,  $\text{Ha}$  Gly], 4.16 [d,  $^2J(\text{He}, \text{He}') = 17.0$  Hz, 1 H,  $\text{He}$ ], 4.25 [d,  $^2J(\text{Ha}, \text{Ha}') = 17.3$  Hz, 1 H,  $\text{Ha}'$  Gly], 5.21 [d',  $^2J(\text{He}, \text{He}') = 16.9$  Hz, 1 H,  $\text{He}$ ], 5.37 (m, 1 H,  $\text{Ha}$  benzazepine), 7.10–7.24 (m, 4 H,  $\text{H}$  arom.), 8.12 [d,  $^3J(\text{NH}-\text{Ha}) = 7.5$  Hz, 1 H,  $\text{NH}$  amide] ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 63 MHz):  $\delta = 22.9$  ( $\text{CH}_3$  Ac), 36.3 ( $\text{CH}_2$   $\beta$ ), 48.0 ( $\text{CH}_2$   $\epsilon$ ), 49.5 ( $\text{CH}_2$  Gly), 52.3 ( $\text{CH}$   $\alpha$  benzazepine), 126.2, 127.8, 129.2, 130.7 ( $\text{CH}$  arom.), 134.5, 135.9 ( $\text{C}_q$  arom.), 169.1, 170.8, 172.2 ( $\text{C}=\text{O}$ ) ppm.

**2-[(4S)-4-Acetylamin-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  $\text{CH}_2\text{Cl}_2$  (12 mL).  $\text{Et}_3\text{N}$  (30  $\mu\text{L}$ , 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  $\text{CH}_3\text{NH}_2\cdot\text{HCl}$  (16.3 mg, 0.242 mmol) and  $\text{Et}_3\text{N}$  (90  $\mu\text{L}$ , 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  $t_{\text{ret}} = 10.55$  min;  $R_f = 0.65$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS 290.1504, found 290.1508.  $[\alpha]_{\text{D}}^{20} = +163$  ( $c = 0.83$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 2.06$  (s, 3 H,  $\text{CH}_3$  Ac), 2.74 [d  $^3J(\text{CH}_3-\text{NH}) = 4.7$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ], 2.91 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 13.5$  Hz, 1 H,  $\text{H}\beta$ ], 3.48 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.0$  Hz,  $^3J(\text{Ha}, \text{H}\beta') = 4.7$  Hz, 1 H,  $\text{H}\beta'$ ], 3.77 [d,  $^2J(\text{Ha}, \text{Ha}') = 16.1$  Hz, 1 H,  $\text{Ha}$  Gly], 3.98 [d,  $^2J(\text{He}, \text{He}') = 16.8$  Hz, 1 H,  $\text{He}$ ], 4.44 [d,  $^2J(\text{Ha}, \text{Ha}') = 16.1$  Hz, 1 H,  $\text{Ha}'$  Gly], 5.22 [d,  $^2J(\text{He}, \text{He}') = 16.8$  Hz, 1 H,  $\text{He}'$ ], 5.43 (m, 1 H,  $\text{Ha}$  benzazepine), 7.10–7.23 (m, 4 H,  $\text{H}$  arom.), 6.57 (br. s, 1 H,  $\text{NH}-\text{CH}_3$ ), 6.93 [d,  $^3J(\text{NH}-\text{Ha}) = 6.3$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ] ppm.  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 500 MHz):  $\delta = 1.92$  (s, 3 H,  $\text{CH}_3$  Ac), 2.59 [d,  $^3J(\text{CH}_3-\text{NH}) = 4.5$  Hz, 3 H,  $\text{NH}-\text{CH}_3$ ], 2.85 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.1$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 13.1$  Hz, 1 H,  $\text{H}\beta$ ], 3.18 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 17.1$  Hz,  $^3J(\text{Ha}, \text{H}\beta') = 4.8$  Hz, 1 H,  $\text{H}\beta'$ ], 3.61 [d,  $^2J(\text{Ha}, \text{Ha}') = 16.4$  Hz, 1 H,  $\text{Ha}$  Gly], 4.07 [d,  $^2J(\text{He}, \text{He}') = 16.7$  Hz, 1 H,  $\text{He}$ ], 4.23 [d,  $^2J(\text{Ha}, \text{Ha}') = 16.4$  Hz, 1 H,  $\text{Ha}'$  Gly], 5.19 [d,  $^2J(\text{He}, \text{He}') = 16.7$  Hz, 1 H,  $\text{He}'$ ], 5.37 (m, 1 H,  $\text{Ha}$  benzazepine), 7.12–7.21 (m, 4 H,  $\text{H}$  arom.), 7.87 [q,  $^3J(\text{NH}-\text{CH}_3) = 4.5$  Hz, 1 H,  $\text{NH}-\text{CH}_3$ ], 8.12 [d,  $^3J(\text{NH}-\text{Ha}) = 7.1$  Hz, 1 H,  $\text{NH}-\text{Ac}$ ] ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta = 22.9$  ( $\text{CH}_3$  Ac), 26.1 ( $\text{NH}-\text{CH}_3$ ), 36.1 ( $\text{CH}_2$   $\beta$ ), 48.6 ( $\text{CH}$   $\alpha$  benzazepine), 51.5 ( $\text{CH}_2$  Gly), 53.0 ( $\text{CH}_2$   $\epsilon$ ), 126.4, 128.3, 128.8, 130.7 ( $\text{CH}$  arom.), 132.1, 134.8 ( $\text{C}_q$  arom.), 168.8 ( $\text{C}=\text{O}$  Gly), 170.1 ( $\text{C}=\text{O}$  Ac), 172.1 ( $\text{C}=\text{O}$  benzazepine) ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 126 MHz):  $\delta = 22.3$  ( $\text{CH}_3$  Ac), 25.2 ( $\text{NH}-\text{CH}_3$ ), 35.7 ( $\text{CH}_2$   $\beta$ ), 47.6 ( $\text{CH}$   $\alpha$  benzazepine), 49.9 ( $\text{CH}_2$  Gly), 51.5 ( $\text{CH}_2$   $\epsilon$ ), 125.6, 127.2, 128.6, 130.1 ( $\text{CH}$  arom.), 133.7, 135.2 ( $\text{C}_q$  arom.), 167.5 ( $\text{C}=\text{O}$  Gly), 168.1 ( $\text{C}=\text{O}$  Ac), 172.15 ( $\text{C}=\text{O}$  benzazepine) ppm.

**[(4S)-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  $\text{CH}_3\text{I}$  (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 evapo-

rated and the residue was divided between water (20 mL) and ether (10 mL). The aqueous phase was extracted with diethyl ether (2  $\times$  10 mL), and the combined organic layer was extracted with saturated aqueous  $\text{NaHCO}_3$  (15 mL). The combined aqueous layer was acidified with 10%  $\text{KHSO}_4$  until pH 3, followed by extraction with EtOAc (3  $\times$  20 mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered and the solvents evaporated. Yield 825 mg (79%). M.p. 110–127 °C. HPLC  $t_{\text{ret}} = 20.5$  min;  $R_f = 0.53$  (EtOAc/MeOH, 2:1). HRMS calcd. 349.1763, found 349.1760.  $[\alpha]_{\text{D}}^{20} = -1.8$  ( $c = 1$ , MeOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta = 1.43$  (s, 9 H,  $t\text{Bu}$ ), 2.97 (br. s, 4 H, N-Me,  $\text{H}\beta$ ), 3.43 (m, 1 H,  $\text{H}\beta'$ ), 4.26 (m, 3 H,  $\text{Ha}$  Gly, 2  $\text{He}$ ), 4.83 (m, 1 H,  $\text{Ha}'$  Gly), 5.15 (m, 1 H,  $\text{Ha}$ ), 7.10–7.41 (m, 4 H,  $\text{H}$  arom.) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 63 MHz):  $\delta = 28.37$  ( $\text{CH}_3$  Boc), 31.75 (N-Me), 34.35 ( $\text{CH}_2$   $\beta$ ), 44.68 ( $\text{CH}_2$   $\epsilon$ ), 53.33 ( $\text{CH}_2$  Gly), 55.64 ( $\text{CH}$   $\alpha$ ), 80.38 ( $\text{C}_q$  Boc), 126.64, 128.13, 128.66, 130.13 ( $\text{CH}$  arom.), 134.55, 135.68 ( $\text{C}_q$  arom.), 156.46 ( $\text{C}=\text{O}$  Boc), 172.92 (2  $\text{C}=\text{O}$ ) ppm.

**[(4S)-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  $\text{HCl}/\text{CH}_2\text{Cl}_2$  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/ $\text{CH}_2\text{Cl}_2$ , 1:9). The desired product **25** was obtained as a white solid. Yield 233 mg (57%). M.p. 128–130 °C. HPLC  $t_{\text{ret}} = 8.4$  min;  $R_f = 0.47$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS calcd. 249.1239, found 249.1244.  $[\alpha]_{\text{D}}^{20} = +0.46$  ( $c = 1$ , MeOH).  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 250 MHz):  $\delta = 2.67$  (s, 3 H, NMe), 3.04 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.3$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 13.2$  Hz, 1 H,  $\text{H}\beta$ ], 3.48 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.3$  Hz,  $^3J(\text{Ha}, \text{H}\beta') = 4.0$  Hz, 1 H,  $\text{H}\beta'$ ], 4.05 [d,  $^2J(\text{He}, \text{He}') = 17.4$  Hz, 1 H,  $\text{He}$ ], 4.25 (m, 2 H, 2  $\text{Ha}$  Gly), 5.20 (m, 2 H,  $\text{He}'$ ,  $\text{Ha}$  Aba), 7.14–7.30 (m, 4 H,  $\text{H}$  arom.), 9.14 (br. s, 1 H,  $\text{NH}$ ) ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 63 MHz):  $\delta = 31.6$  ( $\text{CH}_3\text{N}$ ), 49.6 ( $\text{CH}_2$   $\beta$ ), 51.9 ( $\text{CH}_2$   $\epsilon$ ), 52.3 ( $\text{CH}_2$   $\alpha$  Gly), 56.4 ( $\text{CH}$   $\alpha$  benzazepine), 126.8, 128.2, 129.4, 130.9 ( $\text{CH}$  arom.), 133.7, 133.9 ( $\text{C}_q$  arom.), 169.3, 170.2 ( $\text{C}=\text{O}$ ) ppm.

**{(4S)-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  $\text{NET}_3$ , and  $\text{Ac}_2\text{O}$  (0.8 mL, 6.4 mmol) was added. Meanwhile the pH was kept at 6 with  $\text{NET}_3$ . 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  $t_{\text{ret}} = 12.1$  min;  $R_f = 0.66$  (EtOAc/BuOH/AcOH/ $\text{H}_2\text{O}$ , 1:1:1:1). HRMS 291.1345, found 291.1340.  $[\alpha]_{\text{D}}^{20} = +1.2$  ( $c = 1$ , DMF).  $^1\text{H}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 250 MHz):  $\delta = 2.02$  and 2.05 (2s, 3 H,  $\text{CH}_3$  Ac), 2.84 and 2.99 (2s, 3 H,  $\text{CH}_3\text{N}$ ), 2.95 and 3.19 [dd,  $^2J(\text{H}\beta, \text{H}\beta') = 16.2$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 3.9$  Hz, 1 H,  $\text{H}\beta$ ], 3.41 and 3.46 (m, 1 H,  $\text{H}\beta'$ ), 4.04 [d,  $^2J(\text{Ha}, \text{Ha}') = 17.6$  Hz, 1 H,  $\text{Ha}$  Gly], 4.15 [d,  $^2J(\text{Ha}, \text{Ha}') = 17.6$  Hz, 1 H,  $\text{Ha}'$  Gly] 4.43 and 4.47 [2d,  $^2J(\text{He}, \text{He}') = 16.3$  Hz, 1 H,  $\text{He}$ ], 4.84 and 5.01 [2d,  $^2J(\text{He}, \text{He}') = 16.5$  Hz, 1 H,  $\text{He}'$ ], 5.21 and 5.61 [2 dd,  $^3J(\text{Ha}, \text{H}\beta') = 12.0$  Hz,  $^3J(\text{Ha}, \text{H}\beta) = 3.9$  Hz, 1 H,  $\text{Ha}$  Aba], 7.10–7.30 (m, 4 H,  $\text{H}$  arom.) ppm.  $^{13}\text{C}$  NMR ( $[\text{D}_6]\text{DMSO}$ , 63 MHz):  $\delta = 22.1$  ( $\text{CH}_3$  Ac), 29.2 and 32.9 ( $\text{CH}_3\text{N}$ ), 33.6 and 34.3 ( $\text{CH}_2$   $\beta$ ), 50.5 and 52.3 ( $\text{CH}_2$   $\epsilon$ ), 53.6 ( $\text{CH}_2$  Gly), 57.3 ( $\text{CH}$   $\alpha$  benzazepine), 126.7, 128.2, 128.9, 130.2 ( $\text{CH}$  arom.), 135.6 and 135.7 ( $\text{C}_q$  arom.), 136.2 and 136.6 ( $\text{C}_q$  arom.), 170.5 ( $\text{C}=\text{O}$  Gly), 170.9 ( $\text{C}=\text{O}$  Ac), 171.6 and 171.9 ( $\text{C}=\text{O}$  benzazepine) ppm.

**2-[(4S)-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-

**NHMeI:** *N*-Ac, *N*-Me-(*S*)-Aba-Gly-OH (**26**, 40 mg, 0.14 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL). Et<sub>3</sub>N (20  $\mu$ L, 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<sub>3</sub>NH<sub>2</sub>·HCl (10 mg, 0.154 mmol) and Et<sub>3</sub>N (60  $\mu$ L, 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  $t_{\text{ret}}$  = 11.0 min;  $R_f$  = 0.54 (EtOAc/BuOH/AcOH/H<sub>2</sub>O, 1:1:1:1). HRMS calcd. 304.1661, found 304.1668.  $[a]_D^{20}$  = +1.2 ( $c$  = 1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  = 2.16 (s, 3 H, CH<sub>3</sub> Ac), 2.82 [d, <sup>3</sup> $J$ (CH<sub>3</sub>-NH) = 4.6 Hz, 3 H, NH-CH<sub>3</sub>], 3.27 (s, 3 H, CH<sub>3</sub>N), 2.89 [dd, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 14.3 Hz, <sup>3</sup> $J$ (Ha, H $\beta$ ) = 5.3 Hz, 1 H, H $\beta$ ], 3.62 [dd, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 14.3 Hz, <sup>3</sup> $J$ (Ha, H $\beta'$ ) = 13.0 Hz, 1 H, H $\beta'$ ], 3.72 [1 H, broadened d, Ha Gly, <sup>2</sup> $J$ (Ha, Ha') = 16.4 Hz], 4.07 [1 H, broadened d, H $\epsilon$ , <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 15.1 Hz], 4.73 [d, <sup>2</sup> $J$ (Ha, Ha') = 16.6 Hz, 1 H, Ha' Gly], 5.05 [d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 15.1 Hz, 1 H, H $\epsilon$ ], 4.24 (dd, 1 H, Ha benzazepine, partially hidden by Ha Gly), 7.21–7.30 (m, 4 H, H arom.), 7.51 (br. s, 1 H, NH-CH<sub>3</sub>) ppm. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 500 MHz):  $\delta$  = 2.05 (s, 3 H, CH<sub>3</sub> Ac), 2.59 [d, <sup>3</sup> $J$ (CH<sub>3</sub>-NH) = 4.5 Hz, 3 H, NH-CH<sub>3</sub>], 2.85 and 3.05 (s, 3 H, CH<sub>3</sub>N), 2.96 and 3.19 [dd, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 15.3 Hz, <sup>3</sup> $J$ (Ha, H $\beta$ ) = 4.7 Hz, 1 H, H $\beta$ ], 3.41 and 3.45 [dd, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 14.8 Hz, <sup>3</sup> $J$ (Ha, H $\beta'$ ) = 12.9 Hz, 1 H, H $\beta'$ ], 3.82 and 3.95 [d, <sup>2</sup> $J$ (Ha, Ha') = 16.2 Hz, 1 H, Ha Gly], 4.01 and 4.17 [d, <sup>2</sup> $J$ (Ha, Ha') = 16.4 Hz, 1 H, Ha' Gly] 4.54 and 4.30 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 16.1 Hz, 1 H, H $\epsilon$ ], 4.66 and 5.00 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ), 1 H, H $\epsilon'$ ] = 16.2 Hz], 5.14 and 5.23 [2dd, <sup>3</sup> $J$ (Ha, H $\beta'$ ) = 12.4 Hz, <sup>3</sup> $J$ (Ha, H $\beta$ ) = 4.4 Hz, 1 H, Ha benzazepine], 7.20–7.30 (m, 4 H, H arom.), 7.75 and 7.83 [q, <sup>3</sup> $J$ (NH-CH<sub>3</sub>) = 4.5 Hz, 1 H, NH-CH<sub>3</sub>] ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta$  = 21.9 (CH<sub>3</sub> Ac), 26.4 (CH<sub>3</sub>NH), 28.2 (CH<sub>3</sub>N), 33.2 (CH<sub>2</sub>  $\beta$ ), 51.8 (CH<sub>2</sub>  $\epsilon$ ), 52.3 (CH  $\alpha$  benzazepine), 53.4 (CH<sub>2</sub> Gly), 127.7, 128.2, 128.6, 129.5 (CH arom.), 136.3, 136.5 (C<sub>q</sub> arom.), 169.9 (C=O Gly), 170.2 (C=O Ac), 171.8 (C=O Aba) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 126 MHz):  $\delta$  = 21.7 (CH<sub>3</sub> Ac), 25.4 (CH<sub>3</sub>NH) 28.8 and 34.3 (CH<sub>3</sub>N), 33.0 and 34.00 (CH<sub>2</sub>  $\beta$ ), 51.4 and 52.1 (CH<sub>2</sub>  $\epsilon$ ), 51.2 and 51.6 (CH<sub>2</sub> Gly), 55.9 and 56.8 (CH  $\alpha$  benzazepine), 127.6, 128.0, 128.8, 129.3 (CH arom.), 135.3, 135.4 (C<sub>q</sub> 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  $\mu$ pore, Aldrich 2800, 1.00 g) was washed with milliQ water (15  $\times$  4 mL) and suspended with the nitrile **27** (1.00 g, 3.03 mmol) in Py/AcOH/H<sub>2</sub>O (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  $\times$  100 mL). The organic layer was dried (MgSO<sub>4</sub>), filtered and the solvents evaporated. A brown oil was obtained (320 mg, 32%); HPLC  $t_{\text{ret}}$  = 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-10*a*-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<sup>II</sup> 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  $t_{\text{ret}}$  = 8.7 min, HRMS calcd. 218.1181, found 218.1172. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz):  $\delta$  = 1.75 (m, 1 H, H<sup>2</sup>), 1.99 (m, 2 H, H<sup>2'</sup> and H<sup>1</sup>), 2.42

(m, 1 H, H<sup>1'</sup>), 3.07 (m, 1 H, H<sup>3</sup>), 3.22 [d, <sup>2</sup> $J$ (H<sup>10</sup>, H<sup>10'</sup>) = 15.4 Hz, 1 H, H<sup>10</sup>], 3.40 [d, <sup>2</sup> $J$ (H<sup>10</sup>, H<sup>10'</sup>) = 15.4 Hz, 1 H, H<sup>10'</sup>], 3.78 (m, 1 H, H<sup>3'</sup>), 4.28 [d, <sup>2</sup> $J$ (H<sup>5</sup>, H<sup>5'</sup>) = 14.0 Hz, 1 H, H<sup>5</sup>], 4.52 [d, <sup>2</sup> $J$ (H<sup>5</sup>, H<sup>5'</sup>) = 14.0 Hz, 1 H, H<sup>5'</sup>], 7.35 (m, 4 H, H arom.) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 63 MHz):  $\delta$  = 22.8 (CH<sub>2</sub> 2), 34.6 (CH<sub>2</sub> 10), 35.6 (CH<sub>2</sub> 1), 51.4 (CH<sub>2</sub> 5), 55.7 (CH<sub>2</sub> 3), 73.7 (C<sub>q</sub> 10*a*), 127.7, 127.8, 128.3, 129.2 (CH arom.), 130.2, 133.7 (C<sub>q</sub> 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<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub> (140 mg, 20 wt.-%) and NaCNBH<sub>3</sub> (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  $\mu$ L, 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<sub>3</sub> (3  $\times$  50 mL), the organic layer was dried (MgSO<sub>4</sub>), 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  $t_{\text{ret}}$  = 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 1.46 and 1.51 (2s, 9 H, *t*Bu), 1.91 (m, 4 H, CH<sub>2</sub> 3 and CH<sub>2</sub> 4), 2.56 and 2.64 [2d, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 14.2 Hz, 1 H, H $\beta$ ], 3.55 and 3.72 (2m, 2 H, CH<sub>2</sub> 5), 3.89 and 3.94 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 14.6 Hz, 1 H, H $\epsilon$ ], 3.99 and 4.11 [2d, <sup>2</sup> $J$ (Ha, Ha') = 17.0 Hz, 1 H, Ha Gly], 4.09 and 4.23 [2d, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 14.2 Hz, 1 H, H $\beta'$ ], 4.55 and 4.72 [2d, <sup>2</sup> $J$ (Ha, Ha') = 17.0 Hz, 1 H, Ha' Gly], 5.09 and 5.14 (2s, 2 H, CH<sub>2</sub> Bn ester), 5.09 and 5.31 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 14.6 Hz, 1 H, H $\epsilon'$ ], 7.27 (m, 9 H, H arom. benzazepine, Bn ester) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta$  = 22.3 and 23.2 (CH<sub>2</sub> 4), 28.5 (CH<sub>3</sub> *t*Bu), 37.9 and 39.7 (CH<sub>2</sub> 3), 39.9 and 40.9 (CH<sub>2</sub>  $\beta$ ), 48.6 and 48.7 (CH<sub>2</sub> 5), 52.9 and 53.2, 53.4 and 53.5 (CH<sub>2</sub>  $\epsilon$ , CH<sub>2</sub>  $\alpha$  Gly), 66.8 and 66.9 (CH<sub>2</sub> Bn ester), 69.0 and 69.3 (C<sub>q</sub>  $\alpha$  benzazepine), 80.0 and 81.1 (C<sub>q</sub> *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<sub>q</sub> 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  $t_{\text{ret}}$  = 22.3 min;  $R_f$  = 0.83 (CH<sub>3</sub>CN/MeOH/H<sub>2</sub>O, 4:1:2);  $R_f$  = 0.30 (EtOAc/*c*Hex, 2:1). HRMS calcd. 388.2236, found 388.2246. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz):  $\delta$  = 1.40 and 1.44 (2s, 9 H, *t*Bu), 1.86 (m, 4 H, CH<sub>2</sub> 3 and CH<sub>2</sub> 4), 2.58 and 2.66 [2d, <sup>3</sup> $J$ (CH<sub>3</sub>-NH) = 4.5 Hz, 3 H, NH-CH<sub>3</sub>], 2.69 [d, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 13.9 Hz, 1 H, H $\beta$ ], 3.46 (m, 2 H, CH<sub>2</sub> 5), 3.69 [d, <sup>2</sup> $J$ (Ha, Ha') = 16.6 Hz, 1 H, Ha Gly], 3.84 and 3.93 [2d, <sup>2</sup> $J$ (H $\beta$ , H $\beta'$ ) = 13.9 Hz, 1 H, H $\beta'$ ], 4.15 and 4.18 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 14.5 Hz, 1 H, H $\epsilon$ ], 4.46 [d, <sup>2</sup> $J$ (Ha, Ha') = 16.6 Hz, 1 H, Ha' Gly], 4.89 and 5.04 [2d, <sup>2</sup> $J$ (H $\epsilon$ , H $\epsilon'$ ) = 14.5 Hz, 1 H, H $\epsilon'$ ], 7.32 (m, 4 H, H arom.), 7.51 and 7.72 (2q, <sup>3</sup> $J$  = 4.5 Hz, 1 H, NH-CH<sub>3</sub>) ppm. <sup>13</sup>C

NMR ([D<sub>6</sub>]DMSO, 63 MHz):  $\delta$  = 22.2 and 23.1 (CH<sub>2</sub> 4), 25.7 and 26.0 (NH–CH<sub>3</sub>), 28.4 and 28.5 (CH<sub>3</sub> *t*Bu), 378.0 (CH<sub>2</sub> 3), 38.8 (CH<sub>2</sub>  $\beta$ ), 48.5 and 48.8 (CH<sub>2</sub> 5), 51.3 and 52.4 (CH<sub>2</sub>  $\epsilon$ ), 53.6 and 54.5 (CH<sub>2</sub>  $\alpha$  Gly), 68.7 and 69.3 (C<sub>q</sub>  $\alpha$  benzazepine), 79.5 and 80.2 (C<sub>q</sub> *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<sub>q</sub> 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<sub>2</sub>Cl<sub>2</sub> (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  $t_{\text{ret}}$  = 9.7 min;  $R_f$  = 0.50 (CH<sub>3</sub>CN/MeOH/H<sub>2</sub>O, 4:1:1). HRMS 288.1712, found 288.1718. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz):  $\delta$  = 2.03 (m, 4 H, CH<sub>2</sub> 3 and CH<sub>2</sub> 4), 2.62 [d, <sup>3</sup>*J*(CH<sub>3</sub>–NH) = 4.5 Hz, 3 H, NH–CH<sub>3</sub>], 3.24 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 15.2 Hz, 1 H, H $\beta$ ], 3.40 (br. s, 2 H, CH<sub>2</sub> 5), 3.56 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 15.2 Hz, 1 H, H $\beta'$ ], 4.08 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.1 Hz, 1 H, Ha Gly], 4.17 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.1 Hz, 1 H, Ha' Gly], 4.66 (s, 2 H, 2 He), 7.30 (m, 4 H, H arom.), 7.96 (q, <sup>3</sup>*J* = 4.5 Hz, 1 H, NH–CH<sub>3</sub>), 8.94 and 9.47 (2s, 1 H, NH Pro) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 63 MHz):  $\delta$  = 23.6 (CH<sub>2</sub> 4), 25.8 (NH–CH<sub>3</sub>), 35.6 (CH<sub>2</sub> 3), 37.1 (CH<sub>2</sub>  $\beta$ ), 45.5 (CH<sub>2</sub> 5), 52.8 (CH<sub>2</sub>  $\epsilon$ ), 53.7 (CH<sub>2</sub>  $\alpha$  Gly), 71.1 (C<sub>q</sub>  $\alpha$  benzazepine), 127.7, 128.6, 129.0, 130.6 (CH arom.), 135.0 and 136.2 (C<sub>q</sub> 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<sub>2</sub>O and NEt<sub>3</sub> (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  $t_{\text{ret}}$  = 22.2 min;  $R_f$  = 0.65 (CH<sub>3</sub>CN/MeOH/H<sub>2</sub>O, 4:1:1). HRMS calcd. 330.1817, found 330.1827. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz, 298 K):  $\delta$  = 1.86–2.16 (m, 4 H, CH<sub>2</sub> 3 and CH<sub>2</sub> 4), 2.13 (s, 3 H, CH<sub>3</sub> Ac), 2.56 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta$ ], 2.86 (d, <sup>3</sup>*J* = 4.5 Hz, 3 H, NH–CH<sub>3</sub>), 3.55 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.8 Hz, 1 H, Ha Gly], 3.74 (m, 2 H, CH<sub>2</sub> 5), 3.88 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.5 Hz, 1 H, He], 4.04 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta'$ ], 5.00 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.8 Hz, 1 H, Ha' Gly], 5.28 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.5 Hz, 1 H, He'], 7.23–7.33 (m, 4 H, H arom.), 7.81 [q, <sup>3</sup>*J*(NH–CH<sub>3</sub>) = 4.5 Hz, 1 H, NH–CH<sub>3</sub>] ppm. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 500 MHz, 298 K):  $\delta$  = 1.80 (m, 2 H, CH<sub>2</sub> 3), 2.04 (s, 3 H, CH<sub>3</sub> Ac), 2.09 (m, 2 H, CH<sub>2</sub> 4), 2.64 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta$ ], 2.64 (d, <sup>3</sup>*J* = 4.5 Hz, NH–CH<sub>3</sub>, 3 H), 3.66 (m, 2 H, CH<sub>2</sub> 5), 3.67 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.5 Hz, 1 H, Ha Gly], 3.88 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta'$ ], 4.14 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.3 Hz, 1 H, He], 4.41 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.5 Hz, 1 H, Ha' Gly], 5.09 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.3 Hz, 1 H, He'], 7.25–7.42 (m, 4 H, H arom.), 7.71 [q, <sup>3</sup>*J*(NH–CH<sub>3</sub>) = 4.5 Hz, 1 H, NH–CH<sub>3</sub>] ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta$  = 23.2 (CH<sub>3</sub> Ac), 23.9 (CH<sub>2</sub> 4), 26.5 (NH–CH<sub>3</sub>), 36.4 (CH<sub>2</sub> 3), 38.6 (CH<sub>2</sub>  $\beta$ ), 49.7 (CH<sub>2</sub> 5), 52.3 (CH<sub>2</sub>  $\epsilon$ ), 54.8 (CH<sub>2</sub> Gly), 70.3 (C<sub>q</sub>  $\alpha$  benzazepine), 127.7, 127.8, 128.9, 130.0 (CH arom.), 136.5, 137.6 (C<sub>q</sub> arom.), 170.0 (C=O Gly), 170.4 (C=O Ac), 173.8 (C=O benzazepine) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 126 MHz):  $\delta$  = 22.7 (CH<sub>3</sub> Ac), 23.1 (CH<sub>2</sub> 4), 25.4 (NH–CH<sub>3</sub>), 35.9 (CH<sub>2</sub> 3), 37.3 (CH<sub>2</sub>  $\beta$ ), 48.7 (CH<sub>2</sub> 5), 50.7 (CH<sub>2</sub>  $\epsilon$ ), 53.9 (CH<sub>2</sub> Gly), 69.2 (C<sub>q</sub>  $\alpha$  benzazepine), 126.8, 127.6, 128.0, 129.6 (CH arom.), 136.7, 138.0 (C<sub>q</sub> 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- $\alpha$ -(*o*-formylbenzyl)proline (**28**) for experimental procedure. The nitrile **33** (3.00 g, 10.42 mmol) was dissolved in Py/AcOH/H<sub>2</sub>O (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  $t_{\text{ret}}$  = 17.6 min (gradient 16% CH<sub>3</sub>CN  $\rightarrow$  40% CH<sub>3</sub>CN + 0.1% TFA in 30 min);  $R_f$  = 0.65 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH, 90:8:2). HRMS calcd. 292.1185, found 292.1180. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz):  $\delta$  = 0.64 (m, 1 H, H<sup>4</sup>), 1.54 (m, 1 H, H<sup>4'</sup>), 2.02 (m, 2 H, CH<sub>2</sub> 3), 2.85 (m, 1 H, H<sup>5</sup>), 3.29 (m, 1 H, H<sup>5'</sup>), 3.55 and 3.65 (2s, 3 H, CH<sub>3</sub> Moc), 3.72 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 13.9 Hz, 1 H, H $\beta$ ], 3.85 [d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 13.9 Hz, 1 H, H $\beta'$ ], 7.35–7.83 (m, 4 H, H arom.), 10.13 and 10.15 (2s, 1 H, CHO) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 63 MHz):  $\delta$  = 22.2 and 22.8 (CH<sub>2</sub> 4), 33.1 and 34.5 (CH<sub>2</sub>  $\beta$ ), 35.1 and 36.8 (CH<sub>2</sub> 3), 48.0 and 48.9 (CH<sub>2</sub> 5), 52.3 and 52.6 (CH<sub>3</sub> Moc), 68.6 and 69.0 (C<sub>q</sub>  $\alpha$ ), 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<sub>q</sub> 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  $t_{\text{ret}}$  = 24.6 min;  $R_f$  = 0.35 (EtOAc/*c*Hex, 1:1). HRMS calcd. 423.1920, found 423.1925. <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz):  $\delta$  = 1.65 (m, 2 H, CH<sub>2</sub> 3), 1.88 (m, 1 H, CH<sub>2</sub> 4), 2.63 and 2.73 [2d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta$ ], 3.49 (m, 2 H, CH<sub>2</sub> 5), 3.56 and 3.59 (2s, 3 H, CH<sub>3</sub> Moc), 3.88 and 4.05 [2d, <sup>2</sup>*J*(H $\beta$ ,H $\beta'$ ) = 14.0 Hz, 1 H, H $\beta'$ ], 4.14 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.8 Hz, 1 H, Ha Gly], 4.33 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.7 Hz, 1 H, He], 4.45 [d, <sup>2</sup>*J*(Ha,H $\alpha'$ ) = 16.8 Hz, 1 H, Ha' Gly], 5.05 [d, <sup>2</sup>*J*(He,H $\epsilon'$ ) = 14.7 Hz, 1 H, He'], 5.06 and 5.14 (2s, 2 H, CH<sub>2</sub> Bn), 7.19–7.37 (m, 9 H, H arom.) ppm. <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 63 MHz):  $\delta$  = 22.4 and 23.1 (CH<sub>2</sub> 4), 37.8 and 39.0 (CH<sub>2</sub> 3), 39.2 and 40.3 (CH<sub>2</sub>  $\beta$ ), 48.2 and 48.8 (CH<sub>2</sub> 5), 51.8–52.8 (CH<sub>2</sub>  $\epsilon$ , CH<sub>2</sub>  $\alpha$  Gly, CH<sub>3</sub> Moc), 65.9 and 66.2 (CH<sub>2</sub> Bn), 69.0 and 69.4 (C<sub>q</sub>  $\alpha$ ), 127.2–130.2 (CH arom.), 136.2, 137.8, 138.4 (C<sub>q</sub> 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.

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