Development of New Amino(oxo)piperidinecarboxylate Scaffolds and Their Evaluation as β-Turn Mimics

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In this paper a synthetic approach for functionalised bicyclic Amino(oxo)piperidinecarboxylate (APC) systems is presented. These systems can potentially be applied as *cis*-peptide bond containing β-turn mimics. The scope and limitations of the synthetic method are discussed and the turn-inducing properties of a model compound are evaluated by means of molecular modelling and NMR analysis.

Introduction

The β-turn is one of the three major motifs of peptide and protein secondary structure. The prevalence of β-turns in peptides and on protein surfaces suggests that they play an essential role in molecular recognition events in biological systems.[1] This has raised the challenge of developing scaffolds that can stabilise these secondary structural elements in order to enhance the biological effect of the peptide probes in which they are incorporated: Limiting the number of solution conformations lowers the entropy cost for binding to the corresponding receptors. Rigidifying the peptide can also increase the in vivo absorption and metabolic stability of the biopolymer and preclude undesired conformations which might induce unwanted biological effects.

In previous communications from our laboratory (Figure 1), the synthesis of β-turn mimics **I**[2a] and **II**,[2b] which meet criteria of functionalisability and rigidity is reported. In the second generation of compounds **II**, extra rigidity is incorporated into the original system through annulation of an extra ring through the *N*-terminus of the APC system. In order to generate more structural diversity into the APC skeleton, we envisaged the synthesis of bicyclic compounds of type **III**. These have the extra rigidity in common with systems of type **II** when compared to systems of type **I**, this time, however, by an alternative annulation scheme.

Compounds **I**, **II** and **III** can be considered rigidified mimics of *cis*-peptide bond containing dipeptides. These *cis*-peptide bonds classically occur in type VI turns containing proline at the *i* + 2 position of the tetrapeptide. Our *cis*-amide models might serve as mimics of *cis*-dipeptide moieties not containing proline, which may occur more frequently than previously thought.[3]

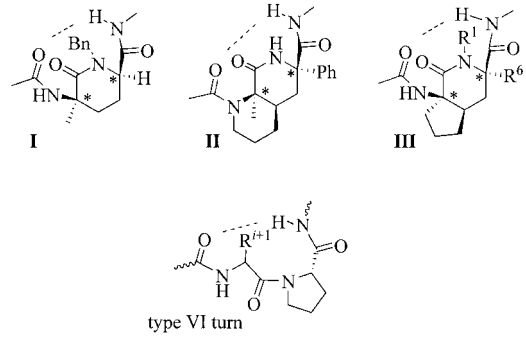
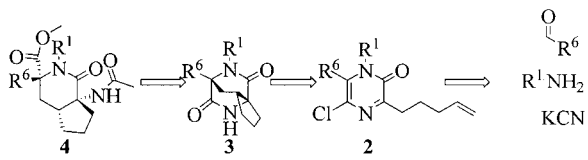


Figure 1. Rigidified mimics of type VI turns.

Results and Discussion

Synthesis

In agreement with our general strategy for the generation of functionalised APC systems, the APC scaffold **4** can be derived from a tricyclic precursor **3** (Scheme 1). These tricyclic lactams can be seen as the reaction product of an intramolecular Diels–Alder reaction of 3-alkenyl-5-chloro-2(1*H*)-pyrazinone **2** followed by hydrolysis of the intermediate imidoyl chloride.



Scheme 1. Retrosynthetic analysis.

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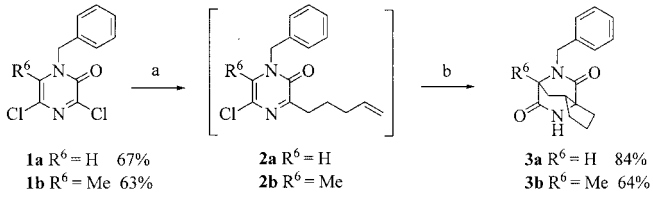
The dichloropyrazinone precursors for compounds **2a**–**b** were synthesised as described previously starting from an amino nitrile.[4] The alkenyl tether was introduced by treating pyrazinones **1a**–**b** with pentenylmagnesium bromide (1.3 equiv.) in THF at –78 °C (Scheme 2). Under these conditions the lactam moiety remains unaffected. In both cases, upon workup at –78 °C with a saturated NH_4Cl solution, extraction with CH_2Cl_2, subsequent drying ($MgSO_4$) and concentration, TLC analysis and mass spectral analysis of the crude extract revealed the presence of alkenylpyrazinone **2**, cycloadduct **3** (also some of its unhydrolysed imidoyl chloride precursor) and a small amount of starting material. In order to simplify the purification, the cycloaddition was driven to completion by refluxing the crude mixture in chloroform for 12 h [open to the air moisture to promote further hydrolysis to the bis(lactam)]. The hydrolysed adduct **3** was purified by column chromatography [silica gel, gradient heptane/EtOAc (50:50 → EtOAc)].



Scheme 2. Synthesis of tricyclic adducts.

^{1}H NMR analysis of the purified cycloadducts **3** revealed the presence of only the *endo* compounds. The *endo* stereochemistry of compound **3a** is apparent from the characteristic coupling constants of the protons H_b and H_c with H_a and with H_d (Figure 2).[5]

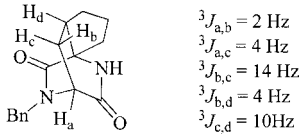


Figure 2. Characteristic coupling constants for **3a**.

When the proton H_a is absent (as is the case in **3b**), the NOESY spectrum confirms the *endo* stereochemistry: An NOE effect is observed between $H_{exo(d+c)}$ and the *ortho*-protons of the benzyl group.

The intramolecular Diels–Alder reaction is completely regio- and stereoselective, hence only one pair of enantiomers is formed. (This is in contrast to intermolecular Diels–Alder reactions with substituted alkenes.[5]) These enantiomers can be separated analytically (and presumably also preparatively) on a chiral stationary phase by means of HPLC (DIACEL, chiralpac OJ). In Figure 3 the separation of **3a** is shown [gradient: hexane/EtOH (60:40 → 0:100); run: 20 min].

The conversion of the bis(lactam) to the APC system is the last step in the development of the dipeptide analogues. In an analogous manner as for bicyclic lactams, the tricyclic bis(lactams) are subjected to acidic methanolysis conditions.[6] Bis(lactams) **3a**,**b** were treated with HCl-saturated methanol overnight. In order to prevent recyclisation upon neutralisation of the reaction mixture, the newly formed primary amines were trapped as acetamides. In the case of adduct **3a** we found the doubly cleaved product **5** together with the desired APC system **4a**. This product **5** is a constrained analogue of (±)-α,ε-diaminopimelic acid, a selective NMDA (*N*-methyl-D-aspartate) antagonist.[7]

This double cleavage was quite surprising because with comparable adducts from intermolecular reactions this behaviour was not observed: After cleavage of the first lactam a tertiary lactam remained unaffected. Probably the first cleavage does not completely relieve the strain which is still present in the bicyclic system.

On the other hand, bis(lactam) **3b** proved to be almost completely inert to both acidic and basic reaction conditions (Scheme 3). Only a small amount of **4b** could be detected in the chemical ionisation mass spectrum. This lack of reactivity of the secondary amide in **4b** can be ascribed to the combined steric hindrance of the angular methyl group and the *endo*-oriented cyclopentane ring. This precludes the formation of a tetrahedral intermediate, which is assumed to be the rate-determining step in the methanolysis.

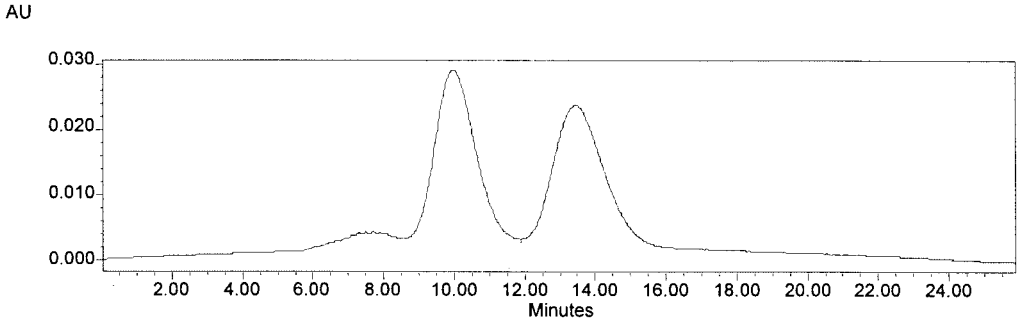
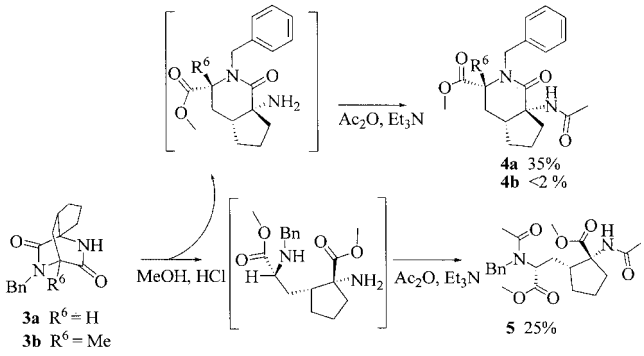


Figure 3. Chromatogram of enantiomers of **3a** (DIACEL, chiralpac OJ).



Scheme 3. Methanolysis of tricyclic bis(lactams) **3**.

New Strategy, New Targets

Because of the limitations in the substitution pattern of the above-mentioned compounds and because of the problem of the "double cleavage", new target compounds were envisaged. From the results described above and from inspection of a model of **3b**, it appears that cleavage of the *endo* secondary lactam group to form the *trans*-fused product **4b** is precluded by the combined steric hindrance of the methyl and the annulated five-membered ring (Figure 4). Moreover, initial cleavage of the bis(lactam) compounds does not usually occur at the tertiary lactam group.[6]

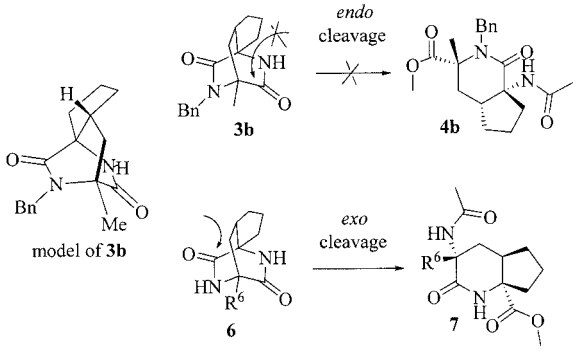
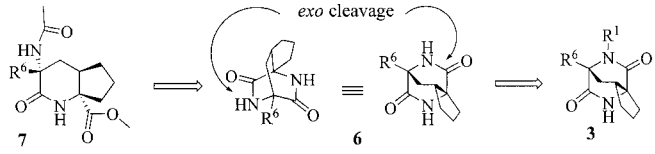


Figure 4. Unreactive *endo*-lactam function in bis(lactam) **3b** and envisaged cleavage of *exo*-lactam function in *N*-debenzylated analogues **6**.

Removal of the *N*-benzyl group could generate a new secondary lactam as in **6,** which in theory is more accessible for methanolysis. The resulting methanolysis products of these compounds will be *cis*-fused this time, but still can be considered as rigidified mimics of *cis*-peptide bond containing dipeptides.

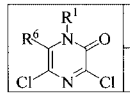
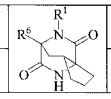
In our new strategy leading to compounds of general structure **7**, the *C*- and *N*-terminal residue of the dipeptide will be switched compared to the compounds of the first strategy (Scheme 4). The substituent R^6 will now be the side chain of the *N*-terminal residue.



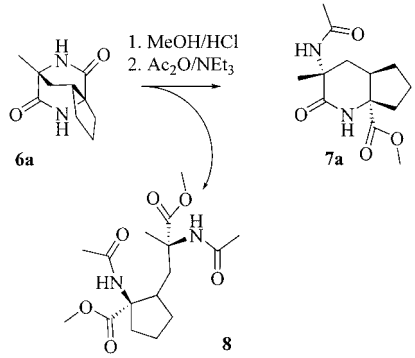
Scheme 4. Alternative synthesis strategy.

The tricyclic target compounds **3** were synthesised as mentioned above. However, based on previous experience with these systems, a PMB protecting group was chosen instead of a benzyl group because it is easier to remove. This imposes no significant changes in the synthetic approach previously described. The yields are given in Table 1.

Table 1. Yields for the PMB analogues.

	**1c** R^6 = Me, R^1 = *p*-OMeBn	57%		**3c** R^6 = Me, R^1 = *p*-OMeBn	53%
	1d R^6 = *i*Pr, R^1 = *p*-OMeBn	66%		**3d** R^6 = *i*Pr, R^1 = *p*-OMeBn	63%

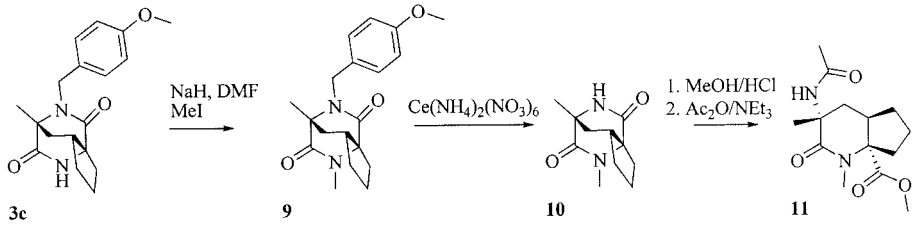
The *para*-methoxybenzyl group of compounds **3c** and **3d** was removed oxidatively using cerium ammonium nitrate (CAN).[8] After chromatographic purification the acid methanolysis conditions were applied to the deprotected adducts **6**. We first discuss the results for adduct **6a** (R^6 = Me) (Scheme 5). Compound **6a** was treated with an HCl-saturated methanol solution for 12 h and the newly formed amine was blocked. This afforded the amino(oxo)piperidinecarboxylate system **7a** (R^6 = Me), which was obtained in 18% yield upon column chromatographic separation. However, the diaminodicarboxylic derivative **8** also was isolated from the reaction mixture (22%). When the reaction time was extended to 21 hours, only the doubly cleaved product was isolated.



Scheme 5. Methanolysis of deprotected bis(lactam) **6a**.

This is in agreement with results from a systematic study we published elsewhere, in which the factors governing reactivity and selectivity in the methanolysis reaction of APC systems were examined.[6]

This study also suggested that there were two solutions to solve the problem of the undesired second cleavage: (a) The amide not to be cleaved could be transformed into a

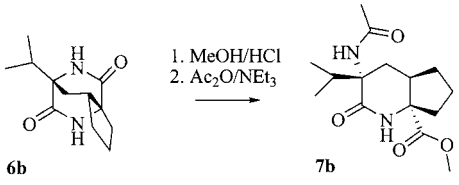


Scheme 6. Synthesis of compound **11**.

tertiary amide, or (b) an isopropyl group could be put next to the carbonyl group that is not be affected by the methanolysis.[6]

Both methods were tested. Before deprotecting adduct **3c**, the secondary lactam was methylated (Scheme 6). Product **3c** was treated with NaH in DMF followed by trapping of the anion with methyl iodide to give **9**.[9] After oxidative removal of the protecting group, product **10** was subjected to the methanolysis conditions. Only the desired APC system **11** was isolated in moderate yield (47%) together with some starting material. No doubly cleaved compound was isolated. Hence *N*-methylation of the *endo*-lactam group of bis(lactam) **3c** effectively prevents subsequent hydrolysis of the corresponding lactam group in the *cis*-fused bicyclic product.

The second method for modulating the reactivity of the APC core was blocking the attack on the carbonyl group by introduction of an isopropyl group in α-position.[6] If this statement holds, there will be no need to alkylate the lactam function. Indeed, adduct **6b** (R^6 = *i*Pr) was selectively cleaved upon treatment with HCl-saturated methanol during 48 h (Scheme 7). After acylation and chromatographic purification (CH_2Cl_2/MeOH, 95:5), the product **7b** was isolated in 54% yield (together with some starting material).

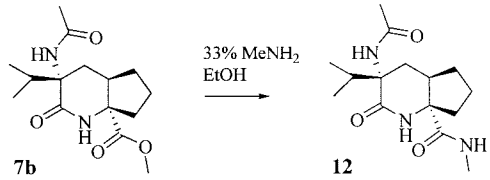


Scheme 7. Methanolysis of deprotected bis(lactam) **6b**.

The new strategy in which the "top" lactam function of the tricyclic system is cleaved appears to be the more flexible one providing access to new APC systems which can potentially induce type VI β-turns.

Analysis

In order to check the β-turn inducing properties of the APC systems synthesised, molecular modelling and NMR analysis were performed on a model compound **12** for a tetrapeptide. The *i* and *i* + 3 residues in the system are simplified to an *N*-methylamide and an acylamide.[2] This model compound was synthesised by direct conversion of **7b** into the *N*-methylamide by reaction with 33% $MeNH_2$ solution in ethanol (Scheme 8). Concentration of the reaction mixture and column chromatography (CH_2Cl_2/MeOH, 95:5) yielded compound **12**.



Scheme 8. Generation of model system **12**.

A β-turn is defined as a tetrapeptide sequence in which the interatomic distance αC_i–αC_{i+3} is smaller than 7 Å. A hydrogen bond is often present between the carbonyl function of residue *i* and NH of residue *i* + 3. Open turns lacking this hydrogen bond also exist. Another criterion that can be checked is the virtual dihedral angle (as defined by Ball) which should be within ±30°.[10]

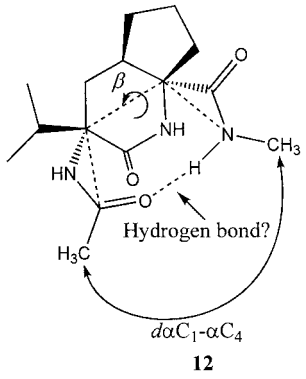
Computational Results

In order to qualify **12** as a β-turn mimic, the structure was checked for the above-mentioned criteria.

The general procedure for the computational analysis is outlined in Figure 5.[2a,10b] A conformational search was performed starting from 2000 random initial conformations (Macromodel, MCMM search, AMBER* force field, solvation models GB/SA $CHCl_3$ and water), and all structures were energy-minimised to 0.05 kcal $Å^{-1}$ mol^{-1}.[11] All conformations found within 5 kcal/mol of the global minimum conformation were checked for the accepted indicators for β-turn properties.

In $CHCl_3$ two conformations were found within 5 kcal/mol of the global minimum, in water five. The global minimum conformations and their properties are depicted in Figure 6. The global minimum in $CHCl_3$ fulfils all of the turn criteria. On the other hand, the minimum in water does not show the hydrogen bond.

In order to obtain an idea about the stability of the turn conformation in the global minimum, a 1000 ps molecular dynamics analysis was performed on the lowest energy conformations both in $CHCl_3$ and water; 10000 snapshots were taken and further analysed for the properties mentioned above. As can be seen from the results summarised in Table 2, 88% of the conformers in H_2O and 74% of them



12

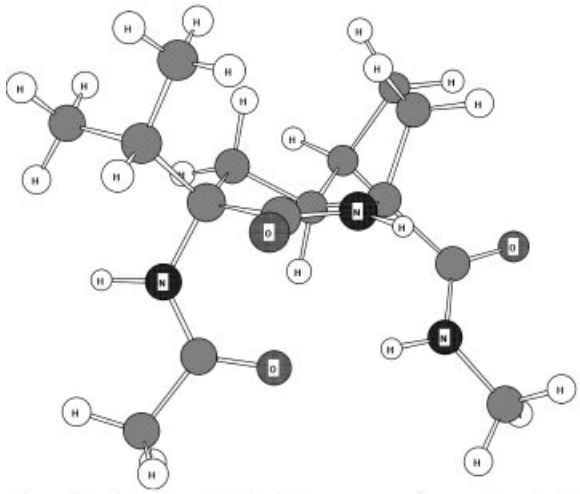
→ Generate 2000 random starting conformations
Energy minimise all conformations, eliminate duplicates
Retain global minimum and conformations within 5 kcal above the global minimum

→ Check for beta turn properties in the conformations retained

→ Perform 1000 ps molecular dynamics analysis on the global minimum found, sample 10000 conformations and again monitor the beta turn properties.

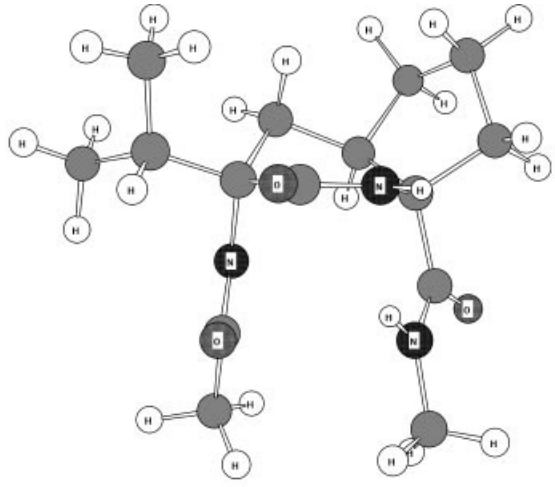
In favour of a β turn:
$d\alpha C_i$-αC_{i+3} < 7A
-30°<β<30°
Hydrogen bond present

Figure 5. Analysis of model compound **12**.



Results for the global minimum conformation in **$CHCl_3$**
* $d\alpha C_1$–αC_4 = 5.89
* β = -21.7°
* Hydrogen bond present

2 conformations were found within 5 kcal/mol of the global miminum.
* $d\alpha C_1$–αC_4 <7Å : 2/2
* number of conformations with -30°<β<30° : 2/2
* number of hydrogen bonded conformations: 2/2



Results for the global minimum conformation in **H_2O**
* $d\alpha C_1$–αC_4 = 3.61
* β = -16.8°
* Hydrogen bond not present

5 conformations were found within 5 kcal/mol of the global miminum.
* $d\alpha C_1$–αC_4 <7Å : 5/5
* number of conformations with -30°<β<30° : 3/5
* number of hydrogen bonded conformations: 2/5

Figure 6. Global-minimum conformations for **12** and its β-turn properties in $CHCl_3$ and H_2O.

in $CHCl_3$ have a virtual dihedral angle β within ± 30°, and almost all of the conformations (99.8%) have a *d* value below 7 Å. Only in $CHCl_3$ is an H-bond present in the majority of cases (76%). Hence, compound **12** largely preserves its β-turn inducing properties in $CHCl_3$ and water.

In Figure 7, the parameter-distribution profiles from the sampled conformations of the dynamics run are depicted. In $CHCl_3$, the global minimum conformation seems to be a stable one, and no major conformational changes are ob-

Table 2. Parameters selected from a molecular dynamics simulation of **12**.

Property	Compound **12** (H_2O)	Compound **12** ($CHCl_3$)
Mean *d* [Å]	4.8	5.9
d within 7 Å [%]	99.8	99.8
Mean β [°]	–19.8	–24.4
β within ± 30° [%]	88	74
H-bonded [%]	30	76

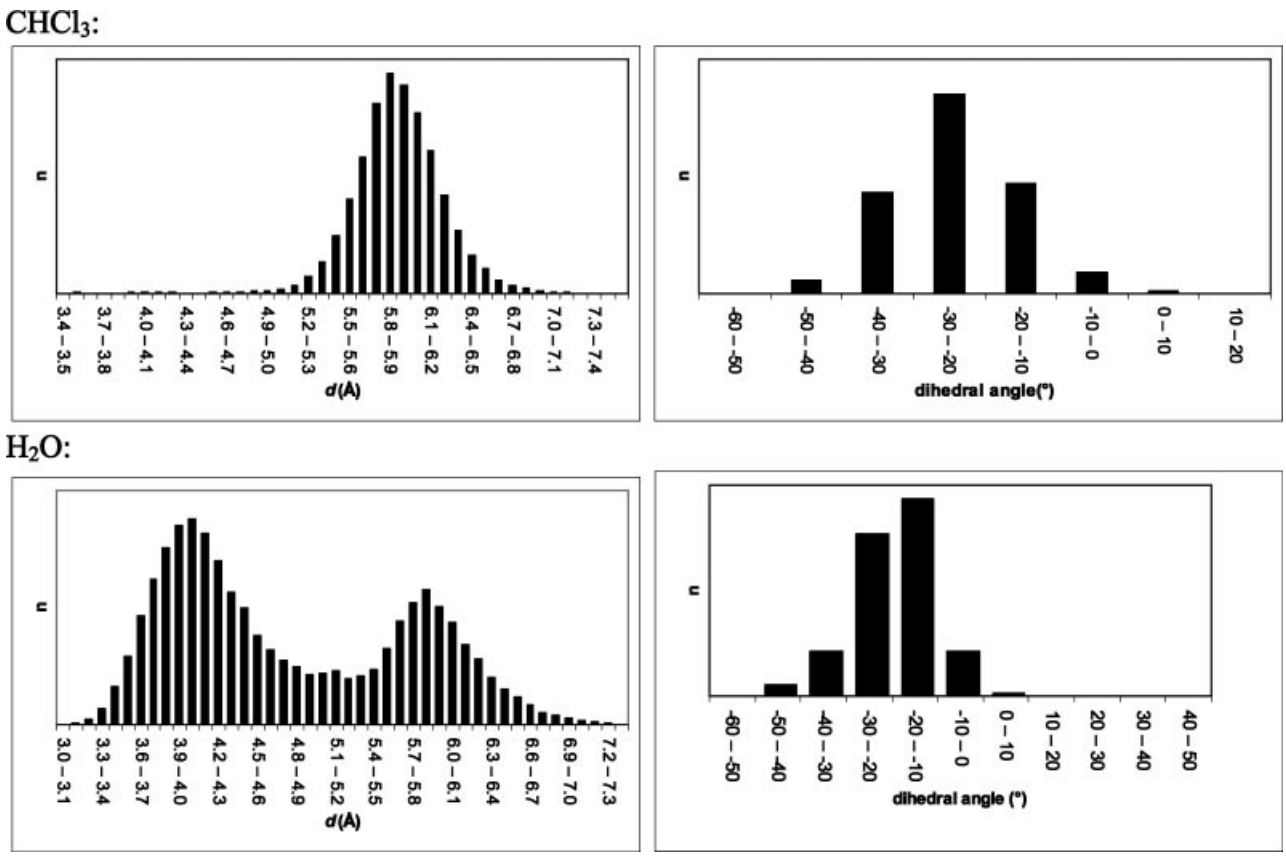


Figure 7. Molecular dynamics analysis of **12** in $CHCl_3$ and H_2O.

served here. Another picture is seen for the conformational analysis in water. Two interconverting classes of conformations are observed. These two classes are identified by visual inspection of the sampled conformations. The major class resembles the non-hydrogen-bonded global minimum with the *N*-methylamide and the *N*-acylamide parallel to one another; the minor conformation with a higher $d(\alpha C_1–\alpha C_4)$ value corresponds to the hydrogen-bonded conformation similar to the one adopted in $CHCl_3$. This analysis is in agreement with the general idea that water is more prone to disrupt intramolecular hydrogen bonding compared to $CHCl_3$.

Notwithstanding the fact that multiple conformations might exist, they all fulfil the 7 Å distance criterion. Hence the modelling analysis points out that the compound is a potential candidate for turn induction.

NMR Analysis

The presence of a hydrogen bond was further checked by ^{1}H NMR spectroscopy of compound **12** in [D_6]DMSO. According to the literature, the temperature dependence of the chemical shift of a hydrogen-bonded amide proton should be small (0 to –3 ppb/K) compared to the temperature dependence of a solvent-exposed proton (< –7 ppb/K).[12] The chemical shifts of the NHCO (singlet at δ = 7.60 ppm; 289 K), $NHCOCH_3$ (singlet at δ = 7.56 ppm; 289 K) and $CONHCH_3$ (quadruplet at δ = 7.41 ppm, 289 K) in [D_6]DMSO were recorded at different temperatures (Figure 8). Linear regression on the collected data points provided the following results: The chemical shift dependence of –1.6 ppb/K for CON*H*CH_3 is consistent with the presence of a hydrogen bond; N*H*CO and N*H*$COCH_3$ on the other hand are more, though not completely, solvent-exposed (shift dependence of –5.3 ppb/K and –5.8 ppb/K, respectively). Possibly the steric bulk of the scaffold is partially shielding these protons from the solvent.

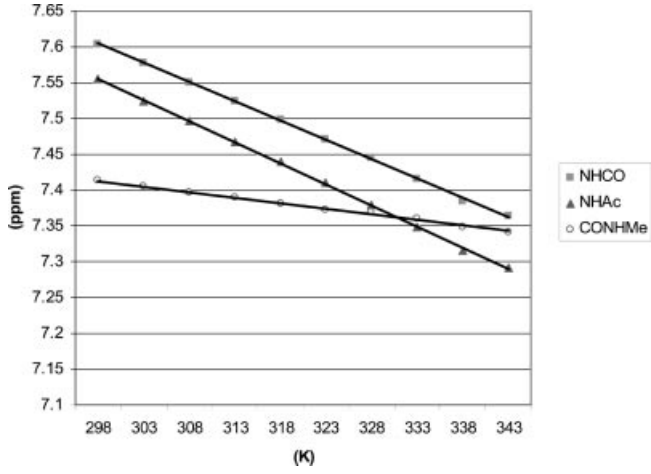


Figure 8. Temperature dependence of the chemical shifts of the NH protons in compound **12**.

The solvent dependency of the chemical shift of the amide protons upon changing the solvent from [D_6]DMSO to $CDCl_3$ was also checked. The results are summarised in Table 3. The small $\Delta\delta$ of the N*H*Me proton confirms the presence of a hydrogen bond. The NMR results are in best agreement with the results obtained for the modelling analysis in $CHCl_3$. If indeed the majority of the conformers would be in a solvent-exposed conformation as seen in the molecular dynamics analysis in water, a larger $\Delta\delta$ would be expected for the NH proton. Hence it is believed that the conformer distribution as shown in the $CHCl_3$ modelling analysis is more representative for the real situation in DMSO (DMSO can only act as a hydrogen-bond acceptor and not as a hydrogen-bond donor as water can do).

Table 3. Solvent dependency of the chemical shifts of the amide protons in **12**.

	δ [ppm] DMSO (298 K)	δ [ppm] $CDCl_3$ (298 K)	$\Delta\delta$ [ppm]
NHCO (s)	7.60	6.19	1.41
NHAc (s)	7.56	5.71	1.85
NHMe (q)	7.41	7.85	–0.44

Conclusions

The intramolecular Diels–Alder reaction of 3-alkenyl-2(1*H*)-pyrazinones, followed by deprotection of the *para*-methoxybenzyl group and cleavage of the strained tricyclic adducts to form the APC system, can be used to construct a novel type of rigid β-turn. The model system **12** for a tetrapeptide has β-turn inducing properties according to molecular modelling and NMR analysis.

Experimental Section

General: Melting points were taken using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 Fourier transform spectrometer. Mass spectra were run with a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10000. For the NMR spectra (δ, in ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. Assignments were made using a combination of 1D and 2D spectra (DEPT-135, COSY, HMBC, HMQC). Analytical and preparative thin layer chromatography were carried out using Merck silica gel 60 PF-224; for column chromatography 70–230 mesh silica gel 60 (E. Merck) was used as the stationary phase.

General Procedure for Pyrazinone Synthesis: For the preparation of the pyrazinones, we refer to the corresponding references. Pyrazinones **1a**–**d:** Ref.[4] for **1a**, ref.[2b] for **1c** and ref.[6b] for **1b**,**d**.

General Procedure for Alkenylation and Subsequent Diels–Alder Reaction: A solution of 5-bromopentene (3 equiv.) in THF, Mg (3.1 equiv.) and a catalytic amount of I_2 was brought to reflux. Upon completion of the formation of the Grignard reagent, the solution was cooled to –78 °C. The pyrazinone **1** (1 equiv.), dissolved in dry THF (5 mL), was slowly added to the solution through a cannula. This solution was kept at low temperature (–78 °C) until completion of the reaction (30 min). The mixture is worked up at low temperature (–78 °C) by addition of aqueous saturated NH_4Cl solution and extracted with diethyl ether. The organic layers were dried with $MgSO_4$, filtered and the solvent was evaporated. The crude compounds **2** were purified by column chromatography (silica gel; CH_2Cl_2 → EtOAc). Partial cycloaddition and subsequent hydrolysis already occurred. In order to simplify the purification, the cycloaddition was driven to completion by refluxing the crude mixture in chloroform (open to the air to promote further hydrolysis) for 12 h. The hydrolysed adduct **3** was purified by column chromatography [silica gel; gradient: CH_2Cl_2/EtOAc (50:50 → 0:100)].

1-Benzyl-5-chloro-6-methyl-3-(4-pentenyl)-2(1*H*)-pyrazinone (2b): Cycloaddition compound was also observed in the spectrum. We only list the signals of compound **2b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (quint, J = 7.2 Hz, 2 H, H-2′), 2.17 (q, J = 7.2 Hz, 2 H, H-3′), 2.36 (s, 3 H, CH_3), 2.84 (t, J = 7.7 Hz, 2 H, H-1′), 4.97 (m, J = 10.2 Hz, 1 H, H-5′), 5.04 (dq, J = 17.2 Hz, 1.8 Hz, 1 H, H-5′), 5.31 (s, 2 H, CH_2Ph), 5.84 (ddt, J = 17.2 Hz, 10.3 Hz, 6.6 Hz, 1 H, H-4′), 7.14 (d, J = 6.6 Hz, 2 H, PhH), 7.27–7.30 (m, 3 H, PhH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0 (CH_3), 26.2 (CH_2), 33.4 (CH_2), 33.9 (CH_2), 48.9 (CH_2Ph), 115.4 (CH=*C*H_2), 126.2 (C-6), 127.1 (PhC), 128.4 (C_{para}), 129.4 (PhC), 133.5(C_{ipso}), 135.2 (*C*H=CH_2), 138.6 (C-5), 156.3 (C-2), 157.5 (C-3) ppm.

8-Benzyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (3a): Yield 52% (1.15 g) (84% if recovered product is accounted for). M.p. 182 °C (hexane/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1657 (s, CO), 1700 (s, CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.42 (m, J = 14 Hz, 4 Hz, 2 Hz, 2 H, H-4 and H-6$_{endo}$), 1.72 (ddd, J = 14 Hz, 9 Hz, 5 Hz, 1 H, H-2), 1.83–1.98 (m, J = 14 Hz, 10 Hz, 4 Hz, 3 H, H-3 and H-6$_{exo}$, H-6$_{exo}$), 1.98–2.12 (m, 2 H, H-5 and H-4), 2.50 (ddd, J = 14 Hz, 10 Hz, 7 Hz, 1 H, H-2), 3.87 (ddd, J = 4 Hz, 2 Hz, 1 H, 1 Hz, H-7), 4.32 (d, J = 15 Hz, 1 H, CH_2Ph), 4.83 (d, J = 15 Hz, 1 H, CH_2Ph), 6.66 (br. s, 1 H, NH),7.22–7.33 (m, 5 H, PhH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 22.6 (CH_2), 25.3 (CH_2), 27.9 (C-6), 28.9 (CH_2), 44.0 (C-5), 47.2 (CH_2Ph), 60.4 (C-7), 68.0 (C-1), 127.2 (PhCH), 127.5, 128.4, 137.4 (C_{ipso}), 171.1 (CO), 171.2 (CO) ppm. EIMS: m/z (%) = 270 (24) [M$^{+\cdot}$], 135 (100) [M$^{+\cdot}$ – BnNHCHO], 91 (31) [$C_7H_7^+$]. HRMS: calcd. for $C_{16}H_{18}N_2O_2$ 270.1368; found 270.1370.

8-Benzyl-7-methyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (3b): Yield: 64% (1.33 g). M.p. 204.1 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 1650 (s, CO), 1710 (s, CO), 3223 (m, NH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3 H, CH_3), 1.47–1.54 (m, 2 H, H-6$_{endo}$ and H-4), 1.71–1.77 (m, 1 H, H-2b), 1.90–1.97 (m, 2 H, H-3), 1.98 (dd, J = 13.4 Hz, 8.6 Hz, 1 H, H-6$_{exo}$), 2.03–2.10 (m, 1 H, H-4), 2.12–2.21 (m, 1 H, H-5), 2.51–2.59 (m, 1 H, H-2a), 4.47 (d, J = 16.0 Hz, 1 H, CH_2Ph), 4.84 (d, J = 16.0 Hz, 1 H, CH_2Ph), 6.13 (s, 1 H, NH), 7.15 (d, J = 7.1 Hz, 2 H, H$_{ortho}$), 7.23–7.31 (m, 3 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 16.5 (CH_3), 22.9 (C-3), 27.2 (C-2), 29.6 (C-4), 37.1 (C-6), 44.1 (CH), 44.6 (CH_2Ph), 62.9 (C-7), 68.2 (C-1), 126.6 (C_{ortho}), 127.3 (C_{para}), 128.7 (C_{meta}), 138.5 (C_{ipso}), 172.6 (CO), 173.3 (CO). EIMS: m/z (%) = 284 (68) [M$^{+\cdot}$], 150 (100) [M$^{+\cdot}$ – BnNHCO], 91 (68) [$C_7H_7^+$]. HRMS: calcd. for $C_{17}H_{20}N_2O_2$ 284.1522; found 284.1530.

8-(4-Methoxybenzyl)-7-methyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (3c): Yield: 53% (1.12 g). M.p. 172.0–173.4 °C. IR (KBr): $\tilde{\nu}$ = 1650 (s, CONBn), 1716 (s, CONH), 3223 (s, NH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, CH_3), 1.44–1.49 (m, 2 H, H-6 and H-4), 1.73–1.79 (m, 1 H, H-2), 1.91–1.98 (m, 3 H, H-3 and H-6), 2.02–2.06 (m, 1 H, H-4), 2.08–2.12 (m, 1 H, H-5), 2.52 (ddd, J = 14.6 Hz, 12.1 Hz, 6.9 Hz, 1 H, H-2), 3.78 (s, 3 H,

OCH_3), 4.40 (d, J = 15.7 Hz, 1 H, CH_2Ph), 4.78 (d, J = 15.7 Hz, 1 H, CH_2Ph), 6.62 (s, 1 H, NH), 6.82 (d, J = 8.6 Hz, 2 H, H_{meta}), 7.09 (d, J = 8.5 Hz, 2 H, H_{ortho}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5 (CH_3), 23.0 (C-3), 27.0 (C-2), 29.6 (C-4), 37.2 (C-6), 44.0 (CH_2Ph), 44.1 (C-5), 55.2 (OCH_3), 62.8 (C-7), 68.1 (C-1), 114.1 (C_{meta}), 128.0 (C_{ortho}), 130.6 (C_{ipso}), 158.8 (C_{para}), 172.6 (CONBn), 173.5 (CONH) ppm. EIMS: m/z (%) = 314 (32) [M^+], 150 (100) [$M^{+\cdot}$ – $CONHCH_2PhOMe$], 121 (60) [$C_8H_9O^+$]. HRMS: calcd. for $C_{18}H_{22}N_2O_3$ 314.1628; found 314.1636.

7-Isopropyl-8-(4-methoxybenzyl)-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (3d): Yield: 63% (1.51 g). M.p. 186–187 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 1612 (s, CONBn), 1692 (s, CONH), 3194 (s, NH) cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 1.04 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.09–1.13 (m, 1 H, CH_2), 1.31 (dd, J = 13.3 Hz, 5.5 Hz, 1 H, H-6$_{endo}$), 1.37 [d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$], 1.48 (dd, J = 13.3 Hz, 9.7 Hz, 1 H, H-6$_{exo}$), 1.55–1.64 (m, 4 H, CH_2), 1.69–1.73 (m, 1 H, H-5), 2.29 [sept, J = 6.7 Hz, 1 H, $CH(CH_3)_2$], 2.49–2.56 (m, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 4.24 (d, J = 15.6 Hz, 1 H, CH_2Ph), 5.09 (d, J = 15.6 Hz, 1 H, CH_2Ph), 6.75 (d, J = 6.5 Hz, 2 H, H_{meta}), 7.17 (d, J = 6.6 Hz, 2 H, H_{ortho}), 7.30 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (CH_3), 19.4 (CH_3), 23.0 (CH_2), 26.9 (CH_2), 28.7 [$CH(CH_3)_2$], 29.8 (CH_2), 33.3 (C-6), 44.2 (C-5), 44.8 (CH_2Ph), 55.2 (OCH_3), 67.6 (C_{quat}), 68.8 (C_{quat}), 114.0 (C_{meta}), 128.3 (C_{ortho}), 130.8 (C_{ipso}), 158.7 (C_{para}), 172.5 (CO), 174.1 (CO) ppm. EIMS: m/z (%) = 342 (25) [M^+], 178 (100) [$M^{+\cdot}$ – CONHBnOMe], 136 (36) [$C_8H_{10}NO^+$], 121 (92) [$C_8H_9O^+$]. HRMS: calcd. for $C_{20}H_{26}N_2O_3$ 342.1947; found 342.1941.

Methanolysis of 3a: A solution of the tricyclic adduct **3a** in MeOH was cooled to 0 °C and saturated with dry HCl gas for 5 min. Upon completion of the reaction, the solution was concentrated under reduced pressure and the crude residue was dissolved in acetic anhydride. The mixture was cooled in an ice bath, and Et_3N was added, until precipitation of triethylammonium salts was observed. After removal of the ammonium salts, the solution was concentrated and the product was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 95:5).

Methyl 7a-Acetylamino-2-benzyl-1-oxo-octahydro-1*H*-cyclopenta-[*c*]pyridine-3-carboxylate (4a): Yield: 35% (111 mg). M.p. 198 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 1590 (s, CO), 1734 (w, CO), 2861 (s, OCH_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.53 (m, 1 H, CH_2), 1.75–1.78 (m, 1 H, H-4), 1.92 (s, 3 H, CH_3), 1.91–2.13 (m, 4 H, H-4 and H_{aliph}), 2.19–2.25 (m, 2 H, CH_2), 2.49–2.50 (m, 1 H, CH_2), 3.74 (s, 3 H, OCH_3), 3.86 (d, J = 15.0 Hz, 1 H, CH_2Ph), 4.02 (dd, J = 10.7 Hz, 4.0 Hz, 1 H, H-3), 5.53 (d, J = 15.0 Hz, 1 H, CH_2Ph), 5.65 (s, 1 H, NH), 7.18 (d, J = 6.8 Hz, 2 H, H_{ortho}), 7.26–7.30 (m, 3 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (C-6), 23.9 (CH_3), 24.8 (C-4), 28.8 (C-5), 30.8 (C-7), 45.0 (C-4a), 49.3 (CH_2Ph), 52.8 (OCH_3), 56.6 (C-3), 65.5 (C-7a), 127.6 (C_{para}), 128.3 (C_{ortho}), 128.7 (C_{meta}), 136.9 (C_{ipso}), 169.6 (CH_3CONH), 171.0 (CO), 174.0 (CH_3OCO) ppm. EIMS: m/z (%) = 344 (6) [$M^{+\cdot}$], 312 (21) [$M^{+\cdot}$ – CH_3OH], 285 (31) [$M^{+\cdot}$ – $CH_3OCO^{\cdot}$], 257 (100) [$C_{16}H_{19}NO_2^+$], 198 (32) [$C_{14}H_{16}N^+$], 91 (89) [$C_7H_7^+$]. HRMS: calcd. for $C_{19}H_{24}N_2O_4$ 344.1735; found 344.1747.

Methyl 1-Acetylamino-2-{2-[acetyl(benzyl)amino]-3-methoxy-3-oxopropyl}cyclopentanecarboxylate (5): Yield: 25% (97 mg), colorless oil. ^1H NMR (400 MHz, C_6D_6, 291 K): δ = 1.36–1.41 (m, 1 H, H-3), 1.49–1.56 (m, 2 H, H-4), 1.79 (s, 3 H, $COCH_3$), 1.80 (s, 3 H, $COCH_3$), 1.95–1.99 (m, 2 H, H-3 and H-1′), 2.06–2.14 (m, 1 H, H-5), 2.29 (ddd, J = 13.8 Hz, 8.4 Hz, 5.5 Hz, 1 H, H-1′), 2.36 (ddd, J = 13.5 Hz, 8.4 Hz, 5.8 Hz, 1 H, H-5), 2.47–2.53 (m, 1 H, H-2), 3.16 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 4.29 (d, J = 16.9 Hz, 1 H, CH_2Ph), 4.33 (d, J = 16.7 Hz, 1 H, CH_2Ph), 5.00 (dd, J = 8.3, 6.4 Hz, 1 H, H-2′), 6.42 (s, 1 H, NH), 7.03–7.16 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (CH_3CO), 22.3 (C-4), 23.3 (CH_3CO), 29.3 (C-1′), 31.3 (C-3), 36.9 (C-5), 44.3 (C-2), 50.7 (CH_2Ph), 51.9 (OCH_3), 52.4 (OCH_3), 56.2 (C-2′), 67.5 (C-1), 126.9 (C_{ortho}), 127.7 (C_{para}), 128.7 (C_{meta}), 136.5 (C_{ipso}), 170.3 (CO), 171.4 (CO), 172.0 (CO), 174.3 (CO) ppm. EIMS: m/z (%) = 418 (4) [$M^{+\cdot}$], 375 (100) [$M^{+\cdot}$ – $CH_3CO^{\cdot}$], 91 (57) [$C_7H_7^+$]. HRMS: calcd. for $C_{22}H_{30}N_2O_6$ 418.2102; found 418.2101.

General Procedure for the CAN Deprotection: The *para*-methoxybenzyl-protected bis(lactam) system **3c**/**3d** was dissolved in acetonitrile and cooled in an ice bath. Then 3 mmol of CAN, dissolved in a minimum amount of H_2O, were added dropwise. After stirring for 3 h, the solution was extracted with CH_2Cl_2 and the combined organic layers were dried with $MgSO_4$. After removal of the solvent, the crude product was purified by chromatography (MeOH/CH_2Cl_2).

7-Methyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (6a): Yield: 81% (287 mg), oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.47–1.55 (m, 1 H, H-4), 1.59 (dd, J = 13.1 Hz, 4.8 Hz, 1 H, H-6), 1.68 (ddd, J = 14.6 Hz, 8.7 Hz, 4.9 Hz, 1 H, H-2), 1.89–1.97 (m, 2 H, CH_2), 2.06–2.11 (m, 1 H, H-4), 2.10 (dd, J = 13.2 Hz, 9.8 Hz, 1 H, H-6), 2.17–2.22 (m, 1 H, H-5), 2.43 (ddd, J = 14.8 Hz, 11.4 Hz, 6.9 Hz, 1 H, H-2), 6.93 (s, 1 H, NH), 6.95 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (CH_3), 22.9 (CH_2), 26.5 (CH_2), 29.6 (CH_2), 36.6 (CH_2), 44.8 (C-5), C_{quat} not resolved, 173.5 (CO), 173.7 (CO) ppm.

7-Isopropyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (6b): Yield: 64% (230 mg). M.p. 330 °C (decomposition). IR (KBr): $\tilde{\nu}$ = 3331 (m, NH), 2980 [s, $CH(CH_3)_2$], 1695 (s, CO) cm^{-1}. ^1H NMR (300 MHz, DMSO): δ = 1.00 [d, ^3J = 6.6 Hz, 3 H, $CH(CH_3)_2$], 1.02 [d, ^3J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.24–1.31 (m, 2 H, H_{aliph}), 1.59–1.79 (m, 3 H, H_{aliph}), 1.91–2.06 (m, 5 H, H_{aliph}), 8.06 (s, 1 H, NH), 8.26 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 17.4 [$CH(CH_3)_2$], 17.5 [$CH(CH_3)_2$], 22.9 (CH_2), 25.3 (CH_2), 28.9 [$CH(CH_3)_2$], 30.0 (CH_2), 32.1 (C-6), 44.3 (C-5), 63.8 (C_{quat}), 67.7 (C_{quat}), 173.4 (CO), 174.3 (CO) ppm. EIMS: m/z (%) = 222 (11) [M^+], 177 (100) [$M^{+\cdot}$ – $CHONH_2$], 151 (27) [$C_{10}H_{17}N^+$]. HRMS: calcd. for $C_{12}H_{18}N_2O_2$ 222.1369; found 222.1364.

Methyl 3-Acetylamino-3-methyl-2-oxo-octahydro-7a*H*-cyclopenta-[*b*]pyridine-7a-carboxylate (7a): The procedure for the methanolysis of **6b** is the same as described for the generation of **3a**. Yield: 18% (60 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, CH_3), 1.63–1.71 (m, 1 H, CH_2'), 1.76–1.84 (m, 3 H, CH_2 and CH_2''), 1.79 (dd, J = 14.0, 8.2 Hz, 1 H, H-4), 1.89 (s, 3 H, $COCH_3$), 2.05 (dd, J = 14.2 Hz, 6.32 Hz, 1 H, H-4), 2.03–2.07 (m, 1 H, CH_2''), 2.13–2.16 (m, 1 H, CH_2'), 2.79–2.86 (m, 1 H, H-4a), 3.78 (s, 3 H, OCH_3), 5.68 (s, 1 H, NH), 5.82 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 ($COCH_3$), 23.8 (CH_2), 24.6 (CH_3), 31.8 (CH_2'), 36.1 (C-4), 38.7 (C-4a), 41.2 (CH_2''), 52.9 (OCH_3), 55.3 (C-3), 68.1 (C-7a), 169.7 ($COCH_3$), 173.5 (CONH), 174.9 ($COOCH_3$) ppm.

Methyl 3-Acetylamino-3-isopropyl-2-oxo-octahydro-7a*H*-cyclopenta[*b*]pyridine-7a-carboxylate (7b): The procedure for the methanolysis was applied as described for product **3a**. Yield: 54% (143 mg) ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.8 Hz, 3 H, CH_3), 0.97 (d, J = 6.9 Hz, 3 H, CH_3), 1.53–1.55 (m, 1 H, H-7), 1.66 (t, J = 13.3 Hz, 1 H, H-4), 1.75–1.79 (m, 1 H, H-5), 1.82–1.86 (m, 2 H, H-6), 1.92 (s, 3 H, $COCH_3$), 2.11–2.22 (m, 2 H, H-5 and H-7), 2.40–2.45 [m, 2 H, $CH(CH_3)_2$, H-4], 2.83–2.86 (m, 1 H, CH), 3.77 (s, 3 H, OCH_3), 5.49 (s, 1 H, NH), 6.09 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 18.3 (CH_3), 23.3 (C-6), 23.9 ($COCH_3$), 31.4 (C-4), 32.8 (C-7), 34.6 [$CH(CH_3)_2$], 36.9

(CH), 40.9 (C-5), 52.8 (OCH_3), 61.4 (C-3), 68.0 (C-7a), 169.7 ($NHCOCH_3$), 172.7 (NHCO), 175.2 ($COOCH_3$) ppm. EIMS: *m*/*z* (%) = 296 (1) [$M^{+\cdot}$], 253 (46) [$M^{+\cdot}$ – $COCH_3$], 237 (35) [$M^{+\cdot}$ – $COOCH_3^{\cdot}$], 211 (100) [$M^{+\cdot}$ –$COCH_3$ – *i*Pr$^{\cdot}$]. HRMS: calcd. for $C_{15}H_{24}N_2O_4$ 296.1736; found 296.1740.

Methyl 1-Acetylamino-2-[2-acetylamino-3-methoxy-2-methyl-3-oxopropyl]cyclopentanecarboxylate (8): Yield: 22% (91 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56–1.51 (m, 1 H), 1.61 (s, 3 H, CH_3), 1.75–1.68 (m, 3 H), 1.98 (s, 3 H, $COCH_3$), 2.00 (s, 3 H, $COCH_3$), 1.96–2.11 (m, 1 H), 2.16–2.25 (m, 4 H), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 5.64 (s, 1 H, NH), 6.49 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (CH_2), 23.3 (CH_3), 23.4 (CH_3), 24.1 (CH_3), 31.2 (CH_2), 35.3 (CH_2), 35.3 (CH_2), 44.5 (C-2), 52.4 (OCH_3), 52.9 (OCH_3), 169.4 (CO), 170.1 (CO), 173.3 (CO), 174.8 (CO) ppm, C_{quat} not resolved.

8-(4-Methoxybenzyl)-7,10-dimethyl-8,10-diazatricyclo[5.2.2.0^{1,5}]-undecane-9,11-dione (9): Sodium hydride [48.5 mg (60% in mineral oil), 1.2 mmol] was added to a stirred solution of the tricyclic compound **3c** (250 mg, 0.86 mmol) in DMF. After stirring at room temperature for 5 min, 1.2 equiv. of MeI (65 μL, 1.04 mmol) was added to this mixture. The reaction mixture was kept at room temperature overnight. The crude product was obtained after workup with saturated NH_4Cl solution followed by extraction and evaporation of the solvent. The product **9** was purified by column chromatography (silica gel; CH_2Cl_2/EtOAc, 70:30). Yield: 80% (225 mg). M.p. 109.4–109.7 °C. IR (KBr): $\tilde{\nu}$ = 1687 (s, CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.26 (m, 1 H, CH_2), 1.33 (dd, *J* = 13.5 Hz, 5.1 Hz, 1 H, H-6), 1.44 (s, 3 H, CH_3), 1.80–1.88 (m, *J* = 13.5 Hz, 9.9 Hz, 2 H, H-6, H-6 and CH_2), 1.95–2.05 (m, 3 H, CH_2), 2.22 (ddd, *J* = 15.4 Hz, 8.8 Hz, 2.9 Hz, 1 H, CH_2), 2.36–2.44 (m, 1 H, H-5), 2.95 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.24 (d, *J* = 15.7 Hz, 1 H, CH_2Ph), 4.81 (d, *J* = 15.4 Hz, 1 H, CH_2Ph), 6.77 (d, *J* = 8.8 Hz, 2 H, H_{meta}),7.03 (d, *J* = 8.8 Hz, 2 H, H_{ortho}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 23.3 (CH_2), 25.1 (CH_2), 29.0 (NCH_3), 29.7 (CH_2), 36.9 (CH_2), 44.3 (C-5), 45.1 (CH_2Ph), 55.6 (OCH_3), 62.8 (C-8), 71.9 (C-1), 114.5 (C_{meta}), 128.4 (C_{ortho}), 130.9 (C_{ipso}), 159.1 (C_{para}), 172.4 (CO), 172.7 (CO) ppm. EIMS: *m*/*z* (%) = 328 (36) [$M^{+\cdot}$], 164 (100) [$M^{+\cdot}$ – CONH*p* – OMeBn$^{\cdot}$], 121 (49) [$C_8H_9O^+$]. HRMS: calcd. for $C_{19}H_{24}N_2O_3$ 328.1787; found 328.1782.

7,10-Dimethyl-8,10-diazatricyclo[5.2.2.0^{1,5}]undecane-9,11-dione (10): The general procedure for the CAN deprotection was applied. Yield: 58% (74 mg), oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29–1.39 (m, 1 H, CH_2), 1.48 (s, 3 H, CH_3), 1.81–1.85 (m, 1 H, CH_2), 1.88–2.15 (m, 4 H, CH_2), 2.17–2.37 (m, 3 H, CH_2), 2.97 (s, 3 H, NCH_3), 6.37 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (CH_3), 23.2 (CH_2), 24.4 (CH_2), 28.9 (NCH_3), 29.7 (CH_2), 36.4 (CH_2), 45.7 (C-5), 58.8 (C_{quat}), 72.4 (C_{quat}), 172.9 (CO), 173.9 (CO) ppm.

Methyl 3-Acetylamino-1,3-dimethyl-2-oxo-octahydro-7a*H*-cyclopenta[*b*]pyridine-7a-carboxylate (11): The general procedure for the methanolysis was applied. Yield: 47% (47 mg), oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, CH_3), 1.54–1.61 (m, 1 H, H-7), 1.66 (dd, *J* = 14.0, 10.0 Hz, 1 H, H-4), 1.90 (s, 3 H, $COCH_3$), 1.81–1.94 (m, 3 H, H-5 and H-6), 2.02–2.07 (m, 1 H, H-7), 2.48–2.54 (m, 2 H, H-4a and H-5), 2.82 (s, 3 H, NCH_3), 2.93 (dd, *J* = 14.0, 5.8 Hz, 1 H, H-4), 3.75 (s, 3 H, OCH_3), 5.85 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8 (CH_3), 24.1 (C-6), 24.1 (CH_3), 32.1 (C-7), 32.3 (NCH_3), 35.0 (C-4), 36.9 (C-5), 40.1 (C-4a), 52.8 (OCH_3), 56.6 (C-3), 74.0 (C-7a), 169.8 ($COCH_3$), 172.6 ($CONCH_3$), 174.9 ($COOCH_3$) ppm.

3-Acetylamino-3-isopropyl-*N*-methyl-2-oxo-octahydro-7a*H*-cyclopenta[*b*]pyridine-7a-carboxamide (12): The piperidinone derivative **7b** (50 mg, 0.17 mmol) was dissolved in a 33% solution of $MeNH_2$ in ethanol (15 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated and the residue was purified by chromatography (CH_2Cl_2/MeOH, 95:5). Yield: 65% (33 mg). M.p. 218.0–219.6 °C. IR (KBr): $\tilde{\nu}$ = 1550 (s, CONH), 1645 (S, CONH), 1689 (s, CONH), 2961 (s, C_{aliph}), 3076 (s, NH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 0.85 [d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.86 [d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.34–1.41 (m, *J* = 13.8 Hz, 2 H, H-4_{ax} with t, H-5), 1.63–1.66 (m, 3 H, H-6 and H-7), 1.75 (s, 3 H, $COCH_3$), 1.77–1.80 (m, 1 H, H-5), 2.02 (dd, *J* = 13.8 Hz, 6.3 Hz, 1 H, H-4_{eq}), 2.06–2.11 (m, 1 H, H-7), 2.29 [sept, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.61 (d, *J* = 4.6 Hz, 3 H, $NHCH_3$), 2.67–2.72 (m, 1 H, H-4a), 7.41 (q, *J* = 4.0 Hz, 1 H, $NHCH_3$), 7.56 (s, 1 H, $NHCOCH_3$), 7.60 (s, 1 H, *NH*CO), ppm. ^{13}C NMR (100 MHz, DMSO): δ = 16.8 [$CH(CH_3)_2$], 18.1 [$CH(CH_3)_2$], 22.7 ($COCH_3$), 23.4 (C-6), 26.0 ($NHCH_3$), 31.9 (C-5), 32.0 [$CH(CH_3)_2$], 32.4 (C-4), 37.5 (C-4a), 39.7 (C-7), 59.0 (C-3), 67.8 (C-7a), 169.2 ($NHCOCH_3$), 170.1 (CONH), 175.4 ($CONHCH_3$) ppm. EIMS: *m*/*z* (%) = 237 (69) [$M^{+\cdot}$ – $CONHCH_3^{\cdot}$], 136 (21) [$C_8H_{10}NO^+$]. HRMS: calcd. for $C_{15}H_{25}N_3O_3$ 295.18957, $C_{15}H_{25}N_3O_3$/$CONHCH_3$ 237.1603; found 237.1603.

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