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Proline Derived Spirobarbiturates as Highly Effective β-Turn Mimetics Incorporating Polar and Functionalizable Constraint Elements

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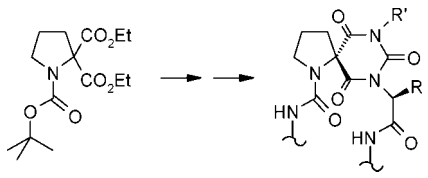

A practical and efficient synthesis of spirobarbiturates of type **III** is reported when NH acidity of the imide function of the hydrophilic linker element allowed the introduction of different substituents. Structural characterization, which was based on both X-ray crystallography and spectroscopic investigations, indicated type II β-turn formation. Introduction of the molecular scaffold into solid phase peptide synthesis gave rise to spirocyclic neuropeptide analogs.

Since reverse-turn motifs play a crucial role in molecular recognition and signal transduction,[1] the development of privileged scaffolds nucleating turn structures has attracted remarkable interest.[2] Upon introduction of constraint elements into biologically active peptides, the number of degrees of conformational freedom and, thus, binding-associated loss of entropy can be decreased.[3] The most powerful β-turn mimetics have been derived from the functionally important amino acid proline[4] when the introduction of suitable constraint elements led to lactam-bridged molecular scaffolds.[5] Employing both saturated and unsaturated constraint elements leading to Freidinger-type (**I**)[6] and dehydro-Freidinger-type (**II**) spirocycles,[7] respectively, we were able to establish a molecular building-kit that allows adjustment of a wide range of dihedral angles (Figure 1).

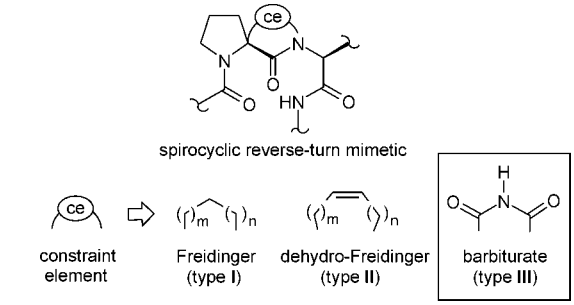

FIGURE 1. Modification of constraint elements.

To complement these investigations, we aimed to construct spirocyclic analogues incorporating polar, "backbone-like" constraint elements. Interestingly, such a concept was described for conformationally constrained nucleosides when a barbituric acid moiety was incorporated into a spirocyclic system.[8]

Following the concept of privileged structures, we planned to synthesize and to conformationally evaluate spirobarbiturates of type **III**. Such molecular scaffolds should be available via cyclocondensation reactions as described for the preparation of barbiturate-type drugs.[9] *NH* acidity of the hydrophilic linker element should allow the introduction of different substituents. These could serve as molecular probes exploring binding pockets of complementary target proteins. We herein present a practical synthesis of model peptide surrogates of type **III**, solid-phase supported application toward two artificial neuropeptide mi-

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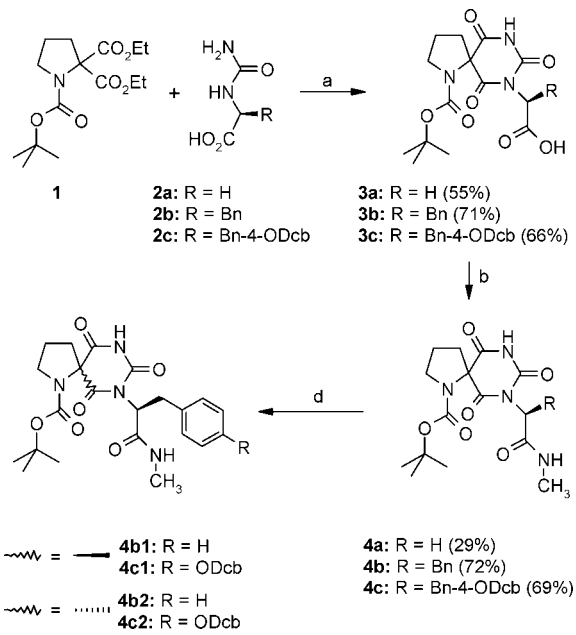
SCHEME 1[a]



[a] Key: (a) *t*-BuOK, DMSO, rt, 16 h; (b) $CH_3NH_2 \cdot HCl$, HATU, DBU, NMP, rt, 15 min–3 h; (d) prep HPLC, silica gel, diisopropyl ether/acetonitrile; Dcb: 2,6-dichlorobenzyl.

metics and structural characterization which was based on both X-ray crystallography and spectroscopic investigations.

The construction of the novel spirocyclic scaffolds was envisioned by a base-promoted cylocondensation reaction of *N*-carbamoyl-substituted amino acids with a suitably *N*-protected α-carboxyproline diester (Scheme 1). Starting from *N*-Boc-protected diethylaminomalonate and 1,3-dibromopropane in the presence of base, the prochiral building block **1**[10] was prepared in 90% yield when the addition of KI significantly increased the efficiency of the cyclization. Our initial attempts to the synthesis of the spirocyclic scaffold including the treatment of the dicarboxylate **1** with *N*-carbamoyl glycine benzylester and EtONa or *t*-BuOK failed. This is putatively due to the high energetic demand for the generation of a 1,2-dianion from the initially formed ester enolate. To circumvent this problem, we planned to react diester **1** with free *N*-carbamoylamino acids in presence of an excess of base, because formation of a carboxylate anion should prevent from deprotonation at C_α and facilitate optical integrity in case of chiral amino acid derivatives. To approach to representative building blocks, the urea derivatives **2a**−**c** were synthesized by *N*-carbamoylation of glycine, (*S*)-phenylalanine and *O*-(2,6-dichlorobenzyl)-(*S*)-tyrosine with KOCN, according to previously reported protocols.[11] In fact, deprotonation of the carbamoyl amino acids **2a**−**c** by 3 equiv of *t*-BuOK in DMSO and subsequent addition of the pyrrolidine dicarboxylic ester **1** resulted in a 55–71% formation of the spirobarbiturate **3a**−**c** (Scheme 1). Employing HATU as an activating agent, carboxamide formation could be performed giving access to the *N*-protected Pro-GlyNHMe surrogate **4a** in racemic form. Furthermore, the conformatively constrained Pro-Phe-NHMe and Pro-Tyr(ODcb)-NHMe analogues **4b** and **4c**, both as 1:1 mixtures of diastereomers, were obtained. Finally, preparative HPLC gave rise to the isomerically pure model peptide surrogates **4b1**, **4b2**, **4c1**, and **4c2**.

X-ray diffraction analysis of the model peptide surrogate **4b1** was performed to provide helpful information on both the conformational properties in solid state and the absolute stereochemistry of the spirocyclic center which clearly revealed (*R*)-configuration (Figure 2). Due to reverse CIP priority-based assignments, the disposition of the backbone-forming carboxamide function of **4b1** is identical to that of natural (*S*)-proline amide. Based on the X-ray structure of the reference scaffold **4b1**, overall similarities of ^1H NMR data and analogous elution profiles allowed determination of the spirocyclic stereogenic centers of **4c1** and **4c2** to be (*R*) and (*S*), respectively.

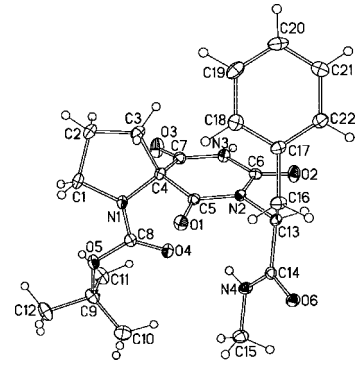


FIGURE 2. Thermal ellipsoid plot of the molecular structure of **4b1** (50% probability ellipsoids).

Taking advantage of the *NH* acidity of our linker elements, we intended to introduce different substituents which can be exploited as biomolecular probes. To facilitate a chemoselective *N*-alkylation, orthogonal protection of the carboxylic acid function should be first conducted. TCE-esters are known to be resistant toward acidic and basic conditions and can be readily removed by reductive cleavage with zinc dust.[12] In detail, EDC/DMAP promoted esterification of **3a**−**c** with 2,2,2-trichloroethanol afforded the 2,2,2-trichloroethyl (TCE) esters **5a**−**c**. Upon deprotonation of the imides **5a**−**c** by NaH and treatment with methyl iodide, benzyl bromide or (DcbO)-benzyl bromide,[13] *N*-alkylation was observed giving access to the functionalized scaffolds **6a**−**e** in 62–85% yield. Zn-mediated TCE deprotection of the representatives **6b**−**e** could be accomplished when we obtained the free carboxylic acid derivatives **7a**−**d**. To approach to the model peptide surrogates of type **8**, HATU-promoted peptide coupling and subsequent aminolysis were performed.

Finally, separation of the diastereomers **8a1/8a2** and **8b1/8b2** was done by HPLC using normal-phase conditions, followed by an NMR-based configurational assignment using **4b1** as a reference structure.

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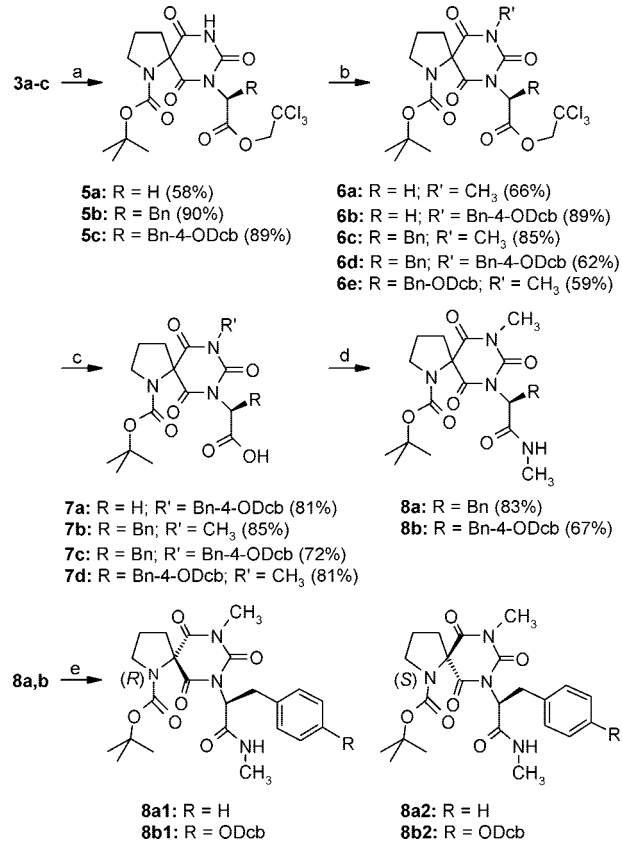
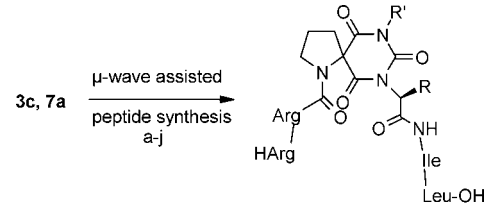
SCHEME 2[a]



[a] Key: (a) 2,2,2-trichloroethanol, EDC, DMAP, CH_2Cl_2, rt, 16 h; (b) CH_3I or 2,6-Cl_2Bn-OBnBr, NaH, DMF, rt; (c) Zn dust, 1 M NH_4OAc, THF, rt, 24 h; (d) $CH_3NH_2 \cdot HCl$, HATU, DBU, NMP, rt, 15 min–3 h; (e) HPLC; Dcb: 2,6-dichlorobenzyl.

To apply our methodology to the synthesis of biologically relevant peptide mimetics, we intended to incorporate our molecular scaffolds of type **III** into NT(8–13) (H-Arg-Arg-Pro-Tyr-Ile-Leu-OH), the active portion of the neuropeptide neurotensin.[14] Since the Pro-Tyr fragment is known to be of special importance for receptor recognition, introduction of the structural congeners **3c** and **7a** should give access to valuable molecular probes of type **9** and **10**, respectively (Scheme 3). Thus, Fmoc-isoleucine was coupled using PYBOP as an activating reagent to *N*-deprotected Leu immobilized on Wang resin. Microwave acceleration proved to be advantageous for both Fmoc-deprotection of the resin and acylation. Subsequently, μ-wave assisted coupling of the building blocks **3c** and **7a** was performed when a second acylation with HATU was necessary to complete the ligation of **3c**. Cleavage of the Boc function was done according to a previously published protocol employing 10% sulfuric acid in dioxan at 8 °C, thus preventing liberation of the peptide from the solid support.[15] Since the pyrrolidine nitrogen of the spirobarbiturate system was not susceptible to acylation reactions with common peptide coupling reagents, we employed the recently introduced BTC (bis-trichloromethylcarbonate),[16] which proved successful for the coupling of Fmoc(Pbf)-arginine to the sterically hindered amine function. After a further deprotection

SCHEME 3[a]



[a] Key: (a) Fmoc-Leu-Wang resin, piperidine/DMF (1:4), μ: 5 × 5 s, 100W, 5× cooling to −10 °C; (b) Fmoc-Ile-OH, PyBOP, DIPEA, HOBt, DMF, μ: 15 × 10 s, 50 W, 15× cooling to −10 °C; (c) (1) Fmoc deprotection (see a), (2) **3c** or **7a,** conditions see (b) for **3c**: reagents for a 2nd μ-assisted coupling: HATU, DIPEA, DMF; (d) H_2SO_4/dioxane (1:9), 8 °C, 2 h; (e) Fmoc-Arg(Pbf)-OH, BTC, 2,6-lutidine, rt, 1 h; (f) (1) Fmoc deprotection (see a), (2) coupling of Fmoc-Arg(Pbf)-OH (see b), (3) Fmoc deprotection (see a); (g) TFA, phenol, H_2O, triisopropylsilane 88:5:5:2, 2 h; (h) RP-HPLC; (i) H_2, 20% $Pd(OH)_2$/C, MeOH; (j) RP-HPLC.

and coupling with Fmoc(Pbf)-arginine, TFA-promoted cleavage, preparative HPLC and palladium-catalyzed hydrogenolysis of the 2,6-dichlorobenzyl group, the target peptides **9** and **10** were isolated in isomerically pure form.

Employing X-ray crystallographic data, we clearly identified a type II β-turn structure for the model peptide scaffold **4b1** (Figure 3) when an intramolecular hydrogen bond with a distance of 2.21 Å[17] could be unambiguously deduced between the methyl amide $N-H_{i+3}$ and the C=O function in position *i*. The backbone dihedral angles of proline (ϕ_{i+1}: −61.1°/Ψ_{i+1}: 137.7°) and phenylalanine (ϕ_{i+2}: 65.9°/Ψ_{i+2}: 17.4°) were deviating by less than 30° [18] from the canonical angles of –60°, 120°, 80°, and 0°, respectively, thus correlating well with the ideal form of a type II β-turn.[19] The distance from the *tert*-butoxy oxygen and the methylamide carbon (d O_i-C_{i+3} representing the distance between $C\alpha_i$ and $C\alpha_{i+3}$, respectively) was found substantially shorter than 7 Å (5.07 Å), indicating that a U-turn is adopted. Additionally, the low pseudodihedral angle β ($C_i-C\alpha_{i+1}-C\alpha_{i+2}-N_{i+3}$) of 9.3° revealed an almost coplanar spatial arrangement and, thus, antiparallel pleated β-sheet nucleating properties.

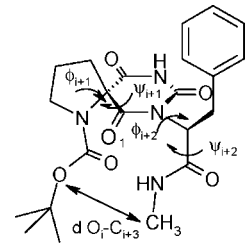


FIGURE 3. Geometric parameters of **4b1**.

To evaluate the structural behavior of the model peptide mimetic **4b1** in solution, we performed conformational studies based on FT-IR and ^1H NMR spectroscopy. To exclude intermolecular interactions, spectra were recorded at 2 mM concentrations.[20]^1H NMR spectra of **4b1** showed two peaks for

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amide *NH*, a major peak at 6.52 ppm (95%) and a minor peak at 5.87 ppm (5%) indicating the presence of two conformers. Temperature dependent chemical shifts as a measure for the stability of secondary structures were studied between 273 and 313 K in $CDCl_3$ recorded in 10 K steps, revealing a low $\Delta\delta\Delta T$ value of –3.1 ppb/K for the *NH* of the major conformer. IR spectra of **4b1** ($CHCl_3$) displayed *NH* stretching vibrations at 3381 cm^{-1} and a very weak shoulder above 3450 cm^{-1}. Thus, we concluded, that an intramolecular hydrogen bond is strongly favored. The above-mentioned diagnostic values for the spirobarbiturates **4a**,**b2**,**c1/2** and **8a1/2**,**b1/2** (δ(NH): 6.41–6.56 ppm; ν(NH): 3380–3402 cm^{-1}; $\Delta\delta\Delta T$: (−4.8)-(−2.4) ppb/K) were very similar to the data measured for reference peptide surrogate **4b1** clearly indicating the preferred formation of type II β-turn secondary structures for all compounds investigated.

In conclusion, an efficient methodology was established that gives access to a novel type of β-turn nucleating scaffolds incorporating polar, "backbone-like" constraint elements.

Experimental Section

General Method for the Synthesis of the Barbiturate Scaffolds 3a−c. To a solution of *t*-BuOK in DMSO (0.5 mmol/mL) was added the respective urea (**2a−c**) dissolved in DMSO (0.15 mmol/mL) at 10 °C. After 10 min of stirring, a solution of pyrrolidine-1,2,2-tricarboxylic acid 1-*tert*-butyl ester 2,2-diethyl ester (**1**) in DMSO (0.3 mmol/mL) was added. The reaction mixture stirred at rt for 20 h, and then 5% aq citric acid was added and extraction with EtOAc was performed. After the organic layer was washed with H_2O and brine and dried with $MgSO_4$, the solvent was evaporated and the residue was purified by flash column chromatography.

General Method for the Synthesis of the Methyl Amides 4a−c and 8a,b. A solution of the carboxylic acid, methylamine hydrochloride, and HATU in NMP (2 mL) was stirred for 10 min at rt, and then a solution of DBU in NMP (2 mL) was added dropwise. After 15 min–3 h, 5% citric acid was added, and extraction with EtOAc was performed. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The product was purified by flash column chromatography.

General Method for the Synthesis of 2,2,2-Trichloroethyl Ester Derivatives 5a−c. To a stirred solution of the respective carboxylic acid, 2,2,2-trichloroethanol, and DMAP in CH_2Cl_2 was added EDC at 0 °C. After 1 h, the solution was allowed to stir at rt for 18 h. Thereafter, the solvent was removed in vacuo, H_2O was added, and a pH ≈ 7 was adjusted by the addition of 5% citric acid. After extraction with EtOAc, the combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash column chromatography.

General Method for the *N*-Alkylation of the Barbiturate Scaffolds to Give 6a−e. An oily suspension of NaH (60%) was washed 2× with dry hexane, and then DMF (4 mL) was added and the mixture cooled to 0 °C. A solution of the corresponding barbiturate derivative in DMF (3–10 mL) was added dropwise. After the development of H_2, a solution of the respective alkyl halide in DMF (3 mL) was added, and the reaction mixture was allowed to stir at rt for 16 h. Thereafter, 5% citric acid was added, and extraction with ethylacetate (3 ×) was performed. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography.

General Method for the Reductive Ester Cleavage To Give 7a−d. To a solution of the respective 2,2,2-trichloroethyl ester in THF was added zinc dust and then an aqueous 1 M NH_4OAc solution. After vigorous stirring for 24 h at rt, the mixture was filtered through Celite and washed with THF. Subsequently, the solvent was removed in vacuo, and the residue was partitioned between 5% citric acid and EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash column chromatography.

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Supporting Information Available: Experimental and analytical data (for compounds **1**, **2c**, and **3–10** including epimerization study of **3b**,**c**, HPLC data and conformational analysis data for **4a**,**b1/b2**,**c** and **8a1/2**,**b1/2** as well as details of the X-ray crystal structure determination of **4b1** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC-668906 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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