Configurational and Conformational Control on Formation and Oligomerization of 2-C Mono-Arylated Pseudo-Proline Dipeptide Building Units by Aromatic Stacking Interactions

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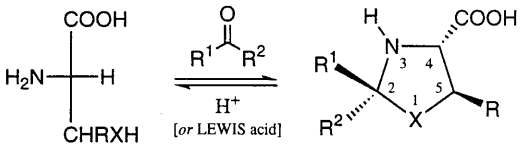
Abstract: Electrophilically induced cyclic acetal formation of the *O*-benzyl dipeptide esters Fmoc-NMeIle-Thr-OBn (**1**) and of Fmoc-Pro-Thr-OBn (**6**) has been observed to lead predominantly to the *(R)* diastereomers **2b** and **8b** at the 2-C position of the resulting substituted 1,3-oxazolidine (ΨPro) unit, while upon acetalization of the corresponding *O*-methyl ester **4** the 2-C*(S)* epimer **5a** is predominantly formed under the same proton catalyzed cyclization conditions. With boron trifluoride etherate as Lewis acid the reaction is particularly fast and leads selectively to the prolyl threonine derived 2-C*(R)* dipeptide building block **8b**, which could conveniently be assembled into a nonamer with a virtually solvent independent CD-spectrum of the polyproline type I (*cis* amide bonds).

Key words: acetals, peptide analogues/mimetics, substituent effects, stereocontrol, *cis/trans*-polyproline

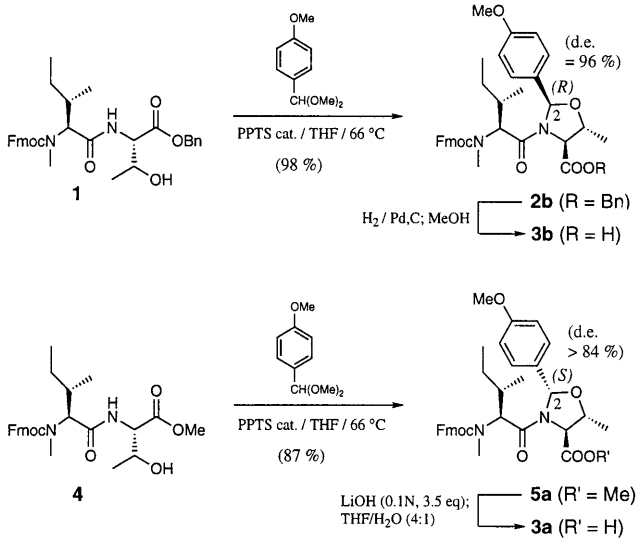
Proline represents the only proteinogenic side chain *N*-cyclized amino acid and therefore has special intrinsic conformational properties extending to the peptide secondary structure segment where it is incorporated.[1] With respect to its other proteinogenic congeners, the conformational space of proline is on one hand restricted around the endocyclic N-C bond to a dihedral angle $\Phi_i = -60\pm15°$, on the other hand, its adjacent exocyclic tertiary amide Ω_{i-1} dihedral angle is subject to greater variation and can undergo receptor or solvent induced conformational switching between the *trans* ($\Omega_{i-1} = 180°$) and the *cis* ($\Omega_{i-1} = 0°$) conformation. The investigation of such transitions are of foremost importance not only to relate observable macroscopic properties such as CD-spectra with molecular conformation,[2] but also to understand biological signaling pathways dependent on ligand-receptor interactions.[3] Biostructural chemistry aims at understanding these equilibria by synthesis of mimetics with defined stereochemical properties.

In the context of our studies to incorporate hetero-alicyclic proline analogues and their chiral substituted derivatives (Scheme 1) into peptide sequences, we recently found a remarkable stereogenic transfer:[4] when the Fmoc protected dipeptide benzyl ester Fmoc-NMeIle-Thr-OBn **1** (Scheme 2) was treated with anisaldehyde dimethylacetal in refluxing tetrahydrofuran in the presence of catalytic amounts of pyridinium *p*-toluenesulfonic acid (PPTS), an initially formed 10:1 mixture of the diastereomeric cyclic 2-aryl-1,3-oxazolidines **2a** (C-2*(S)*) : **2b** (C-2*(R)*) was nearly quantitatively (2:98) transformed into the C-2*(R)* derivative **2b**.



Pseudo-prolines [Xaa(ΨPro)] : Xaa = serine (X = O, R = H) and threonine (X = O, R = CH_3) derived oxazolidines; Xaa = cysteine (X = S, R = H) derived thiazolidines.

Scheme 1



Scheme 2

The latter diastereomer was isolated by a standard work-up and both diastereomers were characterized after HPLC separation and hydrogenolysis of the benzyl ester to the corresponding acids **3a** and **3b**.[4,8] ^{1}H 2D NMR analysis showed that the β-proton of the cyclized threonine residue gives rise to a very strong NOE cross peak to the *ortho*-protons of the *p*-methoxyphenyl (pmp) residue, which is therefore oriented to the same side of the five-membered ring (Figure 1).

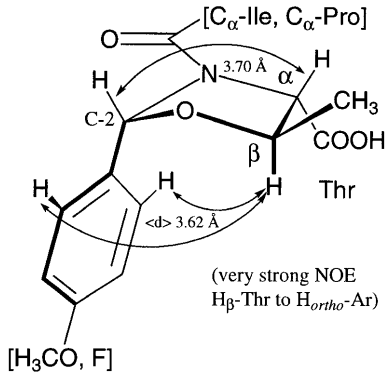


Figure 1

Given this stereochemistry for the main acetalization product **2b**, molecular modeling using the MAB-force field[5] lead us to a plausible rationalization for this stereoselectivity: The two diastereomers C-2*(R)* and C-2*(S)* differ in energy primarily in their non-bonding distant ($n_{bonds} > 4$) interactions term which was calculated to amount to 6.5 kcal in favor of the C-2*(R)* isomer (Figure 2). For reactions proceeding exergonically, it is generally accepted to assume a product-like transition state which is bound to be different for the two pathways leading to the *(R)*- and the *(S)*-diastereomers respectively. Therefore the transacetalization leading to the C-2*(R)* isomer is estimated to be favored significantly with respect to the epimeric conversion, and this result emerges even without explicit inclusion of solvent in the force-field approach. Since the reaction does not proceed at all in an aromatic lipophilic solvent like toluene,[4] a more direct proof by solvent interference is not possible. However, the mechanistic hypothesis is confirmed by the fact that under the same conditions the methyl ester substrate **4** is predominantly transformed to the C-2*(S)* isomer **5a** which is devoid of such a transannular stacking relay, but can on the other hand dispose all of its five-membered ring substituents in an equatorial mode.

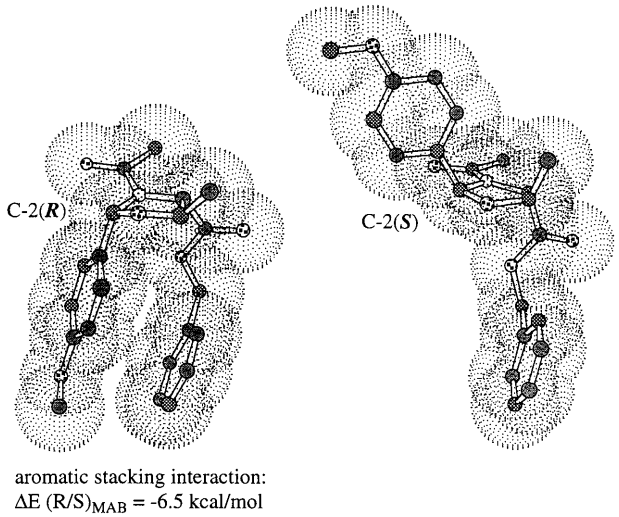
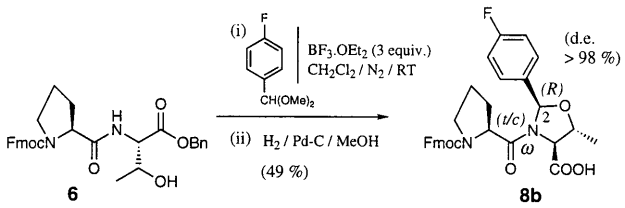
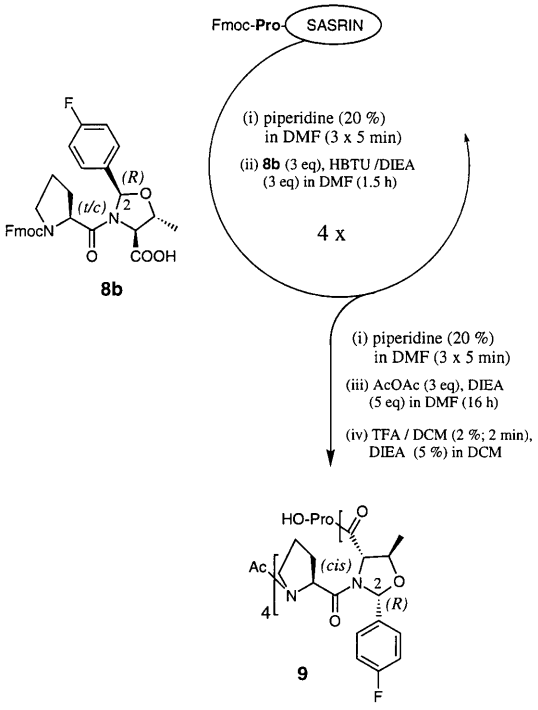


Figure 2

The above bifurcation of the reaction coordinate seems to hold only partially for the Lewis acid driven reaction conditions, where under prolonged acetalization under the conditions given in Scheme 3 even in the methyl ester case predominant formation of the R-isomer is observed. The more so, when the proline containing dipeptide Fmoc-Pro-Thr-OBn **6** (Scheme 3) was subjected to acetalization with *p*-fluoro-benzaldehyde dimethyl acetal in the presence of boron trifluoro etherate, the reaction was improved to occur to completion already at room temperature without the detection of an alternant stereoisomer by HPLC analysis. The more electron deficient aromatic aldehyde was used to increase stability towards acid-catalyzed ring opening in the further elongated oligomer. The dipeptide isomer was further isolated by hydrogenolysis and chromatography on silicagel.[9] Although stereochemically uniform according to HPLC and NMR, the product **8b** was observed to be conformationally inhomogeneous (main conformer: ω-trans; 80%), similarly as has been documented previously by ^{1}H 2D NMR for a series of related R-configured ΨPro derivatives.[6]



Scheme 3



Scheme 4

Can we further take advantage of intramolecular stacking of aromatic substituents to increase stereochemical homogeneity? When assembled into peptide oligomers of alternating Pro-ΨPro constitution (Scheme 4), a related Pro-aromatic stacking effect may be responsible for directing the *cis/trans* equilibrium along the substituted amide bonds into a homogeneous *cis* (polyproline type I) conformation. The CD-spectrum of the nonamer Ac-[Pro-Thr($\Psi^{(R)\text{-}p\text{-F-Ph,H}}$pro)]-Pro-OH **9** (Figure 4) is virtually solvent independent and altered only marginally to a stationary curve with a slight decrease of absorption at 215 nm. This result is significant not only because the CD-curve of the all-*trans*-polyproline has been reported[2] to virtually take up the shape of a mirror image with respect to the wavelength axis (at least above 200 nm where no aromatic absorbance interferes), but also because in high-resolution ^{1}H 2D NMR[10] only one set of signal is observed for the C-2 proton of each of the ΨPro residues. In addition, a coherent series of *cis*-characteristic $C_{\alpha H}$-$C_{\alpha H}$ NOE signals is observed. In contrast to the parent oligoproline constitution, no transition to the more extended, backbone exposed *trans* (polyproline II) conformation could be enforced by solvent exchange, an observation which we correlate to the stabilization of the more compact polyproline I like helix by intramolecular interactions of the addressed aromatic stacking type.

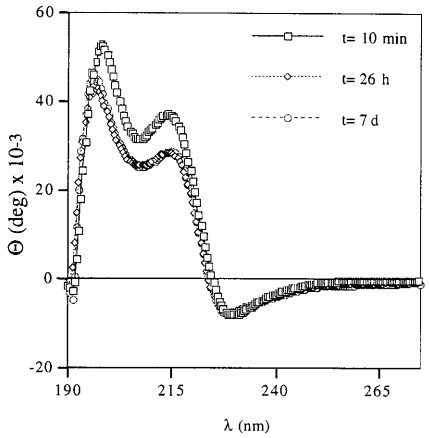


Figure 3. Circular dichroism experiments of peptide Ac-[Pro-Thr($\Psi^{H,para\text{-F-Ph}}$pro)]$_4$-Pro-OH. For this experiment, 0.1 mg peptide was dissolved in propanol from which 100 μL were taken and diluted with 200 μL water to give a final peptide concentration of 0.033 mg/mL. This sample was measured at the indicated times after addition of water: 10 min (squares; identical with the spectrum in pure isopropanol), 26 h (rhombi) and 7 days (circles). Several recordings of the sample between 26 h and 7 days after mixing were carried out, but the absorptions were merely identical. In a separate experiment, a peptide sample (0.033 mg/mL) in water containing 0.33 % of propanol showed a very similar curve typical for polyproline type I.

Historically, the ΨPro-concept was developed as a solubilizing, structure disrupting protection technique to render difficult sequences accessible to solid phase peptide synthesis and to set free the protected hydroxyl groups by concentrated acidolysis after the oligomer assembly.[7] In the present work we showed that the synthetic concept of ΨPro can further be exploited to the general problem of secondary structure stabilization. In particular, the results presented here are most promising for the understanding and control of the polyproline I/II conformational transition.

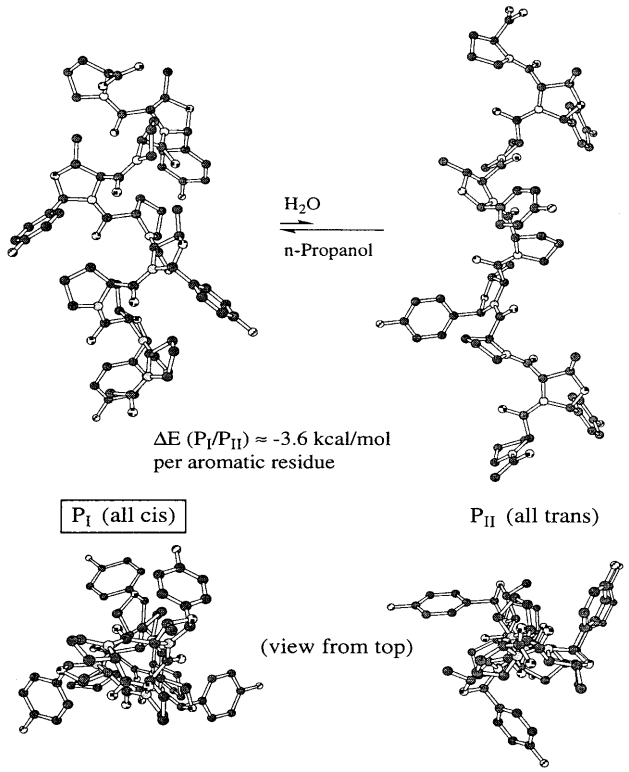


Figure 4

Acknowledgement

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(8) Experimentals to **Scheme 2**: ***Fmoc-NMeIle-Thr(*$\Psi^{H,pmp}$**pro)-OBn (2)** $C_{41}H_{44}N_2O_7$ = 676.8 *Fmoc-NMeIle-Thr-Bn* (**1**; 50 mg, 0.09 mmol) was dissolved in THF (2 ml). PPTS (6.8 mg, 0.3 equiv) and anisaldehyde dimethylacetal (0.096 ml, 5 equiv) added and heated under reflux for 7h. Samples were taken after 1h, 3h and 7h in order to follow the reaction by HPLC: isomer 2-C*(S)* **2a**: r_t = 22.48 min, isomer 2-C*(R)* **2b**: r_t = 23.47 min, 50-100% B, C_{18} (A = water containing 0.09% TFA; B = acetonitrile for HPLC-R containing 10% water and 0.09% TFA; *cf.* Scheme 2 in lit.[4]). Complete conversion to 2-C*(R)* **2b** was stated after 7 hours. The solvent was evaporated and replaced by AcOEt (20 ml) and washed subsequently with aqueous Na_2CO_3 (0.5 M, 20 ml, 3x) and water (20 ml, 3x). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. To the slightly yellow oily residual was added methanol (0.10 ml), before addition of ether (5 ml) to yield oxazoline **2b** as a white precipitate (98%), which was collected on a glass filter and recrystallized from methanol (0.1 ml) / ether (5 ml). HPLC: 23.52 min (95% purity; no other isomer detected). MS-ESI (m/z): 676.8 $[M+H]^+$. *Separation of the diastereomers*: In a separate reaction, the same conditions as above described were used, but the reaction was stopped after 1.5 h and the isomers separated by means of reversed phase HPLC, using an isocratic gradient 40% A and 60% B to 100% B, to obtain 20 mg of each epimer (**2a** and **2b**) separately. ***Fmoc-NMeIle-Thr(*$\Psi^{H,pmp}$**pro)-OH (3)** $C_{35}H_{38}N_2O_7$ = 586.7 Deblocking of the benzyl protecing group was achieved under hydrogen atmosphere in methanol (5 ml) using Pd/C as catalyst. After completion of the deprotection, the suspension was filtered over Celite and all solvent evaporated. HPLC: 2-C*(R)* epimer **3b** 15.9 min (95% purity; no other isomer), 2-C*(S)* epimer **3a** 15.1 min (single peak), 50-100% B, C_{18}; MS-ESI m/z) 559.8 $[M+H]^+$. ^{1}H NMR(400MHz, 10mg/ml, $CDCl_3$, 300 K):2-C(***R***)-stereo-isomer (**3b**; *all-trans* in $CDCl_3$): δ (ppm) 7.8 (*d*, 2H, *J* = 7.6 Hz, Fmoc), 7.62 (*d*, 2H, *J* = 7.6 Hz, Fmoc), 7.55 (*d*, 2H, *J* = 8.8 Hz, *o*-pmp), 7.42 (*d*×*d*, 2H, Fmoc), 7.35 (*d*×*d*, 2H, Fmoc), 7.28 (*s*, $CHCl_3$), 6.94 (*d*, 2H, *J* = 8.8 Hz, *m*-pmp), 6.73 (*s*, 1H, 2-H), 4.6 (*d,* 1H, β-Thr), 4.59 (*d*, 1H, Fmoc-CH), 4.46 (*m*, 1H, Fmoc-CH_2), 4.4 (*m*, 1H, β-Ile), 4.3 (*m*, 1H, Fmoc-CH_2'), 4.29 (*d*, 1H, *J* = 8 Hz, α-Thr), 3.835 (*s*, 3H, OMe), 2.88 (*s*, 3H, NMe), 2.03 (*m*, 1H, β-Ile), 1.46 (*d*, 3H, *J* = 6 Hz, β-Thr), 0.721 (*m*, 3H, δ-Ile), 0.472 (*d*, 3H, *J* = 6.8Hz, γ-Ile). 2-C(***S***)-stereoisomer (**3a**; 40% *cis* and 60% *trans* in DMSO-d_6): 7.8 (*d*, 1H, *J* = 6.8 Hz, *m*-pmp *trans*), 7.74 (*d*, 1-2H, *J* = 6.0 Hz, *m*-pmp *cis*), 7.6 (*d*, 1H, *J* = 6.2 Hz, *o*-pmp *trans*), 7.52 (*d*, 1-2H, *J* = 6.4 Hz, *o*-pmp *cis*), 7.29-7.33 (*m*, 4-6H, Fmoc *cis* and *trans*), 7.04 (*d*, 1-1.5H, *J* = 8.8 Hz, Fmoc), 6.86 (*d*, 1-1.6H, *J* = 8.8 Hz, Fmoc), 6.15 (*s*, 0.2-0.5H, α-Thr trans), 6.09 (*s*, 1-2H, α-Thr *cis*), 5.89 (*s*, 1-1.5H, 2-H *trans*), 5.49 (*s*, 0.8-1.2H, 2-H *cis*), 4.28 (*d*, 1H, *J* = 7.8 Hz, β-Thr), 4.11 (*m*, 0.5-1H, α-Ile *cis*), 4.05 (*m*, 0.3-0.7H, α-Ile *trans*), 3.87 (*m*, 1-2 H, Fmoc-CH *cis* and *trans*), 3.79 (*s*, 3H, NMe), 3.74 (*s*, 3H, OMe), 3.66 (*m*, 2-3H, Fmoc-CH_2), 3.3-3.5 (*s*, H_2O), 2.65 (*m*, 1H, β-Ile *cis*), 2.65 (*m*, 1H, β-Ile *trans*), 2.49 (*s*, DMS*O*-d_6), 1.79 (*m*, 2-3H, β-Ile-CH_3, *cis*), 1.72 (*m*, 3-4H, β-Ile-CH_3 *trans*), 1.43 (*d*, 3-4H, *J* = 5.6 Hz, β-Thr-CH_3 *trans*), 0.91 (*d*, 2-3H, β-Thr-CH_3 *cis*), 0.8 (*m*, 3-4H, γ-Ile-CH_3 *trans*), 0.72 (*d*, 2-3H, J = 6.8 Hz, γ-Ile-CH_3 *cis*). ***Fmoc-NMeIle-Thr(*$\Psi^{H,pmp}$**pro)-OMe (5)** $C_{36}H_{40}N_2O_7$ = 600.8. Fmoc-NMe-Ile-Thr-OMe (**4**; 50 mg, 0.083 mmol), PPTS (7.8 mg, 0.3 equiv) and anisaldehyde dimethylacetal (0.11 ml, 5 equiv) in THF (2.5 ml) were heated under reflux for 16 h. The reaction was followed by HPLC (Gradient 50-100% B, 20 min, C_{18}). After 7h at 80 °C, only one isomer could be observed by HPLC. Heating at 80 °C was continued for another 10 h; very weakly, a second peak close to the peak assigned to the *(R)*-epimer **5b** was observed. To the yellowish liquid was added EtOAc (20 ml), and the solution washed with Na_2CO_3 (10%, 20 ml) and water (20 ml) before drying the organic layer over $MgSO_4$. Deprotection of the methylester was achieved using LiOH (3.5 equiv in THF/H_2O = 4:1, 5 ml, 2 h). The epimers now were separated on the same gradient as above. The relation between the 2-C *(R)* and *(S)*-iomer only changed slightly to 8:92. *(S)*-epimer **3a**: t_R = 15.13 min, *(R)*-epimer **3b**: t_R = 15.84 min (50-100% B, 20 min, C_{18}). The product was purified by flash chromatography over silica using $CHCl_3$/CH_3OH (100:15) as eluent to obtain 2-C*(S) Fmoc-NMeIle-Thr(*$\Psi^{H,pmp}$pro)-OH. $C_{35}H_{38}N_2O_7$ = 586.7. Yield:56 mg, 96%. MS-ESI (m/z) 587.6 $[M+H]^+$. Co-injection of the purified 2-C*(S)* compound with the isolated kinetic product of the *O*-benzyl reaction gave one single peak in HPLC.

(9) Experimentals to **Scheme 3**: ***Fmoc-Pro-Thr(*$\Psi^{H,p\text{-}F\text{-}Ph}$**pro)-OBn (7)** $C_{38}H_{35}N_2O_6F$ = 634.7. *Fmoc-Pro-Thr-OBn* (**6**; 1.3g, 2.05 mmol) was dissolved in CH_2Cl_2 (130 ml) before adding *para*-fluorobenzaldehyde dimethylacetal 2.1 ml, 10 equiv) under nitrogen atmosphere. To the clear solution was added $BF_3.OEt_2$ (965 *ml*, 7.8 mmol) and stirred. The solution first turned to yellow and after two minutes to bordeaux red. After 20 min, the reaction was stopped by adding a solution of Na_2CO_3 (10%, 50 ml). The organic layer was washed with water (50 ml, 2) and dried over $MgSO_4$. All solvent was evaporated and replaced with CH_3OH. To this solution of crude acetal **7**, Pd-C (130 mg) was added and hydrogen bubbled through the solution for 1.5 h. After filtration over Celite and evaporation of the filtrate, a yellowish oil was reconstituted, which was purified on silica using $CHCl_3$/CH_3OH/HOAc (100/10/1 ml) as eluent. 660 mg (1.21 mmol, 49%) of a white solide was isolated and identified as ***Fmoc-Pro-Thr(*$\Psi^{H,p\text{-}F\text{-}Ph}$**pro)-OH** (**8b**; assigned to 2-C*(R)* based on a preliminary ^{1}H 2D NMR NOESY experiment) $C_{31}H_{29}N_2O_6F$ = 544.7. MS-ESI (m/z) 545.2 $M+H^+$. HPLC t_R = 12.38 min (50-100% CH_3CN), 93% purity (only one isomer). ^{1}H NMR (400 MHz, $CDCl_3$, 10 mg/ml, 295 K; two conformers; 80% ω-trans): δ (ppm) 7.8 (*d*, 2H, aromatic Fmoc), 7.65 (*dd*, 2H, *ortho* H-*p*-F-Ph), 7.6 (*t*, 2H, aromatic Fmoc), 7.4 (*t*, 2H, aromatics Fmoc), 7.3 (*t*, 2H, aromatic Fmoc), 7.27 (*s*, $CDCl_3$), 7.1 (*t*, 2H, *meta* H-*p*-F-Ph), 6.7 (*s*, 1H, 2-H oxazolidine; ω-trans), 6.45 (*s*, 0.08H, 2-H oxazolidine; further conformational isomer), 6.0 (*s*, 0.17H, 2-H oxazolidine, ω-cis), 4.5 (*t*, 1H, β-Thr), 4.4 (*dd*, 1H, α-Thr and Fmoc-CH), 3.6 (*m*, 1H, γ-Pro), 3.5 (*m*, 1H, γ-Pro), 2.1 (*m*, 1H, δ-Pro), 1.95 (*m*, 1H, δ'-Pro), 1.75 (*m*, 1H, β'-Pro), 1.5 (*m*, 1H, β'-Pro), 1.45 (*d*, 3H, β-CH_3-Thr; ω-trans), 1.25 (*d*, 0.8H, β-CH_3-Thr; ω-cis).

(10) Experimentals to **Scheme 4**: Solid Phase Synthesis of ***Ac-Pro-Thr(*$^{H,para\text{-}F\text{-}Ph}$***Pro)*$_4$***-OH (9)***. Standard protocols for Fmoc-chemistry on Sasrin resin were used. Commercially available Fmoc-Pro-Sasrin (0.64 mmol/g resin, *BACHEM*, Bubendorf, Switzerland) was dried in vacuo over night before use. 50 mmol/g resin (ca. 0.03 mmol) was swelled in DMF (dimethylformamide) for 30 min and washed with CH_3OH (10 ml, 1x), CH_2Cl_2 (10 ml, 3x) and DMF (10 ml, 3x). Fmoc deprotection was carried out using piperidine in DMF (20%, 3 × 5 min). Coupling reagent HBTU (3 equiv, 35 mg, *ALEXIS*, Läufelfingen, Switzerland), deprotection base DIEA (diisopropylethylamine, 6 equiv, 35 *ml*). For each coupling, 3 equivalents of Fmoc-Pro-Thr($^{H,para\text{-}F\text{-}Ph}$Pro)-OH (50 mg) were taken. Solvent for the couplings was DMF (5 ml). Couplings (1.5 h) were verified upon their completion by reversed phase HPLC of a small aliquot cleaved from the resin be 2% TFA in

CH_2Cl_2 after each coupling step. After the last coupling and deprotection, the sequence was *N*-capped by acetylation using acetic anhydride (3 equiv, 10 *ml*) in the presence of DIEA (5 equiv, 35 *ml*) in DMF (5 ml) during 16 h. Finally, the assembly was cleaved from the support by 2% TFA in CH_2Cl_2 (2 min) and immediately neutralized with 3 equivalents of DIEA (5%, CH_2Cl_2) to prevent ring opening of the oxazolidine. The organic layer was washed with citric acid (20 ml, 3x) and water (millipur, 20 ml, 3x), dried over $MgSO_4$ and the solvent removed under vacuo. The peptide was further purified by semipreparative HPLC using a gradient of 20-50% (30 min) CH_3CN containing 0.09% TFA, and the peptide containing fractions lyophilized to obtain 6.2 mg of pure peptide. ***Ac-Pro-Thr($^{H,para\text{-}F\text{-}Ph}$Pro)$_4$-OH*** **(9)**

$C_{71}H_{79}N_9O_{15}F_4$ = 1374.5 MS-ESI (m/z) 1375.5 $M+H^+$. HPLC t_R = 10.46 min (50-100% acetonitrile, 20 min). ^1H NMR (400 MHz, $CDCl_3$, 5 mg/ml, 298 K): δ (ppm) 8.0 (*m*, 6-7H, *ortho*-H *p*-F-Ph), 7.29 (*s*, $CDCl_3$), 7.1 (*m*, 5-6H, *meta*-H *p*-F-Ph), 6.75 (*s*, 1H, 2-H oxazolidine), 6.67 (*s*, 2H, 2-H'/H'' oxazolidine), 6.62 (*s*, 1H, 2-H''' oxazolidine),1.5-5 (33H, α,β,γ,δ–Pro, α,β-Thr), 2.08 (*s*, 3H, Ac), 1.25-1.5 (4*d*, 12H, β-CH_3-Thr).

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