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Stereocontrol During the Formation of 2-C Mono-Arylated Pseudo-Prolines by Aromatic Stacking Interaction

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Abstract

When treated with anisaldehyde dimethylacetal the *O*-benzyl ester protected dipeptide Fmoc-NMeIle-Thr-OBzl (**2**, cf. Scheme 3), cyclizes to the 2-C(*S*) epimer **3b** assigned by NMR spectroscopy to chirality (*R*) at the 2-C position of the resulting substituted 1,3-oxazolidine (ΨPro) unit, while in the acetalization of the corresponding *O*-methylester Fmoc-NMeIle-Thr-OMe (**6**), the 2-C(*S*) epimer **7a** is predominantly formed stereoselectively and in quantitative yield. The course of the reaction can be rationalized by aromatic stacking interactions involving the benzyl ester and aryl ether groups in a transition state close to a product structure of (*R*) chirality, whereas the lack of such interactions in the case of the methyl ester can be used to direct the acetalization towards the 2-C(*S*) epimer.

Keywords: Acetals; Peptide analogues/mimetics; Substituent effects; Stereocontrol.

The particular role of proline in chemistry and biology has evoked considerable interest since a couple of decades. While the chemist aims to delineate the unique role of this single cyclic amino acid present in natural peptides and proteins through its systematic replacement by proline-like surrogates [1], the biologist evaluates further implications in receptor-ligand interaction [2] and protein refolding [3]. For a detailed understanding of these most important processes, model compounds have been designed for mimicking or enhancing the native effects of Pro [4]. We have recently introduced a class of Pro mimics referred to as pseudo-prolines (ΨPro, *cf. Scheme 1*) [5]. Their use as a tool to prevent secondary structure formation and self-aggregation of the growing peptide chain during solid phase peptide synthesis (SPPS) [6] or as inducer of *cis* imide bonds into peptide backbones has been demonstrated extensively [7].

From a rather synthetical methodological point of view, pseudo-prolines are commonly used in peptide chemistry as orthogonal hydroxyl and thiol protection technique for Cys, Thr and Ser. Whereas Cys-derived thiazolidines are stable to be isolated as a monomeric building block, Thr- and Ser-derived oxazolidines are in equilibrium with the open ring form and must be synthesized by the so called *post*-insertion route via dipeptides. This way of synthesis is complicated by the formation of epimeric mixtures upon condensation of aldehydes with Ser/Thr containing dipeptides. Here, we study the mechanism of the stereocontrolled insertion of arylaldehydes into dipeptides.

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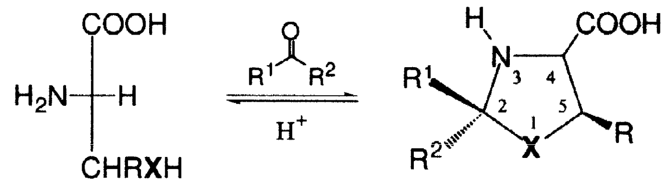
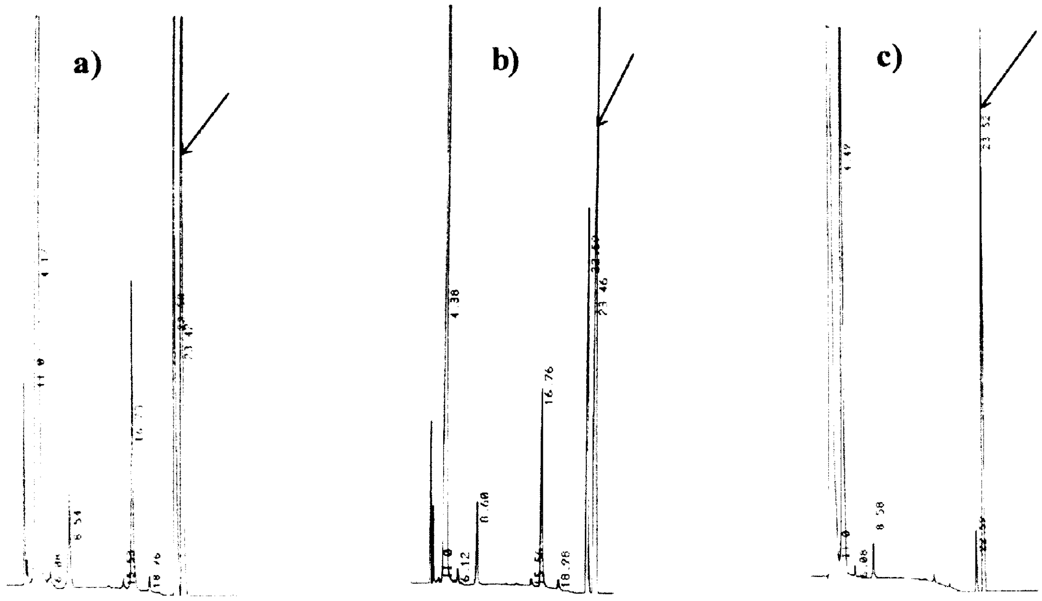


Pseudo-prolines [Xaa(ΨPro)] : Xaa = serine (X = O, R = H) and threonine (X = O, R = CH_3) derived oxazolidines; Xaa = cysteine (X = S, R = H) derived thiazolidines.

Scheme 1

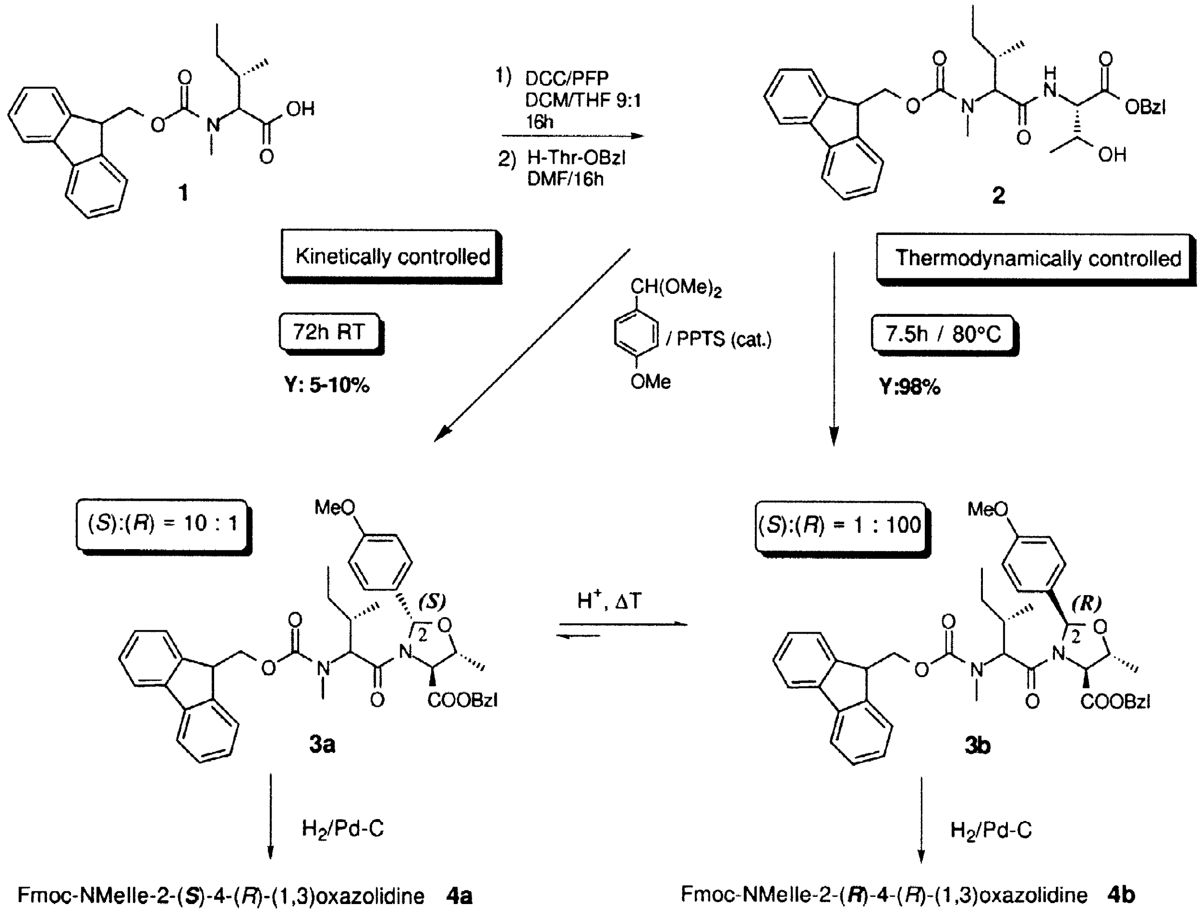
The ready synthetic access of ΨPro derivatives allows for the preparation of a variety of 2-C substituted Pro surrogates exhibiting novel structural and chemical features. For example, by condensation of aldehydes to the α-NH_2 and the nucleophilic function of the side chain (*i.e.* hydroxyl or sulfhydryl; see Scheme 1), two diastereomers 2-C(*R*) and 2-C(*S*) are obtained. However, this occurrence of epimers clearly was undesired in the first instance, since it required their separation by reversed phase HPLC. In our efforts to understand the stereomechanism of these effects, we found that by using benzyl esters (Bzl) as the carboxyl protection group for Thr and Ser, a thermodynamically controlled course of the reaction leads quantitatively to one single isomer, the 2-C(*R*) epimer.



HPLC profile of the reaction of Fmoc-NMeIle-Thr-OBzl (**2**, r_t = 16.7 min) with anisaldehyde dimethylacetal in THF. **a**) after 1h/66°C, **b**) after 3h/66°C, **c**) after 7h/66°C. Gradient: 50→100% B [acetonitrile/water 90:10, 0.09 % TFA], whereas A [water containing 0.09 % TFA]; 20 min; C_{18}. The 2-C(*R*) epimer **3b** is eluted ca. 1 min. after the 2-C(*S*)-epimer **3a**, in chromatogram **c** at r_t = 23.52 min (cf. arrows). The stereochemical assignment is carried out on the level of the isolated and deprotected amino acids (**4a**/**4b**; cf. Scheme 6 and exp. part).

Scheme 2

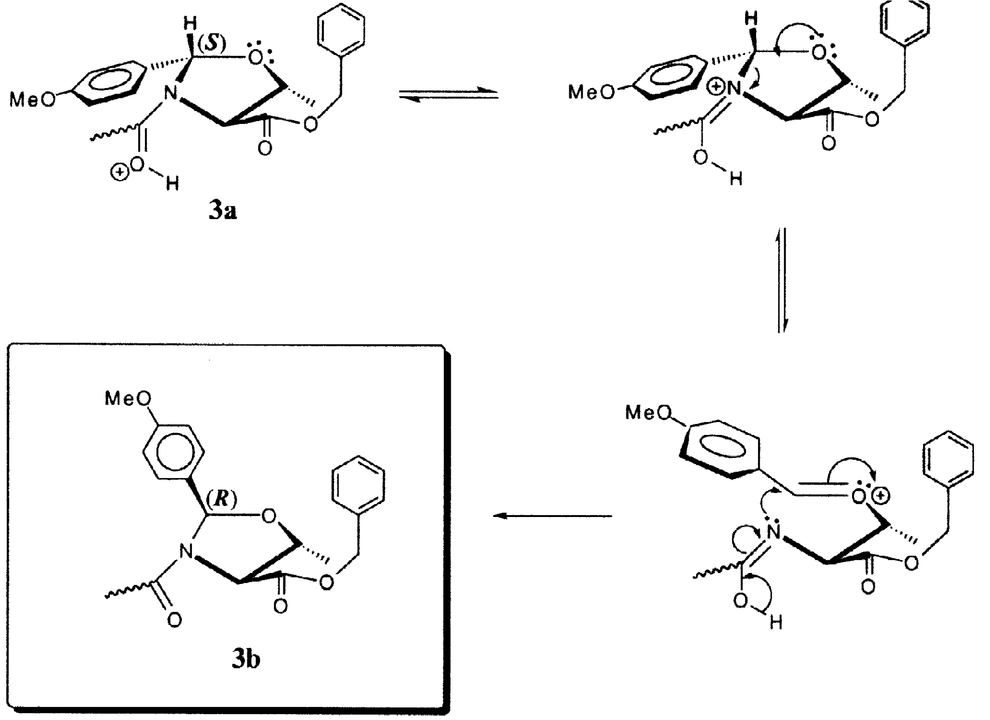
After one hour reaction time (Scheme 2a), two peaks of identical mass and intensity are detected, corresponding to the 2-C stereoisomers. In the course of the reaction, one epimer continuously transforms into the second one; after seven hours (c), the reaction carried out at 66°C is completed to virtually one single stereoisomer, designated as 2-C(*R*). Interestingly, at room temperature, a preference for the 2-C(*S*) epimer is observed; however, in this case the reaction proceeds very slowly and stops at 5-10% of product formation (Scheme 3).



Thermodynamic *versus* kinetic control of the *post*-insertion of anisaldehyde dimethylacetal into Fmoc-NMeIle-Thr-OBzl (**2**) under acidic conditions. In the 2-C(*S*) derivative **3a** (*left*), the 2-C substituent is *trans* to C_α-COOBzl, while in the 2-C(*R*) epimer **3b**, it is *cis* (*right*).

Scheme 3

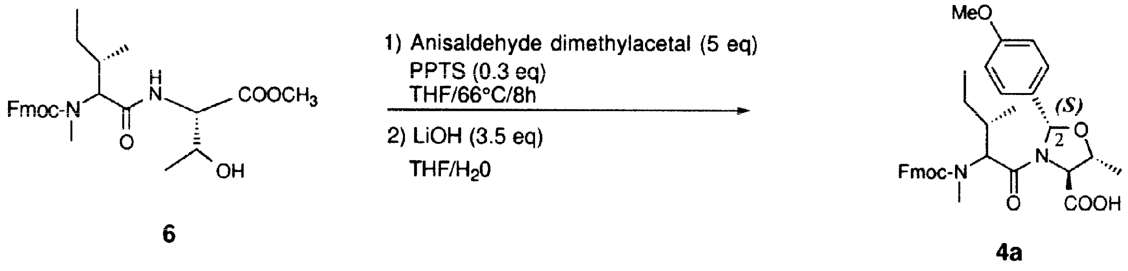
These observations are consistent with an acid catalyzed ring opening mechanism as depicted in Scheme 4[8]. In a first step, the kinetically controlled stereoisomer 2-C(*S*) **3a** is formed[9]. The acid (PPTS) catalyzed opening of the intermediate oxazolidine allows for the conversion to the thermodynamically preferred epimer 2-C(*R*) **3b**, which is quantitatively formed after 7.5 h of reaction (Scheme 4).



Proposed mechanism for the epimerization reaction at 2-C during the *post*-insertion reaction of Fmoc-NMeIle-Thr-*O*Bzl (**2**, cf. Scheme 3) with anisaldehyde dimethylacetal. A favourable aromatic stacking interaction between the two aromatic rings drives the equilibrium towards the 2-C(*R*) epimer **3b**.

Scheme 4

In order to exclude side chain effects arising from the steric propensity of the amino acid side chains, the insertion reaction was applied to the dipeptide Fmoc-Val-Ser-OBzl (**5**) (Table 1). The above results on the stereocontrol of the reaction were fully confirmed. Interestingly, the reaction does not proceed if toluene is used as solvent for none of the dipeptides used (Table 1). This finding is most probably due to a solvent effect; however, it is somewhat surprising that no reaction at all occurs. The described intramolecular stacking interactions are expected to be counteracted by stacking with aromatic solvents, *i.e.* toluene, and hence the stereoselectivity to be lost by reaction in such a solvent. However, a kinetically driven reaction product may emerge all the same, and the observed stereoselectivity might therefore be reduced to a solvent effect and not inherently correlated to the structure of the reactant. To verify this mechanism, the dipeptide Fmoc-NMeIle-Thr-OCH_3 **6** was prepared, which is devoid of any favourable stacking interactions during oxazolidine formation. Most notably, stereoselective formation of the 2-C(*S*) epimer **4a** occurred after boiling for 7 hours at 66 °C in THF (Scheme 5); further continuation of heating under reflux during 16 h did not change the ratio (*R*):(*S*) substantially, as detected by reversed phase HPLC (see Table 1).



Scheme 5

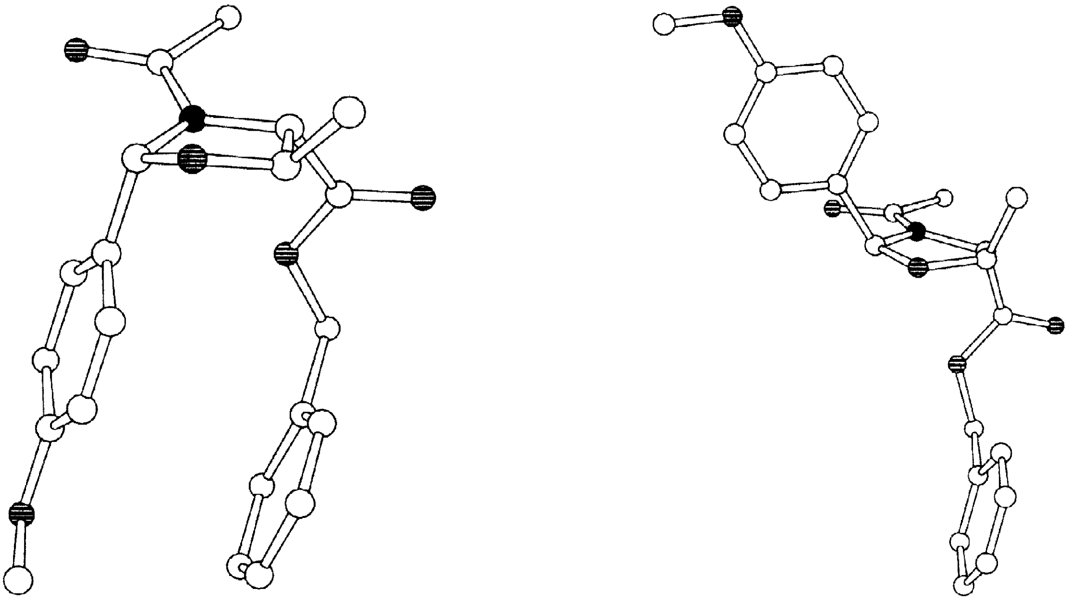
Remarkably, the same reaction is not occurring in toluene. These results suggest a strong solvent dependence of the *post*-insertion reaction independent of the *C*-terminal protecting group.

Table 1. Stereocontrol During the Formation of 2-C Monoarylated ΨPro Containing Dipeptide Derivatives.

dipeptide	dimethylacetal	solvent	temperature [°C]	(*S*)/(*R*)[a] [1h]	(*S*)/(*R*) [7h]
Fmoc-NMeIle-Thr-OBzl (**3**)	anisaldehyde	THF	66	50:50	2:98
		toluene	80	n.r.	n.r.
Fmoc-NMeIle-Thr-OMe (**6**)	anisaldehyde	THF	66	95:5	92:8
		toluene	80	n.r.	n.r.
Fmoc-Val-Ser-OBzl (**5**)	anisaldehyde	THF	66	30:70	10:90
		toluene	80	n.r	n.r.

[a] (*S*)/(*R*) ratios were determined by integration of their absorption in the HPLC (cf. Scheme 1). (*S*) and (*R*) designates 2-C of ΨPro (see Scheme 3). *Legend*: n.r. is no reaction. THF is tetrahydrofuran.

Molecular modelling studies using the MAB-force field [10] support favourable stacking interactions between the two aromatic ring systems *p*-methoxy-phenyl at 2-C of ΨPro and the benzyl (Bzl) protection group of the carboxyl moiety of Thr (Scheme 6).

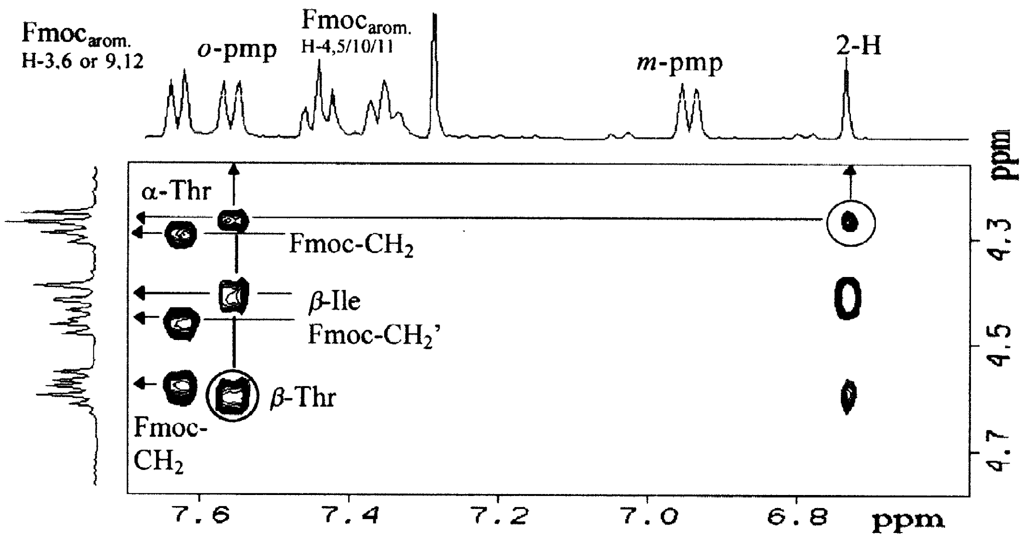


Molecular modelling shows the thermodynamic preference of the *cis*-*p*-methoxy-phenyl [2-C(*R*), *left*] over the *trans* [2-C(*S*), *right*] isomer due to aromatic stacking interactions inherently present in the *cis*-diastereoisomer.

Scheme 6

The two epimers differ in their non-bonding energy interaction energy terms by -6 kcal/mol in favour of the 2-C(*R*) epimer. Such interactions lack in the case of the methylester as the carboxyl protecting group.

The stereochemistry of the 2-C position was determined on the basis of ROE cross peaks between the 2-C proton of the ΨPro ring and the Cα-proton of the ΨPro derived amino acid (*i.e.* Thr) being observed for the 2-C(*R*) epimer **4b** (Scheme 7) [4]. Further evidence is obtained from a strong ROE cross peak between the Cβ-proton (Thr) and the resonances of the *ortho*-protons of the *p*-methoxyphenyl (pmp) ring. Importantly, the corresponding cross peaks are missing in the case of the 2-C(*S*) epimer **4a**.



Expanded region of the 2D ^{1}H NMR ROESY spectrum of Fmoc-NMeIle-Thr($\Psi^{H,pmp}$pro)-OH (4) showing the assignment of the stereochemistry of 2-C(*R*) epimer **4b** by a cross peak (circled) between C_αH-Thr (4.27 ppm) and 2-CH-ΨPro (6.73ppm), further the β–Thr (circled) and the *ortho*-protons of *para*-methoxy-phenyl (*o*-pmp, 7.55 ppm).

Scheme 7

In conclusion, using the model peptides Fmoc-NMeIle-Thr-OBzl (**2**) and Fmoc-NMeIle-Thr-OMe (**6**), we have shown that a stereocontrol of the *post*-insertion reaction can be achieved by appropriate choice of the carboxyl-protecting group to form either 2-C(*S*)-(**4a**) or 2-C(*R*)-Fmoc-NMeIle-Thr($\Psi^{H,pmp}$pro)-OH (**4b**) with nearly quantitative stereoselectivity. The initial predominant formation of the 2-C(*S*) oxazolidine **3a** suggests an isomerization mechanism involving acid catalyzed ring opening and reclosure to the thermodynamically more stable 2-C(*R*) isomer **3b**. Due to the presence of two aromatic ring systems in close spatial proximity, a favourable aromatic stacking interaction shifts the equilibrium towards the 2-C(*R*) epimer **3b**. This finding is of utmost relevance for *post*-insertions using aromatic dimethylacetals for the stereoselective formation of ΨPro containing peptides.

Experimental

Materials. Reagents and solvents were purchased from Fluka (Buchs, Switzerland) and used without further purification. HPLC was performed on Waters equipment using columns packed with Vydac Nucleosil 300Å 5 μm C_{18} particles unless otherwise stated. Analytical columns (250 × 4.6 mm) were operated at 1 mL/min and preparative columns (250 × 21 mm) at 18 mL/min, with UV monitoring at 214 nm.

Solvent A is water (purified on a Milli Q Ion exchange cartridge) containing 0.09% TFA, and solvent B is acetonitrile HPLC-R (containing 10% water and 0.09% TFA), purchased from Biosolve, Valkenswaard, Netherlands. Mass spectra were obtained by electron spray ionization (ESI-MS) on a Finnigan LC 710. ^{1}H NMR spectra were obtained on a Bruker DPX-400 with trimethylsilane as internal standard for intermediate compounds. Abbreviations were used as followed: NMM = N-methylmorpholine, THF = tetrahydrofuran, DCM = dichloromethane, DMSO-d_6 = dimethylsulfoxyde deuterated, DMF = dimethylformamide, PPTS = pyridinium-*para*-toluene-sulfonic acid. The synthesis of compound **5** and a detailed ^{1}H NMR analysis is described in reference 4.

Fmoc-NMeIle-OH (**1**)

$C_{22}H_{25}NO_4$ = 367.4 H-NMeIle-OH (1g, 7 mmol) was dissolved in a solution of sodium carbonate (10%, 8.5 mL) before addition of Fmoc-OSu (2g, 7 mmol) in dioxane (14 mL). After 3 h reaction time, water (20 mL) was added and the aqueous phase extracted with ether (50 mL, 2×). The aqueous layer was acidified to pH 3 with hydrochloric acid (2N) to give a heavy precipitate, which was extracted with ethyl acetate (50 mL, 4×). The organic layers were unified and dried over sodium sulfate. Purification of the product was carried out by flash chromatography (eluent: ethyl acetate/ MeOH = 10:1) to obtain 1.15 g (45%) of Fmoc-NMeIle-OH (**1**). TLC analysis: R_f = 0.4 (ethyl acetate / MeOH = 10:1). MS-ESI (m/z): 368.2 $[M+H]^+$. HPLC r_t = 21.20 min, 50-100% B, C_{18}, 99.4% purity.

Fmoc-NMeIle-Thr-OBzl (**2**)

$C_{33}H_{38}N_2O_6$ = 558.7 To Fmoc-NMeIle-OH (**1**, 735 mg, 2 mmol) was added pentafluorophenol (405 mg, 1.1 equiv) and dicyclohexylcarbodiimide (454 mg, 1.1 equiv) in DCM (20 mL) and THF (20 mL) before stirring for 16 h. The white suspension was filtrated over Celite and the solvent removed under *vacuo*. To this white solid, H-Thr-OBzl hemioxalate (837 mg, 2 equiv) and NMM (463 *m*L, 2.1 equiv) in DMF (10 mL) was added and stirred for 16 h. The solvent was evaporated and ethyl acetate (50 mL) was added. The organic layer was washed with aqueous citric acid (50 mL 5%, 3×) and water (50 mL, 3×) and dried over magnesium sulfate. Purification of the dipeptide was effected by flash chromatography using $CHCl_3$/MeOH/HOAc = 100/10/1 mL as eluent. 436 mg (40%) of pure Fmoc-NMeIle-Thr-OBzl (**2**) was obtained. MS-ESI (m/z): 559.7 $[M+H]^+$, HPLC: r_t = 16.76 min, 50-100% B, C_{18}, single peak.

Fmoc-NMeIle-Thr($\Psi^{pmp,H}$pro)-OBzl (**3**)

$C_{41}H_{44}N_2O_7$ = 676.8 50 mg (0.09 mmol) of the above synthesized dipeptide **2** was dissolved in THF (2 mL). PPTS (6.8 mg, 0.3 equiv) and anisaldehyde dimethylacetal (96 *m*L, 5 equiv) was added and heated under reflux for 7 h. Samples were taken after 1h, 3h and 7h in order to follow the reaction. HPLC: isomer 2-C(*S*) **3a**: r_t = 22.48 min, isomer 2-C(*R*) **3b**: r_t = 23.47 min, 50-100% B, C_{18}. Complete conversion to 2-C(*R*) **3b** was stated after 7 h. The solvent was evaporated and replaced by ethyl acetate (20 mL) and washed subsequently with aqueous sodium carbonate (0.5 M, 20 mL, 3×) and water (20 mL, 3×). The organic layer was dried over magnesium sulfate, filtered and the solvent removed under *vacuo*. To the slightly yellow oily residual was added methanol (100 *m*L), before addition of ether (5 mL) to give oxazolidine **3b** as a white precipitate, which was collected on a glass filter and recrystallized from methanol (100 mL) / ether (5 mL). HPLC: 23.52 min (95% purity). 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 mixture 40% A and 60% to obtain 20 mg of each epimer (**3a** and **3b**) separately.

Fmoc-NMeIle-Thr($\Psi^{H,pmp}$pro)-OH (4)

$C_{35}H_{38}N_2O_7$ = 586.7 Deblocking of the benzyl protecting 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 **4b** 15.9 min (95% purity), 2-C(*S*) epimer **4a** 15.1 min (single peak), 50-100% B, C_{18}. MS-ESI (m/z) 587.3 $[M+H]^+$.

^{1}H NMR (400 MHz, 10 mg/mL, $CDCl_3$, 300 K): **2-C(*R*)-stereoisomer** (*ω-trans* in $CDCl_3$): 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 (40%:60% *ω-cis/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*, DMSO-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-OMe (6)

$C_{22}H_{25}NO_4$ = 367.4 To Fmoc-NMeIle-OH (670 mg, 1.83 mg) in DCM (10 mL) was added DCC (415 mg, 1.1 equiv) and pentafluorophenol (371 mg, 1.1 equiv) and stirred for 16 h, before filtrating over Celite and evaporating the solvent. To the remaining white solid was dissolved in DMF (10 mL) before the addition of H-Thr-OMe (925 mg, 3 equiv) and NMM (1 mL, 5 equiv) and stirred for 4 h. The white suspension was washed with citric acid (10 mL, 2×) and water (10 mL, 2×), dried over magnesium sulfate and all solvent evaporated.

Fmoc-NMeIle-Thr($\Psi^{H,pmp}$pro)-OMe (7)

$C_{36}H_{40}N_2O_7$ = 600.8   Fmoc-NMeIle-Thr-OMe **6** (50 mg), PPTS (7.8 mg, 0.3 equiv) and anisaldehydedimethylacetal (110 μL, 5 equiv) in THF (2.5 mL) were heated under reflux for 16 h. In the course of the reaction, samples were taken and analysed by HPLC (Gradient 50—100 % B, 20 min, C_{18}). After 7 h/80°C, the reaction was finished. 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 was observed. To the yellowish liquid was added ethyl acetate (20 mL) and washed with sodium carbonate (10%, 20 mL) and water (20 mL) before drying over magnesium sulfate. Deprotection of the methylester was achieved using LiOH (3.5 equiv in THF/H_20 = 4:1, 5 mL, 2 h). The epimers now were separated on the same gradient. The relation between the 2-C (*R*) and (*S*)-isomer only changed slightly to 8:92. (*S*)-epimer: r_t = 15.13 min, (*R*)-epimer r_t = 15.84 min (50—100 % B, 20 min, C_{18}). The product was purified by flash chromatography over silica using chloroform/methanol (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 *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. Yield: 56 mg, 96%. MS-ESI (m/z) 587.6 $[M+H]^+$. Further 2D and 1D ^{1}H NMR spectra and HPLC analyses available upon request to the corresponding author.

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