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## COMMUNICATION

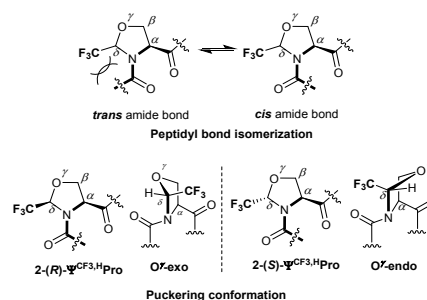
CF<sub>2</sub>H as hydrogen bond donor group for the fine tuning of peptide bond geometry with difluoromethylated pseudoprolinesN. Malquin,<sup>a</sup> K. Rahgoshay,<sup>a</sup> N. Lensen,<sup>\*a</sup> G. Chaume,<sup>\*a</sup> E. Miclet<sup>b</sup> and T. Brigaud<sup>\*a</sup>Received 00th January 20xx,  
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**CF<sub>2</sub>H-pseudoprolines obtained from difluoroacetaldehyde hemiacetal and serine are stable proline surrogates. The consequence of the incorporation of the CF<sub>2</sub>H group is an important decrease of the *trans* to *cis* amide bond isomerisation energy and a remarkable stabilisation of the *cis* conformer by an hydrogen bond.**

Because of the unique properties of fluorine atom, fluorinated compounds are increasingly recognized as highly promising for the discovery of new bioactive compounds.<sup>1</sup> Considering the specific case of peptides, the incorporation of fluorinated amino acids in peptides has been shown to impart remarkable properties.<sup>2</sup> It can modulate the peptide conformation and assembly,<sup>3</sup> the local hydrophobicity,<sup>2,4</sup> and the resistance towards proteolysis.<sup>5</sup> Moreover fluorine atoms are very useful as highly sensitive labels for <sup>19</sup>F-NMR spectroscopy because of <sup>19</sup>F 100% natural abundance and the absence of background signals in natural and biological media.<sup>6</sup> Although several methods have been reported for the synthesis of trifluoromethylated amino acids, the preparation of difluoromethylated one's is much less common.<sup>2,7</sup> It is a lack because the CF<sub>2</sub>H group presents unique features and we believe that this group will play an increasing role in peptides chemistry. The main property of the CF<sub>2</sub>H group is to act as a lipophilic hydrogen bond donor group bioisostere of a hydroxyl or a thiol.<sup>8</sup> These original bioisosteric properties have recently been highlighted in medicinal chemistry.<sup>9</sup> Because of its cyclic structure, the proline residue is recognized to play a unique and crucial role on peptide backbone conformation. When included into a peptide, the pyrrolidine ring cannot act as an hydrogen bond donor and restrain the  $\phi$  dihedral angle to about  $-60^\circ$ .<sup>10</sup> The Xaa-Pro peptide bond is characterized by a small free energy difference ( $\Delta G^\ddagger_{tc}$ ) between the *trans* and the

*cis* amide bond conformers, combined with a high activation energy ( $\Delta G^\ddagger_{tc}$ ) for the *cis-trans* isomerization.<sup>11</sup> This isomerisation is considered to play a key role in regulating many important biological processes in proline containing peptides and proteins, including protein folding.<sup>12</sup> However, studies of protein folding or control of the peptide or protein function are often hampered by the heterogeneity of the X-Pro peptide bond geometry and the scientific community has constantly been on the lookout for either a *cis* or a *trans* stabilizing proline analogue or surrogate.<sup>13</sup> In the fluorinated series, CF<sub>3</sub>-substituted prolines have recently emerged as very attracting tools for the control of peptides conformation and hydrophobicity.<sup>14</sup> On the other hand, very few examples of difluoromethylated prolines have been reported in the literature,<sup>15</sup> and to our knowledge the synthesis of enantiopure 5-CF<sub>2</sub>H-prolines has not been reported so far. Pseudoprolines ( $\Psi$ Pro) obtained from the condensation of serine and aldehydes appear as very useful surrogates of  $\delta$ -substituted prolines to control the conformation of peptides.<sup>16</sup> Since several years we investigate the scope of trifluoromethylated pseudoprolines (CF<sub>3</sub>- $\Psi$ Pro) in peptide chemistry.<sup>17</sup> We reported that the ratio of *cis* conformation of the Xaa-CF<sub>3</sub>- $\Psi$ Pro peptide bond is increased compared to proline itself. The 2-(*S*)-CF<sub>3</sub>- $\Psi$ Pro presents a  $\gamma$ -*endo* puckering of the oxazolidine ring while the 2-(*R*)-CF<sub>3</sub>- $\Psi$ Pro adopts a  $\gamma$ -*exo* puckering (Fig. 1).<sup>17</sup> Moreover, a remarkable feature of the 2-(*R*)-CF<sub>3</sub>- $\Psi$ Pro is the decrease of the *trans* to *cis* isomerization barrier of the amide bond ( $-4.17$  kcal.mol<sup>-1</sup> compared to proline).<sup>1</sup>

Fig. 1 Peptidyl bond isomerization and puckering of CF<sub>3</sub>- $\Psi$ Pro

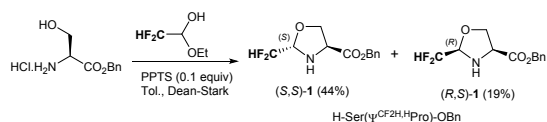
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## COMMUNICATION

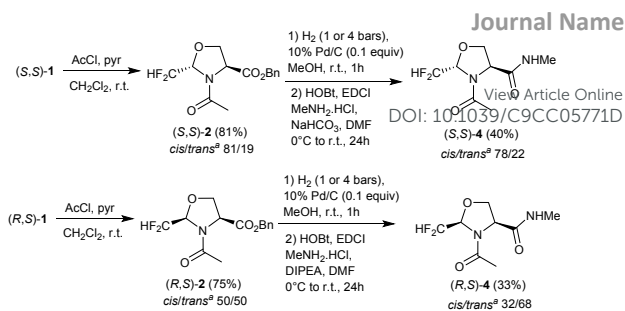


**Scheme 1** Synthesis of H-Ser( $\Psi^{CF_2H,H}$ Pro)-OBn (*S,S*)-1 and (*R,S*)-1

Considering the growing importance of the difluoromethyl group, we wish to present herein our results dedicated to difluoromethylated pseudoprolines ( $CF_2H$ - $\Psi$ Pro). A particular attention is paid to the possibility of interactions through hydrogen bonds.

The oxazolidine ring of the  $CF_2H$ -pseudoproline was built by condensation of difluoroacetaldehyde ethyl hemiacetal with serine benzyl ester under an acidic catalysis (Scheme 1). Both diastereomers (*S,S*)-1 and (*R,S*)-1 were conveniently separated by silica gel chromatography. According to our previous investigations in the trifluoromethylated series,<sup>17a</sup> the *cis* relative configuration of (*R,S*)-1 has been assigned by nuclear Overhauser effect experiments showing a correlation between the  $C_\alpha$  and the  $C_\delta$  protons. In order to investigate the electronic and geometric consequences due to the  $CF_2H$  group incorporation of  $CF_2H$ - $\Psi$ Pro in a peptide chain, the Ac- $\Psi$ Pro-NHMe model tripeptides (*S,S*)-4 and (*R,S*)-4 have been synthesized in a multi-step procedure (Scheme 2). The *N*-acetylation of (*S,S*)-1 with acetic anhydride under iodine catalysis provided a mixture of Ac- $\Psi$ Pro-OBn (*S,S*)-2 (21%) and (*R,S*)-2 (39%). In order to circumvent the epimerization of the  $C_\delta$  atom through an acidic catalysis,<sup>17a,b</sup> the reaction was performed with acetyl chloride in pyridine. These experimental conditions led to the expected *N*-acetylated oxazolidines (*S,S*)-2 and (*R,S*)-2 in 81% and 75% yield respectively without epimerisation.

The *cis/trans* ratio of the acetyl- $\Psi$ Pro bond was determined by  $^1H$  and  $^{19}F$  NMR integration in  $CDCl_3$ . For that purpose, we first assigned each conformers by comparing the  $\alpha$ ,  $\beta$ , and  $\gamma$   $^{13}C$  chemical shifts of the *cis* and the *trans* isomers according to Lubell et al.<sup>18a</sup> For the *trans* isomer, the  $\alpha$  and  $\beta$ -carbons appear upfield while they appear downfield in the *cis* isomer. Conversely, the  $\delta$  carbon for the *trans* isomer appears downfield relative to that of the *cis* isomer. Once acetylated on their *N*-terminal position, we checked the acidic stability of the  $CF_2H$ -oxazolidines (*S,S*)-2 and (*R,S*)-2. Experiments showed that, similarly to the  $CF_3$ - $\Psi$ Pro, they are stable in an acidic medium (5% TFA in  $CHCl_3$ ), whereas pseudoprolines of the non-fluorinated series are generally prone to ring opening.<sup>16a</sup> Even when exposed to more concentrated acidic medium for several hours (3h in TFA/ $H_2O$  95:5) no ring opening or epimerization occurred. The  $CF_2H$ -oxazolidines are therefore suitable for SPPS strategy.



<sup>a</sup> *cis/trans* conformers ratio of the peptidyl- $\Psi$ Pro bond measured by NMR in  $CDCl_3$ .

**Scheme 2** Synthesis of Ac- $\Psi$ Pro-NHMe (*S,S*)-4 and (*R,S*)-4

After removal of the benzyl ester function by hydrogenolysis in quantitative yields, the *N*-methyl amides (*S,S*)-4 and (*R,S*)-4 were obtained in 40% and 33% yield using classical peptide coupling conditions (Scheme 2).

The *cis-trans* bond isomerisation of the  $CF_2H$ -oxazolidine-containing peptide models (*S,S*)-4 and (*R,S*)-4 was studied by  $^1H$  NMR analysis in water at various temperatures. The coalescence temperatures were determined to estimate the rotational barriers for the *cis-trans* isomerisation. The results are reported in the Table 1 and compared with those reported for regular proline<sup>18</sup> and pseudoproline<sup>17c</sup> as well as those previously obtained in the  $CF_3$  series.<sup>17c</sup> The difference of isomerisation energy between the two diastereomers of the  $CF_3$  series (ca. 2.5 kcal.mol<sup>-1</sup>) is no longer observed in the  $CF_2H$  series, the energy barriers are low for both  $CF_2H$ -pseudoprolines. It is interesting to note that the energy barriers for amide isomerisation of both  $CF_2H$ -pseudoproline is ca 5.0 kcal.mol<sup>-1</sup> lower than for proline.<sup>18</sup>

The *cis* amide bond contents were significantly higher when the  $CF_3$  substituent was replaced by the  $CF_2H$  group. Indeed in the apolar chloroform solution, the *cis* population of (*S,S*)-4 reached even 78%. This enrichment may be due to the presence of a new H-bond involving the  $CF_2H$  group.<sup>8</sup> Conversely, it was previously demonstrated that the *trans* amide bond conformer of the 2-(*R*)- $CF_3$ - $\Psi$ Pro analogue was stabilized by a H-bond between the *C*-terminal amide NH and the carbonyl of the *N*-terminal acetyl group.<sup>17c</sup> Two antagonist H-bonds may thus compete in the compound (*R,S*)-4 (Fig. 2). This balance was slightly in favour of the  $CF_2H$  H-bond in water (53% *cis* population) and underlines the hydrophobicity of the fluorinated group which partially preserves the stability of the H-bond in polar solvents such as methanol and water (see supplementary information).

Finally, the puckerings of the  $CF_2H$ -five-membered rings were determined by NMR from the coupling constants between the  $\alpha$  and the  $\beta$  protons as previously reported in the  $CF_3$  series (see supplementary information).<sup>17c</sup>

The results showed that the Ac-(2*S*,4*S*)- $CF_2H$ - $\Psi$ Pro-NHMe (*S,S*)-4 adopted a  $\gamma$ -*endo* pucker conformation for the two

**Table 1** Thermodynamic properties of (*S,S*)-4 and (*R,S*)-4 determined by NMR. <sup>(a)</sup> Populations (%) observed in  $CDCl_3$ . <sup>(b)</sup> Populations (%) and <sup>(c)</sup> energies observed in  $H_2O:D_2O$  90:10. All energies are given in kcal.mol<sup>-1</sup>

	Pro	$\Psi$ Pro (ref 17c)	2-( <i>S</i> )- $CF_3$ - $\Psi$ Pro (ref 17c)	2-( <i>S</i> )- $CF_2H$ - $\Psi$ pro ( <i>S,S</i> )-4	2-( <i>R</i> )- $CF_2H$ - $\Psi$ pro ( <i>R,S</i> )-4	2-( <i>R</i> )- $CF_3$ - $\Psi$ Pro (ref 17c)
<i>cis/trans</i> <sup>(a)</sup>	13:87 (ref 18b)	27:73	40:60	78:22	32:68	24:76
<i>cis/trans</i> <sup>(b)</sup>	24:76 (ref 18b)	34:66	43:57	60:40	53:47	45:55
$\Delta G_{t-c}^\ddagger$ <sup>(c)</sup>	20.40 (ref 18a)	18.41	18.06	15.19	15.82	15.63
$\Delta G_{c-t}^\ddagger$ <sup>(c)</sup>	19.83 (ref 18a)	17.93	17.88	15.45	15.90	15.51

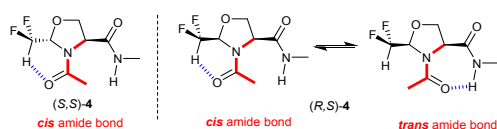
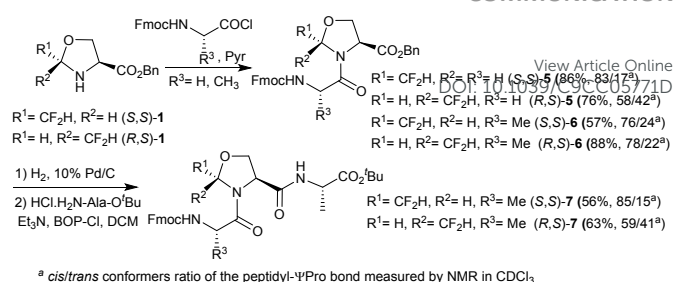


Fig. 2 Possible intramolecular H-bonds for Ac- $\Psi$ Pro-NHMe (*S,S*)-**4** and (*R,S*)-**4**

geometries of the peptide bond. The same observation was made for the 2-(*S*)-CF<sub>3</sub>- $\Psi$ Pro analogue.<sup>17c</sup> Conversely the compound (*R,S*)-**4** underwent a puckering switch when the amide bond geometry was reversed.

Instead of maintaining an *exo*-puckered oxazolidine ring for both the *cis* and the *trans* amide conformers, as observed with 2-(*R*)-CF<sub>3</sub>- $\Psi$ Pro,<sup>17c</sup> the *cis* rotamer of (*R,S*)-**4** showed a slight preference for the *endo* puckering to allow the CF<sub>2</sub>H H-bond. These structural features can be understood by analyzing the unusual NMR parameters of the CF<sub>2</sub>H groups. First, a high chemical shift difference ( $\Delta\delta$ ) of the diastereotopic <sup>19</sup>F informed about a restricted dynamic of the difluoromethyl group. For the *cis* conformers,  $\Delta\delta$  was above 5 ppm, whereas  $\Delta\delta \approx 3$  ppm for their corresponding *trans* conformations (see Fig. 3 and supplementary information). Second, the measured vicinal couplings reflected a very limited rotameric averaging of the CF<sub>2</sub>H group for the *cis* conformers. In particular the Ac-(2*S*,4*S*)-CF<sub>2</sub>H- $\Psi$ Pro-NHMe (*S,S*)-**4** displayed the following values: <sup>3</sup>J<sub>H $\delta$ -F<sub>1</sub> = 3.2 Hz; <sup>3</sup>J<sub>H $\delta$ -F<sub>2</sub> = 18.2 Hz; <sup>3</sup>J<sub>H $\delta$ -H $\delta$  = 1.0 Hz. These three couplings are compatible with a single H<sup>c</sup>-C<sup>c</sup>-C <sup>$\delta$</sup> -H <sup>$\delta$</sup>  dihedral angle of  $\sim 50^\circ$  (see supplementary information). Such a restricted rotation of the CF<sub>2</sub>H group likely arose from the H-bonding observed in the *cis* forms since the oxygen of the preceding acetyl group is facing the positively charged CF<sub>2</sub>H proton in this conformation (Fig. 3). The *endo* puckering of the oxazolidine ring may be needed for the CF<sub>2</sub>H H-bonding establishment in the *cis* conformers, whereas the *exo* puckering was required for the NH...O=C H-bond in the *trans* form.<sup>17c</sup> This provides an explanation for the *trans*-*exo* to *cis*-*endo* transition observed for the compound (*R,S*)-**4**. The (*S,S*)-**4** diastereoisomer adopts preferentially the *endo* conformation which explains the high stability of the CF<sub>2</sub>H...O=C H-bond in the *cis* conformer. In the *trans* conformers, the CF<sub>2</sub>H group cannot establish any H-bond since the O=C acceptor of the acetyl is moved away and replaced by the methyl group. As a result, several rotamers of the CF<sub>2</sub>H group are present as attested by the averaged NMR parameters (Fig. 3).</sub></sub></sub>

In order to expand the scope of the incorporation of CF<sub>2</sub>H-pseudoproline in peptides, a preliminary methodological study of the peptide coupling reactions at their *N*- and *C*-position was undertaken. We already demonstrated that the presence of a CF<sub>3</sub> group at the  $\delta$  position of an oxazolidine unit is detrimental for coupling reactions because of its powerful withdrawing effect. Although the CF<sub>2</sub>H group is less deactivating, typical protocols using HOBt, EDCI, DIPEA or IBCF reagents failed to achieve the *N*-coupling reaction of (*S,S*)-**1** and (*R,S*)-**1** with Fmoc-Gly-OH. However, the peptide coupling could be achieved in good yields while using the most electrophilic Fmoc protected glycine and alanine amino acid chloride (Scheme 3). When the reaction was performed in the presence of pyridine, the epimerization of the  $\delta$  carbon of the oxazolidine ring through a dynamic kinetic resolution (DKR) process<sup>17b</sup> was avoided or limited. The expected dipeptides (*S,S*)-**5**, (*R,S*)-**5**, (*S,S*)-**6** and (*R,S*)-**6** were obtained in 86%, 76%, 57% and 88% yield respectively (Scheme 3). It should be



<sup>a</sup> *cis/trans* conformers ratio of the peptidyl- $\Psi$ Pro bond measured by NMR in CDCl<sub>3</sub>

Scheme 3 Incorporation of CF<sub>2</sub>H-pseudoproline in a peptide chain

noticed that in any cases the *cis* conformer of the amide bond was the major one. The *cis/trans* conformers ratio of the peptidyl- $\Psi$ Pro bond measured by NMR in CDCl<sub>3</sub> were ranging from 58/42 to 83/17. After having successfully solved the challenging coupling reaction at the *N*-terminal positions of the CF<sub>2</sub>H-pseudoproline, suitable experimental conditions were investigated for the *C*-terminal coupling. The removal of the benzyl ester was carried out by palladium mediated hydrogenolysis without impacting the *N*-Fmoc protecting group. The free carboxylic acid was then used in the next step without further purification. Typical protocols involving HOBt, EDCI, DIPEA at room temperature were not suitable for the coupling reaction between dipeptides **6** and HCl.H<sub>2</sub>N-Ala-O<sup>t</sup>Bu. However, the coupling of the CF<sub>2</sub>H-dipeptides using BOP-Cl in the presence of TEA afforded the expected tripeptides (*S,S*)-**7** and (*R,S*)-**7** in 56% and 63% yield respectively. <sup>19</sup>F and <sup>1</sup>H NMR measurements in CDCl<sub>3</sub> revealed a 85/15 *cis/trans* ratio for (*S,S*)-**7** and 59/41 for (*R,S*)-**7**.

In conclusion, original enantiopure (*S,S*) and (*R,S*) CF<sub>2</sub>H-pseudoproline have been synthesized as stable 5-substituted proline surrogates which can be incorporated in a peptide chain. The CF<sub>2</sub>H group provides a strong decrease of the *trans* to *cis* amide bond isomerisation energy and enhances the *cis* conformation content compared to the CF<sub>3</sub> series, by acting as an efficient hydrogen bond donor. These CF<sub>2</sub>H-proline surrogates will provide outstanding tools for the fine tuning of the dynamic and the secondary structure of peptides, in particular type VI  $\beta$ -turns.<sup>13d</sup> Such conformations are known to play important roles in protein structures and molecular recognition. New non-natural amino acids able to stabilize the *cis*-isomer backbone geometry and/or type VI  $\beta$ -turns are still in demand for the design of potent and selective prototypes for drug discovery.<sup>19</sup>

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## Conflicts of interest

There are no conflicts to declare.

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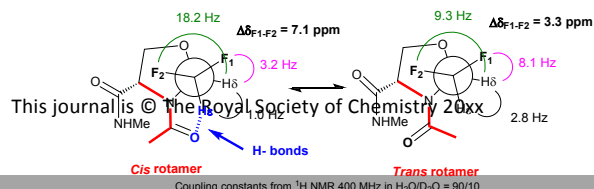


Fig. 3 NMR parameters and conformational features of (*S,S*)-**4**

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