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# Stereoselective synthesis of original spiro lactams displaying promising folded structures

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## Abstract

25 Access to diastereoisomeric forms of original spiro lactam frameworks and investigation of their folded  
potentials are depicted here. Taking advantage of a stereoselective ring-contraction reaction, the  
Transannular Rearrangement of Activated Lactams (TRAL), followed by two unprecedented tandem  
reactions, we described here an efficient access to elegant spirocyclic scaffolds. After dimerization,  
NMR analyses, Circular Dichroism, SEM and Molecular Modelling highlighted an attractive edifice  
30 able to fold and behave as a PPII helix, a common yet neglected peptidic secondary structure.

## Introduction

Spirocyclic moieties are encountered in many natural products<sup>1-6</sup> which made this particular bicycle a  
35 key platform for medicinal chemists.<sup>7-10</sup> Due to their highly constrained structures,<sup>11-13</sup>  
spirocompounds were also described for their interesting properties as folded materials<sup>14-16</sup> and for  
their efficiency as catalysts<sup>17</sup> or molecular actuators.<sup>18</sup> However, very few articles have reported their  
use as peptidomimetics or tools to explore protein-protein interactions<sup>19-23</sup> which are largely mediated  
by the recognition of proline-rich modules generally described to be structured in polyproline II helices  
40 (PPII). They represent attractive targets for the medicinal chemist,<sup>24-28</sup> being the architectural hallmark  
of linear sequences recognizing protein-protein interaction modules such as SH3, WW and EVH1  
domains.<sup>24-26,29</sup> Formerly neglected, the significance of this unique extended structure and its

implication in crucial pathologies<sup>29,30</sup> have recently stimulated few chemists to synthesize PPII mimics.<sup>31</sup> They essentially concern the synthesis of polyimide-based foldamers,<sup>32–34</sup> PTAAAs,<sup>35–37</sup> triproline mimics,<sup>38,39</sup> Ser-Pro dipeptide<sup>40</sup> or Pro-Pro dipeptide mimics.<sup>41</sup> However, compared to the ever-growing field of  $\alpha$ -helices or  $\beta$ -turn mimics, only few approaches have been described to emulate the PPII structure. Then, the discovery of pertinent PPII scaffolds to target protein-protein molecular interactions is still completely relevant to understand their biological significance.

In this context, we wished here to present the access to dimeric spiro lactam structures, one of which was capable of behaving as polyproline II helix. We reported our first steps in the development of a new class of artificial bio-inspired PPII compounds, part of a challenging research on pertinent tools for the understanding of protein-protein interaction.

In order to build spiro lactam platforms, the Transannular Rearrangement of Activated Lactams (TRAL) has proven to be a central and optimal tool. More particularly, we described in this article a careful study on the stereochemical potential of this rearrangement for the design of unprecedented heterocyclic frameworks. Starting from *N,N'*-bis-Boc-activated diketopiperazines (DKP), the six- to five-membered ring-contraction yielded aminotetramate scaffolds with high stereoselectivity.<sup>42</sup> The broad interest of the reaction was previously demonstrated by the preparation of diverse scaffolds such as statins or pentacins analogues.<sup>43–45</sup> While a protonation in aqueous medium yielded TRAL product, addition in the reaction mixture of an alkylating agent allowed the formation and isolation of the TRAL-alkylation product (Scheme 1).

In the present work, we deliberately chose the commercially available Shöllkopf's DKP, given the exceptional stereoselectivity of the TRAL, as a model to further access spiro lactam moieties. We herein reported a preliminary pathway to such constrained structures in a first part, using the TRAL-alkylation tandem reaction, the quickest way to prepare substituted pyrrolidine-2,4-diones. In the second part of our study, we then disclosed an alternative access to spiro lactam constructs, highlighting an attractive edifice able to fold and behave as a PPII helix.

## 30 Results and Discussion

### First route to spiro lactam scaffolds

The TRAL-alkylation found hence its interest in the construction of substituted pyrrolidine-2,4-diones with a high to total diastereoselectivity, depending on the steric hindrance of the starting DKP's side-chain. After a preliminary protection/activation step of the lactams using  $\text{Boc}_2\text{O}$  and DMAP, the resulting activated *N,N'*-bis-Boc-*cyclo*-[Gly-(D)-Val] model was submitted to the TRAL-alkylation conditions using ethyl 2-(bromomethyl)acrylate as the alkylating agent (Scheme 2). The reaction proceeded with a total diastereoselectivity furnishing the *R,R*-diastereoisomer 2 with a yield of 38%. As we recently reported,<sup>44</sup> it is always difficult to propose a predictable and rational chemical reactivity for the TRAL-alkylation, the major by-product here resulting from a direct alkylation of the starting DKP.

After a facile deprotection of the Boc-moieties allowing isolation of the trifluoroacetate salt of the primary amine, we chose to increase functional diversity on our scaffold. Taking advantage of the acrylate moiety, a benzylamino group was located in the following step *via* a suitable Michael addition. At this stage we observed the 1,4-addition of benzylamine, concomitant with the

spirocyclisation, without any detectable trace of 1,2-addition. Excess of benzylamine under microwave irradiation triggered a one-pot spirocyclisation concomitant with an aza-Michael addition. This tandem reaction led to 95% of conversion of the starting material into the functionalized original spiro lactam 3. Concurrently, the presence of a keto group caused the formation of a Schiff base which needed to be further hydrolysed with aqueous 1 N HCl. This unprecedented reaction which is in fact a combination of three different synthetic steps – a 1,4-addition of benzylamine on the ethyl acrylate moiety, and an intramolecular cyclization concomitant with a Schiff base formation – opened thus access to innovative spiro lactam scaffolds with excellent yield.

10 Only one epimer was isolated (3a, for details, please refer to Electronic Supporting Information), which then underwent a stereocontrolled reduction using sodium borohydride to provide a crystalline spiro lactam 4.

NOESY experiments performed on compound 4, revealing strong correlations between hydrogen 7, 16 and 17, allowed us to confirm the 9*R*,11*R*,16*S*,17*S* configuration for this compound. Access to the crystal structure permitted us to validate those NMR data, certifying the relative stereochemistry of the stereogenic centre created during the aza-Michael addition and the configuration of the asymmetric quaternary carbon 11, previously generated during the TRAL-alkylation. The stereoselectivity of the reduction step could be supported by the literature which described the reduction of substrates bearing a hydrogen bond donor (HBD) on an asymmetric carbon in the  $\alpha$ -position of the carbonyl to reduce.<sup>46</sup> The hydride source, supposedly positioned in the same plane than the HBD, could explain the produced selectivity during the reduction step, thanks to a dihydrogen bond formation.<sup>47</sup> A second plausible explanation to the observed total stereoselectivity could also be the steric hindrance at the *Si* face generated by both alkyl groups in  $\alpha$  and  $\alpha'$  position of the ketone. Consequently, the attack of the hydride would occur by the less hindered *Re* face, yielding only the 17*S* diastereoisomer.

Benefiting from these results, we decided to turn our attention to the simple version of the TRAL, which presents the advantage of a quantitative yield. Thus switching from the TRAL-alkylation to the TRAL reaction followed by an appropriate alkylation step, we envisioned to apply the precedent synthetic pathway.

### Second route to spiro lactam scaffolds

The activated *N,N'*-bis-Boc-*cyclo*-[Gly-(D)-Val] model was here submitted to the TRAL conditions, allowing the synthesis of the aminotetramate 5. When *O*-alkylation conditions, using ethyl 2-(bromomethyl)acrylate, were applied to the TRAL product, a concomitant and opportune Claisen rearrangement took place, giving us access to compound 6 in a single step (Scheme 3).

Based on a previous study on *O*-alkylation of aminotetramates,<sup>43</sup> we postulated that the reaction did not proceed through a direct *C*-alkylation. We could notice here that the subsequent Claisen rearrangement was completed at room temperature without any addition of catalyst, which is unusual for such a sigmatropic rearrangement.<sup>48</sup> The main advantage of this step lies in its total diastereoselectivity, which could be explained by a representation of the Zimmerman-Traxler chain-like transition state (Scheme 3).<sup>48</sup> The isopropyl side chain creates a strong steric hindrance, preventing the formation of the *R,R* isomer. Compound 6 was prepared here with a greatly improved yield of 70% compared to its diastereoisomeric construct synthesized by the first route.

Following our preliminary study, Boc protecting groups were removed in pure TFA before neutralizing the TFA salt,<sup>49</sup> to generate compound 7 (Scheme 4). The tandem reaction described for

the first route, involving a spirocyclisation concomitant with an aza-Michael addition and an imine formation, was then applied to this pyrrolidine-2,4-dione yielding, after a suitable acidic work-up, 95% of a functionalized spiro lactam 8. Purification of the mixture of the two diastereoisomers allowed us to isolate 8a and 8b with 40% and 45% respective yields.

5

Compound 8a was then submitted to a stereoselective reduction step to yield 10a, unfortunately uncrystallisable. Unexpectedly, cautious 2D-NMR experiments performed on compound 10a and meticulous comparison with data obtained earlier during the synthesis of product 4, led us to highlight a remarkable epimerisation of the asymmetric carbon bearing the isopropyl group.

10

We were intrigued to observe in this second route, and not in the first one using the TRAL-alkylation (Scheme 2), a quasi-total inversion of configuration of one stereogenic center (>90% *de*), instead of a more expected partial loss of stereochemistry due to the imine-enamine intermediate equilibrium.

15 Regarding opposite and equal specific rotations, but also identical 1D NMR spectra, of 10a and 4, it appeared obvious that we were in the presence of two enantiomers. Careful NOESY experiments confirmed those data by highlighting a strong correlation between H17 and H16 and between H17 and NH7 while no sign of correlations between H16 with H10 and H10' were detected. We founded of interest to develop arguments to explain this serendipitous epimerisation, which seemed to be related  
20 to the formation of the undesired imine during the tandem reaction.

To understand precisely at which step this epimerisation exactly occurred, we performed similar NOESY experiments on the spiro lactam 9, prepared by simply heating primary amine 7 in absolute ethanol, using microwave irradiation, without any addition of benzylamine. NMR analyses of  
25 compound 9 revealed this time no correlation between H11 and NH5, confirming the retention of the configuration of C11 during the heating step. The same epimerisation could be further observed, with an identical diastereomeric excess, only when the spiro lactam 9 was converted into compound 8 in presence of benzylamine under microwave heating. As a first conclusion, the epimerisation seemed to be clearly induced by the presence of benzylamine and could find its explanation in the Schiff base  
30 formation.

A proposed mechanism which could explain the high stereoselectivity of this epimerisation process is depicted in Scheme 5. We suggested here that in the imine/enamine equilibrium, the C11 could switch from  $sp^3$  to  $sp^2$  allowing us to easily consider a potential epimerisation of the product. To explain the  
35 observed quasi total inversion, promoting the formation of one epimer in favour of another, we proposed a pericyclic reaction involving the lactam group borne by cycle A and the enamine group of the cycle B. In the representation proposed in the Scheme 5, due to the bottom face localization of the lactam, the  $sp^2$  carbon C11 seems to have no choice but to catch the NH proton *via* the same *Re* face to become  $sp^3$  again, resulting in the inversion of configuration of C11. This postulated mechanism is  
40 also coherent with the absence of epimerisation observed initially for spiro lactam 4. Following a similar representation, the lactam would be located, this time, at the top face of cycle A, the pericyclic reaction resulting in the retention of the configuration of C11.

### En route to the construction of folded edifices

45

Having efficient access to spiro lactam building blocks, helpful for the construction of folded edifices, we then intended (*i*) to firstly take advantage of the hydroxyl group generated previously for crystallization, thinking that this additional point of functionalization could be useful to decrease the keto reactivity but also to further build larger structures, (*ii*) to secondly remove the benzyl protecting

group to release a free amino group in order to link the two spiro lactams units, (iii) to finally proceed to the dimerisation itself.

Reduction of the spirocycles 8a or 8b using sodium borohydride furnished monomers 10a and 10b with an excellent yield and a total diastereoselectivity, while an hydrogenolysis of 8a or 8b, using Pd/C 10% under a hydrogen atmosphere in an acidic medium, easily led to the desired primary amines 11a and 11b. The linking of the two monomers 10 and 11 was then performed on each diastereoisomer by creating an urea bond in presence of triphosgene and DIPEA.<sup>50</sup> Dimers 12a and 12b were finally isolated with a good yield after purification by preparative HPLC (Scheme 6).

To summarize this chemical part of our report, TRAL reaction products were used as spiro lactam precursors and helped us to highlight an unprecedented total inversion of configuration based on a pericyclic reaction. An elegant 6-step pathway was developed, leading us to access to innovative constrained dimeric spirocyclic constructs with a good overall yield of 47-49%.

To gain information on local secondary structures of our dimers, we then decided to use circular dichroism (CD) analytical technic. Obviously, this is the most popular technique to determine spatial arrangement of chiral molecules, especially conformations of proteins, peptides and more particularly polyproline II secondary structures.<sup>24,51</sup>

CD results of the synthesized spiro lactam constructs will be then presented afterward to explore their conformational state of the synthesized spiro lactam constructs, although our structures were not related to peptides and being aware of the fact that CD spectra interpretation can be misleading when dealing with non-peptidic structures.

### **Folded potential of compound 12a**

CD spectra of monomers and dimers were recorded, analyzed and compared with the CD spectrum of the hexapeptide H-(Pro)<sub>6</sub>-NH<sub>2</sub> synthesized in our laboratory. The CD spectrum of H-(Pro)<sub>6</sub>-NH<sub>2</sub> in phosphate buffer, as PPII helices, showed a positive  $\pi$ - $\pi^*$  band around 204 nm and a negative  $n$ - $\pi^*$  band around 226 nm. The spectral features were extremely characteristic, easy to differentiate from other secondary structures, and typically intensified in the presence of a chaotropic agent such as guanidine hydrochloride, which favored the PPII structure (for details refer to Electronic Supporting Information).<sup>51,30,52,53</sup>

As expected, CD spectra of all monomers presented data which were not in favour of a PPII folded potential but which could be more qualified as unordered forms (for details refer to Electronic Supporting Information). However, the behaviour of our artificial dimer 12a in CD analyses was exceptionally and remarkably similar to the one observed with the well-known PPII hexaproline.<sup>51,53,52,30,54,55</sup>

In phosphate buffer, a negative band followed by a positive one of greater magnitude were observed, with an exact bathochromic effect compared to PPII spectra, which could be correlated with the presence of a benzyl moiety or a *cis*-configuration of amide bonds in lactams.

To reinforce this first assumption of a similar behaviour in CD between our molecule and a natural PPII, extensive CD studies involving the effect of increasing temperature, and more especially the concentration effect in presence of chaotropic agent, were performed underlining a bio-inspired PPII

conformation of dimer 12a. Regarding the literature,<sup>29,51,30,52,53</sup> among the helical structures, PPII helix is known for decades to be more resistant to an increase of temperature than any other helix.

Additional temperature-based variation analyses by CD revealed a PPII characteristic temperature effect on the CD spectrum of 12a (Figure 1). The conformational change between two forms occurring at 50°C, indicated by the presence of an isodichroic point, is reversible since we recorded, at 5°C, after this experiment, the same spectrum as before the heating. This point clearly indicated that the dimeric construct could assume a preferred folded state. Comparable results were obtained when performing CD studies in less polar solvent such as TFE.

10 The most striking observation was nevertheless the typical intensification of 12a molar ellipticity, similar to the one of the hexaproline, in the presence of increasing concentrations of a chaotropic agent, a typical behavior only displayed by PPII helix among natural secondary structures.<sup>51,30,52,53</sup> The comparable comportment of our dimer and a natural PPII in the presence of chaotropic agent,<sup>52</sup> displayed through a signal reinforcement, which is exceptional with chemical compounds unrelated to 15 peptides, are strong arguments in favour of a bio-inspired PPII conformation of 12a. Even though this dimer copied some of the properties of the PPII helix, we could not affirm that 12a literally mimics a PPII helix.

To confirm that CD spectra do not result from the sum of the CD spectra of each building block, the 20 same experiments were performed with an equimolar mixture of 10a and 11a corroborating the importance of the carbamide linker in the PPII-like behaviour of the dimer 12a (for details refer to Electronic Supporting Information).

Polyproline II conformation being critical for majority of protein-protein interaction modules, 25 molecular modelling analysis was also initiated to illustrate how such a chemical entity could recognize a SH3 domain. Consequently, compound 12a was docked on the 3D structure of a relevant SH3 domain without applying any restraints to the system and using a flexible algorithm to illustrate how such conformers could interact and recognize SH3 domains.

30 Then, a 3D model of a PPII-bound conformation was achieved by a flexible docking of the spiro-compound 12a onto the SH3 domain of the Fyn kinase, a very well described PPII interacting partner (PDB code 1EFN).<sup>56</sup> The top solutions from the docking simulation were filtered using NMR restraints observed in aqueous solution (for details refer to Electronic Supporting Information) and the most representative conformation was compared to a pentaproline (Figure 2). The resulting conformation of 35 this polyproline demonstrated the potentiality of our heterocyclic framework to mimic the three-dimensionality of PPII helices with a conserved shape, end-to-end distances and 3D-pharmacophoric properties (Figure 2).

According to our first results, we have highlighted here efficient access to chemical constructions able 40 to fold into artificial structures hypothetically acting as natural polyproline oligomers.

Although the correlation between the spirocyclic structures with proline moieties seems unusual, molecular modelling studies suggested that the two nitrogens of each spiro groups could be correlated to two consecutive nitrogens of a Pro-Pro sequence (Figure 2). The resulting construct could possibly 45 be seen as a series of two over-constrained proline bio-inspired structures linked by a flexible arm, increasing the extended PPII-structural ability of the edifice.

Inspired by biological systems, chemists manage to design and synthesize artificial oligomers able to spontaneously fold into well-defined edifices.<sup>57</sup> Recently, H.-S. Lee *et al.* introduced the concept of

"foldectures" where artificial protein fragments with particular secondary structure self-assembled to provide original 3D molecular architectures.<sup>58,59</sup> To learn more about the "foldecture" potential of our edifice having a specific rigidity and folding predisposition to act as a PPII helix, we undertook Scanning Electron Microscopy (SEM) experiments under solvophobic conditions. The SEM images 5 revealed 3D shape of an important quantity of diverse rods and sticks, which are ca. 75  $\mu\text{m}$  in length for the longest with widths of ca. 8.5  $\mu\text{m}$  (Figure 3).

Only a biological evaluation of optimized compounds actually under investigation would permit to conclude if 12a indeed behaves as the natural PPII helix does and if specific moieties of the molecule 10 are more active than others, such as the carbonyl moieties for example.

For this purpose, the affinity of the dimer needs to be improved by adding specific amino acids sequences on the compounds side chain to possibly bind specific receptors and hope to be able to crystallize the compound in the presence of this biological target such as SH3 domain.

15

### Folded potential of compound 12b

Unexpectedly, analysis of CD spectra of dimer 12b, whose structure differs from 12a only by the configuration of two stereogenic centres, was incompatible with PPII helix features. The CD spectrum 20 displayed a weak negative band around 208 nm and a strong positive band at 227 nm, the signature of a folded state. One can tentatively compare the shape of the signal with the one of a class B  $\beta$ -turn, exhibiting a weak negative band around 187 nm and a strong positive band around 209 nm, a well-known secondary structure.<sup>54</sup> A bathochromic effect compared to class B  $\beta$ -turn spectra could here again be correlated with the presence of a benzyl moiety or a *cis*-configuration of amide bonds in 25 lactams. The folding propensity of 12b could be easily disturbed by a chaotropic agent or by increasing the temperature above 25°C as proven by the loss of its signature, a completely opposite behaviour compared to 12a. This particularity was hypothetically consistent with a possible  $\beta$ -turn conformation, acknowledged to be stabilized by intramolecular hydrogen bonds. It is important to note that for both dimers, the conformational changes induced by the heating were reversible, since we noticed the 30 reappearance of the exact same spectrum when cooling back to room temperature. To confirm that CD spectra do not result from the sum of the CD spectra of each building block, the same experiments were performed with an equimolar mixture of 10b and 11b corroborating the importance of the carbamide linker in the folding potential of the dimer 12b (for details refer to Electronic Supporting Information).

35

While an ever-growing interest on  $\beta$ -turn mimics make this work perhaps less relevant compared with neglected PPII mimics, additional studies are actually under investigation to confirm this hypothesis.

### Conclusion

40

We described here an efficient access to two dimers capable of adopting a well-defined organization in solution, one of these heterocyclic frameworks seeming to behave as polyproline II helix. Its folding potential, strongly dependent upon the configuration of its asymmetric carbons, was evaluated using CD experiments under various conditions, and molecular modelling based on the nOe constraints 45 obtained from advanced NMR analyses. We are confident this work could open a way to the synthesis of bio-inspired foldamers which could find their use in the comprehension of protein-protein interactions but also more generally useful for molecular recognition, catalysis or nanoscience.

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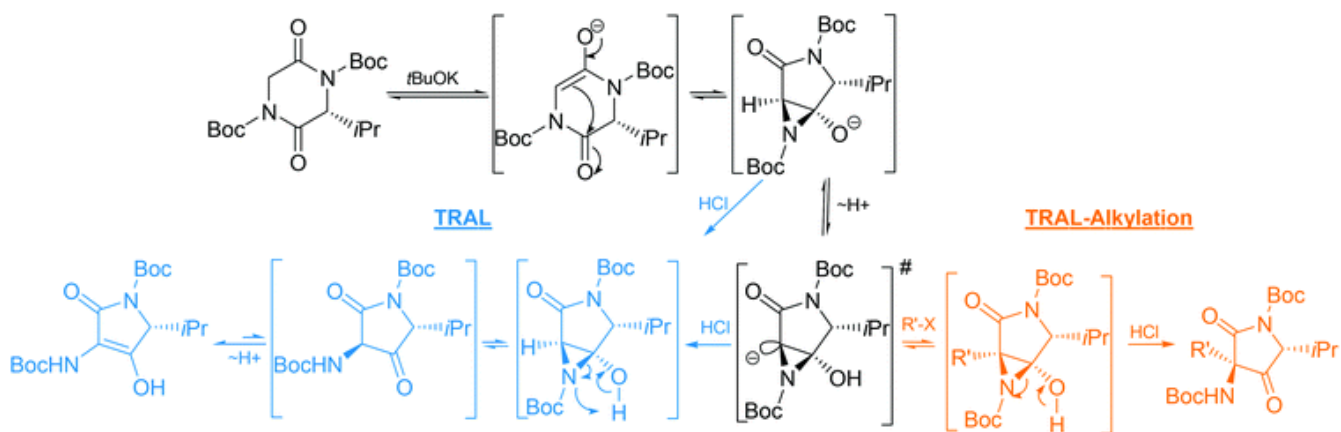
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## Notes and references

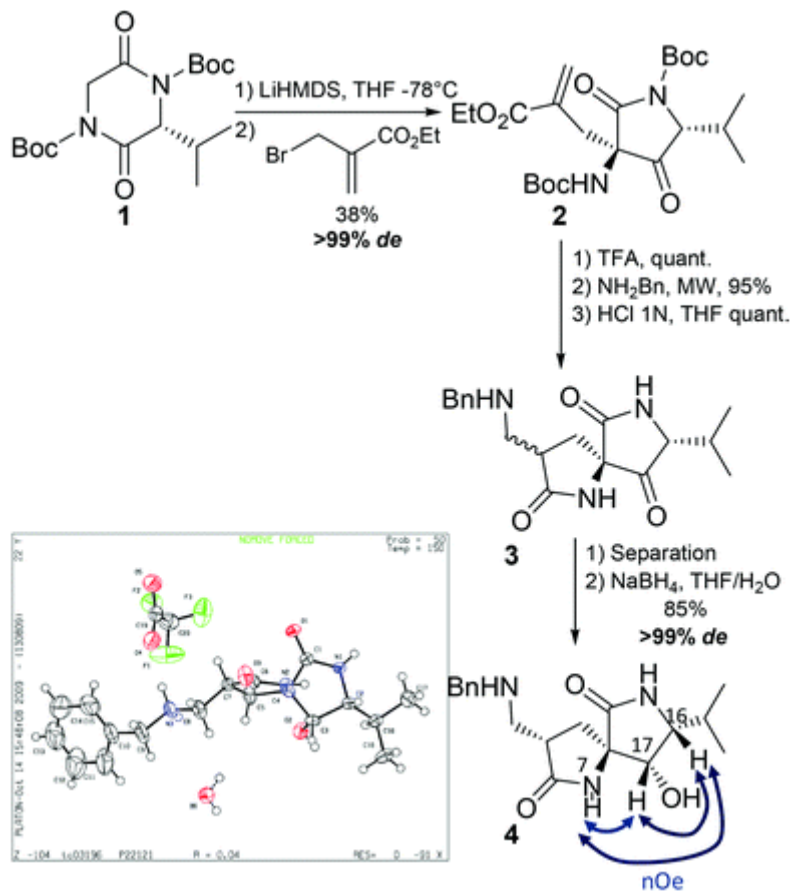
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## 20 Figures

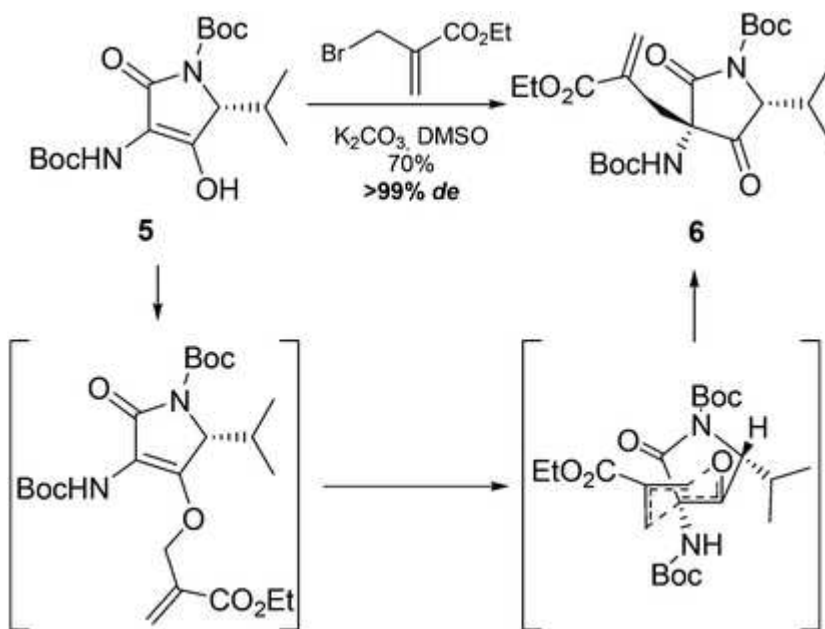


**Scheme 1** Proposed mechanism for the TRAL and the TRAL-alkylation.

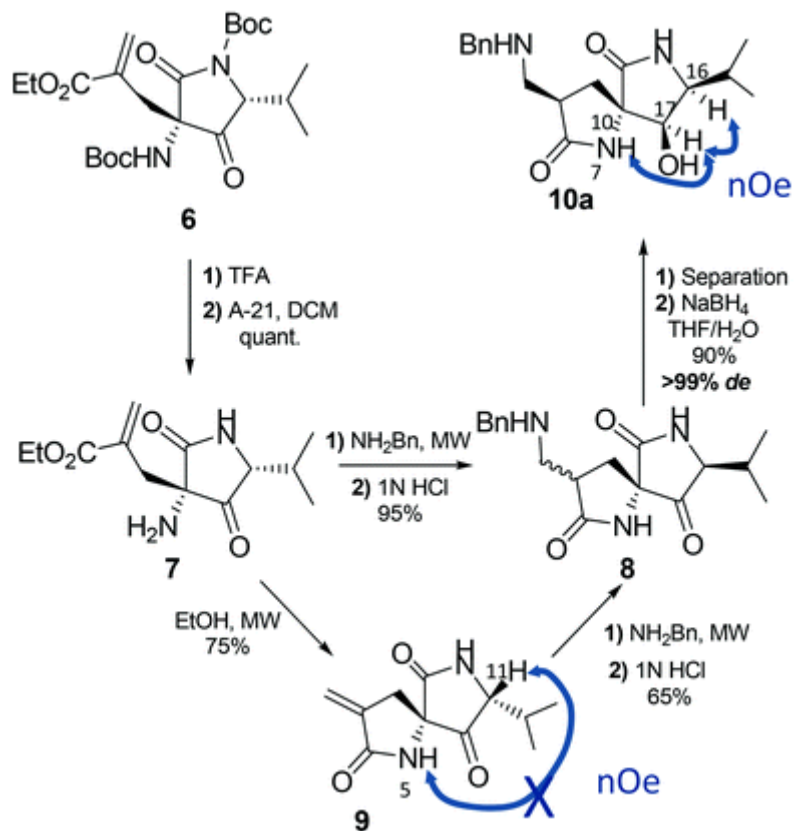


**Scheme 2** Synthesis of spirolactams using the TRAL-alkylation reaction.

5

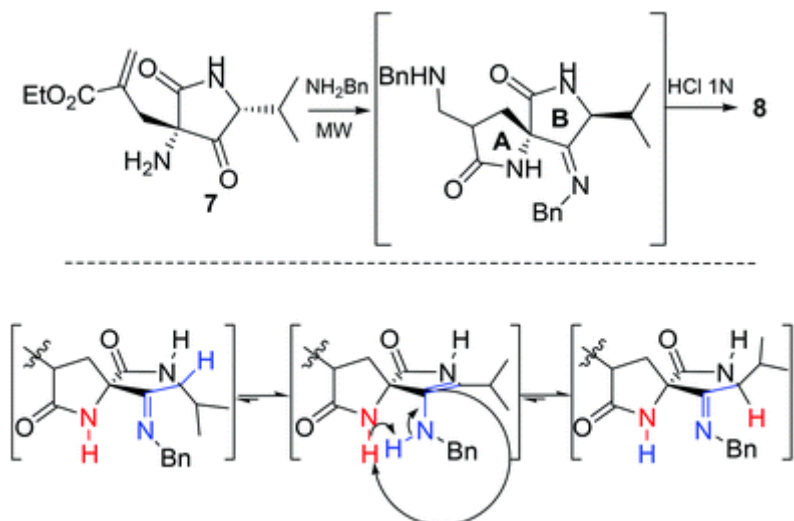


**10 Scheme 3** Diastereoselective O-alkylation-Claisen rearrangement tandem reaction.



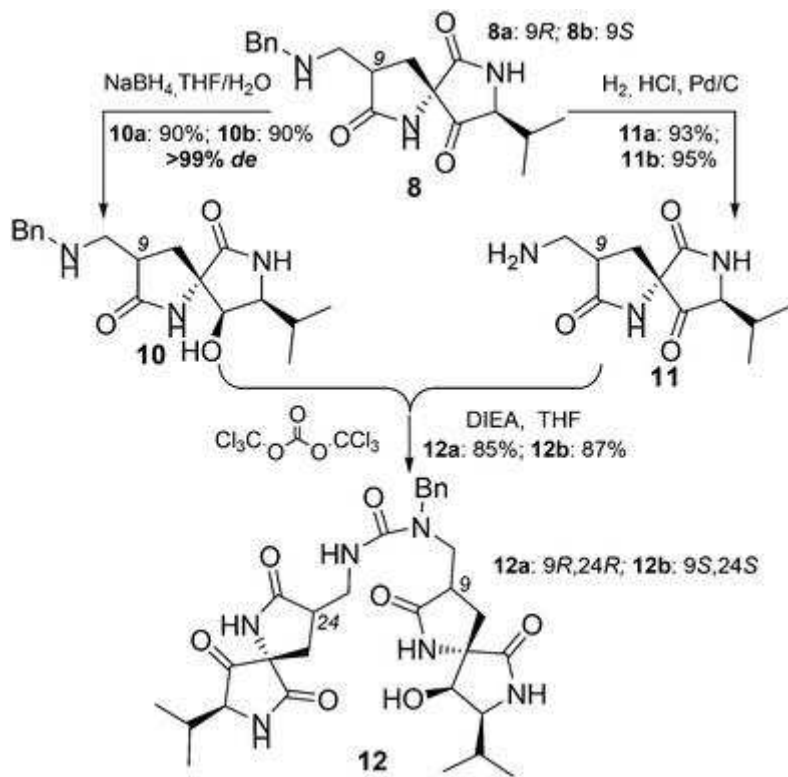
**Scheme 4** Synthesis of spiro lactam diastereomeric mixture 8.

5

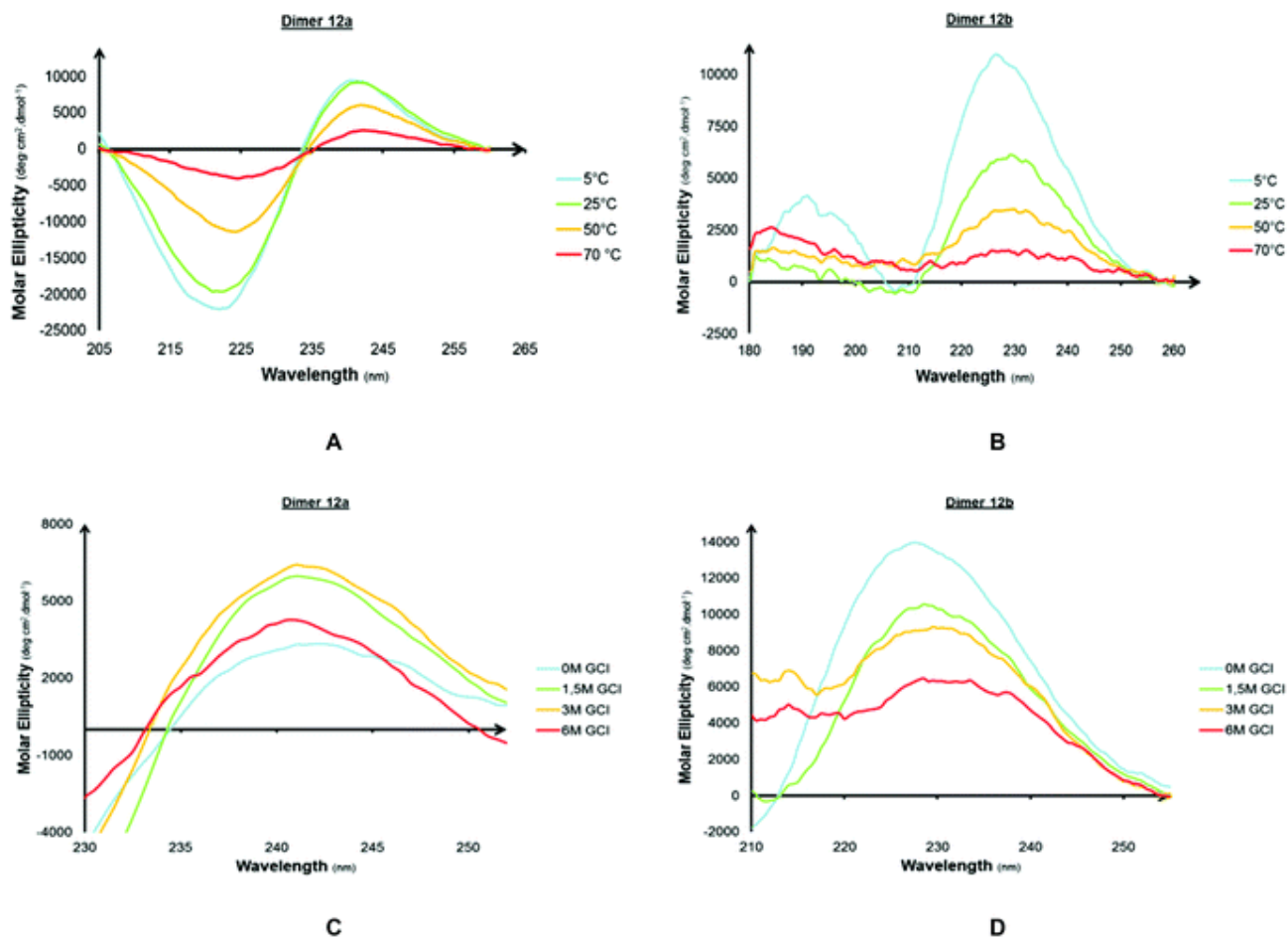


**Scheme 5** Proposed pathway for the highly stereoselective epimerisation process.

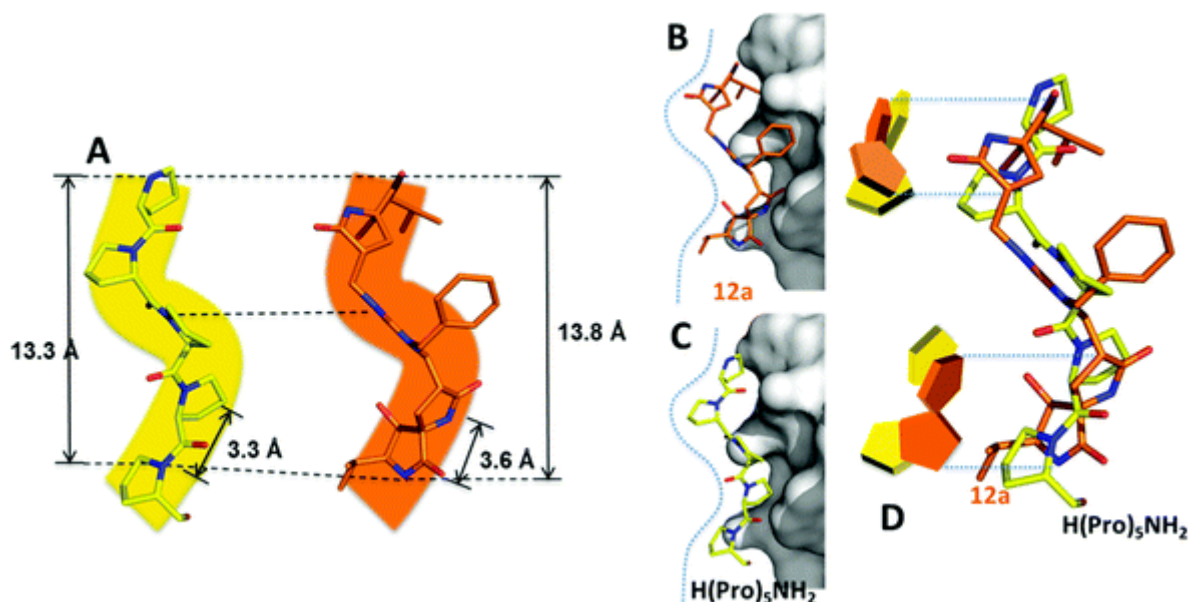
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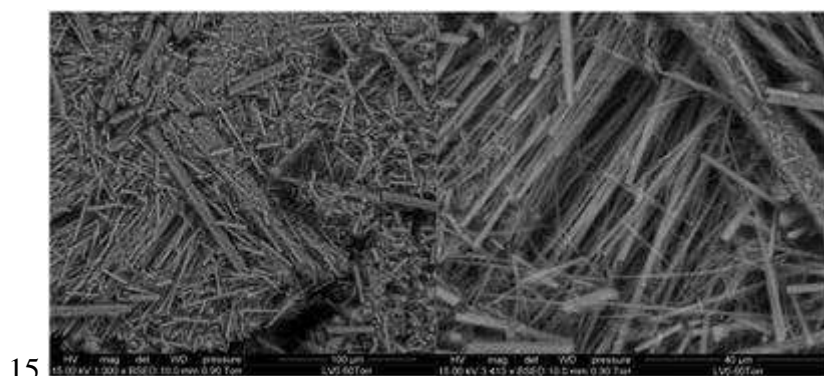
**Scheme 6** Dimerisation of spirolactams **8a** and **8b** to access **12a** and **12b**.



**Fig. 1** CD experiments in phosphate buffer; A and B: effect of the increasing temperature on the global shape of **12a** and **12b** signals respectively; C and D: effect of increasing concentrations of guanidinium 5 chloride on the global shape of **12a** and **12b** signals, respectively.



**Fig. 2** (A) Representation from modelling studies of PPII bio-inspired spirocyclic dimers 12a (right) and a pentaprolinone in PPII conformation (left) (modelled from PDB code 1EFN). (B) Representation of the crystallographic structure between Nef polyproline (sticks with atoms colour-coded option) and SH3 from Fyn kinase protein (PDB code 1EFN, Connolly-type surface representation with depth-colour coded option). The side chains of the pXXp from Nef (residues XX-XX) have been replaced by prolines; (C) docking mode of action of 8a after a fully flexible docking by surflex-GeomX and compatibility assessment with NMR restraints observed in solution; (D) schematic analysis of the relative orientation of the spiro groups (orange) with the N- and C-term Pro-Pro (yellow).



**Fig. 3** SEM images of the self-assembled structure of dimer 12a.

Electronic supplementary information (ESI) available. CCDC [751234](https://doi.org/10.1039/c3ob40643a). For ESI and crystallographic data in CIF or other electronic format see DOI: [10.1039/c3ob40643a](https://doi.org/10.1039/c3ob40643a)