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Concerted Synthesis of a Spirobicyclic Type-VI β-Turn Mimic of Pro-Pro-Pro-NH_2

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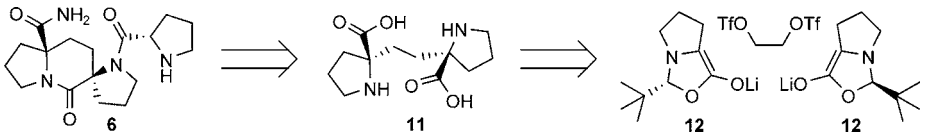
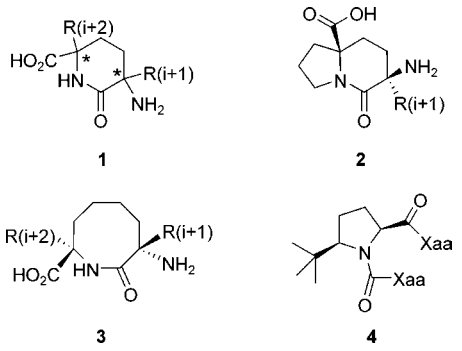
ABSTRACT



A highly concerted strategy for the synthesis of symmetrical type-VI β-turn mimics was formulated. A proof of concept is presented in the synthesis of a spirobicyclic peptidomimetic of Pro-Pro-Pro-NH_2, compound 6. The formation of an unusual adduct that was encountered in the process also is reported. This approach is potentially general for type-VI β-turn mimics where the *i* + 1 and *i* + 2 residues are identical.

In our ongoing investigations into the conformation-bioactivity relationships of peptidomimetics of the allosteric dopamine receptor modulator Pro-Leu-Gly-NH_2, we were faced with the need to constrain Pro-Pro-Pro-NH_2 in a type-VI β-turn conformation. In the past, the conformational mimicry of this *cis*-amide containing turn has been achieved through the utilization of either the (rac) *cis*-3-amino-6-carboxypiperidone (**1**),[1] indolizidinone (**2**),[2] or *trans*-3-amino-8-carboxyazocanone (**3**)[3] skeletons. Alternatively, induction of the *cis*-amide isomer has been achieved through the use of 5-*tert*-butyl proline (**4**).[4]



In our case, we deemed the indolizidinone (piperidone)-based mimic of Germanas to be the most appropriate due to its minimal steric deviation from the parent peptide. Incorporation of this type of mimic into the tripeptide Pro-Pro-Pro-NH_2 (**5**) gives the novel spirobicycle **6** (Figure 1).

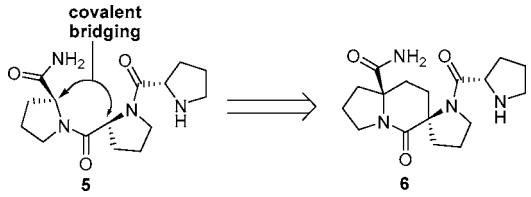


Figure 1. Design of the spirobicyclic type-VI β-turn mimic.

We initially envisioned an approach to the spirobicyclic framework of **6** that would employ a but-3-enyl substituted system such as **8**. Such a system could be prepared from **7** according to Germanas' methodology (Scheme 1).[2] Functionalization at the terminal alkene would give alcohol **9**, which in turn could be cyclized by an intramolecular Mitsonubu reaction[5] to potentially afford the desired spiro-

(1) Rogiers, J.; Borggraeve, W.; Topper, S.; Compernolle, F.; Hoornaert, G. *Tetrahedron* **2003**, *59*, 5047−5054.

(2) Kim, K.; Dumas, J.; Germanas, J. *J. Org. Chem.* **1996**, *61*, 3138−3144.

(3) Creighton, C.; Allen, R. *Org. Lett.* **2001**, 893−895.

(4) Bélec, L.; Slaninova, J.; Lubell, W. D. *J. Med. Chem.* **2000**, *43*, 1448−1455.

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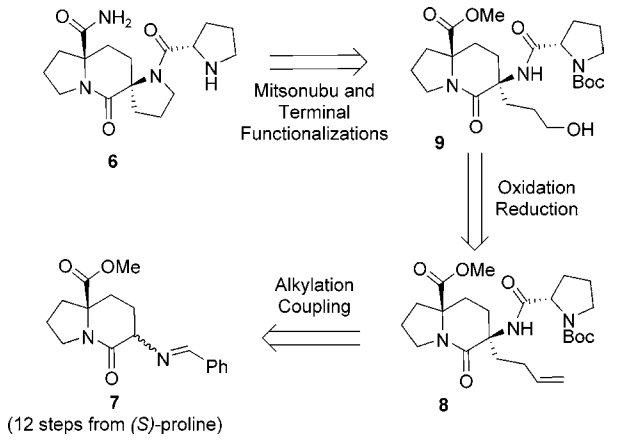
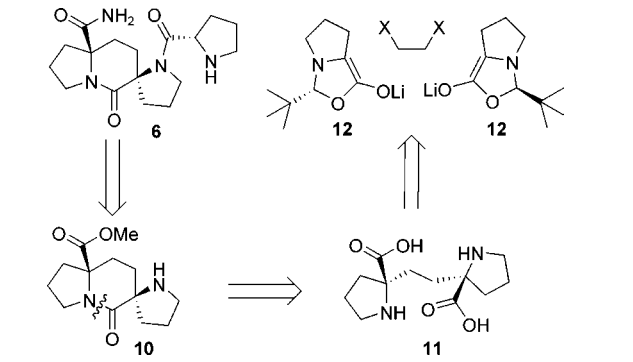
bicycle. This linear approach (approximately 18 steps) plus the fact that it hinged on the sequential creation of two stereocenters seemed daunting. We thus explored a potential concerted approach to **6**.

Scheme 1. Retrosynthetic Approach to Spirobicycle **6** via Germanas' Methodology



One of the features in **6** that sets it apart from the other known type-VI β-turn mimics is the fact that the $i + 1$ and $i + 2$ amino acids are identical. They are, in essence, substituted prolyl residues. This presents an opportunity to disconnect the lactam bond in **10**, thereby leading to a symmetrical 2,5-diaminoadipic acid-like derivative **11** that essentially is two prolines linked enantioselectively with a 2-carbon linkage at their α-carbons (Scheme 2). The reported

Scheme 2. Retrosynthetic Concerted Approach to Spirobicycle **6** Involving a C2-Linked Biproline

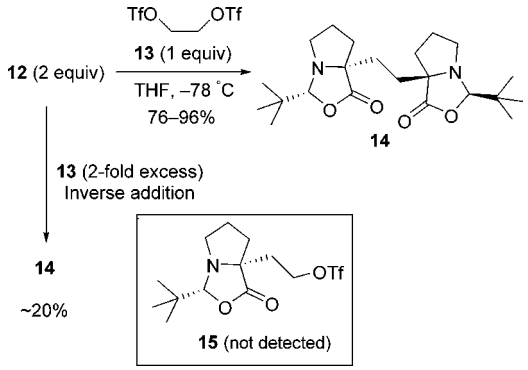


propensity of 2,5-diaminoadipate esters to spontaneously form a monolactam[6] and the stability of such monolactams over the diketopiperazine led us to believe that **11** could be a suitable entry into the spirobicyclic framework of **6**.

For such an approach, the lithium enolate of Seebach's oxazolidinone (**12**)[7] was seen as a suitable system for enantiocontrol due to the complete diastereoselectivity of its alkylation and the cleanliness of reactions that it undergoes. Our initial efforts with vicinal dihalides, both symmetrical and asymmetrical, failed to afford the required dimer. However, we recently reported the stereochemical details of a dehydrodimerization that occurred when 1,2-dibromoethane was used in such a reaction.[8] We hence concluded that the "onium" character of the dihalo electrophiles, which is a result of the dipole distortion induced by the second halo function, was responsible for their unusual reactivity (1,2-dibromoethane) or their unreactivity (1-bromo-2-chloroethane). This prompted us to turn our attention to other leaving groups, the sulfonate esters being the next obvious choice.

Glycol bis-tosylate was insoluble/unreactive in THF below −30 °C (the stability limit of **12**), while glycol bis-mesylate failed to react. However, the bis-triflate **13** reacted with **12** almost instantaneously, giving the highly crystalline dimer **14** in excellent yields ranging from 76 to 96% over multiple runs (Scheme 3). A cursory attempt at producing the

Scheme 3. Reaction of Glycol Bis-triflate with **12**



potentially very useful monosubstituted product **15** by adding enolate **12** to a solution containing a 2-fold excess of the bis-triflate was unsuccessful. The reaction led only to a modest yield of **14**, and no **15** was detected. The reaction did contain a number of side products, but none corresponded to any of the possible solvolysis or ring-opened products of **15**. This suggested that the disturbance in normal dipole moment is relevant even in the highly reactive bis-triflate.

In our initial attempts at forming **14** when we were rather unsure about the reactivity of glycol bis-triflate, we used 4 equiv of **12**. In these runs, we also isolated a crystalline byproduct as a single diastereomer, whose structure was elucidated by NMR to be **16**. This structure and the stereochemical assignment were confirmed by X-ray crystallography (Figure 2). The backbone of **16** appears to have been formed through a nucleophilic attack of **12** on an electrophilic iminium species derived from proline and pivalaldehyde (see Scheme A in the Supporting Information for a postulated pathway to the formation of **16**).

(5) Genin, M. J.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L. *J. Org. Chem.* **1993**, *58*, 2334−2337.
(6) Lyssenko, K.; Lenev, D.; Kostyanovsky, R. *Tetrahedron* **2002**, *58*, 8525−8537.
(7) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398.
(8) Vartak, A. P.; Young, V. G., Jr.; Johnson, R. L. *Org. Lett.* **2005**, *7*, 35−38.

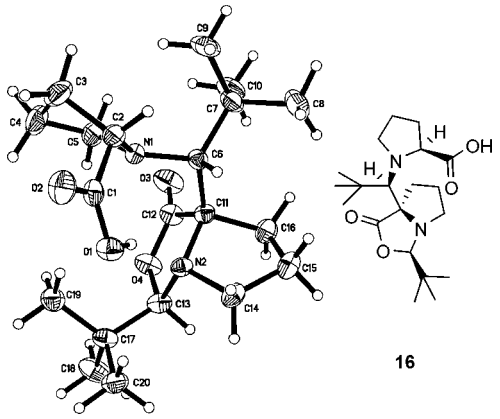
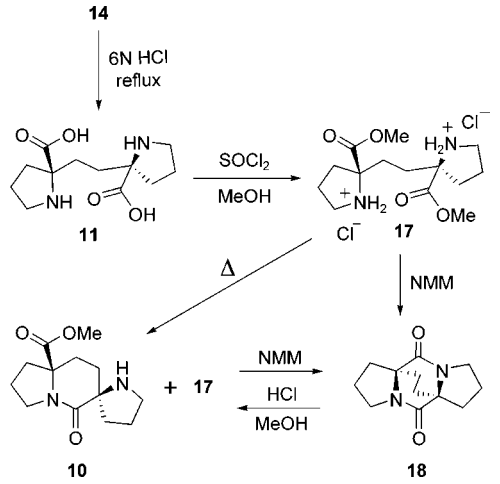


Figure 2. X-ray crystal structure of **16**.

Acid hydrolysis of the dimer **14** afforded **11** in a quantitative yield. Fischer esterification led to the dimethyl ester **17**, which could be cyclized (even in its hydrochloride form!) to give predominantly the monolactam **10** either when **17** was heated at reflux in toluene for 8 h or when it was heated neat under aspirator vacuum at about 60 °C for 30 min (Scheme 4).

Scheme 4. Formation of Spirobicycle **10** and Tetracyclic Diketopiperazine **18**

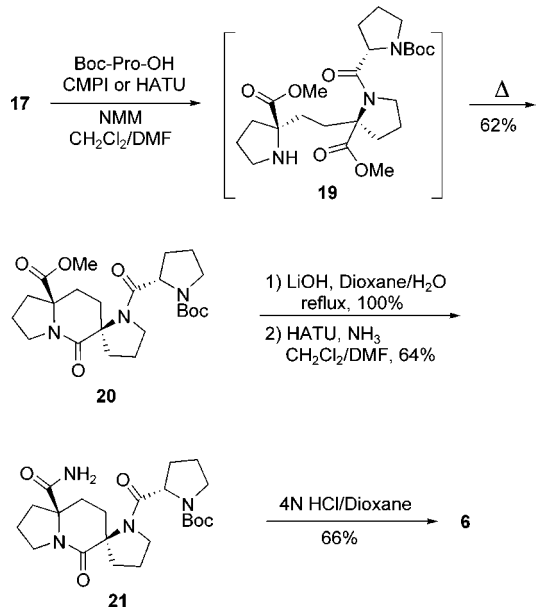


Exposure of **10** to 1 equiv of NMM for approximately 10 min or exposure of **17** to 2 equiv of NMM for 1−2 h led to the formation of the tetracyclic diketopiperazine **18**. This is in contrast with the observations of Lyssenko et al.[6] in the case of the simple 2,5-diamino dimethyladipate, wherein a strong base was required to induce formation of a diketopiperazine, while the monolactam formed readily. We attribute this difference to the fact that the basic nitrogen in the monolactam in our case is positioned axial due to the boat conformation of the six-membered lactam component of the indolizidine, which in turn is induced by the *cisoid* fusion with the five-membered pyrrolidine ring. Acidic methanolysis of **18** gave rise to a mixture of **10** and **17**, and **10** was the predominant component.

We next attempted to trap **10** with an activated ester of Boc-proline. As expected, the yields of **20** were generally abysmal with weaker coupling reagents such as EDC and DCC, with or without DMAP. In these cases, the predominant byproduct was **18**. Mukaiyama's reagent, 2-chloro-*N*-methyl pyridinium iodide (CMPI), only gave yields of 5−10%.

We serendipitously found that when **17** or mixtures of **10** and **17**, where **17** was the predominant component, were exposed to these coupling conditions, the yields of **20** increased dramatically. The most reproducible yields (∼30%) were obtained when CMPI was used as the coupling reagent along with 2 equiv of Boc-proline (Scheme 5). It appeared

Scheme 5. Synthesis of **6**



from these observations that the acylation reaction with the formation of **19** takes place before the lactamization. True to this possibility, diluting the reaction mixture to 10× its volume and refluxing it for an extra day increased the yields of **20** to a range of 50−62%.

The methyl ester function of **20** resisted direct amidation under a variety of conditions (cyanide catalysis, heating, and Weinreb's amidation). It could, however, be broken down very easily to the acid with LiOH and then coupled to ammonia using 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU) as the coupling reagent to obtain the primary carboxamide (**21**), which was deprotected to afford the target mimic **6**.

The ability of the indolizidinone skeleton to mimic the type-VI β-turn has been well-studied by Germanas et al.[2] A hydrogen bond between the *i* carbonyl and the $i + 4$ NH hydrogen is typical of the type-VIa1 subclass. In the case of the Boc-protected precursor **21**, the terminal carboxamide

hydrogens appear in a typical H-bonded conformation, with the H-bonded hydrogen being downfield at 8.62 and 8.51 ppm (rotameric signals) and the non-H-bonded hydrogen being unusually upfield at 5.56 and 5.51 ppm (rotameric signals). This is mirrored in spirocycle **6** as well, with the hydrogens appearing at 7.65 and 6.31 ppm. The bias of **6** toward the type-VIa1 β-turn subclass is likely to be enhanced by the natural ϕ dihedral angle of $-60°$ of the $i + 1$ prolyl residue, the ideal value of type-VIa1 β-turn.

In summary, we have successfully explored a more convergent strategy toward the required triproline type-VI β-turn mimic. A salient feature of our route is that the core mimic can be synthesized in only seven steps instead of 18 steps as would be required in the linear approach. Our approach is independent of the identity of the $i + 2$ residue since formation of the $i + 1$ α-center is not dependent on the *cisoid* fusion of the indolizidinone skeleton. It is, however, at this time limited to cases where the $i + 2$ and $i + 1$ residues are the same. Further investigations aimed at exploring the generality of this approach and extension to cases where $i + 1 \neq i + 2$ are in progress.

Acknowledgment. We thank Benjamin Kucera and Dr. Victor Young, Jr. of the Department of Chemistry's Crystallographic Laboratory for solving the X-ray crystal structure of **16**. This work was supported by NIH Grant NS20036.

Supporting Information Available: Experimental procedures and spectroscopic data for **6**, **11**, **14**, **16**, **18**, **20**, and **21**, X-ray crystallographic data for **16** in CIF format, and a scheme depicting a postulated pathway for the formation of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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