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A new bicyclic proline-mimetic amino acid

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Abstract—A new constrained bicyclic α-amino acid proline-mimetic was developed. The synthesis was achieved starting from derivatives of the chiral pool, thus allowing to prepare analogues of either L- or D-proline by choosing appropriate stereoisomers of serine and α,β-isopropylidene-glycerol derivatives. The scaffolds were prepared as *N*-Fmoc-amino acid suitable for solid-phase peptide synthesis.

β-turns are ten-membered ring hydrogen-bonded structures, which play an important role in proteins for folding and generating compact structures, and their structural mimics have been extensively studied.[1] Indeed, considerable effort has been focused on developing conformationally restricted mimics of these structures, which show particular conformation of backbone geometry and side-chain orientations, and exhibit intramolecular hydrogen bonding.[2] Among the naturally occurring amino acids, proline is often involved in the nucleation of reverse turn structures such as β-turns and β-hairpins. Moreover, the ability of proline to form *cis* peptide bonds and undergo *cis*/*trans* isomerization is well known. Depending upon the *cis*/*trans* stereochemistry of the Xaa-Pro amide bond, proline is involved either in type I-II or in type VI β-turn. Specifically, *cis* geometry of proline amide bond causes peptide backbone to fold in a type VI β-turn in which proline occupies the *i*+2 position, while type I and type II β-turns show a structure in which proline is in position *i*+1 and generates a *trans* amide bond with the preceding amino acid in position *i*. These structural properties of proline and its derivatives result in characteristic and unique constraints on the conformational space of peptide sequences containing proline or hydroxyproline.[3] Numerous mimetics and analogues of proline have been developed and applied in the synthesis of biologically active compounds, with the aim of modulating the *cis*/*trans* ratio of acyl-Pro bonds, constraining the conformation of the peptide bond and producing proline-like reverse turn inducers.[2,4]

During recent years we have developed a new class of bicyclic 3-aza-6,8-dioxa-bicyclo[3.2.1]octane scaffolds as γ/δ amino acids named BTAa[5] and BTKa,[6] obtained from tartaric acid and amino carbonyl derivatives, which proved to be valuable dipeptide isosteres when inserted in peptide chains. In particular, compounds belonging to the 7-*endo*-BTAa sub-class showed marked properties as reverse turn inducers in both cyclic[7] and linear[8] peptide sequences, acting as mimetics of *i*+1-*i*+2 central dipeptidic sequence of a typical β-turn motif, in which the rigidity imposed by ten-membered ring hydrogen bond was retained by the scaffolds architecture.

With the aim of exploring the capabilities of BTAa scaffolds to revert the direction of peptide backbone in another fashion, we developed a new set of bicyclic compounds named BGS, in which the carboxyl moiety of 7-*endo*-BTG is shifted from position 7 to 4, thus generating a constrained unnatural α-amino acid showing structural features similar to proline (Fig. 1).

In particular, owing to the structural asset of the bicyclic structure, BGS and BgS amino acids, having *R* absolute configuration at C-4, could be considered the

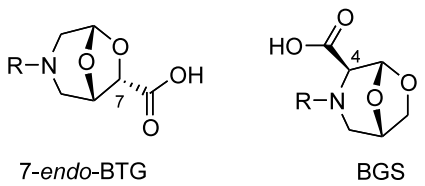

Figure 1. Shift of carboxylic function from position 7 to 4.

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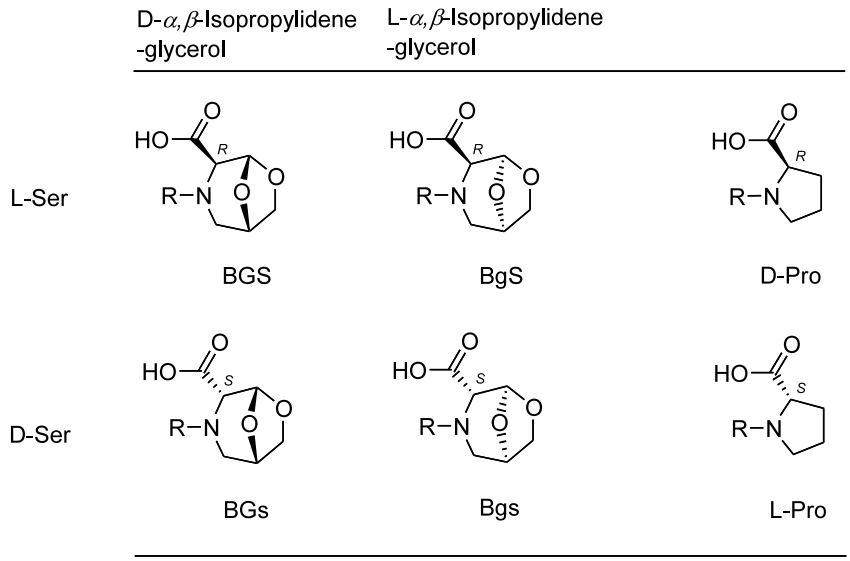


Figure 2. Stereochemical differences of BG(g)S(s) scaffolds depending upon the chirality of starting materials, and structural analogies with D- and L-proline amino acids.

bicyclic analogues of D-proline, while BGs and Bgs, having C-4 with *S* absolute configuration, showed similarity with L-proline, as shown in Figure 2.

BG(g)S(s) molecules displayed different geometrical presentation of side-chain functions depending on the stereochemistry of the starting precursors. BGS scaffold, which was prepared from the combination of D-α,β-isopropylidene-glycerol and L-serine derivatives, showed the carboxyl function in 4-*exo* position, while BGs compound, obtained from D-α,β-isopropylidene-glycerol and D-serine derivatives, displayed the COOH moiety in 4-*endo* position (Fig. 2). The corresponding enantiomers Bgs and BgS were obtained from L-α,β-isopropylidene-glycerol derivative.

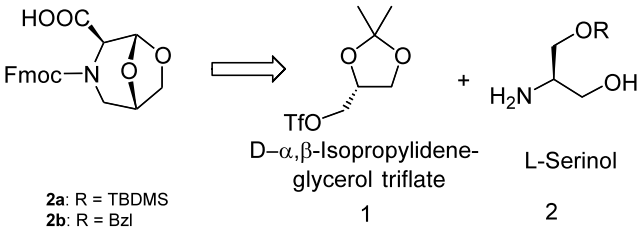
The synthesis of BGS scaffold was achieved starting from D-α,β-isopropylidene-glycerol triflate[9] and *O*-protected L-serinol derivatives (see Scheme 1), and consisted of a coupling step, followed by amine protection and oxidation of alcohol to aldehyde, to obtain the title scaffold after acid cyclization.

Initially, following the information achieved in a previous work about the preparation of BTS scaffolds,[10] we focused our attention on the synthesis of *O*-benzyl-protected BGS amino alcohol, starting from *O*-benzyl-serinol (**2b**) and D-α,β-isopropylidene-glycerol triflate (**1**) (Scheme 2). Compound **2b** was prepared as reported,[11] and **1** was obtained in good yield following the reported procedure.[12] The coupling was achieved in dichloromethane after overnight stirring at room temperature, thus obtaining the desired amino alcohol adduct together with 15% of dialkylated product. After protection of the amine function as Fmoc urethane, the oxidation step was performed with Dess–Martin periodinane, in agreement with previous consideration about the tendency of the desired aldehyde to undergo β-elimination to the more stable α,β-unsaturated aldehyde when Swern conditions were employed.[10]

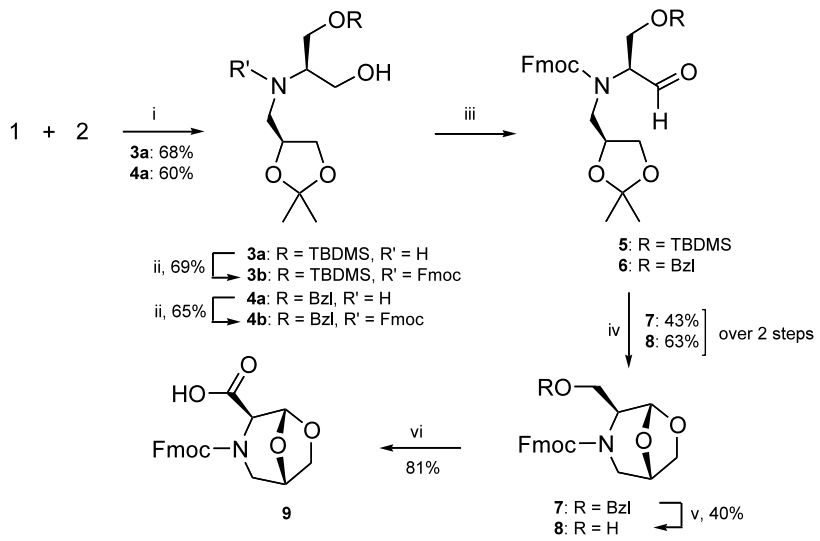
Cyclization of the Fmoc-aminoaldehyde proved to be more difficult than the analogous BTS scaffold, in which an endocyclic amide was present. In particular, cyclization conducted in refluxing benzene with H_2SO_4–SiO_2 catalyst, led to the desired product with poor yield. On the contrary, when cyclization was performed at room temperature in pure TFA, a better yield (43%) was obtained, though not convenient enough for preparative purposes.

Moreover, the *O*-benzyl deprotection showed unexpected difficulties. In fact, the benzyl group showed resistance towards hydrogenolysis in MeOH and EtOH with Pd/C and $Pd(OH)_2$/C, unless high pressures of hydrogen were employed. Alternatively, deprotection was achieved using Lewis acids, and, in particular, $FeCl_3$[13] proved to be more efficient than $TiCl_4$, while $SnCl_4$ showed no reaction. The main drawback of using Lewis acids was the low yield, which was found in all cases to be not higher than 40%.

The need for an efficient strategy to allow the preparation of a larger amount of final *N*-protected amino acids, prompted us to replace *O*-benzyl-serinol **2b** with a more suitable starting reagent in terms of costs and compatibility with the synthetic path. In a work of Meyers et al.,[14] an efficient method for the preparation of *O*-TBDMS-serinol **2a** compounds was described.



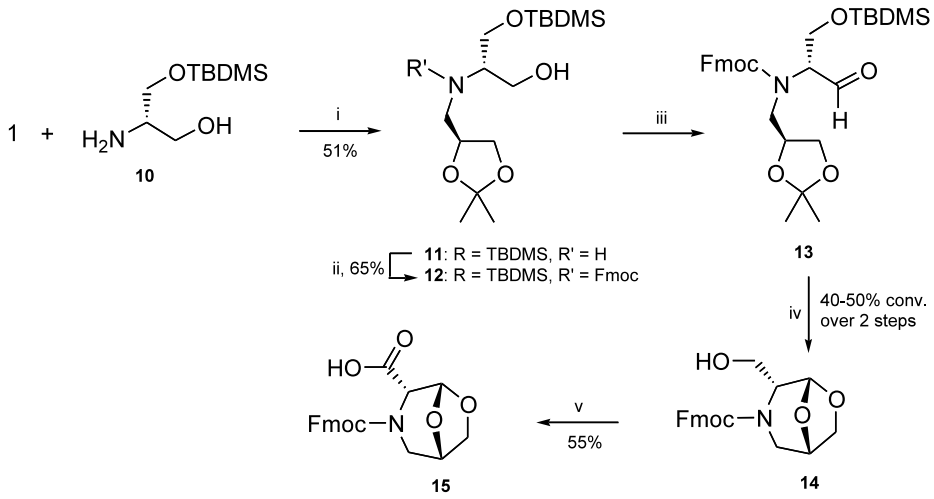
Scheme 1. Retrosynthetic approach to BGS scaffold.



Scheme 2. *Reagents and conditions*: (i) DIPEA, CH_2Cl_2, rt, overnight; (ii) Fmoc-*O*-Su, THF, 2,6-lutidine, 0°C, 4 h, then rt, overnight; (iii) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (iv) TFA, rt, 2 h; (v) $FeCl_3$ 2 equiv., CH_2Cl_2, rt, 30 min; (vi) Jones reagent, acetone, rt, overnight.

Thus, the silylated amino alcohol was prepared in gram quantities and coupled with glycerol–triflate derivative **1** (Scheme 2). The alcohol oxidation was performed with Dess–Martin periodinane using standard work-up with $Na_2S_2O_3$–$NaHCO_3$ solution, as no β-elimination to give corresponding α,β-unsaturated aldehyde was observed. Finally, acid cyclization with TFA gave BGS scaffold **8** with free OH group, as TBDMS group is known to be acid sensitive, giving the deprotected scaffold in 63% yield over two steps. Thus, final *N*-Fmoc-amino acid **9** was obtained with Jones oxidation in 81% overall yield (Scheme 2). BGS scaffolds **7**–**9** showed two rotamers on ^{1}H NMR in about 1:1 ratio, as often observed for *N*-Fmoc-BTAa bearing a substituent in 4-*exo* position.[5]

In the case of BGs, the 4-*endo*-carboxyl-scaffold was obtained in lower yield (Scheme 3). The difficult cyclization as a consequence of steric restrictions was known for similar compounds carrying an exocyclic double bond,[10] and in bicyclic scaffolds having a carboxylic group shifted from *exo* to *endo* position.[15] In particular, cyclization with acid silica in refluxing benzene proved to be difficult and not reproducible on larger scale, giving BGs scaffold with poor conversion. When using TFA as a cyclizing agent the final product was obtained with 40–50% conversion, though after purification the yield lowered to 11%.[16] Jones oxidation gave final BGs amino acid in lower yield than corresponding BGS isomer, thus confirming the instability of BGs. Both the amino alcohol and amino acid BGs scaffolds presented a unique rotamer as a consequence of steric restriction imposed by carboxyl function in equatorial position, as already observed in other BTAa scaffolds.[5,8]



Scheme 3. *Reagents and conditions*: (i) DIPEA, CH_2Cl_2, rt, overnight; (ii) Fmoc-*O*-Su, 2,6-lutidine, THF, 0°C, 4 h, then rt, overnight; (iii) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (iv) TFA, rt, 2 h; (v) Jones reagent, acetone, rt, overnight.

The corresponding enantiomers obtained from L-α,β-isopropylidene-glycerol showed similar behavior, as Bgs scaffold, being the enantiomer of BGS, belonged to the matched case, while BgS showed mismatched behavior in analogy with BGs molecule.

In conclusion, a new strategy for the development of bicyclic analogues of both D- and L-proline was achieved, obtaining Fmoc-BG(g)S(s) amino acids readily available for SPPS synthesis of new modified reverse turn peptides. The use of silylated serinol compounds was found to be more effective in terms of yields, thus developing a more viable synthetic protocol. The synthesis of BGs or BgS scaffolds, carrying a substituent in 4-*endo* position proved to be more difficult than the corresponding 4-*exo* diastereomer, as a consequence of difficult cyclization and increased instability of the final product, thus showing the match/mismatched behavior of these molecules, depending upon the relative configuration of side chain functionality in position 4 of the scaffold.

Acknowledgements

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