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Synthesis of a constrained tricyclic scaffold based on *trans*-4-hydroxy-L-proline

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Abstract—Drug discovery research has taken advantage of peptidomimetic chemistry in order to achieve new leads possessing structural and functional characteristics of bioactive peptides together with enhanced metabolic resistance towards proteases. Herein is reported the synthesis of a tricyclic peptidomimetic scaffold derived from the combination of *trans*-4-hydroxy-L-proline and tartaric acid derivatives by means of amidation and acid *trans*-acetalisation reactions. Further manipulations of the hydroxylic function on the pyrrolidine ring gave access to a new set of amino acid scaffolds possessing high rigidity and a fixed arrangement of the functional groups.

In recent years, drug discovery has focused on bioactive peptides as therapeutics. The severe pharmacological limitations such as poor absorption and low oral bioavailability have led researchers to develop the concept of 'peptidomimetic chemistry',[1–5] which allowed one to generate compounds able to preserve peptide-like activity and to increase resistance towards proteases. Many templates have been developed so far, and unnatural amino acids proved to be of great interest as new building blocks for the development of peptidomimetics possessing enhanced diversity and structural constraints.

Following our interests, in generating constrained scaffolds for peptidomimetic design, we focused our attention towards polycyclic structures carrying functional groups in a well-defined topological arrangement. In particular, we explored the chemistry of a 6,8-dioxa-3-azabicyclo[3.2.1]octane scaffold,[6] which proved to act as a constrained scaffold for the generation of rigid amino acids,[6–10] and for asymmetric synthesis.[11,12] Different synthetic strategies using sugar or tartaric acid derivatives with amino acid derivatives allowed us to obtain different sub-classes of scaffolds named BTKa (bicycles from tartaric acid and keto amines)[8] and BTAa (bicycles from tartaric acid and amino acids),[9,10] based on the same heterocyclic core. The key step to obtain the bicyclic scaffold is an acid-catalysed *trans*-acetalisation of a 1,2-diol moiety with a free or protected aldehyde function. In particular, a masked aldehyde as an acetal allowed to achieve final compounds in higher amounts due to easier access and relatively cheaper chemistry.[9]

trans-4-Hydroxy-proline has been widely used for the generation of new-proline-based compounds,[13–15] and the three functional groups on the pyrrolidine ring have been also used for the generation of combinatorial libraries on solid support.[16] According to the general retrosynthetic path to achieve BTAa scaffolds, condensation of amino aldehydes derived from α-amino acids with tartaric acid derivatives could give access to bicyclic compounds having a carboxylic group at position 7 and a secondary amino group at position 3.[6] On the contrary, by using the secondary α-amino acid proline, a tertiary amide bond and an additional cycle in the 6,8-dioxa-3-azabicyclo[3.2.1]octane template are introduced, thus increasing the conformational rigidity, though losing the possibility of functionalising the amino group at position 3. Thus, 4-substituted proline was chosen in order to keep two functional groups in the scaffold architecture, with a well-defined topology and an increased distance between them. Moreover, compound **2** was chosen in order to reduce the synthesis of the scaffold to two steps, namely amidation and acid catalysed *trans*-acetalisation (Fig. 1).

Keywords: Peptidomimetics; Drug design; Peptides; Amino acids.
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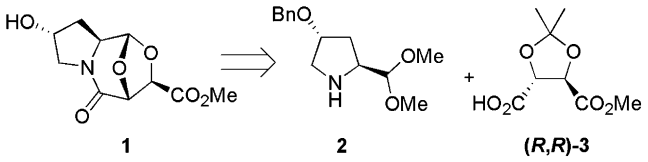
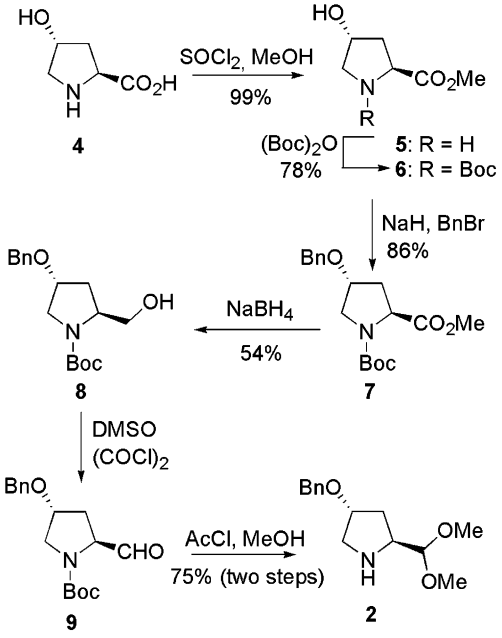


Figure 1.

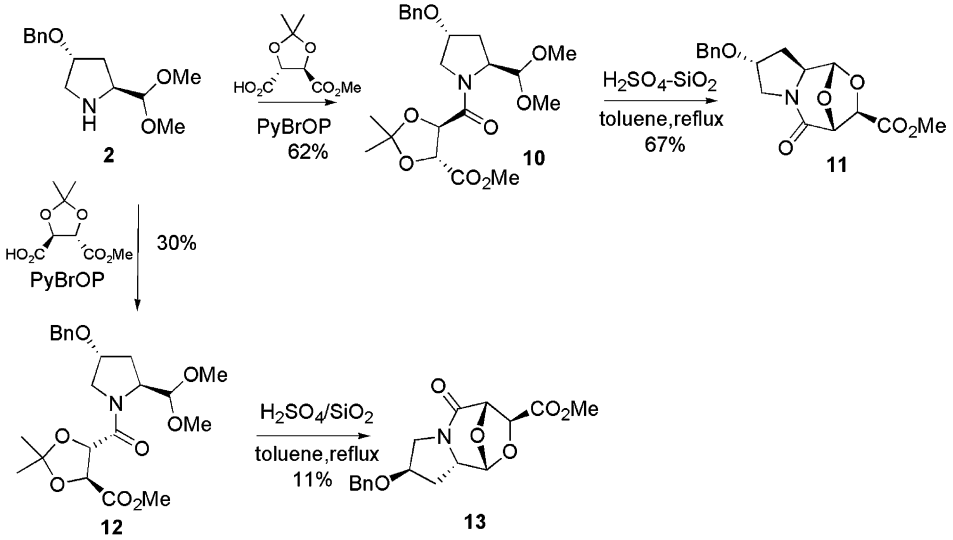


Scheme 1.

Amino acetal **2** was obtained from *trans*-4-hydroxy-L-proline in six steps according to Scheme 1.

Fisher esterification of **4** produced compound **5**, which was successively converted to the Boc-protected amino ester **6**. Subsequent protection of the hydroxyl group was accomplished by treatment with NaH, followed by alkylation with benzyl bromide in 86% yield.[17] Reduction of the ester function of **7** by means of $NaBH_4$ afforded the corresponding protected amino alcohol **8**, which was subjected to Swern oxidation to give aldehyde **9**. Treatment of **9** with a methanolic solution of HCl, obtained by reaction of MeOH with acetyl chloride, allowed us to achieve directly the final amino acetal **2** in 75% yield after two steps, as a consequence of simultaneous acetalisation and Boc-deprotection.

With the amino acetal **2** in hand, the synthetic route to the polycyclic scaffold consisted in a two-step process, that is, amide bond formation and acid-catalysed intramolecular cyclisation, as showed in Scheme 2. Amide bond formation was achieved using PyBrOP as the carboxylic acid activator, giving product **10** in 62% yield after purification. Interestingly, the coupling of monoester **3** with *trans*-4-(*O*-benzyloxy)-prolinol, corresponding to the Boc-deprotected derivative of **8**, did not produce the related amide in satisfactory yield (30%), and an ester by-product was observed as main product, as a consequence of the reaction of the primary hydroxyl group instead of the secondary amine. Thus, it was hypothesised that there was an interaction between the hydroxyl and the amine group resulting in the deactivation of the latter, hence disfavouring the reaction with the tartaric acid derivative. Intramolecular cyclisation was carried out in refluxing toluene and in the presence of acid silica gel, (prepared by slow addition of concentrated sulfuric acid to a suspension of silica gel in dichloromethane, followed by solvent evaporation),[6] giving **11** in 67% yield. It was found optimal to increase the reaction time to an hour, instead of the few minutes required for other BTAa compounds, as a consequence of the increased constraint of the final compound carrying an additional cycle. Compound **11** showed both the proton at C-4 and the hydroxyl function in *endo* configuration relatively to the six-membered ring. On the contrary, the reaction of amino acetal **2** with monoester derivative (*S*,*S*)-**3** of D-tartaric acid gave access to the diastereomeric scaffold **13**, having both the proton at C-4 and

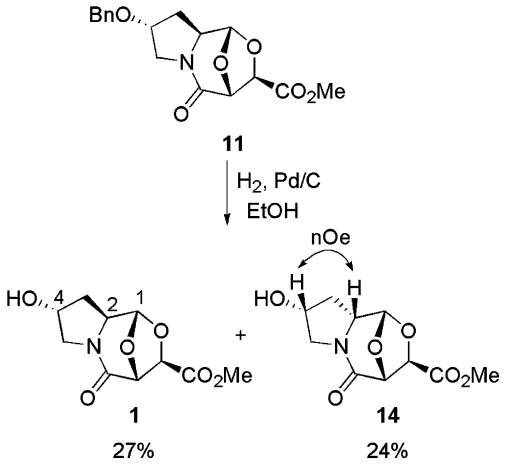


Scheme 2.

the hydroxyl function oriented in *exo* with respect to the six-membered ring (Scheme 2). In this case, acid-catalysed cyclisation of **12** to give **13** occurred with high difficulty, giving the desired product in a yield lower (11%) than that for the diastereomeric **11**.

The stability of the new polycyclic system bearing an acetal moiety was assessed by treating **11** for several hours in refluxing toluene. It showed complete resistance towards epimerisation on heating, although partial degradation was observed. Moreover, compound **11** in a $CDCl_3$ solution containing 1% TFA showed complete stability towards epimerisation and ring opening, even upon addition of small quantities of water. Successively, in order to test the versatility of the tricyclic scaffold, the hydroxyl group on the pyrrolidine ring was further processed in order to achieve a new constrained amino acid. Thus, the benzyl group of **11** was removed by hydrogenolysis to give the corresponding hydroxy ester **1**. Surprisingly, epimerisation at the C-2 stereocentre was observed, giving **1** and **14** as a 1:1 mixture of diastereoisomers (Scheme 3).

Structural determination of these two isomers was achieved by X-ray analysis of **1**[18] (Fig. 2) and by NOE experiments (Scheme 3). Compound **1** did not show



Scheme 3.

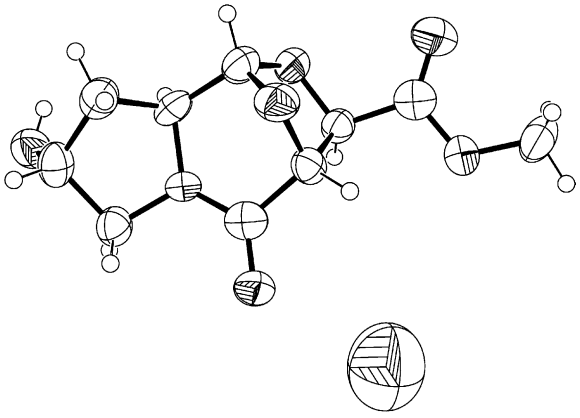


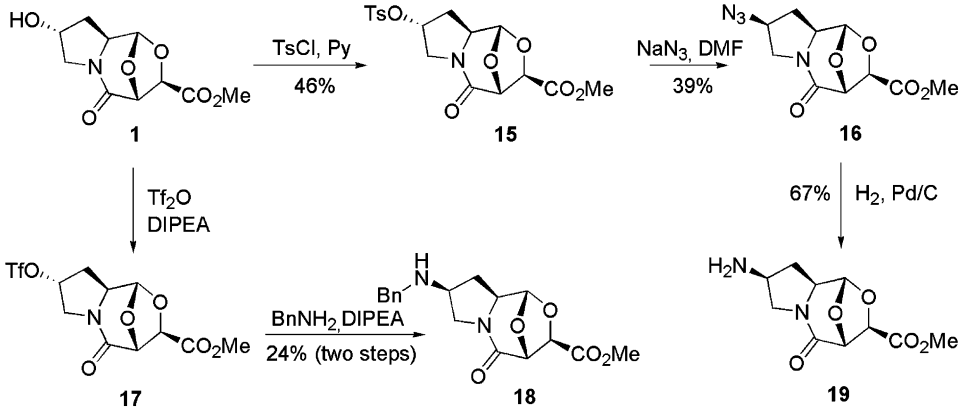
Figure 2. X-ray structure of compound **1**.

any NOE effect between 2-H and 4-H of the tricyclic system, whereas an intense NOE interaction was observed for the isomer **14**.

Interestingly, the X-ray analysis of compound **1** showed the preferred *syn* orientation of the carbonyl group of the ester at C-9 with respect to the C-9–O-10 bond in the solid state. This is in contrast to the preferred *anti* orientation observed from molecular modelling calculations for other BTAa scaffolds.[6] Moreover, the measured distance between the carbonylic carbon atom of the ester group at C-9 and the oxygen at C-4 was 7.247 Å, corresponding approximatively to the length of a tripeptide sequence.

Successively, two strategies were explored for the synthesis of a new tricyclic amino acid (Scheme 4). Initially, compound **1** was reacted with tosyl chloride to give **15** in 46% yield, which was successively treated with NaN_3, to give the amino acid precursor **16**. Final hydrogenolysis with catalytic Pd/C afforded the target amino acid **19**. Alternatively, the hydroxyl group of **1** was transformed to the corresponding triflate **17**, which was treated with benzylamine to give the resulting *N*-benzyl amino acid **18** in 24% yield over two steps.

In conclusion, a new tricyclic scaffold was synthesised from *trans*-4-hydroxy-L-proline and tartaric acid deriva-



Scheme 4.

tives, having an extremely rigid structure, which could find applications in peptidomimetic design as a rigid template carrier of two functional groups of a pharmacophore. Such new molecular platform was demonstrated to be versatile to various transformations, and a new tricyclic amino acid was achieved with two convergent approaches, thus giving a new constrained tripeptide isostere.

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Supplementary data

Experimental procedures and characterisation data for compounds **1**, **2**, **11** and **13**–**19**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.021.

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18. Crystallographic data (excluding structure factors) for the structure **1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 278480. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].