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Spirobicyclic diamines 2: Synthesis of homochiral diastereoisomeric proline derived [4,4]-spirolactams.

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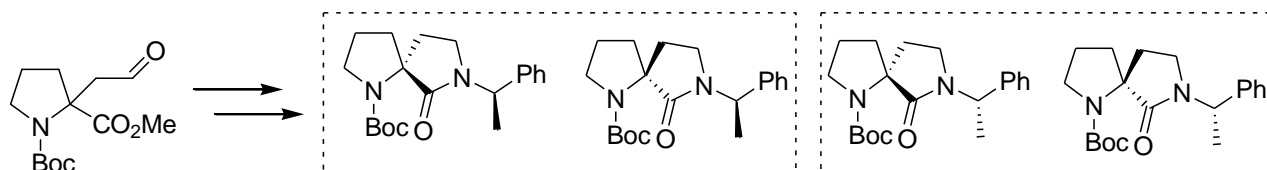
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Graphical abstract :

Spirobicyclic diamines 2: Synthesis of homochiral diastereoisomeric proline derived [4,4]-spirolactams.

Fintan Kelleher* and Sinead Kelly

Reductive amination of homochiral primary amines ((*R*)- or (*S*)- α -methyl benzylamine, and (*R*)- or (*S*)-alanine methyl ester) with a racemic proline derived aldehyde, followed by cyclisation gave diastereoisomeric [4,4]-spirolactams.



Spirobicyclic diamines 2: Synthesis of homochiral diastereoisomeric proline derived [4,4]-spirolactams.[†]

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Abstract:

L-Proline derived diastereoisomeric [4.4]-spirolactams have been prepared by a reductive-amination reaction of (*R*)- or (*S*)-alanine methyl ester followed by thermal cyclisation of the resulting amine onto the proline ester group in refluxing toluene. Under similar conditions (*R*)- or (*S*)-phenylalanine methyl ester gave no cyclisation products, while *R*- or *S*- α -methylbenzylamine required treatment with NaNH₂ in refluxing toluene to induce cyclisation giving diastereoisomeric [4.4]-spirolactams.

There are currently a large number of methods for the synthesis of spirocyclic compounds and they can also be easily formed in a stereocontrolled manner.¹ Although Freidinger was the first to incorporate a lactam constraint into the backbone of a peptide in order to rigidify the peptide tertiary structure into a more defined conformation,² this is now a widely used method to constrain the secondary structures of peptides. Of the range of methods available for lactam synthesis one of the most common is the cyclisation of an amino group (primary or secondary) onto a carboxylic ester, with concomitant loss of an alcohol. Many of the reactions take place spontaneously at ambient temperature, while others require heating in a suitable solvent.^{2b,3} The overall efficiency of the cyclisation is dependent on a number of factors including the size of the ring being formed, the nature of the amino substituent in the case of a secondary amine, any substituents on the resulting ring and the structure of the alkyl moiety of the ester group.

[†] see reference 4.

L-Proline derived spirolactams have, in particular, been studied for their use in constraining peptides with L-proline residues to mimic a β -turn, a very important component of peptide secondary structures.³ As part of a program to synthesise both homochiral and racemic proline derived [4.4]-spirolactams, we recently reported on our studies on the preparation of racemic spirolactams by a thermal intramolecular ester aminolysis method.⁴ The route we employed is shown in Figure 1, where *N*-Boc L-proline methyl ester was α -alkylated with allyl bromide, using LiHMDS as base. The alkene of the allyl group was oxidatively cleaved by the OsO₄/NaIO₄ system to give the aldehyde **4**. Reductive amination of the aldehyde with allyl amine, benzylamine or glycine methyl ester gave the desired secondary amines **5** as suitable cyclisation precursors. Heating solutions of the amino esters **5** in refluxing toluene gave [4.4]-spirolactams **6** in yields of 66-90%. Since the amines used in this study were achiral, the resulting spirolactams were obtained as racemic mixtures. It was of interest to us to examine the extension of the scope of the reaction by employing chiral amines, for example *R*- or *S*- α -methylbenzylamine. This would result in diastereoisomeric amino esters which would, in each case, give a mixture of two spirolactams after cyclisation. It was expected that these diastereoisomeric compounds would be separable by column chromatography, giving us a route to all four homochiral [4.4]-spirolactams from a common racemic precursor, namely aldehyde **4**.

Reductive amination of **4** with either *R*- or *S*- α -methylbenzylamine cleanly gave **5a** and **5b**, the desired precursors to the spirolactams. Using the conditions employed in our previous studies, i.e. stirring in toluene at reflux, did not give any of the desired [4.4]-spirolactam cyclisation products, with only starting material being isolated in each case, even after prolonged heating. It was therefore apparent that the extra steric hindrance in the system with the addition of an extra methyl group in the position α to the nitrogen of the amine compared to benzylamine, was sufficient to stop cyclisation from occurring. We surmised that converting the secondary amine cyclisation precursor to a secondary lithium or sodium amide ion, by deprotonation with a sufficiently strong base would give a stronger nucleophile which might be able to overcome the inherent steric hindrance of the system. Since we had done all our cyclisations in refluxing toluene and sodium amide is commercially available as a

50% solution in toluene, this was the strong base that we employed. Treating solutions of the secondary amines **5a** or **5b**, dissolved in toluene, with NaNH₂ in toluene, gave no indication of cyclisation after stirring at ambient temperature, but when the solutions were stirred at reflux, cyclisation proceeded with the desired spiro lactams **6a-d** (as pairs of diastereoisomers which were separable by column chromatography) being isolated in yields of 30% and 51% from aldehyde **4** (Scheme 1). In both cases the ratio of diastereoisomers isolated was approximately 1:1.

Although the stereochemistry of the α -methyl benzyl substituent was known from our choice of the starting homochiral amine we were unaware of the absolute stereochemistry of the spiro centre in each of the four isolated diastereoisomers. We were unable to obtain crystals of sufficient quality for X-ray analysis of the structure. Molecular modelling⁵ was used to give minimised energy conformations of the *RR* and *SR* diastereoisomeric pair **6a** and **6b**. It was immediately evident from the minimised structures (Figure 2) that in the *SR* diastereoisomer the hydrogens of the Boc protecting group and the meta hydrogens of the phenyl group were close in space (closest distance of 2.67 Å), whereas in *RR* isomer the Boc and phenyl groups were a large distance apart. As a result of this it was expected that NOE NMR experiments would be able to distinguish between the two diastereoisomers. We were pleased to find that irradiation of the signal for the hydrogens of the Boc group of the diastereoisomer assigned as *SR* did indeed show an NOE to the phenyl hydrogens, whilst no similar NOE was observed in the case of the *RR* diastereoisomer. Although this is not conclusive proof of the absolute stereochemistry of the spiro centre we have now tentatively assigned the stereochemistry, based on the molecular modelling and NOE studies, of all four diastereoisomers.

We next examined the synthesis of diastereoisomeric spiro lactams with carboxylic ester side-chains on the lactam nitrogen. Previously we had found that when glycine methyl ester was used cyclisation was very efficient. The use of (*R*)-alanine methyl ester, with the incorporation of a methyl group in the position α to the nitrogen was expected to reduce considerably, or possibly completely stop, cyclisation from taking place under the thermal ester aminolysis protocol. We found that using the thermal cyclisation method the two diastereoisomeric spiro lactams **6e** and **6f** were obtained in

a much reduced yield of 40% even after stirring for 3 days in refluxing toluene, compared to the 90% for glycine methyl ester after stirring for 24 h in refluxing toluene (Scheme 2). The diastereoisomeric ratio in this case was 6:1. Repeating the synthesis, but this time using (*S*)-alanine methyl ester again for 3 days in refluxing toluene, gave the two diastereoisomeric spiro lactams **6g** and **6h** in a slightly improved yield of 54%. The diastereoisomeric ratio in this case was 1.75:1. As before, we were unable to obtain crystals of sufficient quality for X-ray analysis from any of the four diastereoisomeric compounds. For both sets of reactions the remaining material was the unreacted amino cyclisation precursors **5c** and **5d**.

We expected that increasing the steric bulk of the amino acid component would cause a further reduction in the isolated yield of the diastereoisomeric spiro lactams. When (*S*)-phenylalanine methyl ester was used no spiro lactam products were isolated with the secondary amine **5f** being isolated as an inseparable mixture of diastereoisomers (one spot by TLC) in a 72% yield, while use of (*R*)-phenylalanine methyl ester gave a similar result with the uncyclised diastereoisomeric amines **5e** being obtained in a yield of 80% (Scheme 3).

In conclusion, it is apparent that the size of the α -substituents on the primary amine component is critical to the overall success of the thermal ester aminolysis method for the synthesis of proline derived [4.4]-spiro lactams, with a group larger than methyl causing the complete absence of any products arising from cyclisation. It would be our recommendation that for the synthesis of homochiral proline derived [4.4]-spiro lactams with larger groups on the lactam nitrogen, the thermal ester aminolysis is not the method of choice. It is more appropriate to synthesise the cyclisation precursor, hydrolyse the proline ester, and then to use peptide coupling methods to induce lactamisation.³ Currently, we are attempting to obtain crystals suitable for X-ray analysis of a number of derivatives of these spiro lactams and we are also examining their chemical properties. The results of these studies will be reported in due course.

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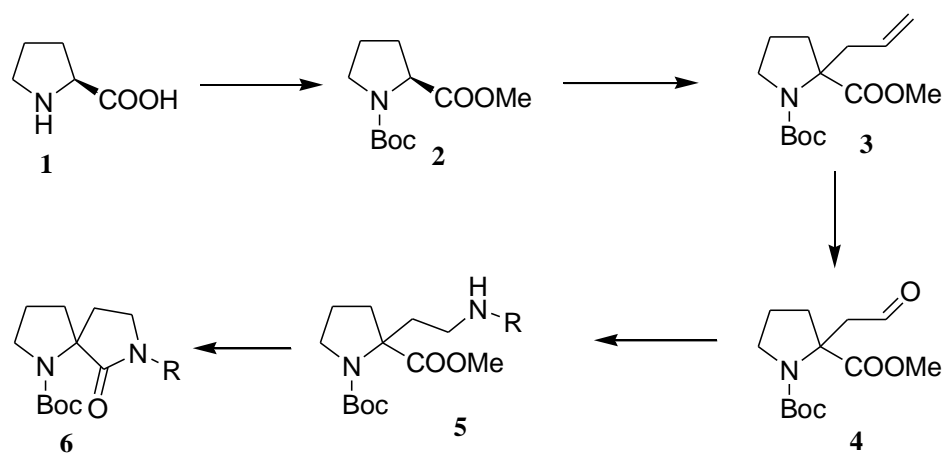
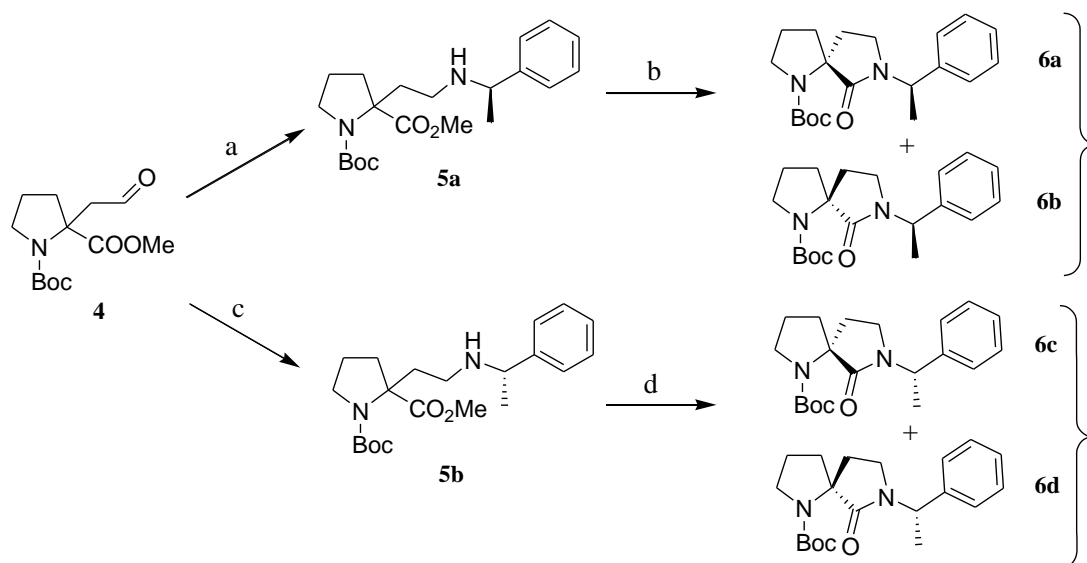
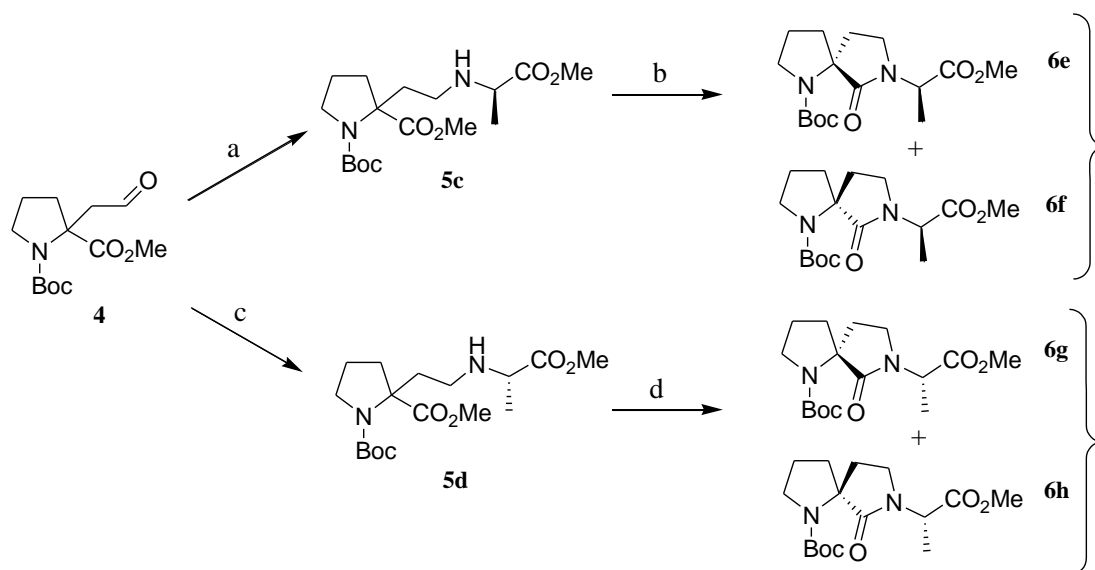


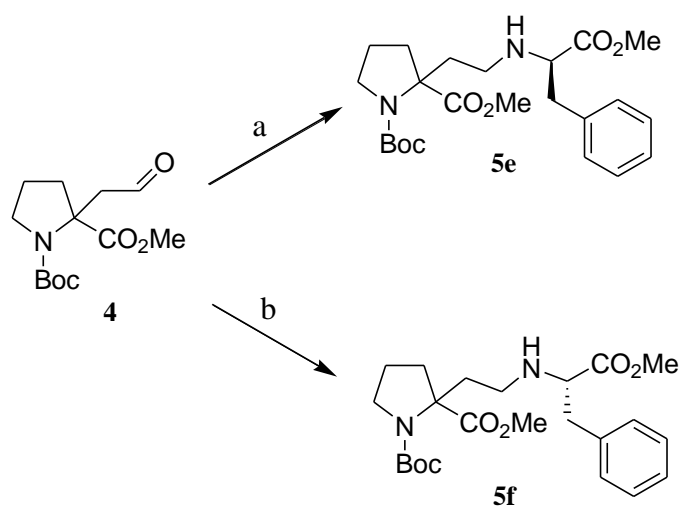
Figure 1. Synthesis of racemic [4.4]-spirolactams.⁴



Scheme 1: Reagents and conditions; (a) i) (*R*)- α -methylbenzylamine, MgSO_4 , MeOH, ii) NaBH_4 , rt; (b) NaNH_2 in toluene, reflux, 30% from **4**; (c) i) (*S*)- α -methylbenzylamine, MgSO_4 , MeOH, ii) NaBH_4 , rt; (d) NaNH_2 in toluene, reflux, 51% from **4**;



Scheme 2: Reagents and conditions; (a) i) (*R*)-alanine, MgSO_4 , MeOH, ii) NaBH_4 , rt; (b) toluene, reflux, 40% from **4**; (c) i) (*S*)-alanine, MgSO_4 , MeOH, ii) NaBH_4 , rt; (d) toluene, reflux, 54% from **4**;



Scheme 3: Reagents and conditions; (a) i) (*R*)-phenylalanine, MgSO₄, MeOH, ii) NaBH₄, rt, 80%; (b) i) (*S*)-phenylalanine, MgSO₄, MeOH, ii) NaBH₄, rt, 72%.

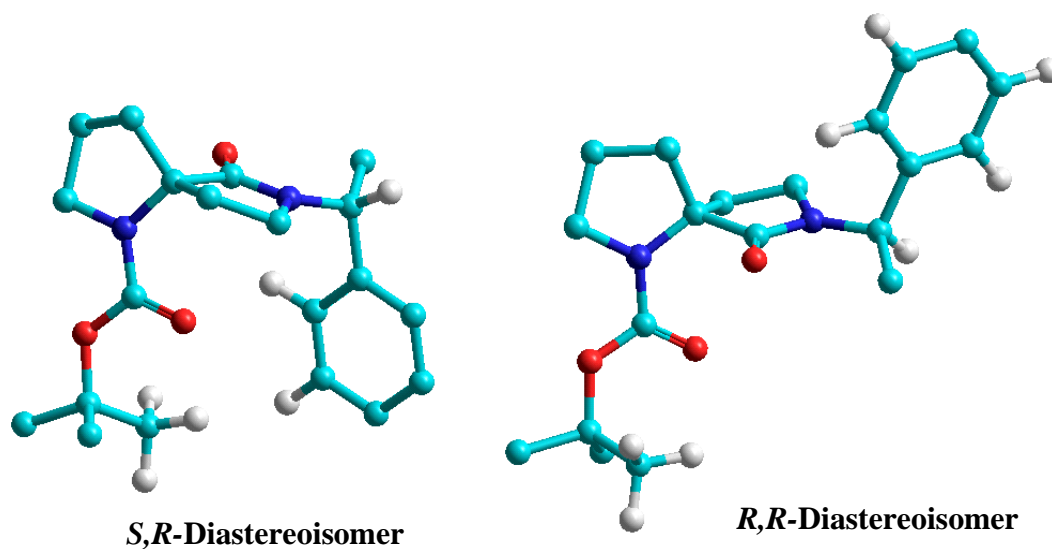


Figure 2. Energy minimised conformations of **6b** (*S,R*) and **6a** (*R,R*).⁵