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Spirobicyclic diamines 1: Synthesis of proline-derived spirolactams via thermal intramolecular ester aminolysis.

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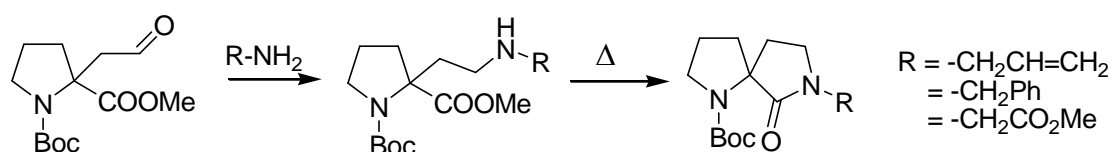
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Graphical abstract :

Spirobicyclic diamines 1: Synthesis of proline-derived spirolactams via thermal intramolecular ester aminolysis.

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Reductive amination of primary amines with a proline derived aldehyde followed by thermal cyclisation in refluxing toluene gave spirolactams in good yields.



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Abstract:

Proline derived [4.4]-spirolactams have been synthesised in good yields by a reductive-amination reaction followed by thermal cyclisation of the resulting amine onto the proline ester group in refluxing toluene. The synthesis of the corresponding [4.5]-spirolactams by the same method gave much reduced yields.

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 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 One of the most common methods for the synthesis of lactams is the cyclisation of an amino group (primary or secondary) onto a carboxylic ester, with concomitant loss of an alcohol. The overall efficiency of the cyclisation is dependent on 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. Many of the reactions take place spontaneously at ambient temperature, while others require heating in a suitable solvent.^{2b,3}

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. A number of different strategies have also been used for the critical final cyclisation step to form the spirobicyclic lactam ring.³⁻⁵ (Figure 1).

As part of a program to synthesise both homochiral and racemic spirocycles we were interested in the synthesis of both enantiomers of proline derived [4.4]-spirolactams, a racemic synthesis allows both enantiomers to be accessible, with the possibility of their resolution at a later stage by, for example, diastereoisomeric salt formation.⁶

The variety of different cyclisation methods used, along with their wide ranging yields, prompted us to study one of the methods, the thermal cyclisation reaction, in more detail in order to investigate whether it was a viable method for the synthesis of a range of proline-derived [4.4]-spirolactams. We were interested in having substituents already in place on the lactam nitrogen which would then allow for further manipulation and derivatisation. Of course this would increase the steric hindrance of the system and might have a detrimental effect on the yield of the cyclisation reaction. This necessitated the synthesis of secondary amines for subsequent cyclisation onto a carboxylic ester (Scheme 1).

Aldehyde **4** was prepared in 4 steps from L-proline by methyl ester formation, Boc protection of the nitrogen, α -allylation using LiHMDS as base with allyl bromide as alkylating agent and oxidative cleavage of the alkene using OsO₄/NaIO₄. We found that it was necessary to efficiently purify the aldehyde by column chromatography to completely free it from any traces of osmium by-products as failure to do so led to reduced yields in subsequent steps. Reductive amination of **4** with allyl amine in ethanol, followed by treatment of the intermediate imine with NaBH₄, gave the required secondary amine spirolactam precursor **5a**. Following the method of Johnson,^{4e,5} an almost quantitative (99%) yield of the spirolactam **6a** was obtained. Although this cyclisation was very efficient, we encountered problems in the work-up in removing excess DMF with a large number of extractions with water being required. As a result we examined the use of a different solvent and refluxing toluene was investigated for the cyclisation step. It was not necessary to purify the secondary amine intermediate prior to cyclisation, but direct reaction of the crude product was possible. Although the work-up procedure was now much simpler, the 66% yield obtained was much reduced. When benzylamine was used in place of allyl amine, using the same reaction cyclisation conditions (refluxing in toluene), the *N*-benzyl

substituted spiro lactam (**6b**) was obtained in a higher yield of 75% (in both cases the cyclisation reactions were performed in the absence of any acids or bases).

In order to investigate the possibility of the use of more synthetically useful amines in the cyclisation step (e.g. amino acids as the amine moiety), the reaction with glycine methyl ester (the free amine was obtained by treatment of the HCl salt with 2 molar equivalents of Hunig's base) was initially attempted. In this case the bicyclic spiro lactam **6c** was isolated in 90% yield. Since the syntheses of **6a** and **6b** were conducted in the absence of added base, these reactions were then repeated in the presence of 1 molar equivalent of Hunig's base. Surprisingly, this resulted in reduced yields of 50% and 61%, respectively, for **6a** and **6b**, compared to the reactions performed in the absence of added base. The reason for this reduction in yield is as yet unexplained.

We next examined the use of the thermal ester aminolysis method for the synthesis of the homologous [4.5]-spiro lactam analogues. This required the synthesis of the homologated aldehyde **8** (Scheme 2), for subsequent reaction to form the spiro δ lactams, under the same conditions as used to prepare the [4.4]-spiro lactams. The aldehyde was prepared from **3** by hydroboration-oxidation of the alkene followed by Swern oxidation⁷ of the resulting alcohol **7**. Reductive amination of crude **8** with allyl amine, and cyclisation in refluxing toluene, gave the required spiro δ lactam **10a** in only 20% yield, the remainder being the uncyclised secondary amine cyclisation precursor **11**. The use of benzylamine in the synthesis of *N*-benzyl spiro δ lactam **10b** gave no product after prolonged heating in refluxing toluene and only a 17% yield of the product was obtained, after treatment of the *N*-benzyl secondary amine analogue of **11**, with sodium hydride in THF at reflux temperature. This was not unexpected since, in general, the formation of 5-membered rings is thermodynamically more favourable than the corresponding 6-membered ring analogues. Johnson^{4e,5} also found a similar outcome when trying to use the thermal cyclisation method to synthesise the [4.5.5]-analogue of the compound in Figure 1. In that case no cyclisation was observed.

The unsubstituted [4.5]-spirolactam N-H analogue was synthesised in order to see how effective the thermal cyclisation of a primary amine onto an ester was in preparing the homologous spirolactam. The primary amine **12** was prepared by alkylation of **2** with the stabase-protected aminopropyl bromide, followed by deprotection with potassium carbonate in methanol, and subsequent stirring at reflux in toluene to induce cyclisation gave the spiro δ -lactam **9** in 30% overall yield from **2**. The *N*-allyl and *N*-benzyl derivatives (**10a** and **10b**) were prepared by alkylation with allyl and benzyl bromide respectively, using sodium hydride as base in THF. Attempts to prepare the compound with a $-\text{CH}_2\text{CO}_2\text{Me}$ (or the ethyl ester equivalent) side-chain by alkylation of the lactam nitrogen with methyl bromoacetate or the more reactive iodoacetate analogue were unsuccessful, with **9** being recovered unchanged, in each case.

In conclusion, the thermal ester aminolysis method allows the preparation of a series of *N*-substituted [4.4]-spirolactams in 60-70% overall yield starting from α -allyl ester **3**. The reactions have been scaled up to 10 g with no loss in yield. This route also allows the introduction of the lactam nitrogen substituent at a late stage in the synthesis and it proceeds from a common intermediate, namely aldehyde **4**. Currently we are studying the extension of this methodology to homochiral α -substituted amines and α -amino acids. The presence of the second chiral centre will allow the easy separation of the diastereoisomeric products. The results of these studies will be reported in due course.

Typical procedure for spirolactamisation, exemplified by the synthesis of 6c. To a stirred solution of glycine methyl ester hydrochloride (1.02 g, 8.10 mmol) in dry methanol (10 ml) was added dropwise diisopropylethylamine (2.58 ml, 14.80 mmol), followed by a solution of **4** in dry methanol (4 ml). After 3 h MgSO_4 (0.53 g, 4.43 mmol) was added and stirring was continued for a further 2 h. The reaction was cooled to -4°C and sodium borohydride (0.45 g, 11.80 mmol) was added portionwise, and the solution was stirred for 1 h and then saturated sodium hydrogen carbonate solution (7 ml) and water (3 ml) were added. The solution was extracted with ethyl acetate (3 x 20 ml), dried over MgSO_4 and concentrated *in vacuo*. The residual oil was stirred at reflux temperature in toluene (12 ml) for 16 h, allowed to cool to

ambient temperature and concentrated *in vacuo*. The residue was chromatographed on silica gel in 10% ethyl acetate/hexane to give **6c** as a pale yellow oil (1.91 g, 90%). R_f 0.33, 60% ethyl acetate/hexane. IR (*thin film*): 2975, 1751, 1700, 1251 cm^{-1} . ^1H NMR (CDCl_3 300.4 MHz, two rotamers present) δ 4.66 (d, 0.5H, $J = 17.7$ Hz, $-\text{CH}_2-\text{CO}_2\text{Me}$), 4.44 (d, 0.5H, $J = 17.5$ Hz, $-\text{CH}_2-\text{CO}_2\text{Me}$), 4.28 (d, 0.5H, $J = 15.0$ Hz, $-\text{CH}_2-\text{CO}_2\text{Me}$), 3.97 (d, 0.5H, $J = 14.5$ Hz, $-\text{CH}_2-\text{CO}_2\text{Me}$), 3.75 (s, 3H, $-\text{CO}_2\text{Me}$), 3.61-3.33 (m, 4H, pyrrolidine $\delta\text{-CH}_2$ and lactam $\gamma\text{-CH}_2$), 2.78-2.25 (m, 2H, lactam $\beta\text{-CH}_2$), 2.15-1.83 (m, 4H, pyrrolidine $\beta\text{-CH}_2$ and $\gamma\text{-CH}_2$), 1.45 and 1.41 (2 x s, 9H, *t*-butyl). ^{13}C NMR (CDCl_3 , 75.4 MHz) δ 175.3 (lactam carbonyl), 169.3 and 169.0 (ester carbonyl), 153.6 and 153.4 (Boc carbonyl), 80.0 and 79.6 (spiro-C q), 66.5 (*t*-butyl C q), 52.1 ($-\text{CO}_2\text{Me}$), 47.9 and 47.6 ($\underline{\text{C}}\text{H}_2\text{-CO}_2\text{Me}$), 44.7 and 44.5 (lactam $\delta\text{-CH}_2$), 43.9 and 43.7 (lactam $\gamma\text{-CH}_2$), 37.3 and 36.7 (lactam $\beta\text{-CH}_2$), 31.1 and 30.0 (pyrrolidine $\beta\text{-CH}_2$), 28.4 (*t*-butyl CH_3), 23.3 and 22.7 (pyrrolidine $\gamma\text{-CH}_2$). Microanalysis: Found: C, 57.38; H, 7.86; N, 8.71%. Calculated for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_5$: C, 57.68; H, 7.74; N, 8.97%.

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References and Notes

1. Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
2. (a) Freidinger, R.; Veber, D.; Perlow, D.; Brooks, J.; Saperstein, R. *Science* **1980**, *210*, 656. (b) Freidinger, R.; Perlow, D.; Veber, D. *J. Org. Chem.* **1982**, *47*, 104.
3. A number of examples are given and the list is far from exhaustive, but are included to just exemplify the methods used: (a) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091. (b) Reddy, P.; Hsiang, B.; Latifi, T.; Hill, M.; Woodward, K.; Rothman, S.; Ferrendelli, J.; Covey, D. *J. Med. Chem.* **1996**, *39*, 1898. (c) Batey, R., Mackay, D. *Tetrahedron Lett.* **2000**, *41*, 9935. (d) Vitry, C.; Vasse, J-L., Dupas, G.; Levacher, V.; Queguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 3087. (e) Nagata, T.; Nishida,

- A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345. (f) Herrero, S.; Garcia-Lopez, M.; Latorre, M.; Cenarruzabeitia, E.; Del Rio, J.; Herranz, R. *J. Org. Chem.* **2002**, *67*, 3866.
4. (a) Castelhana, A. Witter, D. *Patent No.* US6638941B1 **2003** (CAN 139:345905). (b) Montserrat Fernandez, M.; Diez, A., Rubiralta, M.; Montenegro, E.; Casamitjana, N. *J. Org. Chem.* **2002**, *67*, 7587. (c) Millet, R.; Goosens, L.; Bertrand-Caumont, K.; Goosens, J.-F.; Houssin, R.; Henichart, J.-P. *J. Pharm. Pharmacol.* **2001**, *53*, 929. (d) Millet, R.; Goosens, L.; Bertrand-Caumont, K.; Houssin, R.; Rigo, B.; Goosens, J.-F.; Henichart, J.-P. *Lett. Peptide Sci.* **2001**, *7*, 269. (e) Khalil, E.; Ojala, W.; Pradhan, A.; Nair, V.; Gleason, W.; Mishra, R.; Johnson, R. *J. Med. Chem.* **1999**, *42*, 628. (f) Witter, D.; Famiglietti, S.; Cambier, J.; Castelhana, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3137. (g) Genin, M.; Gleason, W.; Johnson, R. *J. Org. Chem.* **1993**, *58*, 860. (h) Ward, P.; Ewan, G.; Jordan, C.; Ireland, S.; Hagan, R.; Brown, J. *J. Med. Chem.* **1990**, *33*, 1848.
5. (a) Genin, M.; Ojala, W.; Gleason, W.; Johnson, R. *J. Org. Chem.* **1993**, *58*, 2334. (b) Hinds, M.; Welsh, J.; Brennan, D.; Fisher, J.; Glennie, M.; Richards, N.; Turner, D.; Robinson, J. *J. Med. Chem.* **1991**, *34*, 1777.
6. Ács, M.; Fogassy, E.; Faigl, F. *Tetrahedron* **1985**, *41*, 2465.
7. Mancuso, A.; Swern, D. *Synthesis* **1981**, 165.

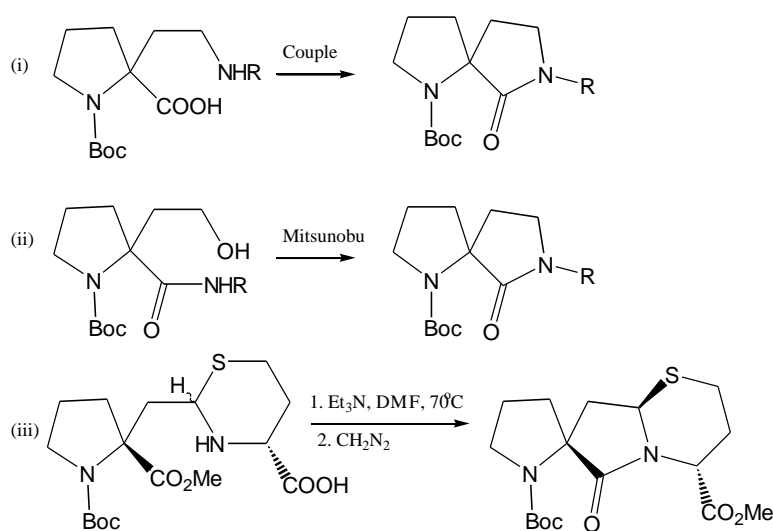
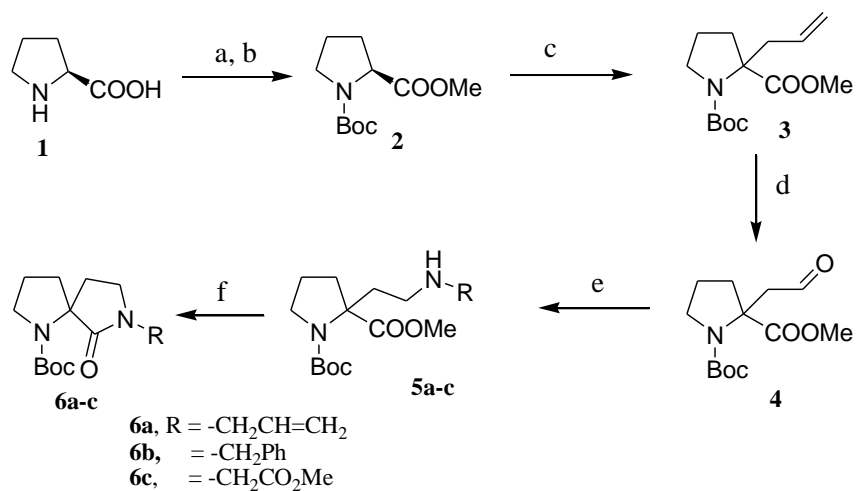
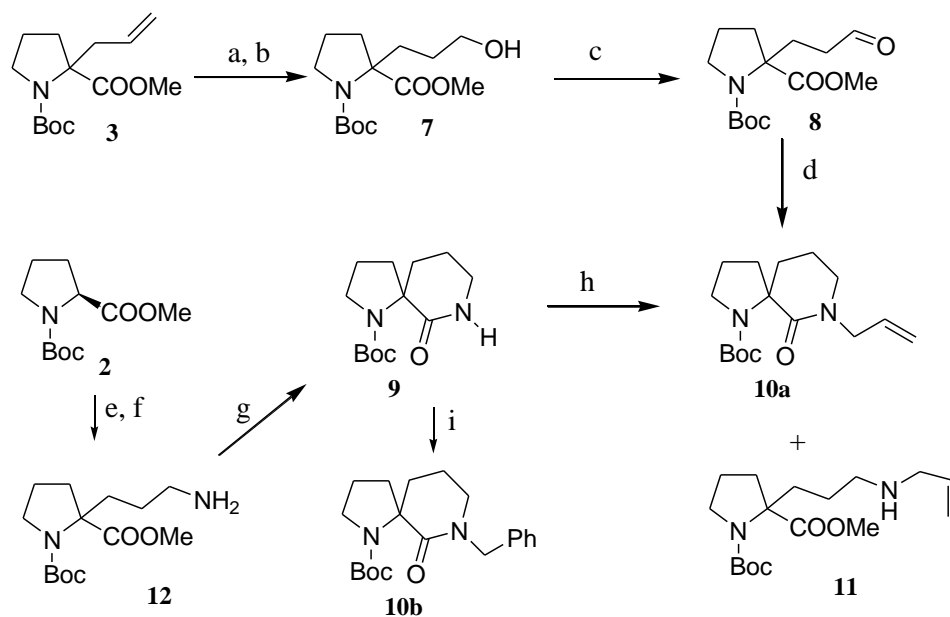


Figure 1: Cyclisation methods for proline-derived spirolactams.³⁻⁵



Scheme 1: Reagents and conditions; (a) SOCl_2 , MeOH, reflux, 94%; (b) $(\text{Boc})_2\text{O}$, DMAP, Et_3N , DCM, rt, 74%; (c) i) LiHMDS, THF, -78°C , ii) allyl bromide, rt, 80%; (d) $\text{OsO}_4/\text{NaIO}_4$, THF: H_2O (4:1), rt, 74%; (e) i) RNH_2 , EtOH, ii) NaBH_4 , rt; (f) Toluene, reflux, 66-90%



Scheme 2: Reagents and conditions; (a) 1M Borane-THF; (b) 30% $\text{H}_2\text{O}_2/\text{KOH}$, 58% from **3**; (c) $(\text{COCl})_2$, Et_3N , DCM, 94%; (d) i) Allyl amine, EtOH, ii) NaBH_4 , iii) Toluene, 100°C , 20%; (e) 1M LiHMDS, THF, 1-(3-Bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane; (f) K_2CO_3 , MeOH; (g) Toluene, reflux, 32% from **2**; (h) NaH, THF, allyl bromide, 75%; (i) NaH, THF, benzyl bromide, 73%.