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Syntheses of templates derived from pyrrolidine *trans*-lactams as potential serine protease inhibitors

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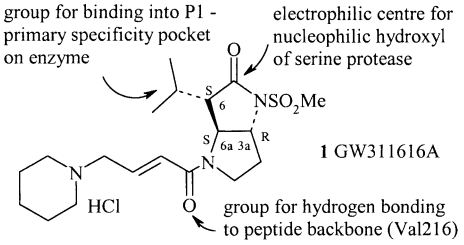
Abstract—The synthesis of templates derived from pyrrolidine *trans*-lactams as potential serine protease inhibitors is described.

1. Introduction

Serine proteases are a class of trypsin-like proteases that are implicated in many disease states.[1] Inhibitors belonging to new structural classes are therefore of enormous interest and potential therapeutic importance both to the pharmaceutical industry and the academic community. GSK have described a novel class of serine protease inhibitors known colloquially as the pyrrolidine *trans*-lactams which are exemplified by **1**, a potent inhibitor of human neutrophil elastase (HNE).[2] The *trans*-lactam template provides an important new broad-spectrum class of inhibitor for serine proteases. Through judicious choice of the substituent α to the lactam carbonyl it is possible to tune selective inhibition of different serine proteases such as chymotrypsin,[2a] cathepsin G,[2a] thrombin,[3] lactamase[4] and cytomegalovirus inhibitors.[5]

We identified **1** as a development candidate for HNE.[2d] In consequence, it became critical to gain a deeper understanding of this unusual ring system and to use the *trans*-lactam template as a springboard for discovering alternative 'second generation' inhibitor templates. In so doing, we aimed to preserve the key binding features we had identified as being necessary for inhibition (see **1**).[2c,d] The targets we have explored are summarised in Fig. 1. From this work we describe here our syntheses of these templates. They demonstrate some new (and sometimes unexpected) insights into the reactivity and chemistry of the *trans*-lactam template.



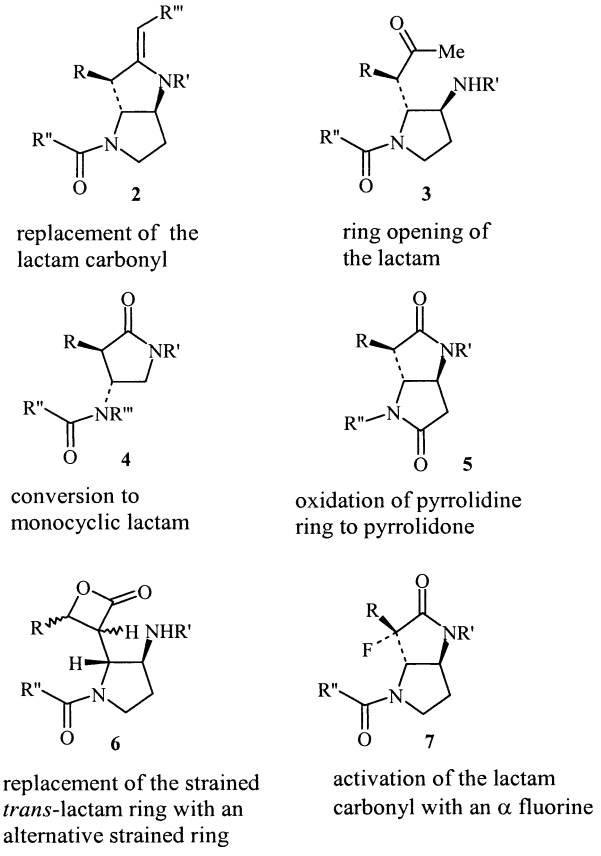


Figure 1.

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2. Chemistry

2.1. Replacing the lactam carbonyl 2

The replacement of the carbonyl group with an alternative electrophilic centre such as an acrylate,[6] proved acutely sensitive to the substrate (Scheme 1). Thus refluxing **8** with methyl (triphenylphosphoranylidene)acetate provided only the retro-Michael adduct **9** together with some reclosed *cis*-lactam **10**. Replacement of the arylsulphonamide with the less electron withdrawing benzylcarbamate **11**, at least facilitated attack at the lactam carbonyl, but with concomitant ring-opening to give the phosphoranylidene **12**. However, under similar conditions, **11** (critically, with R = Boc) did give, in an incomplete reaction, a 9% yield of the desired adduct **13**.

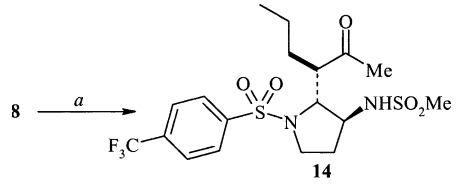
2.2. Ring-opened lactam 3

The ring-opened lactam is perhaps one of the simpler changes to the *trans*-lactam motif but provides a notably different conformation of the key binding substituents. Based on the experience above, we anticipated that reaction of the *trans*-lactam carbonyl with the Tebbe reagent[7] ([μ-chloro-μ-methylene[bis(cyclopentadienyl)titanium]dimethylaluminium]) should lead to an enamine unstable to hydrolysis and indeed, a 78% yield of the methyl ketone **14** resulted (Scheme 2).

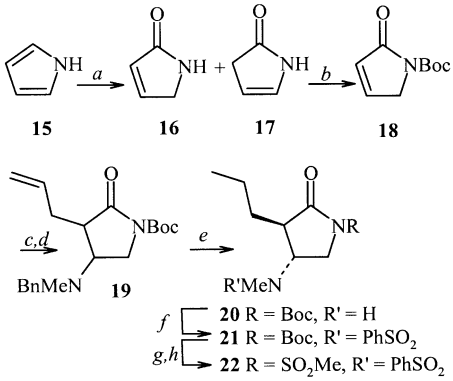
2.3. The monocyclic lactam 4

The monocyclic template is conformationally less rigid and planar than the pyrrolidine *trans*-lactam system.[8] However it was known that the electrophilicity of the lactam carbonyl could be tuned to the required reactivity through the lactam *N* substituent.[2c]

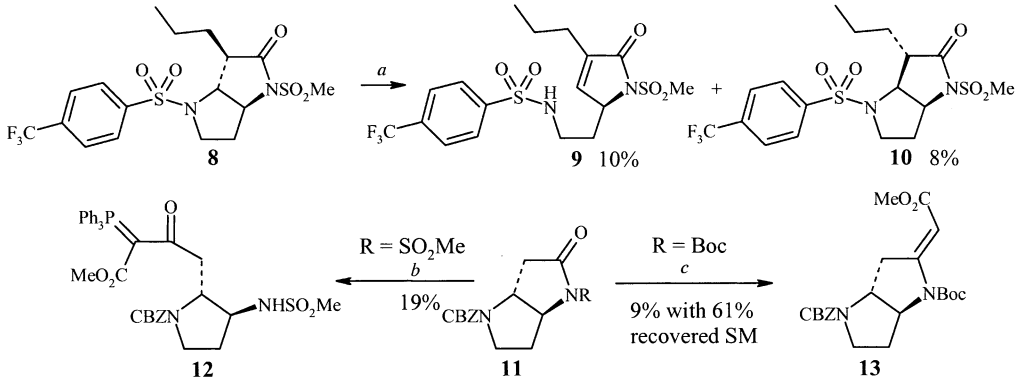
Oxidation of pyrrole with hydrogen peroxide catalysed with barium carbonate gave a 9:1 mixture of unsaturated lactams **16**:**17** (Scheme 3).[9] Protection of the crude mixture as the *t*-butylcarbamate derivatives, gave, after purification, **18** in 36% yield over two steps. Conjugate addition of methylbenzylamine to **18** in DMF, followed by the introduction of the allyl group gave **19** as one major isomer in 43% yield. Removal of the benzyl group and reduction of the allyl group then allowed derivation of the amine **20** to the sulphonamide **21** in 61% yield. The lactam *N* protecting group was cleaved with TFA and the *trans* stereochemistry was confirmed by nOe experiments. Deprotonation of **21** and treatment with mesyl chloride[2b] gave the acyl sulphonamide **22** in 37% yield.[10]



Scheme 2. All structures racemic. *Reagents and conditions*: (a) Tebbe reagent (1 equiv.), 0°C to rt, 5 h, then aq. MeOH, 78%.



Scheme 3. *Reagents and conditions*: (a) $BaCO_3$ (10 mol%), 30% aq. H_2O_2 (1 equiv.), H_2O, reflux, 3 h; (b) Boc_2O, DMAP (5 mol%), MeCN, rt, 45 min, 36% over two steps; (c) BnMeNH (1 equiv.), DMF, rt, 18 h; (d) $LiN(SiMe_3)_2$ (1.1 equiv.), THF, −70°C, 30 min, then allyl iodide (2 equiv.), −70°C, 2 h, 43% over two steps; (e) $Pd(OH)_2$ (cat.), H_2, EtOAc, rt, 18 h; (f) $PhSO_2Cl$ (3 equiv.), Et_3N, (3 equiv.), DCM, rt, 61% over two steps; (g) TFA (50 equiv.), DCM, rt, 4 h; (h) $LiN(SiMe_3)_2$ (1.5 equiv.), THF, −70 to 0°C, 15 min, recool to −70°C, $MeSO_2Cl$ (2.5 equiv.), 2 h, 37% over two steps.



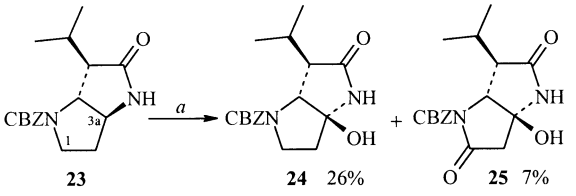
Scheme 1. All structures racemic. *Reagents and conditions*: (a) Ph_3PCHCO_2Me, PhMe, reflux, 46 h; (b) Ph_3PCHCO_2Me (1.6 equiv.), PhMe, reflux, 32 h; (c) Ph_3PCHCO_2Me, PhMe (1.6 equiv.), reflux, 93 h.

2.4. Oxidation of the pyrrolidine ring 5

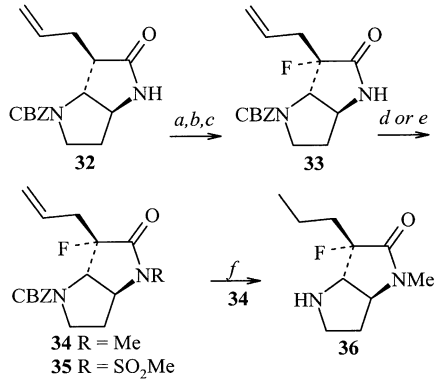
Introduction of a carbonyl group into the pyrrolidine ring provides both a more planar conformation of the bicycle and an alternative hydrogen bonding acceptor to the carbamate carbonyl. We expected this system would be readily accessible from the lactam **23** by oxidation with ruthenium oxide. However, oxidation occurred initially at C3a giving **24**; extended treatment led to subsequent oxidation at C1 (**25**) (Scheme 4). Oxidation at C3a results in inversion of the ring geometry presumably driven by the conformational preference for the *cis*-fused ring system. Alternative approaches to the *trans*-fused ring system were not pursued.

2.5. Replacing the *trans*-lactam ring with an alternative ring 6

Four membered ring compounds such as β-lactams, are known elastase inhibitors.[11] The β-lactone **28** was prepared from the activated *trans*-lactam **26** by deprotonation and reaction, from the α-face of the enolate,[12] with acetaldehyde (Scheme 5). Reaction of the intermediary alkoxide **27** with the activated *trans*-lactam carbonyl leads to **28** (IR carbonyl stretching frequency 1816 cm^{-1}) in 30% yield. An alternative, competitive pathway for **27** is reaction with further acetaldehyde leading to the unassigned acetal isomers **29** and **30** in 15 and 32% yields, respectively. The alcohol derived from **27** was not observed in the crude reaction mixture. The β-lactone **28** can be converted into the γ-*trans*-lactam **31** by deprotection of the *t*-butylcarbamate (78%) and treatment with *t*-butyl magnesium chloride (43%). Presumably the attenuated electrophilicity of the lactam carbonyl of **31** compared with the starting lactone carbonyl of **28**, prevents regeneration of the β-lactone from the magnesium alkoxide of **31** generated in the reaction mixture.



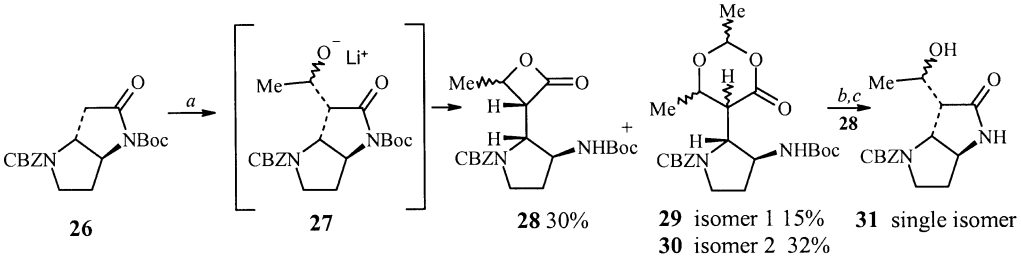
Scheme 4. All structures racemic. *Reagents and conditions*: (a) RuO_4 (7 mol%), 10% aq $NaIO_4$ (xs), EtOAc, 5 h, rt.



Scheme 6. All structures racemic. *Reagents and conditions*: (a) Boc_2O (4 equiv.), Et_3N (1 equiv.), DMAP (0.25 equiv.), MeCN, rt, 18 h, 66%; (b) $LiN(SiMe_3)_2$ (1.1 equiv.), THF, −78°C, 30 min then $(PhSO_2)_2NF$ (5 equiv.), THF, −78°C, 3 h; (c) 10:1 DCM:TFA, rt, 30 min, 74% for two steps; (d) $LiN(SiMe_3)_2$ (1.1 equiv.), THF, −70 to 0°C, 15 min, recool to −70°C, MeI (6 equiv.), then warm to rt, 4 h, 84%; (e) $LiN(SiMe_3)_2$ (1.3 equiv.), THF, −70 to 0°C, 15 min, recool to −70°C, $MeSO_2Cl$ (2.5 equiv.), 1 h, 75%; (f) 10% $Pd(OH)_2$ (cat.), H_2, rt, 5 h, 96%.

2.6. Lactam carbonyl activation by α-fluorination 7

Trifluoromethyl ketones are well established inhibitors of HNE.[1] Thus fluorination alpha to the carbonyl may reduce the need for a powerful electron withdrawing substituent on the lactam *N*. After protection of **32** as its *t*-butyl carbamate derivative, deprotonation and treatment with excess *N*-fluorodibenzenesulphonamide, introduced the fluorine stereoselectively (Scheme 6). Deprotection of the crude material, followed by purification gave the lactam **33**[13] in 74% yield for two steps. It was not possible to confirm the stereochemistry of the fluorine substituent until conversion to **36**; however it is unlikely that the stereochemistry changes once the fluorine is introduced. Fluorination from the lower face is explained in terms of reducing steric hindrance between the strained and rigid lithium enolate and the incoming electrophile.[12] The methyl and mesyl lactams **34** and **35**[13] were readily prepared by treatment of the lithium salt of **33** with the appropriate electrophile. Removal of the CBZ group from **34** to give the amine **36** allowed assignment of the stereochemistry by nOe NMR experiments. The infra-red carbonyl stretching frequencies of **34** and **35** showed no substantial difference to the des-fluoro analogues.



Scheme 5. All structures racemic. *Reagents and conditions*: (a) $LiN(SiMe_3)_2$ (1 equiv.), THF, −78°C, 15 min then MeCHO (1 equiv.) 1.5 h; (b) 4 M HCl, 1,4-dioxan, rt, 45 min, 78%; (c) ^tBuMgCl (3 equiv.), THF, rt, 30 min, 43%.

3. Conclusion

Described herein are the syntheses of a variety of templates derived from pyrrolidine *trans*-lactams. We found much of the chemistry of the *trans*-lactam ring system to be governed by the planarity of the bicylic template, the propensity for lactam opening or equilibration to the corresponding *cis*-fused system. These templates have a range of inhibitory activities against HNE. The details of activity and further medicinal chemistry of these templates will be described elsewhere.

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10. The carbonyl stretching frequency of **22** is 1735 cm^{-1} compared with 1745 cm^{-1} for a typical pyrrolidine *trans*-lactam such as **1**.
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13. Infra-red carbonyl stretching frequencies for **33** (1726 cm^{-1}), des-fluoro analogue (1720 cm^{-1}), **35** (1765 cm^{-1}), des-fluoro analogue (1768 cm^{-1}) (all values measured using KBr diffuse reflectance).