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Piperidones: from alkaloids to pseudopeptides

Pilar Forns, Mario Rubiralta, and Anna Díez*
Laboratori de Química Orgànica. Facultat de Farmàcia. Universitat de Barcelona

Abstract

Our early work on the synthesis of alkaloids that contain a piperidine ring led us to prepare diversely functionalised piperidines as scaffolds for building more complex structures. Since then we have prepared a number of piperidone synthons, and we have applied these to the preparation of biologically interesting compounds which range from alkaloids to conformationally constrained pseudopeptides. We provide here a brief historical introduction, followed by eight sections, dedicated to our most relevant piperidine synthons: i) 2-aryl-4-piperidones, ii) Δ^3-piperidein-2-ones and 2-cyanopiperideines, iii) 3-amino-2-arylpiperidin-4-ones, iv) 3-aminopiperidin-2-ones, v) glutarimides, vi) 3-amino-Δ^5-piperidein-2-ones, vii) oxazolopiperidones, and viii) hydroxylactams.

Resum

Els nostres treballs inicials sobre la síntesi d'alcaloides que contenen un anell de piperidina en llur estructura, ens va portar a la preparació de sintons piperidínics diversament funcionalitzats sobre els quals construir molècules més complexes. Des de llavors hem sintetitzat algunes piperidones, que hem emprat per a la obtenció de compostos amb interès biològic. Al llarg dels anys, aquests compostos van des dels alcaloides fins a pseudopèptids de conformació restringida. Aquest article consta, per tant, d'una breu introducció històrica, seguida de vuit capítols corresponents als sintons piperidínics més rellevants que hem desenvolupat: i) 2-aril-4-piperidones, ii) Δ^3-piperidein-2-ones i 2-ciano-Δ^3-piperideïnes, iii) 3-amino-2-arilpiperidin-4-ones, iv) 3-aminopiperidin-2-ones, v) glutarimides, vi) enamides, vii) oxazolopiperidones i viii) hidroxilactams.

Keywords: 2-aryl-4-piperidones, 3-aminolactams, indole alkaloids, pseudopeptides, peptidomimetics.

1. Introduction

In the early 1980's our group was working on the synthesis of monoterpene indole alkaloids and their derivatives. We were particularly interested in four families: *Corynanthe*, *Vinca-Eburnane*, *Strychnos* and *Aspidosperma* (Figure 1). Some representatives of these families still find clinical use; vincamine, is used as a brain vasodilator in geriatric patients, and vincristine is used as an antineoplasic agent in the treatment of certain cancers. The widespread use of these drugs is only possible, however, because chemical synthesis provides them in quantities not obtainable from natural sources, where the amounts of the active principles are too low. In addition, these drugs are highly toxic. Less toxic and more specific synthetic analogues could lead to the improvement of the quality of life of patients under treatment.

The four families of indole alkaloids mentioned above were attractive as targets for synthesis because they share a common structural feature, a 2-indolylpiperidine unit. Our general synthetic approach was to focus on this moiety, using functionalized piperidine synthons as scaffolds to build more complex molecules. The first piperidine synthon we prepared was a 2-aryl-4-piperidone, reviewed in Section 2. We have subsequently developed a number of piperidones and applied them to the preparation of piperidine compounds with biological interest.

* Author for correspondence: Anna Díez, Laboratori de Química Orgànica. Facultat de Farmàcia. Universitat de Barcelona. Av. Diagonal 641. 08028 Barcelona, Catalonia (Spain). Tel. 34 934035849. Fax: 34 934024540. Email: adiez@farmacia.far.ub.es

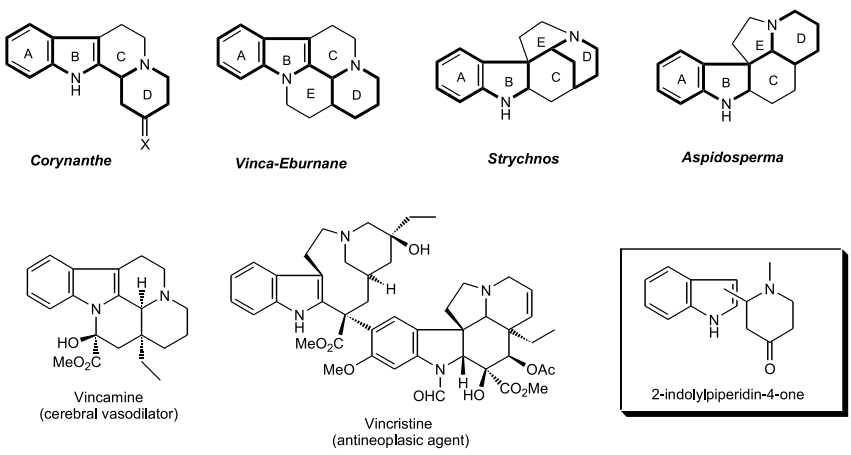


Figure 1

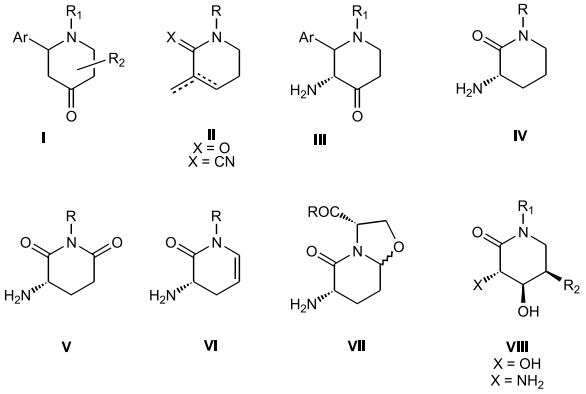


Figure 2

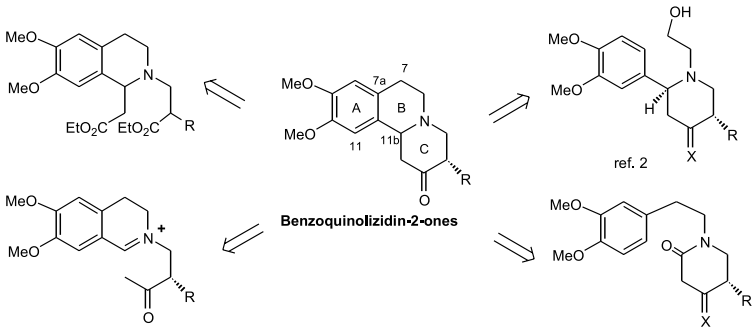


Figure 3

At about this time, models to explain how biological receptors operate were beginning to appear [1], although the relationship between structure and biological activity remained largely mysterious. Thus, compounds of similar structure proved to have different biological properties, and compounds with very different structures were found to be useful against the same disease. The possibility of using rational design to improve molecules showing potential clinical efficacy was, consequently, very tempting. Indeed, progress in understanding the modes of action of compounds has since aided the rational design of new «drug leaders». Many compounds act by mimicking the action of endogenous peptides, and peptide mimetics has become an intensely active field of pharmacological study. As our research has advanced, we have continued to seek structures that contain the piperidine core and that have potential use in the pharmacological field. By modifying our piperidine synthons we have widened their scope, and our research has evolved towards molecules that might act as small peptidomimetics. The focus of our most recent work is the preparation of 3-aminopiperidin-2-ones (Figure 2) whose backbone makes them intrinsically biologically interesting (see for example, Section 4.1). In addition, they can be considered as conformationally constrained dipeptide surrogates (see section 5), and can be used to improve the activity of known peptides.

This review is organized into eight sections, each devoted to one of the most relevant synthons on which we have focused our work: 2-aryl-4-piperidones (**I**), unsaturated valerolactams and 2-cyanopiperideines (**II**), 3-amino-2-arylpiperidin-4-ones (**III**), 3-aminopiperidin-2-ones (**IV**), glutarimides (**V**), enamides (**VI**), oxazolopiperidinones (**VII**), and hydroxylactams (**VIII**).

2. 2-Aryl-4-piperidones (I)

We developed our first synthon, 2-aryl-4-piperidone **I** (Figure 2), with the aim of forging a new route to the benzoquinolizidine alkaloids. At the time, the known methods for obtaining this tricyclic structure were closure of ring C by either Dieckmann cyclization or the Mannich reaction, and formation of the 11a-11b bond through a Bishler-Napieralsky reaction (Figure 3). Our approach was to close ring B by formation of the 7-7a bond [2], for which we had first to prepare the appropriate 2-phenyl-4-piperidone, a system that had never been described.

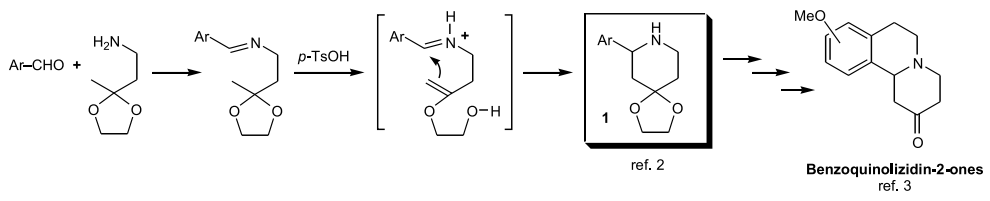
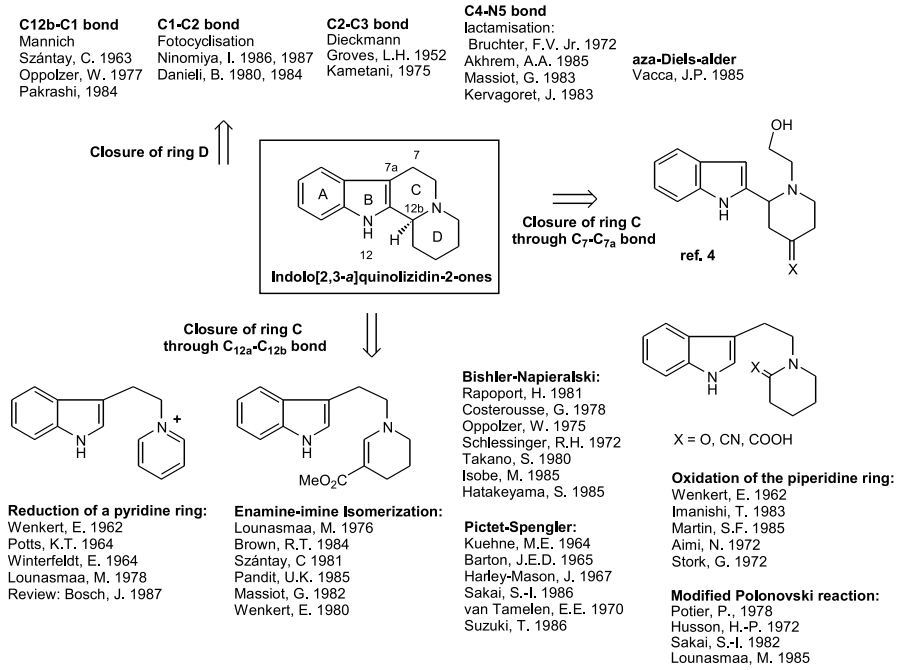


Figure 4



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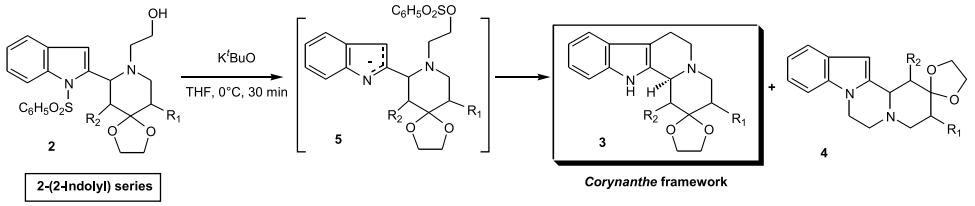
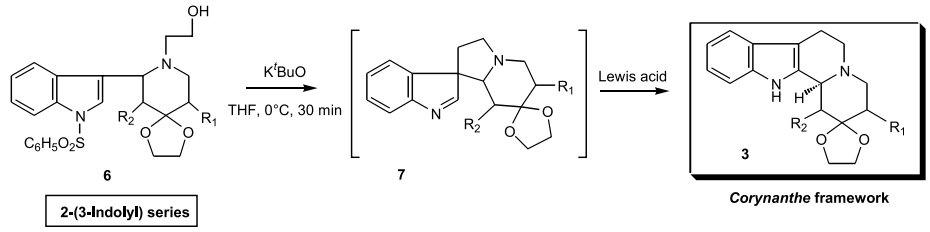


Figure 6



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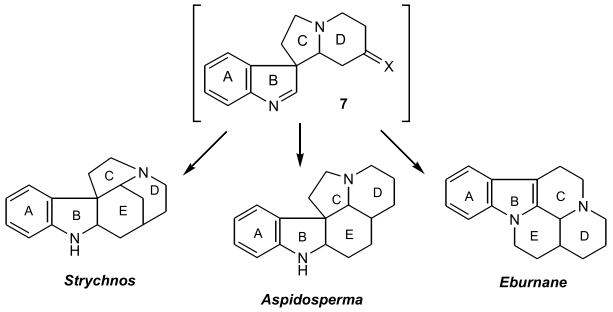


Figure 8

The synthesis of the required 2-phenylpiperidin-4-one was achieved by condensation of the suitable primary aminoacetal with benzaldehyde, followed by an acid-promoted Mannich-type cyclisation (Figure 4) [3]. Indeed, in a dry acid medium the protonation of the acetal allows the formation of an enol ether which attacks the intramolecular iminium salt. This proved to be a general method for obtaining protected 2-aryl-4-piperidones **1**, by using any aromatic aldehyde.

2.1. ***Corynanthe*** alkaloids

Our interest in the quinolizidines led us to attempt the preparation of *Corynanthe* indole alkaloids. The reported methods for synthesis of the indolo[2,3-α]quinolizidine ring system were based on closure either of ring C through formation of the C_{12a}-C_{12b} bond, or of ring D (Figure 5). We planned to explore the possibility of applying our method to close ring C by formation of the C_7-C_{7a} bond.

We discovered that the treatment with K^{t}BuO of a 2-(2-indolyl)piperidine **2**, whose indole nucleus was protected with a phenylsulfonyl group and whose piperidine nitrogen atom carried 2-hydroxyethyl chain, yielded directly the indoloquinolizidine system **3** (Figure 6). However, pyridopyrazinoindole **4** was also obtained. This result, together with

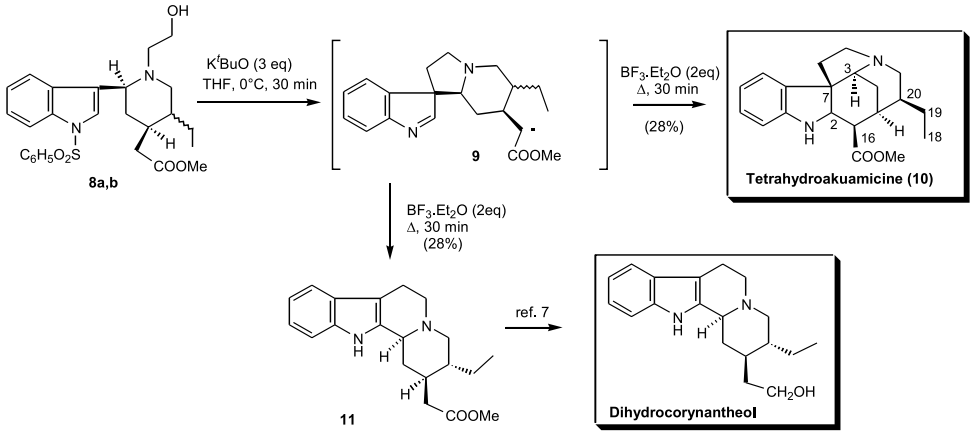


Figure 9

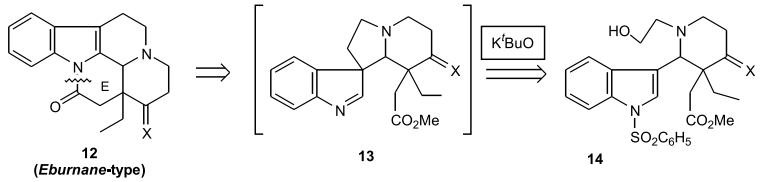


Figure 10

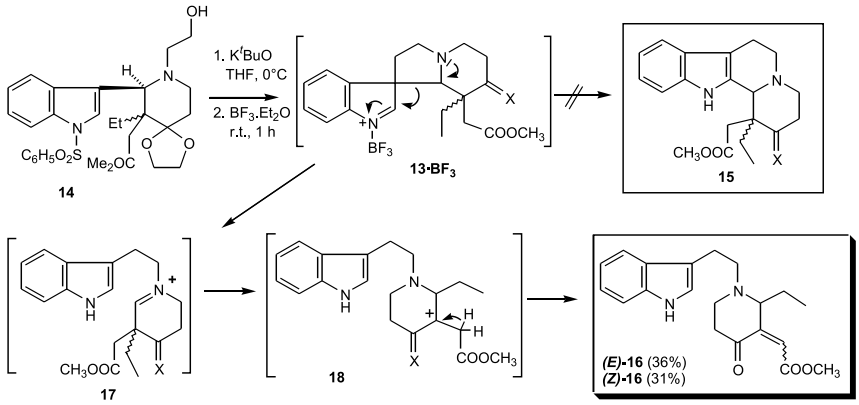


Figure 11

those of other experiments, allowed us to give a mechanistic explanation [4].

The K^{t}BuO acted as a nucleophile on the sulfonyl group, allowing its migration to the alcoholate *via* transesterification. The resulting intermediate **5** underwent intramolecular attack of the bidentated indole anion on the sulfoxyl leaving group. Thus, the indoloquinolizidine system was obtained in one step as a product of cyclisation on the indole 3-position, although inevitably accompanied by the pyridopyrazinoindole that results from cyclisation on the indole nitrogen atom.

To avoid the formation of the undesired regioisomer, we applied the reaction to a 2-(3-indolyl)piperidine **6**. In this case, the intermediate formed with K^{t}BuO would be a spiroindolenine **7**, which was known to rearrange to the desired quinolizidine upon treatment with a Lewis acid (Figure 7) [5].

Structurally, the intermediate spiroindolenines **7** constitute the ABCD ring system characteristic of *Aspidosperma* and *Strychnos* alkaloids, so we considered the possibility of building the fifth E ring by integrating a carbonated chain between the imine carbon atom and positions 3 or 4 of the piperidine ring, respectively (Figure 8). In addition, an appropriate substitution on the piperidine C3 position might also be used to obtain the *Eburnane* framework after rearrangement to an indoloquinolizidine.

2.2. Synthesis of ***Strychnos***-type compounds ***via*** protected 2-indolyl-4-piperidones

To synthesize *Strychnos*-type compounds, we first prepared 2-(3-indolyl)piperidines **8a** and **8b** following our methodology (Figure 9) [6]. Piperidines **8a** and **8b** bear an acetate chain on the 4-position, *cis* with respect to the indole substituent, and are epimeric on C-5. Treatment of the mixture of **8a** and **8b** with an excess of K^{t}BuO followed by addition of BF_3.Et_2O to the reaction medium provided a mixture of compounds **10** and **11** (Figure 9). Indoloquinolizidine **11** was already known to be a precursor of dihydrocorynantheol [7], and compound **10** was identified as tetrahydroakuammicine. We had thus achieved a formal synthesis of dihydro-

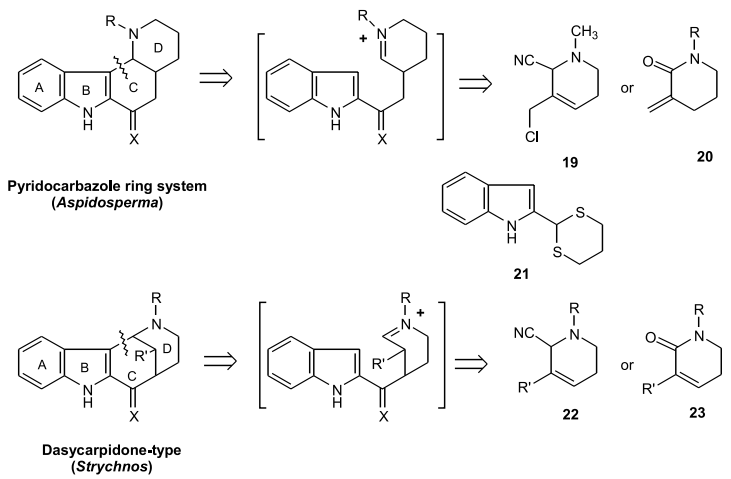


Figure 12

corynantheol, and opened a new synthetic route to the pentacyclic *Strychnos* structure [8,9].

2.3. Attempts to synthesize the ***Eburnane*** and ***Aspidosperma*** alkaloids

According to our reasoning (Figure 8), it should be possible to synthesize the *Eburnane*-type structure **12** by closing the C_{16}-N_1 bond after rearrangement of a spiroindolizidine **13** to the corresponding quinolizidine (Figure 10). Compound **13** would be obtained from 2-indolylpiperidine **14** by treatment with K^{t}BuO.

However, when we treated piperidine **14** with K^{t}BuO under the conditions normally used to obtain spiroindolenine **13**, and then induced rearrangement to the indoloquinolizidine **15** using $BF_3.Et_2O$, the only products obtained were tryptophylpiperidines **16** (Figure 11) [10].

We had already observed that spiroindolenines carrying substituents on the piperidine C3 [11] or the indole C2 [12] positions evolve naturally to tryptophylpiperidines type **17** through opening of the pyrrole ring by anchimeric assistance of the nitrogen atom. It appeared that the ring opening was quicker than the rearrangement because of the steric interaction. In the absence of a nucleophile or oxidizing agent [5b], the resulting iminium salt (type **17**) would usually evolve to the corresponding enamine. However, in the present case, the lack of a hydrogen atom on C3 prevents the tautomeric equilibrium of **17**, and a Wagner-Meerwein rearrangement of the ethyl chain takes place, followed by elimination to give the stable unsaturated ester **16**.

In any case, the high instability of the intermediate spiroindolenine **13** rendered our strategy unsuitable for obtaining either *Eburnane* or *Aspidosperma* alkaloids.

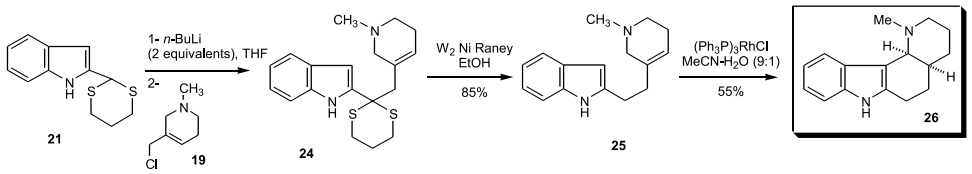


Figure 13

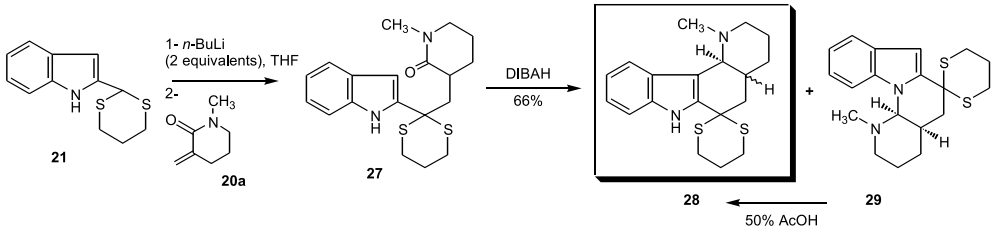


Figure 14

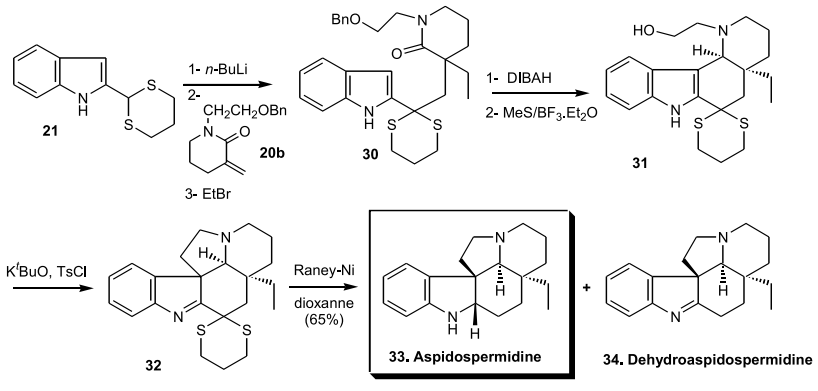


Figure 15

3. Unsaturated valerolactams and 2-cyanopiperidines (II)

In the light of our previous results, we planned to obtain both the *Aspidosperma* and the *Strychnos* frameworks by closing the pyrrole C ring (Figure 8) on a suitable ABED tetracyclic system, a strategy that had already been reported [13]. The bridged tetracyclic framework of the *Strychnos* alkaloids constitutes the structure of dasycarpidone alkaloids. In the case of *Aspidosperma*, the preparation of a pyridocarbazole was necessary.

We devised a single approach for synthesis of both tetracyclic ring systems, with the key step being the closure of the bond between the indole nucleus and the piperidine C2-position (Figure 12). We chose 2-cyanopiperidines **19** and **22** as latent iminium salts, with lactams **20** and **23**, whose partial reduction would also provide the desired iminium salts, as alternatives. The nucleophile indole synthon in both cases would be 2-(1,3-dithian-2-yl)indole **21**.

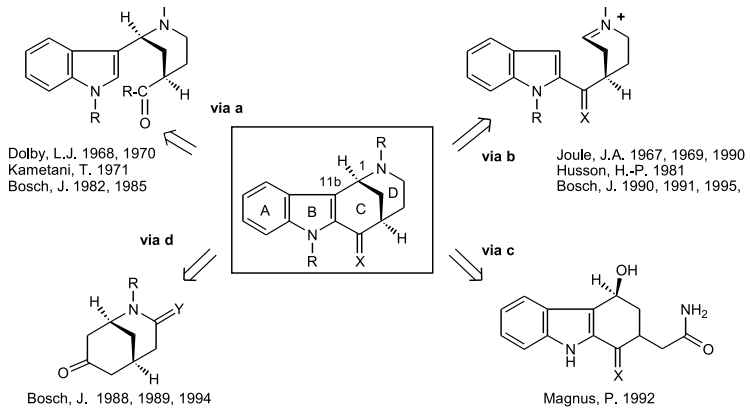


Figure 16

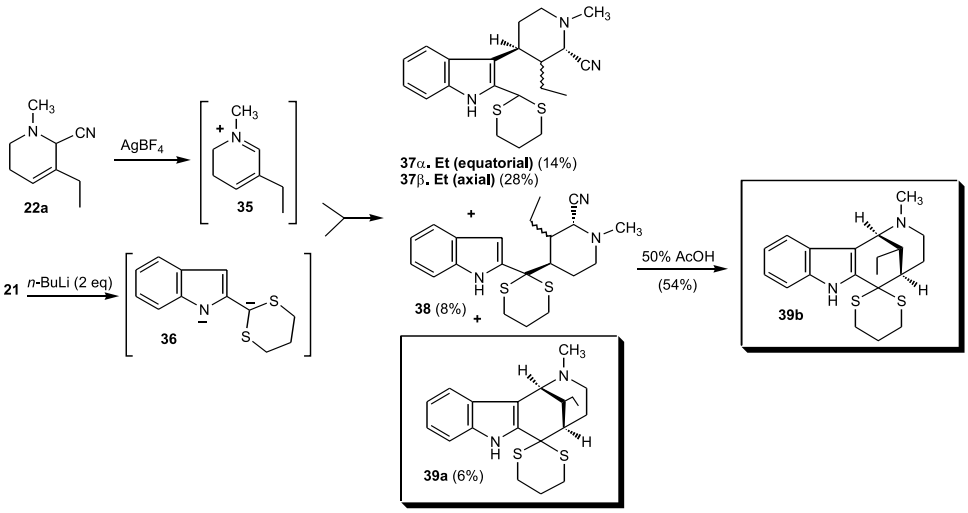


Figure 17

3.1. Synthesis of *Aspidosperma*-type compounds

We first carried out the condensation of 3-chloromethylpiperideine **19** with the dianion of indolyldithiane **21**, to obtain compound **24**. Sequential Ni-Raney reduction and cyclization with rhodium chloride triphenylphosphine complex [14] then led to the target compound **26** (Figure 13) [15]. However, this method did not allow cyclization in the presence of the sulfur atoms, and thus limited considerably the possibilities of functionalizing the system.

To circumvent this problem, we prepared the pyridocarbazole tetracycles **28** by conjugate addition of the dianion of dithiane **21** on 3-methylenelactams **20a**, followed by treatment of the adduct with DIBAH (Figure 14). The reduction takes place with spontaneous cyclization of the iminium salt to give the desired pyridocarbazoles **28** (C/D ring junction *cis* and *trans*) and their regioisomer, the naphthyridoindole **29** [16]. Naphthyridoindole **29** was isomerised to compound **28** in 50% aqueous AcOH.

Subsequently, we introduced an ethyl chain on C3 by a tandem conjugate addition-alkylation reaction, using lactam **20b** as the starting material. In this case, only the C/D *cis* pyridocarbazole was obtained, and closure of the pyrrolidine ring followed by reduction of the dithiane ring yielded the alkaloid aspidospermidine (Figure 15) [16].

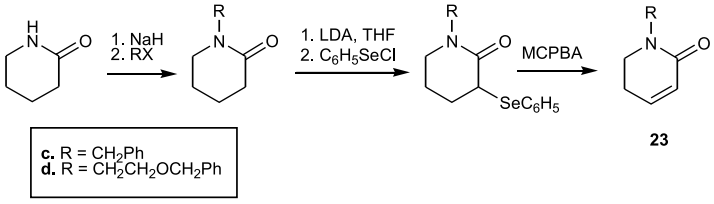


Figure 1

3.2. Synthesis of dasycarpidone-type alkaloids

Previous synthesis of the dasycarpidone ring system (Fig. 16) had been based on closure of ring C (a, b) or ring D (c), or by indolization (d).

To obtain the dasycarpidone ring system, we generated the iminium salt **35** by treating the 2-cyanopiperidine **22a** with $AgBF_4$ (Figure 17). The dianion of indolyldithiane **21** was generated in an adjacent reaction, and then added *via* cannula to the dihydropyridinium salt. The major adducts derived from this reaction were **37**, derived from condensation on the indole 3-position. The minor products were compound **39a**, identified as the direct precursor of 20-epidasycarpi-

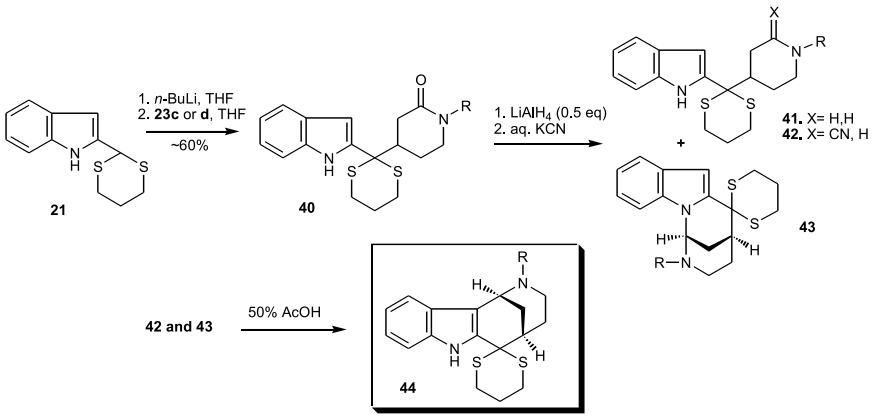
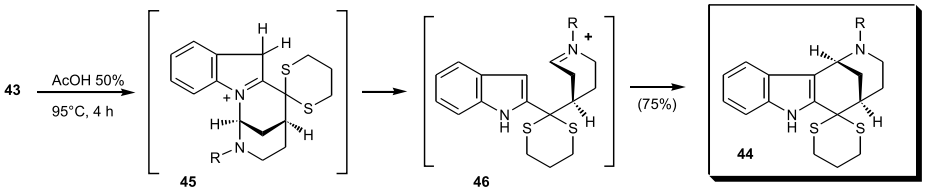


Figure 19



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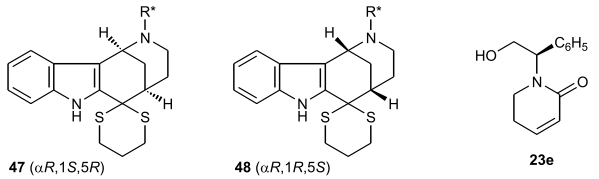


Figure 21

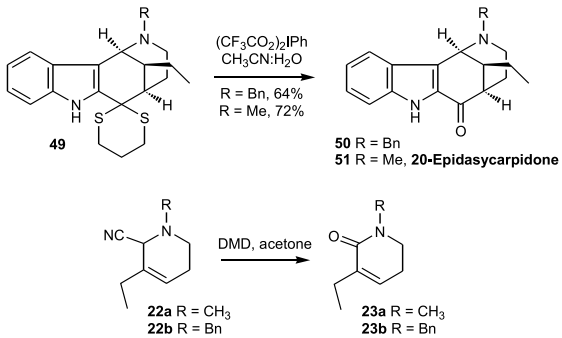


Figure 22

done, and 2-cyanopiperidine **38**, which yielded the dasycarpidone precursor **39b** upon cyclization with AcOH [17]. Thus, the target compounds were obtained, but in very low yield owing to the poor regioselectivity of the condensation.

To avoid the regioselectivity problem, we performed the conjugate addition of the indolyldithiane anion on the α,β-unsaturated lactam **23c** or **23d** (Figure 18). Lactams **23c** and **23d** were prepared from δ-valerolactam by *N*-alkylation, phenylselenylation on the 3-position and subsequent oxidation/elimination of the selenide by treatment with MCPBA.

The Michael-type addition of the dianion of indolyldithiane **21** on lactam **23c** or **23d** in THF yielded the expected adduct **40** as the only product (Figure 19). Partial reduction of lactam **39** was achieved with LiAlH4 in the presence of cyanide anions, and led to a mixture of piperidine **41**, 2-cyanopiperidine **42** and methanodiazocinoindole **43**. Treatment of compounds **42** and **43** with 50% aqueous AcOH transformed both to the target dasycarpidone-type tetracycle **44**, in high yield.

We envisioned the isomerization of methanodiazocinoindole **44** occuring as depicted in Figure 20. In the acid medium the indole 3-position is rapidly protonated leading to formation of the iminium salt **45**. This, through an imine-enamine tautomerism, then cyclises to give the regioisomeric dasycarpidone methanoazocinoindole ring system.

We subsequently applied this strategy to the diastereoselective synthesis of compounds **47** and **48** (Figure 21), using the chiral lactam **23e** as the electrophile [18]. Lactam **23e**, an *(R)*-(-)-phenylglycinol derivative, was prepared by oxidation of the corresponding saturated lactam [19]. In this study, the reduction/cyclisation step was improved by the use of Red-Al®.

We also applied the methodology to the preparation of compounds **49** (R = Bn, Me), which were converted to the corresponding acylindole derivatives **50** and the alkaloid 20-epidasycarpidone, respectively (Figure 22) [20]. In this case, the unsaturated valerolactams required **23a** and **23b** were obtained by DMD oxidation [21] of the corresponding 2-cyano-3-ethyl-Δ^3-piperidein-2-ones **22a** and **22b**.

3.3. Lactam Pseudopeptides: 3-Amino-4-indolyl-2-piperidone

The use of unsaturated lactams as Michael acceptors had proved to be a very efficient synthetic procedure. Moreover, the conjugate addition of aromatic moieties on Δ^3-piperidein-2-ones indicated a possible entry to 4-aryl-2-piperidone synthons, which, together with our experience in the preparation of 3-aminopiperidine derivatives (see Section 4.1), led us to focus on the preparation of 3-amino-4-indolylpiperidin-2-ones type **54** (Figure 23). Compound **54** was designed as a conformationally constrained analogue of the dipeptide Trp-Gly (see Section 6), in which the restriction caused by

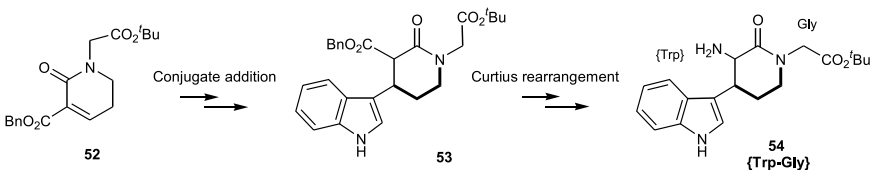


Figure 23

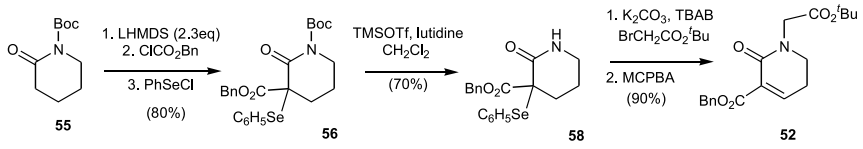


Figure 24

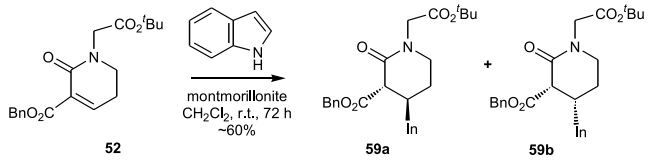


Figure 25

cyclization between the β-carbon of tryptophan and the nitrogen atom of glycine constrains the conformational space occupied by the indole nucleus of Trp. Furthermore, the dynamics of the ring imposes the orientation of its substituents, and as a result, the ϕ torsion angles of both Trp and Gly are also restricted. The synthesis of compound **54** was envisaged as occuring through a conjugate addition of indole on lactam **52** followed by a Curtius rearrangement to introduce the amino group on C3 (Figure 23) [22].

The synthesis of the unsaturated lactam **52** was started from *N*-Boc-δ-valerolactam **55** (Figure 24). Acylation on C3 with benzylchloroformate, followed by phenylselenylation on the same position, yielded lactam **56**. The successive deprotection of the nitrogen atom and introduction of the acetate chain was done at this stage, since the unsaturated secondary lactam **57** was highly unstable. Alkylation of **58** in basic medium, and addition of MCPBA to the reaction, gave the desired lactam in 60% yield.

The conjugate addition of indole was performed in the presence of Montmorillonite® [23], yielding a mixture of the racemics *cis* and *trans* **59** (Figure 25). Compounds **59a** and **59b** were separated by analytical reverse phase HPLC. However, in the presence of SiO_2, epimerization of C3 resulted in partial interconversion of **59a** and **59b**.

When the mixture of lactams **59** was submitted to the Curtius rearrangement using DPPA and Et_3N in the presence of dibutyltin dilaureate, carbamate **60** (Cbz/O^{t}Bu) was obtained. Only the *trans*-isomer was observed. In order to adapt our {Trp-Gly} pseudodipeptide for solid phase peptide synthesis, we also prepared the Fmoc/O^{t}Bu derivative **61** by standard methods.

4. 3-amino-2-arylpiperidin-4-ones

4.1. 3-Aminopiperidines as Substance P inhibitors

In the early 1990's we became interested in preparing 3-aminopiperidine derivatives, since many compounds that contained this substructure showed medically relevant activities. For instance, the marine pseudodistomines (Figure 27) showed antitumor properties, cyclo-arginine is a component of antithrombotic agents, and other derivatives were active at different levels of the nervous system. The introduction of a 3-amino moiety on our piperidine synthons therefore appeared likely to enhance the pharmacological interest of our synthetic chemistry.

Particularly interesting was the peptide mimetic CP-9,994 [24], which inhibits *in vitro* the undecapeptide known as Substance P (SP). SP is found in the central and the peripheral nervous system, and was known to participate in processes of inflammation and pain [25]. The discovery of CP-9,994 stimulated great scientific excitement at the time, since the regulation of SP levels appeared to be a possible key to the treatment of inflammatory diseases. We designed a structural analogue of CP-9,994, compound **62**, as a syn-

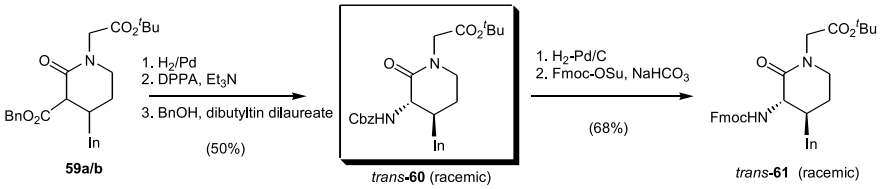


Figure 26

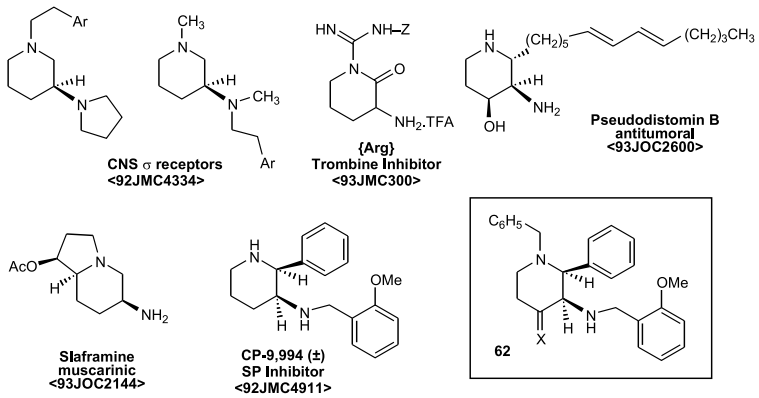


Figure 27

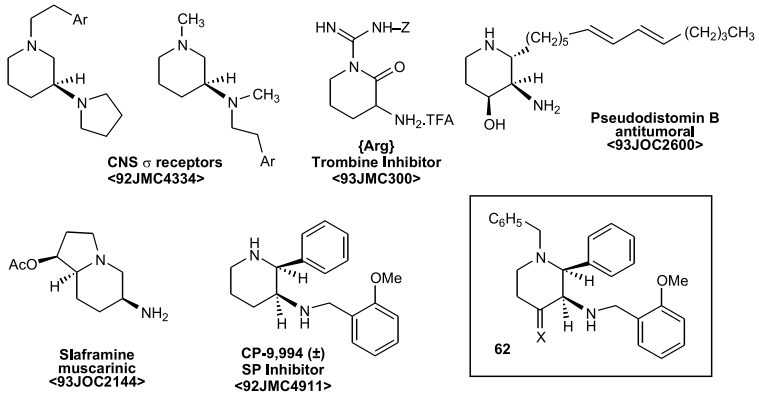


Figure 28

thetic target potentially able to inhibit SP.

The first problem was to establish a method for introducing an amino group on the 3-position. Of the known amination methods, we chose to try the Neber rearrangement, an old reaction that allows the introduction of an amino group on the α-position of ketones [26]. On the other hand this reaction had never been shown to work on nitrogenated substrates. We first verified that the method works on *N*-benzylpiperidin-4-one, by formation of the oxime, tosylation, and treatment of the tosyloxime with NaEtO in EtOH (Figure 28). When the method was applied to substrates arylated on C2, the rearrangement yielded both, the 3– and the 5-amino derivatives **66** and **67**. We observed that the regioselectivity of the rearrangement depended on the stereochemistry of the intermediate tosyloxime. Thus, the amination took place «*anti*» with respect to the tosyloxime, which indicated that the intermediate azirine **69** was formed by a *backside* attack of the anion on the nitrogen atom. The subsequent opening of the azirine ring occured by the action of the EtOH used as solvent, to give acetal **70**. In this way we obtained a small collection of 3-amino-2-arylpiperidin-4-ones. These proved to be inactive as SP inhibitors. However, we had demonstrated for the first time the usefulness of the Neber rearrangement on a piperidone.

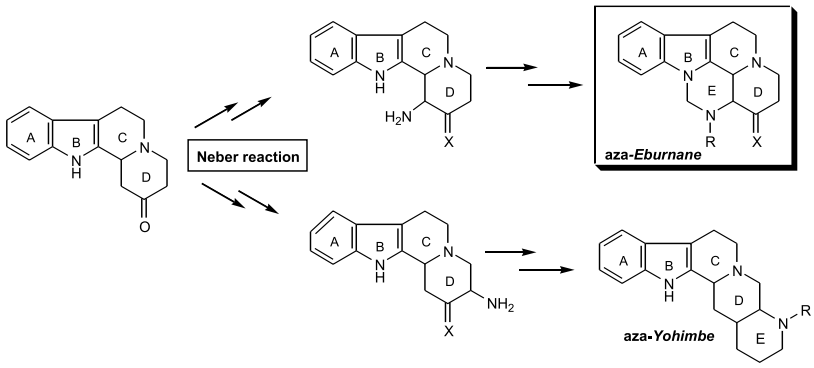


Figure 29

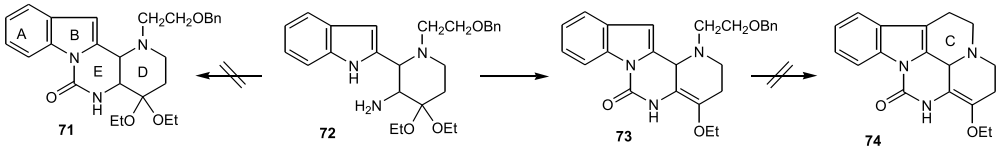


Figure 30

4.2. Aza-***Eburnane*** alkaloids

In connecting our studies on the Neber rearrangement to the indolo[2,3-*a*]quinolizidine alkaloids (see Section 2), we decided to prepare 1– and 3-aminoindolo[2,3-*a*]quinolizidin-2-ones (Figure 29). These compounds would lead respectively to the pentacyclic aza-*Eburnane* and aza-*Yohimbe* alkaloids, in which the extra nitrogen atom is located in ring E. Similar aza-*Eburnane* systems had shown to be able to modify the induction of tyrosine hydroxylase [27]. We planned two approaches for the synthesis of aza-*Eburnane* compounds, *via* closure of ring C or of ring E in the last step.

Since the pyridopirimidinoindole tetracyclic system of compound **71** (Figure 30) was unprecedented in the literature, we studied its preparation first. Treatment of 3-amino-2-indolylpiperidine **72** with benzyl chloroformate yielded only compound **73** in very low yields, whose structure was inferred from its analytical data. We concluded that even if the ABED tetracycle was formed, its functionalization provoked a spontaneous elimination in the reaction conditions, and that the loss of the ma-

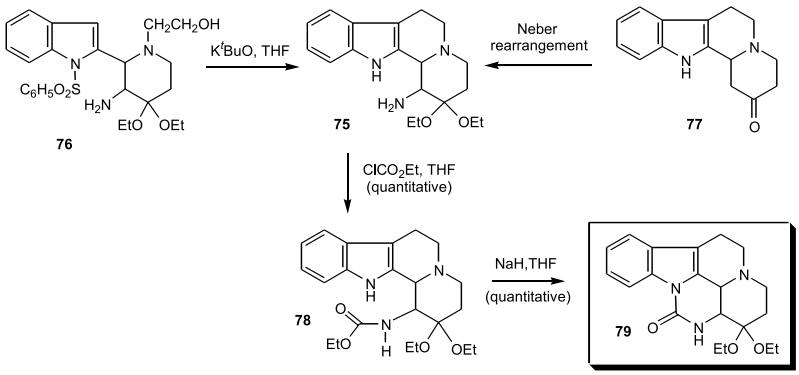


Figure 31

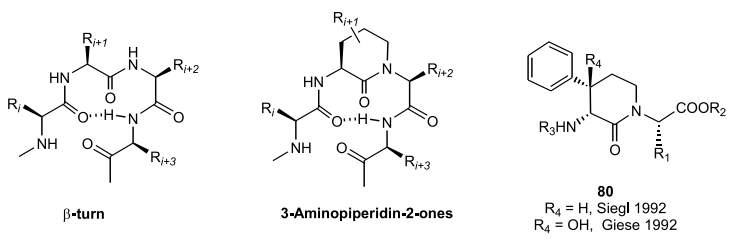


Figure 32

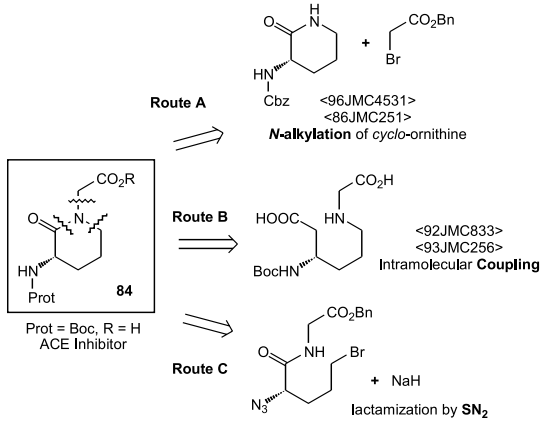


Figure 33

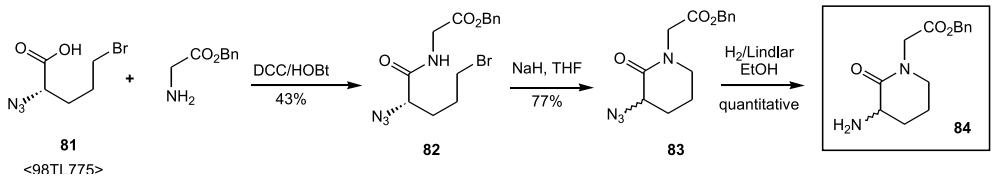


Figure 34

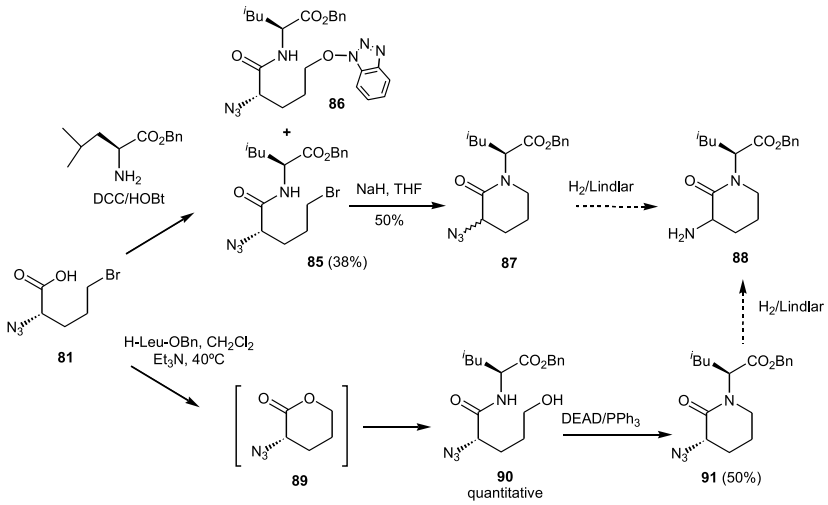


Figure 35

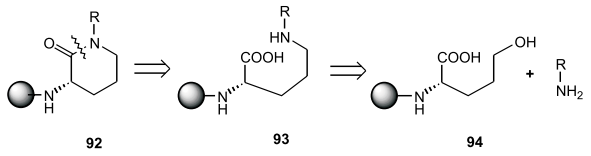


Figure 36

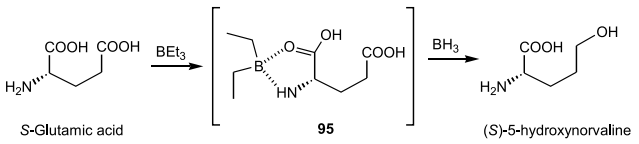


Figure 370

jority of the product could be the result of a subsequent aromatization.

Closure of ring C on compound **73** to give the aza-*Eburnane* type compound **74** was unsuccessful, which was explained by the high rigidity of the substrate and the decreased nucleophilicity of the indole C3-position.

The second approach to the synthesis of aza-*Eburnane* systems was started by the preparation of 1-aminoindoloquinolizidine **75** (Figure 31). This was done either by closure of ring C on aminopiperidine **76**, or by amination of indoloquinolizidin-2-one **77**. The pentacyclic system was obtained quantitatively from **75** by formation of the carbamate **78** followed by base-induced cyclization [28].

5. 3-aminolactams

5.1. Introduction

In the early 1990s we became interested in the possibility that piperidones might be used as pseudopeptides and as peptide mimetics. As drugs, peptides and proteins tend to suffer from low bioavailability and rapid degradation. Furthermore, the larger and more flexible the molecule, the more likely it is to interact with a wide range of receptors, with corresponding loss of specificity. Small molecules with a longer half-life that bind to a particular receptor may thus be more active than the native peptides or proteins they mimic. Another aspect to be taken into account is that the interaction between the receptor and the peptide active site depends on the conformation of both. Since small molecules have more limited conformational variability, productive interaction with their receptors is likely to be more frequent than that of larger peptides.

One of the major structural motifs that characterise receptor recognition sites of peptides is the β-turn (Figure 32) [29]. 3-Aminolactams were first reported to be able to induce β-turns by Freidinger in 1982 [30]. Since then numerous structures that mimic or induce β-turns have been developed. In 1992 Siegl reported a synthesis of 4-phenyl lactam **80**, as a constrained analogue of phenylalanine [31]. This, together with the relevance that peptide mimetics were acquiring in the pharmacological field, focused our attention on the synthesis of diversely functionalized 3-aminopiperidin-2-ones. Not only do our structures present interesting biological activities *per se* as enzyme inhibitors, but they can also be used as dipeptide surrogates to study structure-activity relationships of known active peptides.

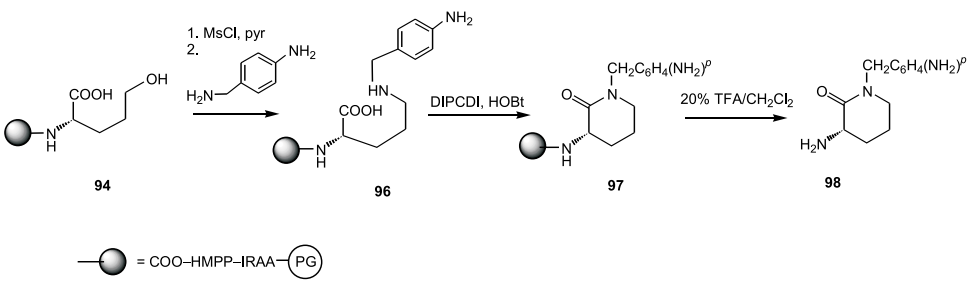


Figure 38

5.2. Simple 3-aminolactams as conformationally restricted surrogates of alanine

We envisaged the synthesis of diversely N_1-substituted 3-aminovalerolactams, since we regarded these as one of the simplest structures that can be considered as constrained derivatives of alanine. The Ala-Gly surrogate **84**, described as an ACE inhibitor [32], has been prepared by two methods: *N*-alkylation of Cbz-cyclo-ornithine with benzyl bromoacetate [33], and lactamisation of N_ω-substituted ornithine (Figure 33) [32,34]. Since our intention was to be able to introduce any substituent on the lactam nitrogen atom, we explored the possibility of closing the C6-N1 bond by intramolecular nucleophilic substitution of an ω-bromoamide [35].

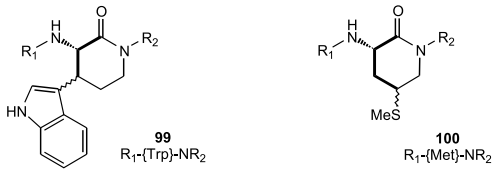


Figure 39

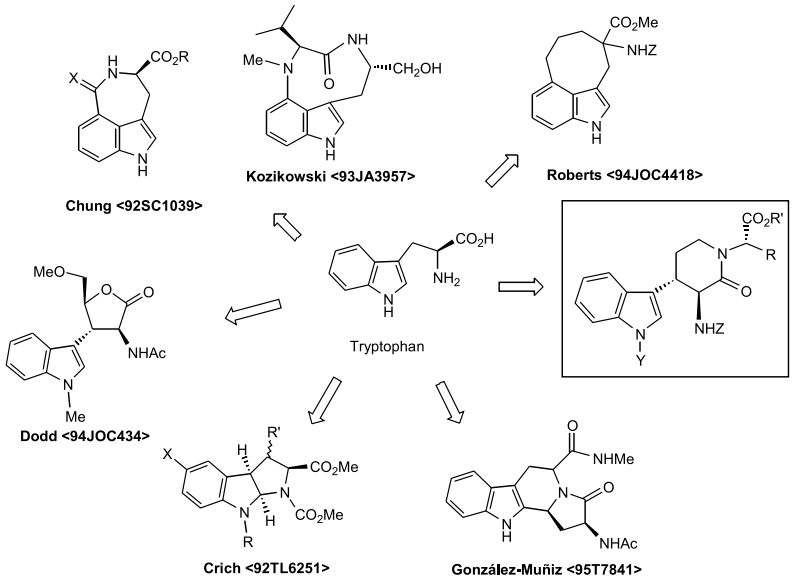


Figure 40

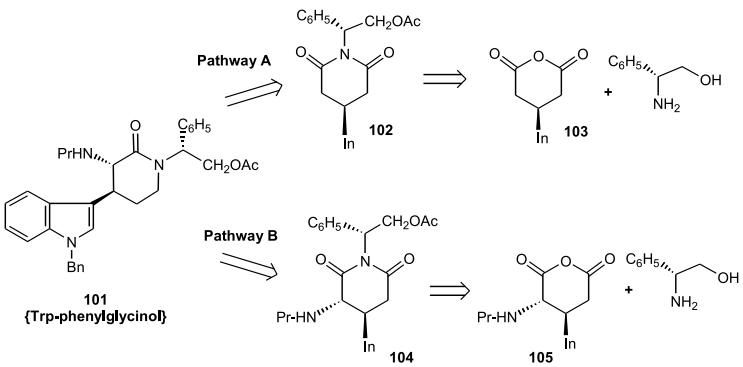


Figure 41

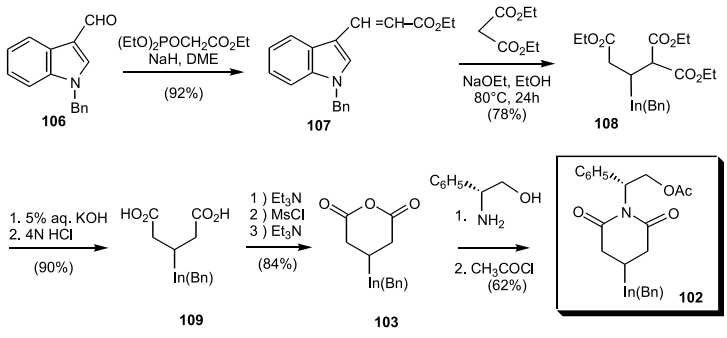


Figure 42

Coupling of bromoacid **81** [36] with glycine-OBn using DCC/HOBt yielded the desired bromoamide **82**, whose treatment with NaH led to the expected valerolactam **83**. Reduction of the azido group by hydrogenation in the presence of Lindlar catalyst yielded the target Ala-Gly surrogate **84**.

We then applied the cyclisation method to the preparation of {Ala-Leu} **88**. Coupling of bromovaleric acid **81** to Leu-OBn using DCC/HOBt gave amide **85** in 38% yield, and treatment of **85** with NaH furnished the expected lactam **87** (Figure 35). However, this series of reactions had two drawbacks. Compound **86**, resulting from nucleophilic attack of HOBt on the bromide, was identified as a by-product of the coupling, which accounted for the mediocre yields obtained, and, most importantly, the NaH cyclisation occured with racemisation at C3.

In order to avoid the SN reaction competing with the coupling, we performed the condensation of the bromoacid with Leu-OBn in the presence of Et_3N. In this manner, the intermediate lactone **89** was generated by cyclisation of the carboxylate, which then reacted with Leu-OBn to give hydroxyamide **90** quantitatively. Treatment of **90** with DEAD/PPh_3 led to the desired azidolactam **91** without racemisation.

In parallel with the previous study, we assayed the solid phase synthesis of 3-aminovalerolactams by formation of the N1-C2 bond through intramolecular coupling of a secondary amine and a carboxyl group (Figure 36). As noted earlier, this strategy had been reported to cyclise N_ω-substituted ornithine [33]. However, we needed to be able to introduce an asymmetric centre α with respect to the N_ω nitrogen atom. For this purpose, we decided to use a suitable amine as a nucleophile on the mesylate of 5-hydroxynorvaline.

We first established a new method for the preparation of (*S*)-5-hydroxynorvaline (Figure 37) [37]. This involved protection of the aminocarboxyl extremity of glutamic acid using BEt_3, and reduction of the γ-carboxylate with BH_3.

(*S*)-5-Hydroxynorvaline was anchored to a solid support (PS(BHA)-IRAA-HMPP resin) by carbonate activation of the resin. The hydroxyl group was replaced by 4-aminobenzylamine *via*

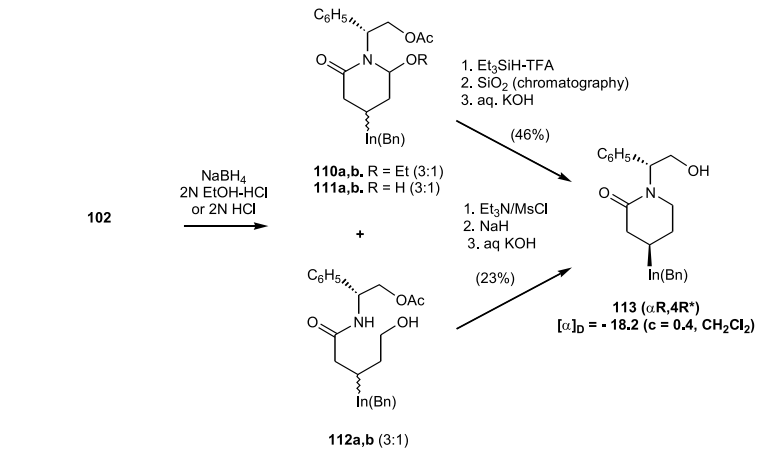


Figure 43

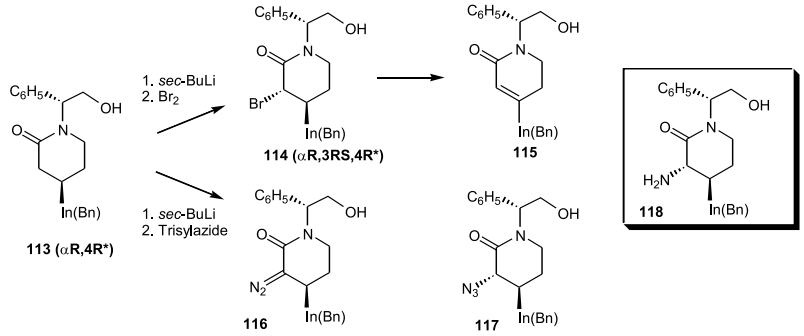


Figure 44

mesylation, to give the open chain aminoacid **96** in high yields (Figure 38). Subsequent cyclisation was effected by intramolecular DIPCDI/HOBt coupling of the secondary amine. The final cleavage from the resin was carried out by a 20% TFA/CH_2Cl_2 treatment to give lactam **98** [38].

We are currently studying the generality and scope of these two methods by the preparation of small libraries of 3-aminovalerolactams, both in solution and on solid support.

6. Glutarimides

A somewhat more ambitious goal was the preparation of 3-aminovalerolactams substituted on positions C4, C5 and C6. In particular we wished to prepare 4-indolylvalerolactam **99** and 5-methylthiolactam **100**, constrained analogues of Trp and Met, respectively (Figure 39).

Various constrained derivatives of tryptophan had already been reported. These can be classified as shown in Figure 40. A first group of derivatives contain the α-position of Trp linked to the indole nucleus 4-position, *via* a carbon bridge that renders Cα quaternary. A variation of this method consists of linking the amino group to the indole 4-position, by either a carbon chain or another aminoacid (here Val) to yield rings of 7, 8, or 9 members. A third class of derivative includes the α- and β-carbons of Trp in a 3-aminolactone ring, whose synthesis was achieved starting from an appropriate carbohydrate. Other derivatives show the cyclisation between the amino group and the indole 2-position, either directly to form a fisostigmine-type compound, or through a carbon atom to yield a β-carboline, *via* a Bishler-Napieralsky condensation of Trp with the aldehyde of Ser followed by coupling.

Our 3-aminovalerolactam was therefore a new derivative of Trp, in which the β-position was tethered to the amino group of the following amino acid residue (aa_2) by a 2-carbon bridge. In this fashion, the ω, ψ(Trp), and χ_1(Trp) dihedral angles are constrained by the six-membered ring, with a concurrent effect on the φ(Trp), χ_2(Trp), and φ(aa_2) dihedral angles which are obliged to move cooperatively with the ring.

Because of our experience with synthesis of (*R*)-phenylgycinol-derived lactams in the dasycarpidone alkaloids (see Section 3.2), we decided to establish the synthetic strategy by preparing 3-amino-4-indolylpiperidin-2-one **101**, by reduction of a 4-indolylglutarimide (Figure 41). We considered two different approaches: performing the amination as the final step of the synthesis, or introducing the C3 amino group on the starting substrates. In both cases the imides would be prepared by reaction of an appropriate anhydride with (*R*)-phenylglycinol, a strategy that should allow us to diversify the synthesis by the use of any primary amine.

6.1. Tryptophan-phenylglycinol derivatives

We first obtained the 4-indolylglutaric anhydride **103** from *N*-benzylindole-3-carbaldehyde (**106**). A Wadsworth-Emmons condensation with ethyl diethylphosphoroacetate, followed by a malonic synthesis, yielded 4-indolylglutaric acid **109** (Figure 42), which was then cyclized by mesylation and base treatment. The condensation of anhydride **103** with (*R*)-

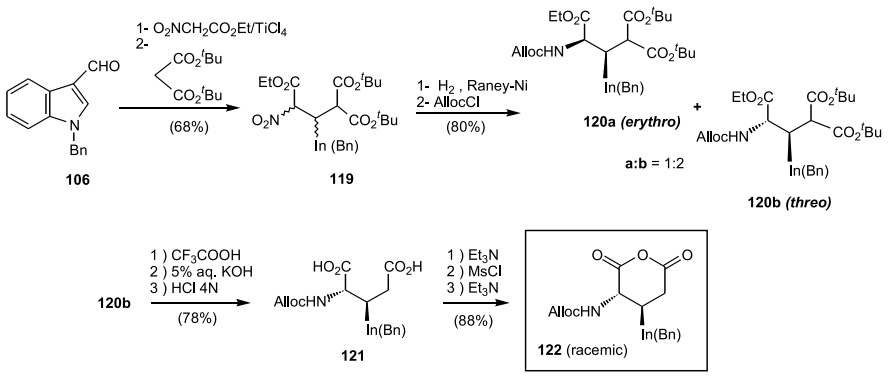


Figure 45

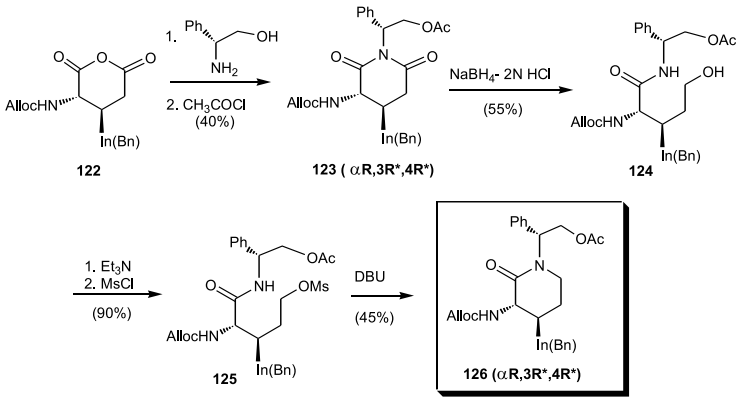


Figure 46

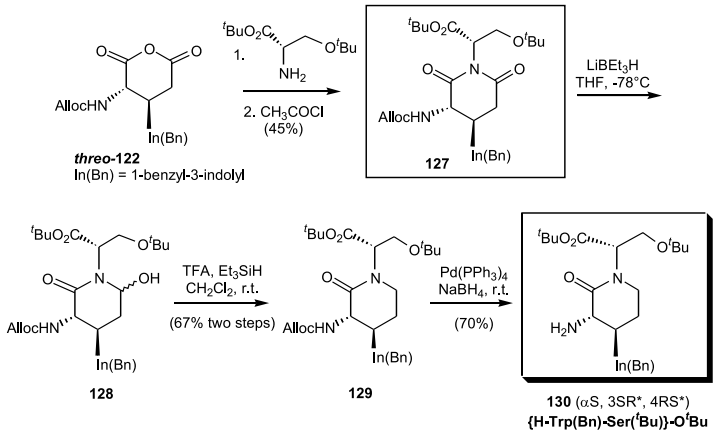


Figure 47

phenylglycinol and the subsequent addition of AcCl led to the desired prochiral glutarimide **102**.

Reduction of imide **102** was performed by treatment with $NaBH_4$ in acid medium, and yielded a mixture of the 6-hydroxylactams **110** and **111**, together with a small proportion of hydroxyamide **112** (Figure 43). Formation of hydroxyamide results from the reduction of the intermediate open-chained aldehyde [39]. Reduction of position C6 by Et_3SiH/TFA, followed by chromathography on SiO_2 and saponification of the acetyl group led to the desired lactam **113**. Lactam **113** was also obtained by cyclisation of the hydroxyamide **112** through mesylation and subsequent treatment with NaH.

The assays of direct amination on C3 using trisylazide did not yield the expected 3-azidolactam **117**, but rather the diazoderivative **116** which we were unable to reduce to the amine (Figure 44). We then prepared 3-bromolactam **114**, but unfortunately the acidity of the proton on C4 was sufficient to make the bromolactam undergo a dehydrohalogenation upon treatment with benzylamine or with NaN_3, resulting in piperideinone **115**.

The second approach circumvented this problem by using a starting substrate bearing the amino group on the C3 position. Thus, 4-indolylglutaric anhydride **122** was prepared from indolyl-3-carbaldehyde **106** in a sequence that involved a Henry-type reaction, followed by a conjugate addition of di-*tert*-butyl malonate to yield triester **119** (Figure 45). The reduction of the nitro group was performed at this stage, and the amino function was Alloc-protected. In this fashion, the *erythro* and *threo* racemic mixtures **120a,b** were obtained, and were separated by column chromatography. The major *threo* triester **120b** was used to prepare the corresponding diacid **121**, which was cyclized as in the previous series to obtain the *trans*-anhydride **122**.

The synthesis of the target lactam **126** from anhydride **122** was carried out by applying the sequence that we had established previously, *i.e.* by formation of the glutarimide (two *trans* diastereomers), reduction and cyclisation [40]. However, in this case, the reduction of imide **123** with $NaBH_4$/HCl led only to the open chain hydroxyamide **124**, whose mesylate **125** was cyclized using DBU as the base (Figure 46).

The same chemistry was applied using the minor *erythro*-triester **120a**, to obtain the *cis* diastereomers.

6.2 Tryptophan-serine derivatives

We next tried to apply the method the synthesis of Trp-Ser surrogates. Thus, condensation of the *threo* anhydride **122** (2 diastereomers) with di-*tert*-butylserine yielded **127**, the glutarimide necessary for our study (Figure 47).

Since, in our experience, the use of $NaBH_4$/HCl as the reducing agent for glutarimides led to mixtures of the open chain hydroxyamide and the hydroxylactam in very variable proportions [41], we tried the reduction of **127** using $LiBEt_3H$. Of the two possible products, only hydroxylactam **128** was obtained. The dehydroxylation was effected by treatment with TFA/Et_3SiH to obtain the desired 3-amino 4-indolylpiperidin-2-one **129**. The selective cleavage of the Alloc protecting group was performed with $NaBH_4$ in the presence of a Pd catalyst to yield the H-{Trp(Bn)-Ser(*t*Bu)}-O*t*Bu pseudopeptide **130**.

However, we were confronted to two major problems: failure to separate the diastereomeric anhydrides, glutarimides, or lactams by standard chromatographic methods, and inability to debenzylate the indole nucleus (Figure 48). The pseudopeptides obtained were therefore neither pure nor easily and selectively deprotected, and were hence unsuitable for further synthetic purposes.

However, we later succeeded in preparing Trp constrained derivatives by using conjugate addition of indole on an appropriate unsaturated lactam, as described in Section 3.3.

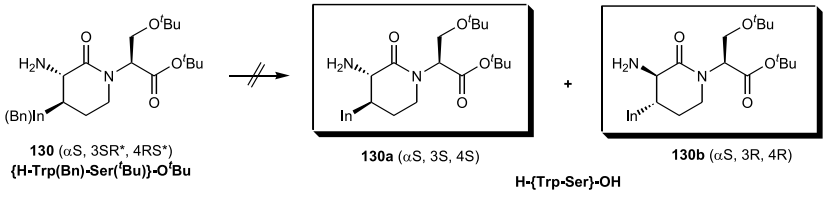


Figure 48

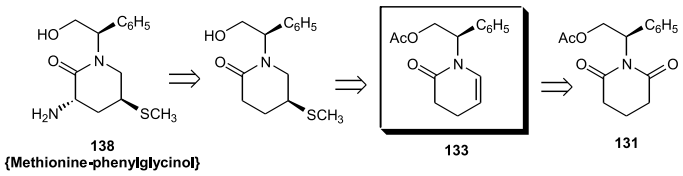


Figure 49

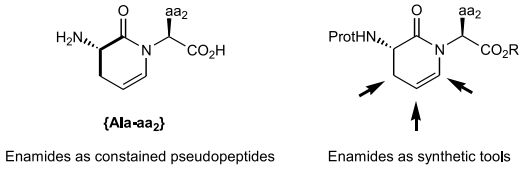


Figure 50

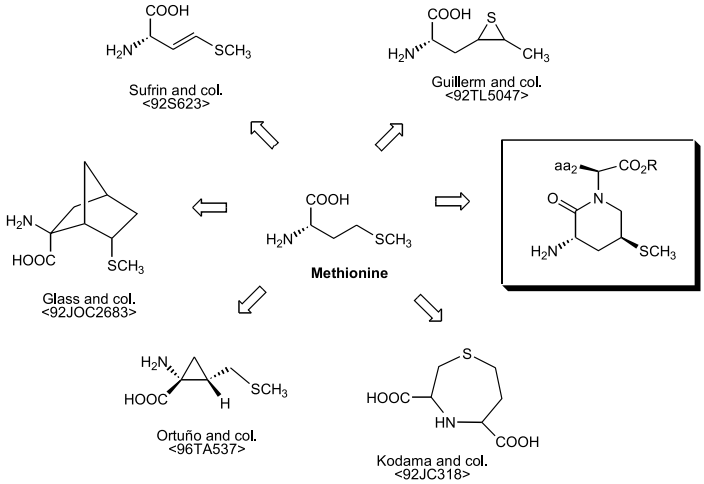


Figure 51

7. Enamides

As outlined in the introduction to Section 6 (Figure 39), we also aimed to synthesize 3-amino-5-methylthiovalerolactams **100**, as constrained surrogates of Met. In conjunction with the studies on glutarimides, we envisaged the possibility of using 6-hydroxylactams to yield cyclic enamides by dehydration, and of using the double bond to functionalize position C5 (Figure 49). Since there was little information on the reactivity of enamides, we decided to prepare the methionine-phenylglycinol derivative **138**, using the intermediate enamide **133** as a model.

The enamides appeared to be very attractive synthons; not only can they be regarded as constrained derivatives of Ala, their potential reactivity should allow functionalization on positions C4, C5, and C6 of the valerolactam ring.

7.1. Methionine-phenylglycinol [42]

Several ways to constrain the mobility of the methionine side-chain had been reported in the literature (Figure 51). When a thiirane ring [43] or of a double bond [44] is introduced the α-position remains tertiary. Otherwise, the α-position is involved in the formation of a bridged bicycle [45] or of a cyclopropane ring [46], yielding quaternary derivatives. Finally, a compound isolated from human urine, contains the structure of methionine as part of a seven-membered ring [47]. Our 3-amino-5-methylthiolactam maintains both the methylsulfide function and the tertiary α-position, and binds the side chain to the nitrogen atom of the following amino acid with an ethylene bridge. As in the case of the Trp derivatives, the level of constraint is high, affecting most dihedral angles of the amino acid.

To prepare compounds **134**, glutarimide **131** was partially reduced with Superhydride®, and the resulting hydroxylactams **132** were dehydrated using TFA to produce the expected enamide **133** in 60% yield (Figure 52). The methylthiolation of C5 was achieved by addition of MeSH to the double bond in the presence of AIBN, whereas the enamide did not react with electrophilic reagents such as MeS-S(O)Me. This demonstrated that the electron withdrawing effect of the carbonyl group (C2) was sufficiently strong to make the double bond of the enamide behave as an isolated alkene rather than as an enamine. As expected, the radical addition yielded an equimolar mixture of the antiMarkovnikov regioisomers, **134a** and **134b**, which were separated by column chromatography.

Amination of the 3-position was carried out by bromination and substitution (Figure 53). Thus, treatment of the methylthiolactam (α*R*,5*S*)-**135** with *sec*-BuLi and bromine led to a 5:1 diastereomeric mixture of 3-bromolactams **136a** and **136b**. The 3,5-*cis* isomer spontaneously epimerized to give the thermodynamically more stable 3,5-*trans* isomer, both in solution and in the presence of SiO_2.

Substitution of the bromine atom by NaN_3 yielded compound **137** as a single isomer, which was reduced to obtain the (*aR*,3*R*,5*S*) {Met-phenylglycinol} **138a**. When the bulkier potassium phthalimide was used as the nucleophile, we obtained a 5:1 C3 epimeric mixture of 3-phthalimidolactams **139**, which were separated by chromatography. Deprotection of isomer **139b** yielded the (*aR*,3*S*,5*S*) {Met-phenylglycinol} **138b**.

7.2. Methionine-serine [48]

Since amination on C3 using a strong base is incompatible with the acidity of the α-proton of amino acids, it appeared advisable to use glutamic anhydride as the starting substrate for the preparation of dipeptide analogues. The key enamides could then be obtained either by partial reduction of the corresponding imide, or by closure of the N1-C6 bond from a formylamide (Figure 54). Both general approaches should

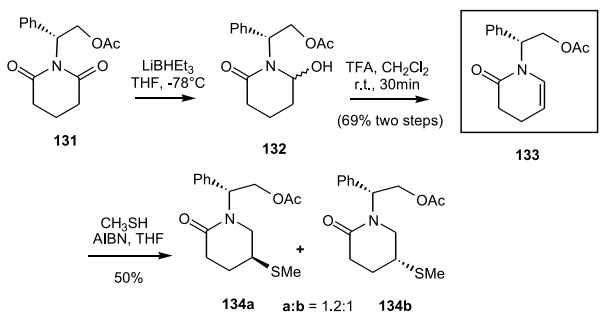


Figure 52

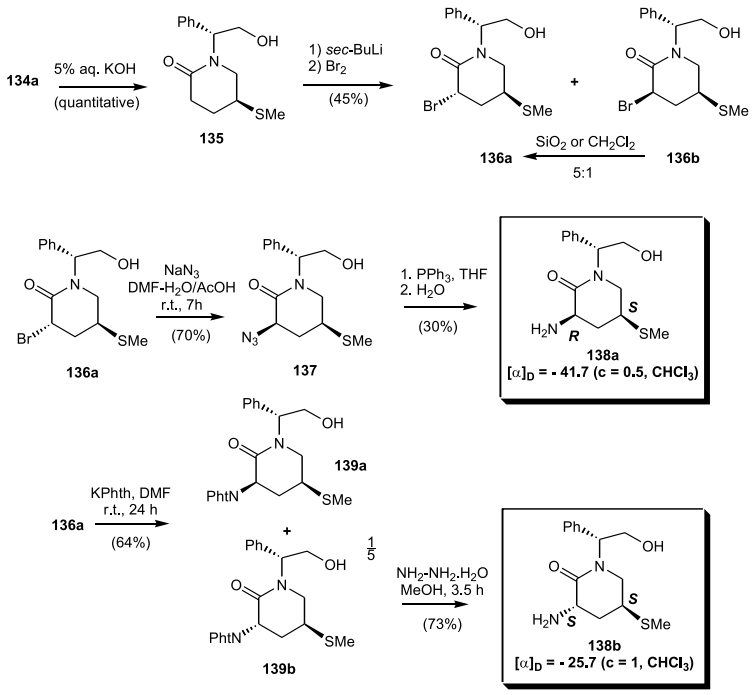


Figure 53

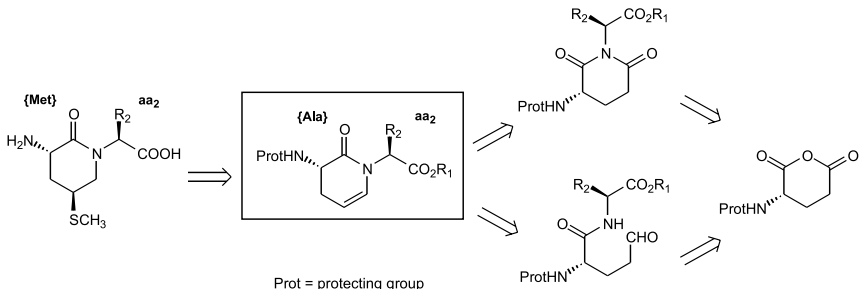


Figure 54

enable us to prepare small series of pseudodipeptides, first by diversifying the second amino acid (aa_2), and eventually, by diversifying the functionalisation of the lactam ring.

Condensation of glutamic anhydride **140** with di-*tert*-butyl serine led to the corresponding imide in 60% yield (Figure 55). The reduction of imide **141** with Superhydride(r) gave the expected 6-hydroxylactam **142** in 50% yield. When we tried the reaction using $NaBH_4$/HCl as the reducing agent, only the open chain hydroxyamide **143** was obtained, and DIBAH led to a mixture of **142** and **143**, but in variable proportions. Although we tried to dehydrate hydroxylactam **142**, the starting substrate remained unaltered under all conditions used (TFA; *p*-TsOH; 1. MsCl/TEA, 2. DBU; $POCl_3$, pyridine; NH_4Br). These unexpected results made us turn our attention to the second approach.

The alternative was to prepare an open chain formylamide **148**, whose cyclisation would yield the target enamide **149** (Figure 56). We decided to generate the aldehyde function by reduction of the corresponding thioester. Thus, treatment of glutamic anhydride **145** with phenylthiol in the presence of dicyclohexylamine yielded thioester **146** quantitatively, and this was condensed with di-*tert*-butyl serine under standard conditions to obtain amide **147**. The reduction of compound **147** using Et_3SiH in the presence of Pd/C in CH_3CN:CH_2Cl_2 led to the key aldehyde **148**, and treatment of **148** with acid generated the desired enamide **149** in 45% yield (2 steps) after column chromatography on SiO_2.

Once the enamide had been obtained, methylhiolation with MeSH in the presence of AIBN in THF gave the target {Met-Ser} constrained derivative **150**.

In order to test the generality of this method for synthesizing {Met-aa_2} derivatives, we repeated the synthetic sequence using other amino acids. Since one of our aims is to determine whether our pseudodipeptides can induce particular conformations once inserted in longer peptide chains, we chose to prepare {Met-Val} and {Met-Leu}. The Ramachandran plots of valine and leucine show that they show high potential for β-sheet and α-helix conformation, respectively.

Condensation of thioester **146** with Val and Leu, followed by the reduction of the thioester function and final acid cycli-

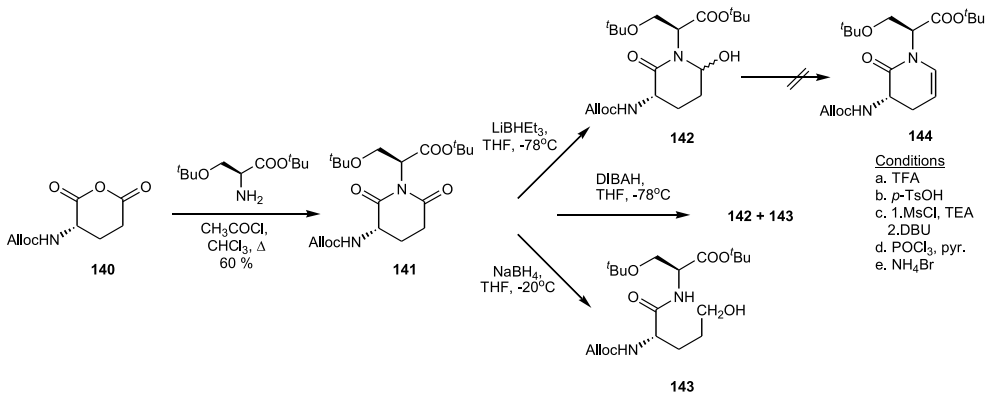


Figure 55

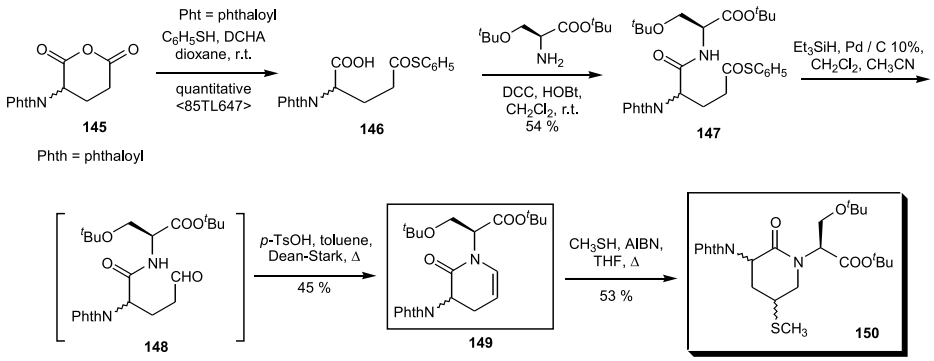


Figure 56

sation of the aldehydes, yielded enamides **153** and **154** (Figure 57). In each case the separation of the two diastereomers was done by serial chromatography. Methylthiolation was performed on the pure diasteromers **153a** and **154a** to give a 3:1 proportion of the methionine-derived pseudopeptides. The major isomers were always the 3,5-*trans* forms (**a**), in which the methylsulfide group was axially disposed. We attributed the unequal proportion to a steric effect of the bulky C3 phthalimido substituent.

7.3. Application to the solid phase synthesis of enamides [49]

Our next aim was to synthesize enamides on solid phase. In this fashion we would be able to diversify their N_1-substituent, and subsequently carry out parallel functionalisations of the ring. This exponential diversification would result in small libraries of lactam pseudopeptides. For this purpose, the above sequence (Figure 57) had to be modified to make it compatible with the resin. The first step was to test the feasibility of the procedure using a carbamate *N*-protection such as Cbz. Since there was no regioselectivity in the ring opening of anhydride **157** (Figure 58) we could not apply the same strategy as that used in the phthalimido series (Figure 56). Hence, Cbz-Glu was transformed to the amidoacid **161** after condensation of the oxazolidinone **160** **[**50**]** with Leu-OMe. The reduction of the acid group in **161** *via* an acid chloride yielded the pyrrolidone **162**, as a result of cyclisation on the carbamate nitrogen atom (Figure 58).

In order to avoid the formation of the pyrrolidone ring, the reduction of the acid group was carried out on compounds **160** [51] *via* a thioester intermediate **163**. The aldehyde was protected as a dimethylacetal, and compound **165** was coupled with Leu-OMe to yield **167**. Various cyclisation conditions were assayed, but only with *p*-TsOH was the desired enamide **168** obtained (6%), together with a more polar compound identified as 5-hydroxyproline **169** (Figure 59).

At present we are optimising this cyclisation to enable us to start the sequence on solid phase using a Tentagel(r)-IRAA-HMPP-O-CO resin.

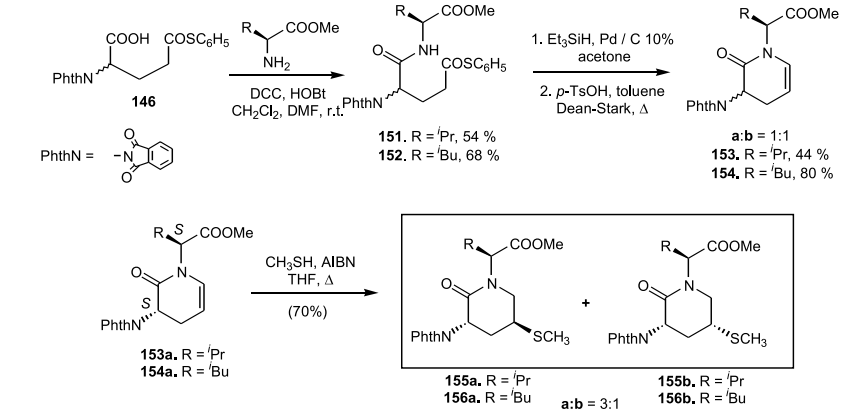


Figure 57

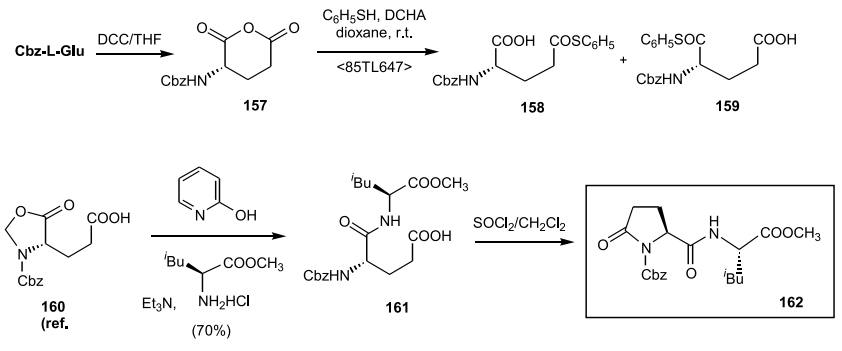


Figure 58

8. Oxazolopiperidines [52]

8.1. Introduction

As explained in Section 5, we are interested in obtaining pseudopeptides that can induce a particular conformation once inserted in a longer peptide chain. More specifically, one of the conformations that we seek is the β-turn, since it is known that bicyclic compounds can be good β-turn mimetics [53]. For instance, compound **170** (Figure 60) [54] has been extensively studied in the context of building active peptide analogues [55-61]. Despite the role played by the β-turn position itself in the interaction with the receptor and the fact that **170** induces a βII' turn conformation in collaboration with the adjacent residues, this β-turn dipeptide seems not to be very useful for improving the activity of small peptides, in which the β-turn position itself plays some role in the interaction with the receptor site [62]. Interestingly, recent molecular modeling calculations on the tetrapeptide Ac-Ala-{**170a**}-Ala-NHMe indicate that the geometry of a turn induced by thiazolopiperidone **170**

differs significantly from that of an ideal β-turn [63]. In addition, the incorporation of either epimer **170a** or **170b** in a bioactive peptide has been shown to provoke distinct changes in its bioactivity [60a].

We thought that the isosteric substitution of the sulfur in the 7-position by an oxygen atom might improve the binding properties of the β-turn dipeptide, since oxygen could act as a better hydrogen bond acceptor on the «external part» of the turn. With the aim of establishing the possible utility of oxazolopiperidones **171** as β-turn mimetics, we have prepared these bicyclic lactams and their derivatives **173** (Figure 61). The conformational analysis of **173**, both by NMR and by molecular modeling calculations, indicate that oxazolopiperidone **173a** mimics a βII' turn and that **173b** adopts a β-turn conformation that does not correspond to the classified types [1b-e,2].

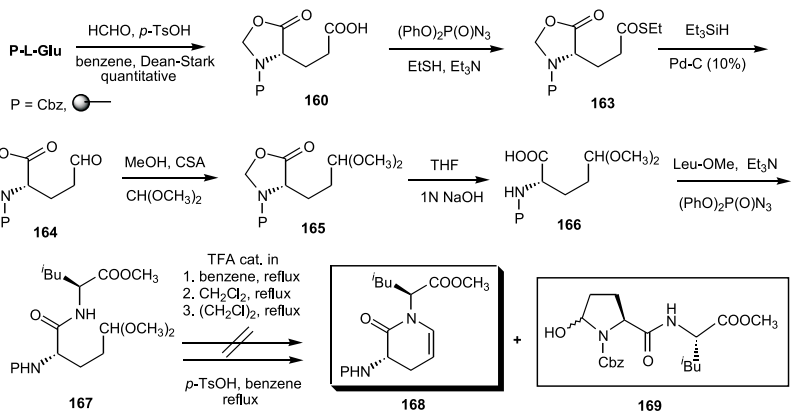


Figure 59

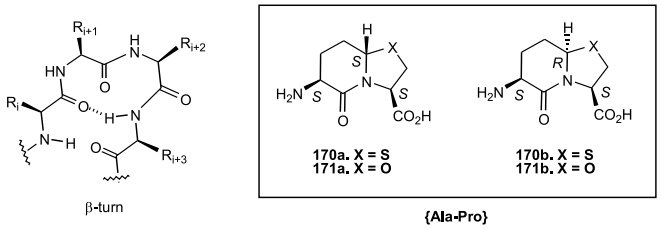


Figure 60

8.2. Synthesis and structural studies

The preparation of oxazolopiperidones **172** was achieved by condensation of aldehyde **164** [50] with methyl serine hydrochloride (Figure 61). When the reaction was conducted at room temperature, isomer (3*S*,6*S*,9*S*)-**172a** was obtained pure, whilst the condensation in refluxing toluene yielded a 1:5 mixture of **172a** and its C6 epimer **172b**. The absolute configuration of each isomer was determined by NOESY experiments. Amidation of compounds **172** with $MeNH_2$ led to compounds **173**, which fulfil all the requirements necessary for studying the conformational tendencies of the bicyclic oxazolopiperidone system.

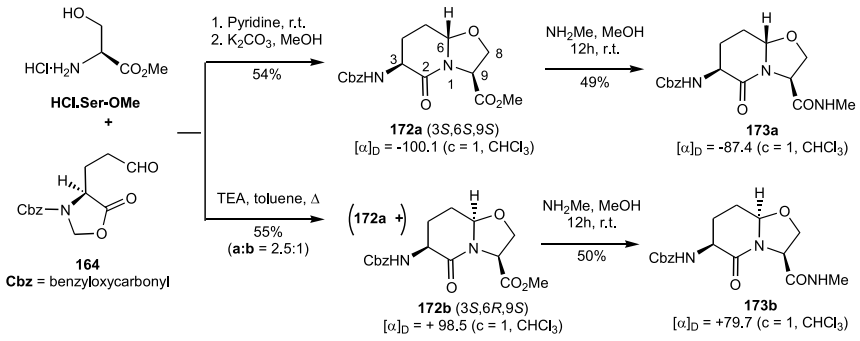


Figure 61

The conformation of **173a** and **173b** was studied by combining molecular modeling calculations and NMR techniques. NMR experiments were used to determine the existence of an intramolecular hydrogen bond between the oxygen atom of the Cbz carbonyl group and the amide NH proton, which is the *sine qua non* for pseudodipeptide occupation of the (*i+1*) and (*i+2*) positions of a standard β-turn. Molecular modeling calculations were used to find the most probable conformations of each isomer (6H-α and 6H-β), and to determine, according to the dihedral angles involved, which kind of β-turn they correspond to.

Similar results were obtained for both isomers **173a** and **173b** by NMR experiments (Figure 62). Thus, following the classification of Scolastico and co-workers [64], chemical shifts in $CDCl_3$, temperature coefficients in $CDCl_3$, and the results of competitive solvent addition (DMSO) experiments

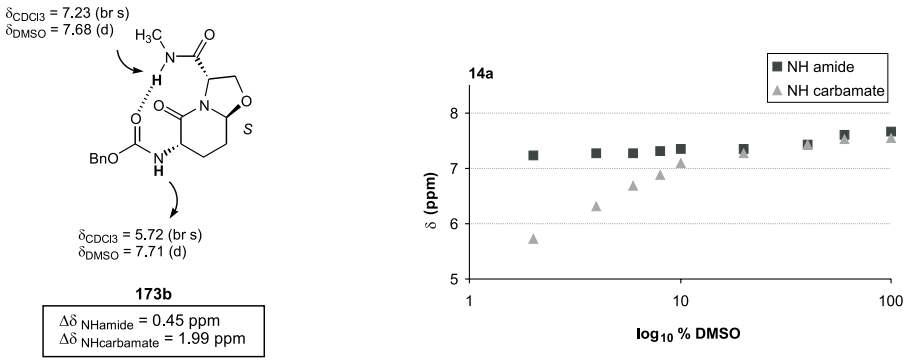


Figure 62a. Solvent dependence of the ^{1}H-NMR chemical shifts for compound 173a.

Figure 62b. ^{1}H-NMR Chemical shift of the NH protons of pseudodipeptide 173a at different proportions of d_6-DMSO in $CDCl_3$ (25ºC).

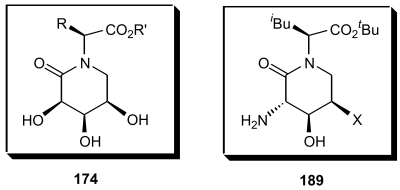


Figure 63

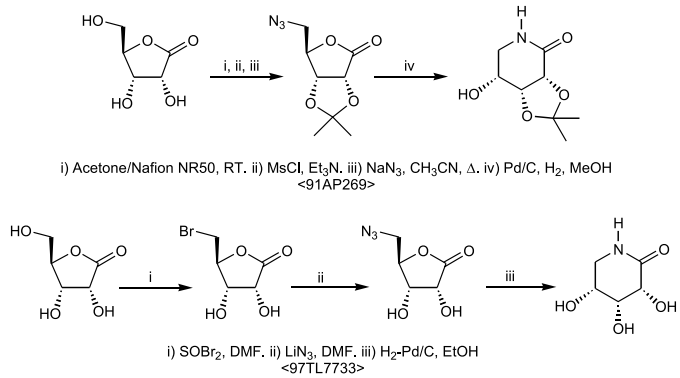


Figure 64

showed that the NH_i carbamate proton was not hydrogen-bonded, and that the NH_{i+3} amide proton was intramolecularly hydrogen-bonded, though weakly. Therefore both isomers showed reasonable potential for action as β-turn mimetics.

Molecular mechanics/dynamics (MM/MD) calculations were performed in continuum, in DMSO, and in H_2O. These demonstrate that **173a** is an excellent βII' turn mimetic, whereas **173b** is more flexible and adopts either unusual β-turns or L-shaped conformations.

The bicyclic system (3*S*,6*S*,9*S*)-**171a** is therefore a new dipeptide scaffold for the synthesis of βII' turn mimetics, which might find application in bioactive peptide-based rational drug design.

9. Hydroxylactams

9.1. Introduction

The last synthon that we present in this review is the polyhydroxylated piperidin-2-one **174** (Figure 63). Since polyhydroxylated lactams have been reported as having interesting biological activities, such as inhibition of glycosidase activity [65], cancer cell metastasis [66], and inflammation [67], we considered the possibility of synthesising a small collection of 3,4,5-trihydroxypiperidin-2-ones **174**, whose activities might be modulated by side chain functionalisation of the amino acid moiety. In addition, transformation of the hydroxyl groups of this synthon offered a wide range of synthetic possibilities. Thus, our first aim was to employ the polyhydroxylated synthon in the preparation of 3-aminovalerolactam **189**, a constrained surrogate of the Ser-Leu dipeptide.

9.2. Synthesis of 3,4,5-trihydroxyvalerolactam 174

The synthesis of compound **174** was directly inspired by the lactamisation reaction of aminolactones derived from carbohydrates (Figure 64). This procedure produces a valerolactam ring with three stereocentres of predefined configuration. Thus, ribonolactone, protected [68] or not [69], can be transformed to its 5-azido derivative, whose hydrogenation yields *N*-unsusbtituted valerolactams by spontaneous cyclisation of the primary amine.

In contrast, our synthesis demanded the cyclisation of an intermediate 5-aminolactone **176** which presented a secondary amino group, since we wanted to introduce a stereocentre adjacent to the N_1-position (Figure 65) [70]. Hydrolysis of the acetal would lead to the target synthon **174**.

Quantitative protection of commercial ribonolactone was carried out by transacetalisation using acetone dimethyl acetal (Figure 66). To introduce the suitable amino moiety, C5 was brominated using NBS-PPh_3 in CH_2Cl_2, and the resulting bromine **179** was treated with Leu-O^{t}Bu in the presence

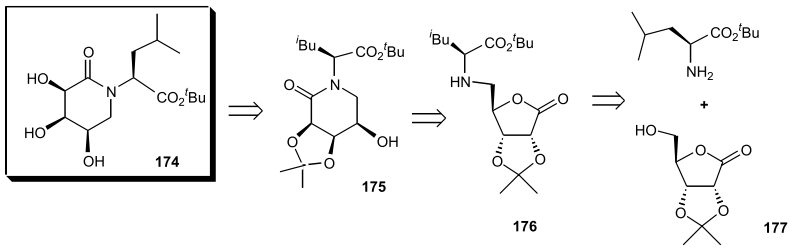


Figure 65

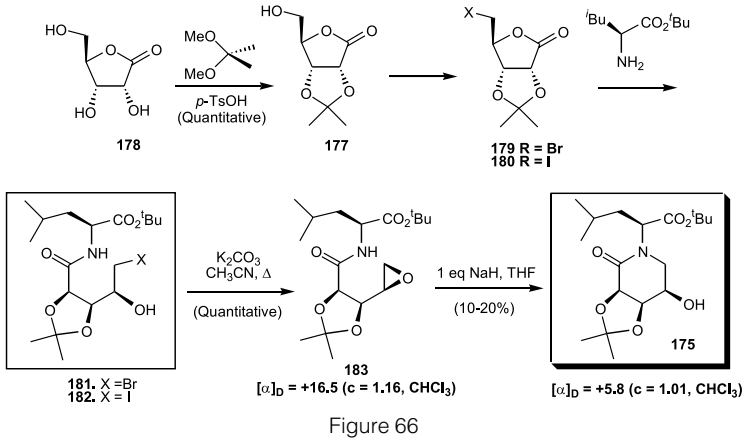


Figure 66

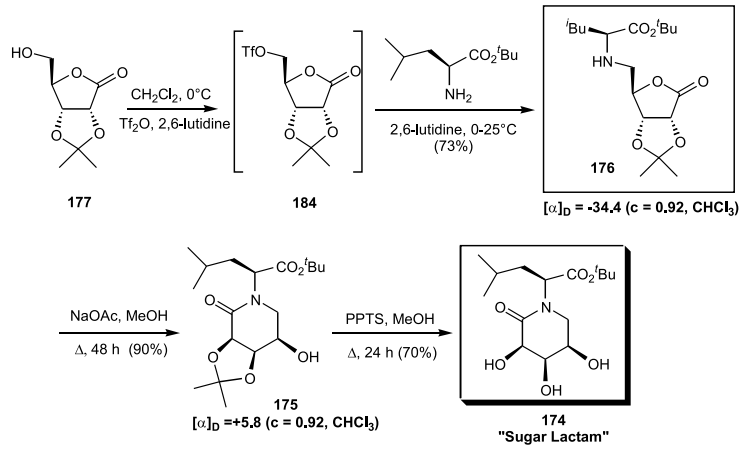


Figure 67

of Et_3N. However, the product obtained was identified as the amide **181**, resulting from opening of the lactone ring, instead of the expected substitution product **176** [71]. When iodide was assayed as the leaving group the same result was obtained. Treatment of amides **181** and **182** with K_2CO_3 led quantitatively to the corresponding epoxyde **183**, which was transformed to the desired lactam **175** on NaH treatment, but in very low yields.

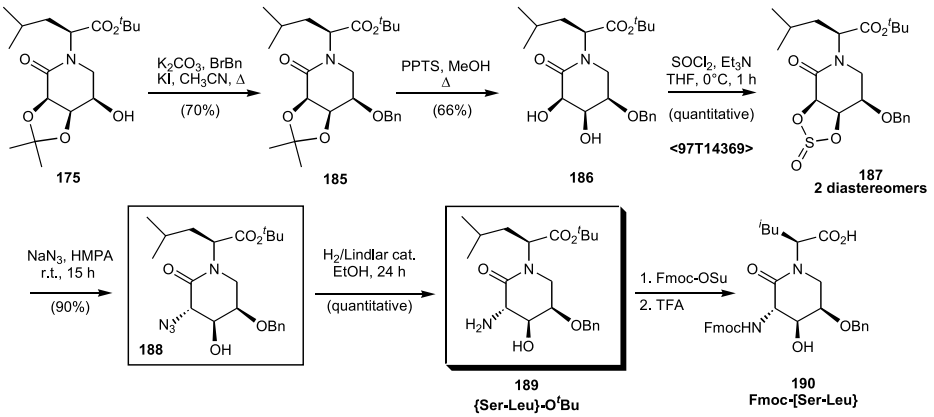


Figure 68

As an alternative, we prepared triflate **184**, whose reaction with Leu-O^{t}Bu yielded the aminolactone **176**, which led to the protected lactam **175** in 90% yield upon treatment with NaAcO (Figure 67). Hydrolysis of the acetal furnished the target trihydroxyvalerolactam **174**.

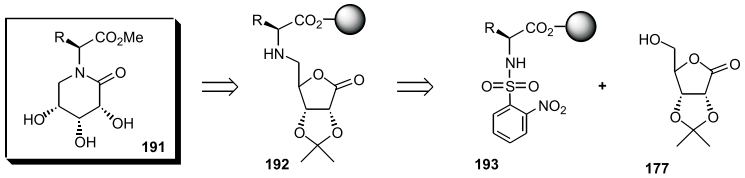


Figure 69

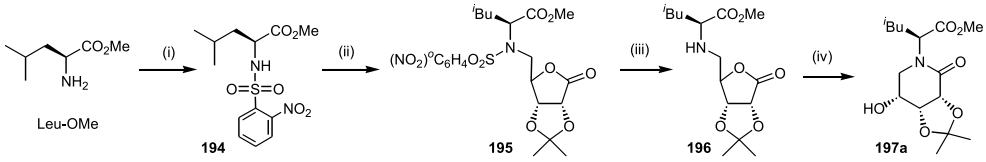
9.3. Serine-Leucine constrained analogues

Once the synthesis of compound **174** had been established, we could proceed to the synthesis of pseudodipeptide **189** as a conformationally restricted Ser-Leu surrogate (Figure 68) [70]. The free alcohol of compound **175** was protected as a benzyl ether, and the acetal was hydrolysed to give compound **186**. The C3 was aminated by reaction of the sulphite **187** with NaN_3 in the presence of HMPA [72]. The sulphite **187** was obtained as a mixture of the 2 epimers on the sulfur atom, which could be separated by chromatography and fully characterized. The subsequent attack by NaN_3 on each isomer led only to the 3*S* isomer of compound **188**. Subsequent reduction of the azide group led to the target {Ser-Leu} pseudopeptide **189**. Compound **189** was suitably *N*-protected and *C*-deprotected to yield the Fmoc/OH derivative **190**, appropriate for further peptide synthesis on solid phase.

We intend now to introduce compound **190** in a small cyclic peptide in order to evaluate its possible application as a β-turn mimetic.

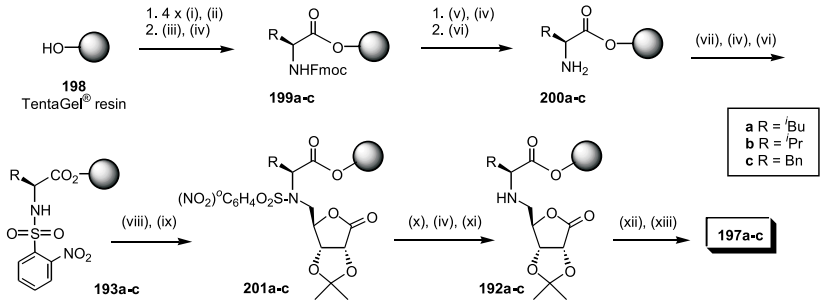
9.4. Solid phase synthesis of hydroxylactams

Once we had established the synthesis of hydroxylated lactams in solution, we examined modified versions of it applicable to solid phase synthesis, which would allow the preparation of a small library of derivatives with various substituents on the N_1 position. Our strategy consisted of anchoring the terminal carboxyl of the aminoacid moiety to a Tentagel$^{(r)}$ resin [73], performing the condensation with D-ribonolactone **177**, and lactamisation (Figure 69). Since lactamisation is accomplished using NaOAc/MeOH, the cleavage of the molecule from the resin would be concomitant with the cyclisation [74], and no linker would be necessary [75].



Reagents and Conditions: i) Et_3N (1.5 equivalents), *o*-NBSCl (1.5 equivalents), CH_2Cl_2, room temperature, 1.5 h (72%); ii) **177** (1.5 equivalents), PPh_3 (1.5 equivalents), DEAD (1.5 equivalents), CH_2Cl_2, 0°C, 5 min, room temperature, 12 h (80%); iii) PhSH (1.1 equivalent), K_2CO_3 (3 equivalents), DMF (87%); iv) NaOAc (5 equivalents), MeOH, reflux, 15 h (96%).

Figure 70



Reagents and Conditions: i) Fmoc-Leu, Fmoc-Val, or Fmoc-Phe (5 equivalents), DIC (5 equivalents), DMAP (0.1 equivalent), HOBt (5 equivalents), DMF/CH_2Cl_2 (1:9, 6 ml/g of resin), 4 h, room temperature; ii) rinsings with CH_2Cl_2/MeOH/Et_2O (3 times each); iii) Ac_2O (1 equivalent), pyridine (2 equivalents), DMF (6 ml/g of resin), 1 h, room temperature; iv) rinsings with DMF/MeOH/Et_2O (3 times each); v) 3 x 20% piperidine-DMF (v/v, 6 ml/g of resin, 5-10-10 min), room temperature; vi) ninhydrine test; vii) Et_3N (5 equivalents), *o*-NBSCl (5 equivalents), DMF (6 ml/g of resin), room temperature, 1.5 h; viii) 4 (5 equivalents), PPh_3 (5 equivalents), DEAD (5 equivalents), THF (6 ml/g of resin), 0°C, 10 min, room temperature 12 h; ix) rinsings with THF/MeOH/Et_2O; x) PhSH (1.5 equivalents), K_2CO_3 (2 equivalents), DMF (6 ml/g of resin), room temperature, 40 min.; xi) chloranyl test; xii) NaOAc (5 equivalents), MeOH, reflux, 24 h; xiii) 1. filtration, 2. evaporation of the MeOH, 3. solution in CH_2Cl_2,filtration

Figure 71

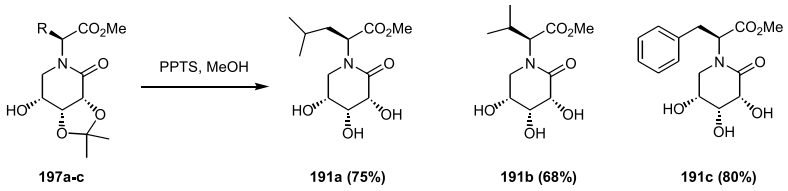


Figure 72

First, we explored the possibility of aminating ribonolactone **177** using a Mitsunobu reaction, which is mild and suitable for solid phase synthesis [76]. This was satisfactorily achieved by *N*-alkylation of the sulfonamide derived from Leu (**194**) with **177** in the presence of DEAD and PPh_3, followed by cleavage of the arylsulfone group of compound **195** with PhSH (Figure 70) [77]. Treatment of the resulting secondary amine **196** with NaOAc/MeOH yielded the expected lactam **197a**.

For the solid phase synthesis we followed Liskamp's method [74] since the TentaGel$^{(r)}$ resin conveniently swells in MeOH, a necessary condition for efficient lactamisation/cleavage. Parallel anchoring of the Fmoc protected aminoacids to the Tentagel$^{(r)}$ resin *via* a Mitsunobu-type reaction [78] yielded compounds **199a-c** which, after capping with Ac_2O, were deprotected to obtain amines **200a-c** (Figure 72). Standard sulfonation of the amines gave the desired compounds **193a-c** [79] which were *N*-alkylated by treatment with ribonolactone **177** in the presence of DEAD and PPh_3 to obtain the corresponding tertiary sulfonamides **201a-c** (Figure 72). The sulfone group was cleaved using PhSH, and subsequent treatment of the secondary amines **192a-c** with NaOAc/MeOH yielded the expected hydroxylactams **197a-c**. After removal of the resin, the MeOH solvent was replaced by CH_2Cl_2 and the products filtered to yield **197a-c** in pure form. The formation of the primary amines and the sulfonamides was confirmed by positive and negative ninhydrine tests, respectively.

Finally, treatment of lactams **197a-c** with PPTS in MeOH yielded the target trihydroxylactams **191a-c** (Figure 72).

10. Conclusion

As every painter has a particular colour that helps him capture very specific feelings or images, we have used the synthetic scope of piperidine to prepare pharmacologically interesting compounds. Thus, by modifying the functionalisation of the piperidine ring we have been able to obtain compounds ranging from alkaloids to pseudopeptides. The reader will realise that this is a dynamic field: we intend to continue contributing to its development.

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About the authors

The authors belong to the Department of Pharmacology and Medicinal Chemistry of the University of Barcelona. The group is specialised in the preparation and the synthetic applications of piperidone building blocks. They first developed two main families of substituted piperidones: 2-arylpiperidin-4-ones and 4-arylpiperidin-2-ones. The former were used to obtain natural alkaloids and derivatives of reserpine and corynantheol. The latter to obtain Aspidosperma and dasycarpidone alkaloids. More recently, with the better understanding of the mode of action of drugs, and the technical development for the design of new potential drugs, the authors developed a collection of 3-aminopiperidin-2-ones. These have a double interest: as peptidomimetics and as restricted pseudodipeptides to be used as surrogates in longer peptide chains. The targets are mostly enzyme inhibitors for diverse therapeutical applications, such as antiinflammatories, antibiotics, and anticancer agents.

Dr. Anna Díez is a Professor at the UB. She did her post-doc in the Institut de Chimie des Substances Naturelles, CNRS (Gif-sur-Yvette, France) in 1988, in the field of alkaloids. Dr. Pilar Forns did her post-doc in the USA (Univeristy of Minnesotta in 1997, and Florida Atlantic University in 1998), specializing in solid phase synthesis. The group has international collaborations in France and the UK, and is part of the «Group of Peptidomimetics and Bioactive Heterocyclic Molecules» of the recently created Science Park of Barcelona, of which Professor Rubiralta is one of the founders.