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Abstract: The importance of, and synthetic routes to, pyrrolidines and piperidines, along with their relevance to natural product synthesis and antibacterial drug discovery, are surveyed in the context of an extended programme of investigation from our own laboratories.

Natural products provide much inspiration for synthetic chemists, and amongst the frameworks which occur in natural product structures, the γ - and δ -lactam moieties are very common, either as an individual sub-unit or embedded in a multicyclic framework.¹ Our interest has been in the chemistry and biology of pyroglutamate and tetramate systems, and one key characteristic of both of these two heterocycles is that they may possess a large number of chemical functional groups and stereochemical information densely packed around the central ring system; this makes for interesting and unexpected interactions and reactivity patterns. A key goal on our part was not so much to engage in total synthesis, but rather to develop simple methodology which provided access to small molecules that might mimic bioactive natural products; this might be one way to address the now widely recognized inefficiency in pharmaceutical drug development,² by increasing the ease of introducing novel chemical matter into medicinal chemistry.³ Our work in this area arose from a project to develop direct routes to functionalised amino acids **1** (Figure 1) via selective formation and alkylation of side chain enolates derived from aspartic and glutamic acids.⁴ While this approach proved to be highly successful, one of its inherent limitations was the need for three protecting groups, two of which were needed to maintain the chirality at the α -position. Of interest was whether a similar strategy might be suitable in a cyclic amino acid, since this would reduce the required number of protecting groups, along with the molecular weight of the intermediates, and moreover introduce the possibility of diastereocontrol by selective facial reactivity of the cyclic system. We chose for immediate study pyroglutamic acid **2** ($R^1=R^2=H$), for its ready availability and potential for the

synthesis of modified amino acids, but also recognising its link to pyrrolidine and pyrrolidinone-containing heterocycles so widely distributed with natural products. At the same time, though, we were developing an interest in heterocyclic systems which were already more highly functionalised, since these seemed to offer significant synthetic potential, and tetramates **3** also became an area of focus. Thus began what was to become a career-long programme, which we set in context below.

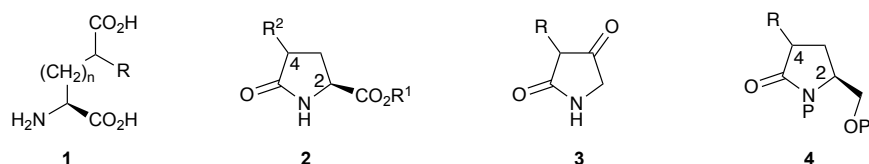


Figure 1

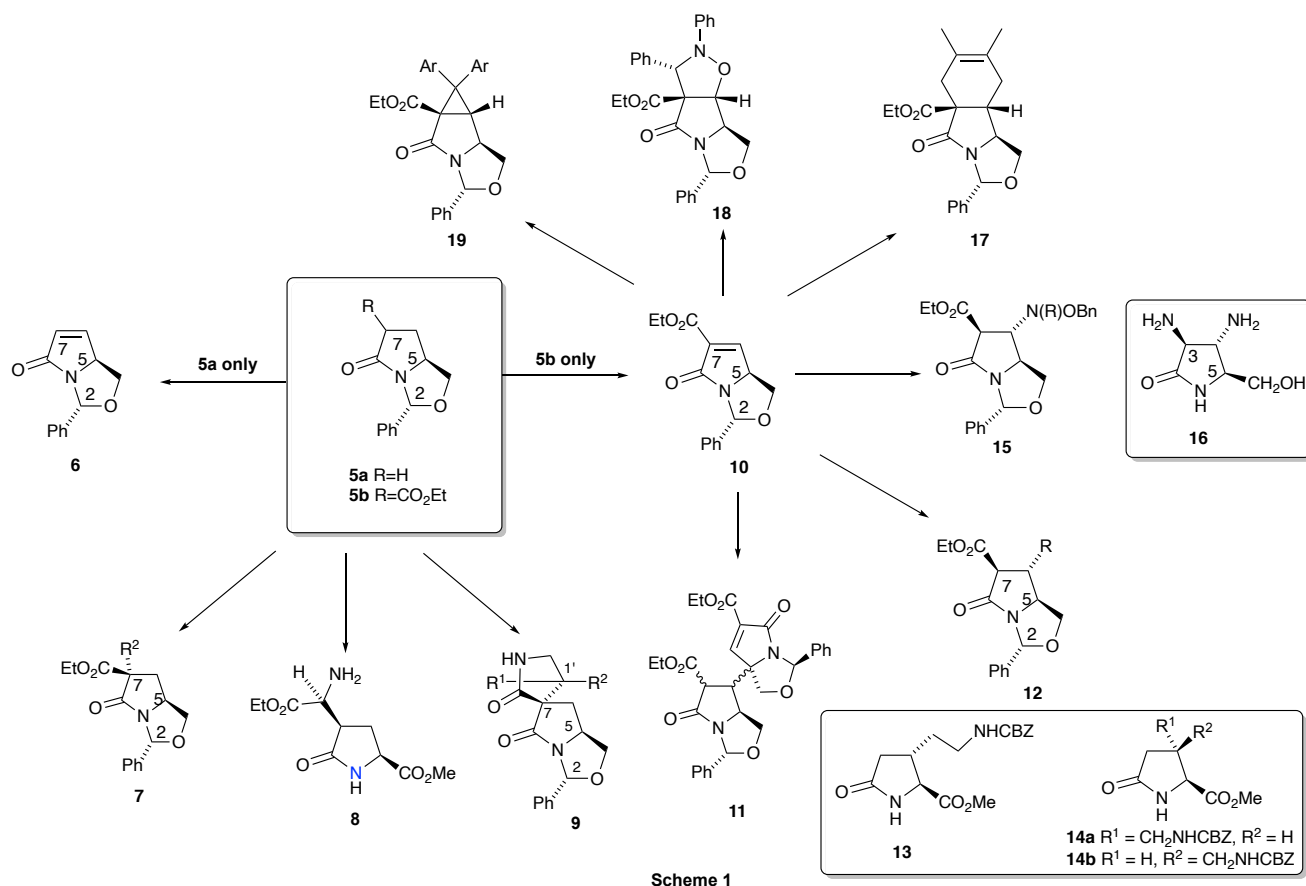
1. Pyroglutamates.

(a) Synthesized by modification of an existing ring.

Pyroglutamates **2** ($R^1=R^2=H$) are of synthetic interest⁵ particularly for their role in chemical biology^{6,7} and drug discovery⁸ and whose medicinal significance continues to develop.^{7,9} The direct modification of pyroglutamates, using an 8-aminoquinoline amide as a directing group for C-H activation, to access functionalized pyroglutamates has recently been reported.¹⁰ Our initial foray into this area sought to modify a pyroglutamate ester **2** ($R^1=Et$) at C-4 by lactam enolate formation followed by alkylation with reactive electrophiles ($R^2 = Me, PhCH_2, CH_2=CHCH_2$), but we had difficulty with deprotonations leading to reactions lacking regio- and diastereoselectivity, and also had concerns with the maintenance of enantiocontrol under the conditions of the reaction.¹¹ We did not follow this up too diligently, but should have, as shown by the elegant work done by others which has been very successful,¹² including the use of protected pyroglutaminol derivatives **4** which at least removed the complication arising from the presence of the acidic α -centre of pyroglutamic acid.¹³ Instead, we moved on to bicyclic lactam **5a** (Scheme 1), originally reported by Thottathil in 1985 for selective alkylations but which initially at least had not been widely followed up within the synthetic community¹⁴ even though some interest was developing in the synthetic application of chiral non-racemic lactams.¹⁵ This system was of particular interest to us, because of its low molecular weight in which two functional groups are protected by a single protecting group, the fact that deprotonations at the α -position are not possible and therefore enantioselectivity could not be compromised, and that the bicyclic structure might be expected to give excellent diastereocontrol.¹⁶ In this, we were not the only ones to recognise its potential, and Langlois,¹⁷ Hamada,^{18, 19} Hanessian,^{20, 21} Meyers^{15, 22} and Madalengoitia^{23, 24} all more or less at the same time developed elegant applications and made major contributions to this area. In our work, we were able to show that that lactam **5a** could be alkylated at C-7 with some diastereocontrol by formation of the lactam enolate.¹⁶ One surprise, though, came

when we accessed enelactam **6**²⁵ by selenation and elimination according to the literature protocol,²⁶ expecting to be able to use conjugate additions to introduce β -functionality as has been found in related cyclopentenones;²⁷ we found this simple system lacked reactivity although conjugate additions¹⁶ and oxygenations were possible.²⁸ However, others were more successful,²¹ and particularly for hydroxylation,²⁹ epoxidation³⁰ and dihydroxylation.^{19, 31, 32} Since generation of the lactam enolate of **5a** also required the use of strong base, we immediately sought to solve both problems simultaneously by the simple expedient of introducing an ethoxycarbonyl activating group at C-7, giving structure **5b**; this was readily done by reflux of bicyclic lactam **5a** with diethyl carbonate and sodium hydride, giving a system which could be readily alkylated under very mild conditions, to give products of type **7**.³³ We found that these reactions were reasonably general in scope, but without full diastereoselectivity; the *exo*- system appeared to be favoured on steric grounds although *endo*-selectivity was possible.^{24, 34, 35} In related work, Liotta concluded that “no portion of the structural framework of these lactam enolates exerts any significant steric or electronic control on the diastereofacial selectivity observed in the alkylation reactions of these bicyclic lactams and that the observed reactivity was best accounted for by solvation of the enolate”,³⁶ and this most likely arises from the very shallow nature of the concave/convex bicyclic ring system which does not offer a strong steric bias. More recently, the understanding of the basis for, and ability to control, diastereoselectivity in lactam alkylations has been very considerably enhanced.^{35, 37} We used these alkylations to access protected penmacric acid **8**³⁸ and novel spirocycles **9**,³⁹ an approach which was also exploited by others.⁴⁰ Of great interest was that selenylation and elimination gave enelactam **10** very efficiently, and this compound proved to be significantly more activated than simpler enone **6**; in fact, it was sufficiently activated that it needed to be made and used immediately, since it was very prone to dimerization, efficiently giving **11** even on standing overnight, and especially under basic conditions.⁴¹ It proved to be superbly reactive to conjugate addition giving products of type **12**,⁴¹⁻⁴³ with high diastereocontrol, and active methylene compounds proved to be excellent nucleophiles which could be used under mild conditions. Reformatsky reagents too, rarely used in conjugate additions, also proved to be ideal nucleophiles for this conjugate addition, since they could be generated under non-basic conditions, and helping to avoid the formation of dimer **11**; we were able to use this approach to access peptidomimetics such as **13** and **14**.⁴⁴ In both cases, the attack to the sterically more accessible *exo*-face giving **12** was favoured, but of particular interest is a recent report which indicates that this may be reversed.⁴⁵ Amine nucleophiles were not suitable, again because these bases facilitated dimerization to **11**, but α -nucleophiles such as hydroxylamines and hydrazines were excellent, giving products of type **15**.⁴⁶ After addition of the hydroxylamino component, it was possible to introduce α -amino groups by reaction of the enolate with an azodicarboxylate, ultimately providing access to diamines of type **16**. Cycloadditions, too, proved to be possible under mild

conditions, giving products **17** and **18** arising from *exo*- addition.⁴⁷ Cyclopropanations using diaryldiazomethanes were efficient in the absence of any catalysis, giving products **19** with exclusive *exo*-attack, such was the reactivity of the enolactam system.⁴⁸ That the concept of using a bicyclic lactam for diastereoselective ring manipulation was an effective strategy, even if we had not optimised it in detail, was shown by its later elegant application by others to large scale synthesis of mesylate **20**⁴⁹ and PF-06650833 **21** (Figure 2).⁵⁰



Scheme 1

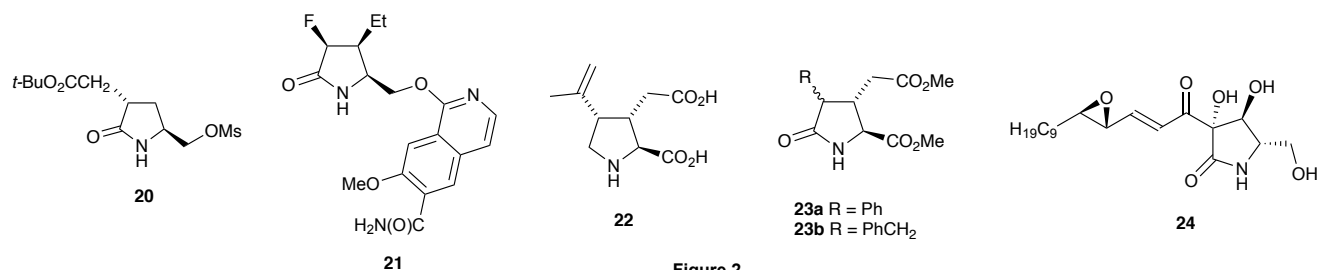
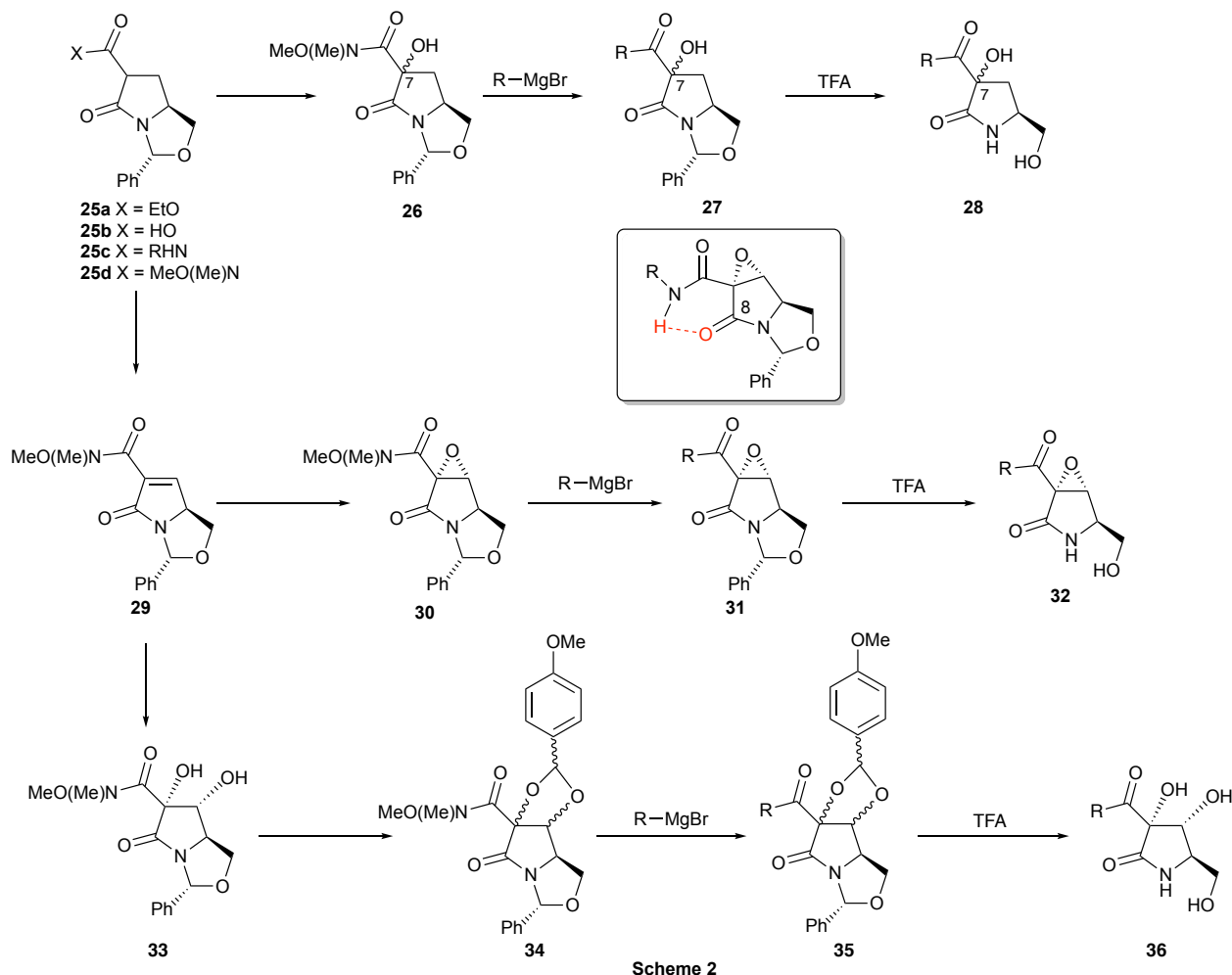


Figure 2

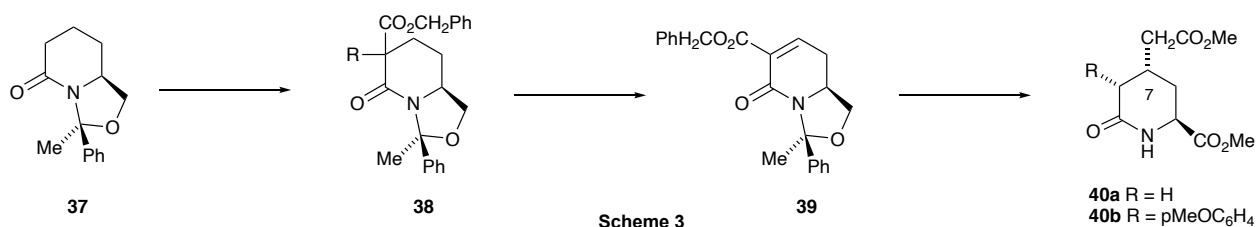
This strategy was applied in a general route to kainoid mimics; kainic acid **22** attracted much interest in the 1990s for its neuroexcitatory activity.⁵¹ The Reformatsky adduct **12** (R= CH₂CO₂tBu) nicely set the required substitution pattern for kainic acid, and we sought to introduce aryl functionality at the C-7 position, since such groups had been shown to have selective binding behaviour at the various

kainoid receptors. For this, we used the α -arylation strategy mediated by lead (IV) and extensively developed by Pinhey,⁵² since at that time, the palladium equivalent later developed by Hartwig⁵³ had not yet become available. Using this methodology, it was possible to introduce a range of aryl substituents and then to elaborate the system to a kainoid mimic, at least as the diester **23a**.^{43, 54} Alkylated versions **23b** were also available by adaptation of this approach.

Another target that became of later interest was pramanicin **24**, discovered by Schwartz and his team at Merck Rahway.⁵⁵ Direct hydroxylation of the lactam system therefore became of interest, but another key issue was introduction of the long alkyl side chain and we found that direct ester-amide exchange of the C-7 ester of lactam **25a** for a variety of amines giving amides **25c** was effective. This strategy could be extended to hydrolysis of lactam **25a** to the intermediate acid **25b**, which with care could be obtained without spontaneous decarboxylation, and direct conversion to Weinreb amide **25d** by CDI-mediated coupling.⁵⁶ Weinreb amide **25d** could be directly hydroxylated to give **26** (as a mixture of *exo*- and *endo*-diastereomers) before conversion to the ketone **27** by chemoselective Grignard displacement, or converted to the enelactam **29** by the usual selenenation/elimination approach, epoxidized to **30**, and converted to the ketone **31** again by chemoselective Grignard displacement.⁵⁶ Dihydroxylation of enelactam **29** was also easily achievable, giving exclusively the *exo*- product **33**, but further elaboration unfortunately required protection to **34**, adding additional steps to the sequence, although the desired product **35** could nonetheless be obtained again by Grignard reaction.⁵⁷ The Grignard displacement on these densely functionalized Weinreb amides was uneventful and highly chemoselective, notwithstanding the high level of chemical functionality in the bicyclic ring system, the only complication arising from the need for additional equivalents of Grignard reagents to account for the additional acidic hydrogens of the substrates. These systems could be deprotected under acidic conditions, providing access to hydroxylated products **28**, **32**, and **36**.^{56, 57} However, the ease of this process leading to epoxypyroglutaminols **32** was surprisingly dependent upon apparently remote side-chain substituents. For example, Weinreb amide **30** and *N*-methylcarboxamide **31** (R = PhN(Me)) were readily hydrolyzed, but carboxamido **31** (R = PhNH) was resistant to hydrolysis under the same conditions. This appears to be due to intramolecular hydrogen bonding of the –NH– group of the amide with the lactam carbonyl oxygen, evidenced from IR and ¹³C spectra (inset, Scheme 2), which reduces electron density of the lactam nitrogen atom, and impedes the acid-catalyzed oxazolidine hydrolysis.

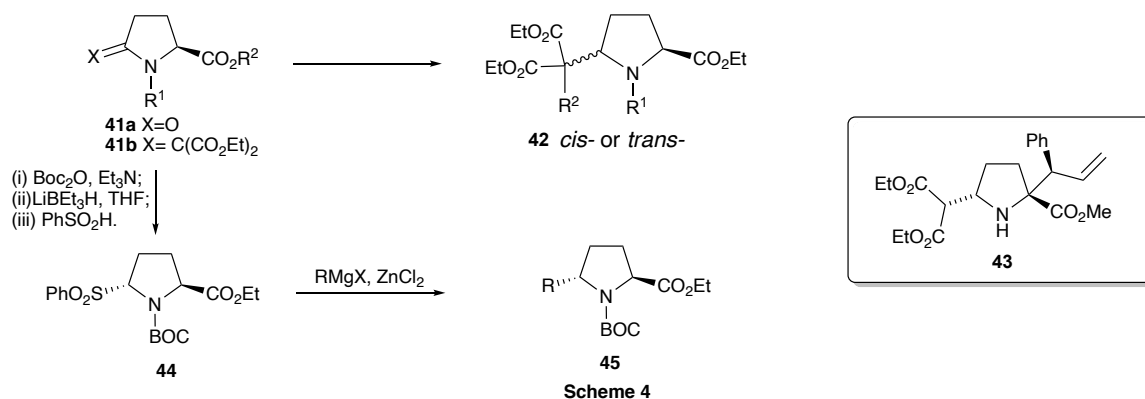


We were also able to further develop this concept for bicyclic piperidinones **37**⁵⁸ leading to key intermediates **38** and **39**, which could be elaborated to products of type **40a,b** analogously to that described above for the γ -lactam series (Scheme 3). Amat extensively developed a similar approach using a more easily accessed bicyclic system,⁵⁹ which has led to a much better understanding of the alkylation of chiral bicyclic lactams.⁶⁰



While the bulk of our work had focused on the reactions of the bicyclic lactam **5a,b**, using the lactam enolate as the entry point, we also found that conversion of the lactam carbonyl of pyroglutamic acid **41a** to enamine systems **41b** using the Eschenmoser thiocarbonyl reaction, followed by reduction, could be used to access 2,5-substituted pyrrolidines **42** with some control of the ring substituent stereochemistry as dictated by the identity of the protecting group R' on the ring nitrogen atom

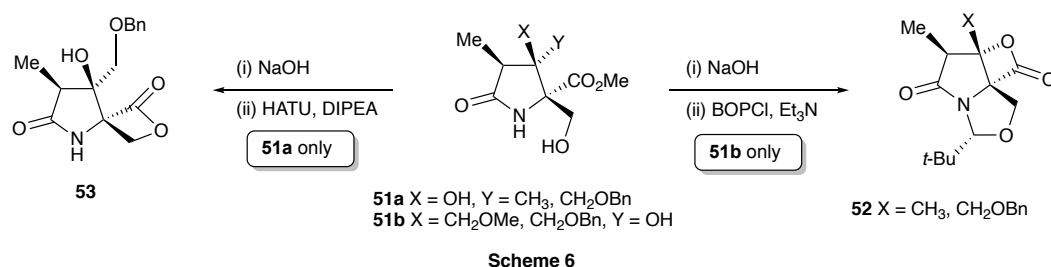
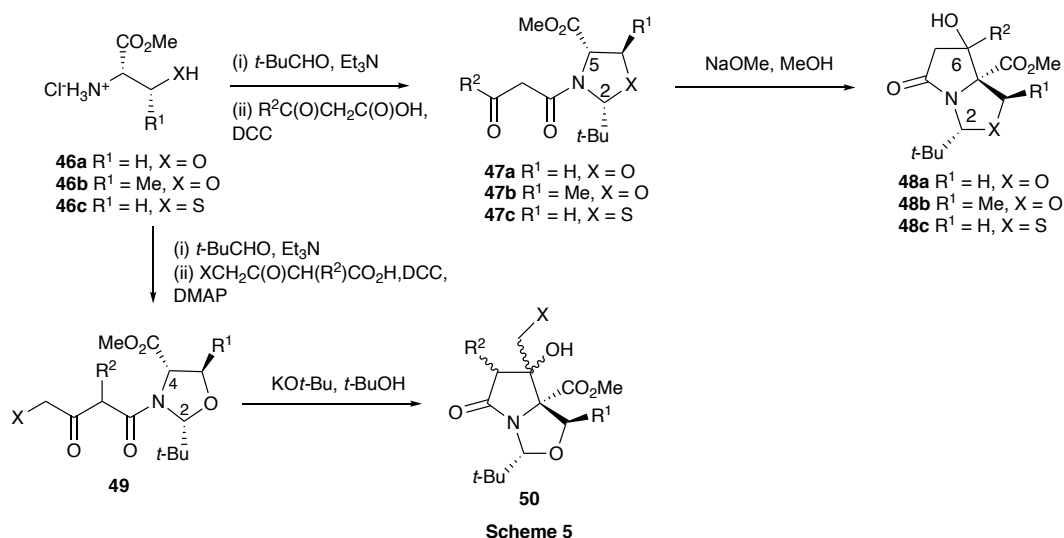
(Scheme 4).^{61, 62} We were able to extend this strategy further to permit double substitutions at the carbon positions flanking the ring nitrogen leading to adducts of type **43**⁶³ by developing an earlier report by Kazmeir,⁶⁴ and to allow effective Grignard additions to an activated sulfone **44** giving *trans*-pyrrolidines **45**.⁶² Similar lactam homologation⁶⁵ has been applied for the formation of (–)-lepadiformine⁶⁶ and epibatidine⁶⁷ and bicyclic thiolactam homologation has been applied to the synthesis of nakadomarin A.⁶⁸



(b) Synthesised by Construction of a New Ring.

While the strategy for the modification of the existing ring described above had been very successful, providing effective routes to highly functionalised pyrrolidines, it was necessarily iterative, requiring a step-wise walk around the heterocyclic ring, initiated by lactam enolate formation, in order to achieve introduction of new substituents. An alternative strategy would be to make the ring in a late step, but already with functionality in place. The key question was how this was to be achieved, and especially with enantiocontrol. A number of elegant approaches to this problem have been devised;⁶⁹ for example, Soloshonok has reported the direct synthesis of pyrrolidines.⁷⁰ Such systems are useful templates for further elaboration to more complex heterocyclic structures.⁷¹ We wondered if we could apply the elegant “Self Regeneration of Stereocentres” concept of Seebach⁷² in an intramolecular manner, and found that highly functionalised pyrrolidines **48a** were directly available by diastereoselective aldol ring closures of ketoacyloxazolidines **47a** which were derived from serine **46a**.⁷³ This reaction also later proved to be suitable for threonine-derived oxazolidine **47b**^{74, 75} and cysteine-derived thiazolidine **47c** templates giving pyrrolidines **48b,c** (Scheme 5)^{76, 77} although these aldol reactions may be reversible.⁷⁸ Similar stereoselective intramolecular aldol reactions of (4*R*)-3-(3-oxobutanoyl)-1,3-thiazolidine-4-carboxylates have been reported and are believed to be directed by 'self-induced' axial chirality.⁷⁹ This reaction proved to be suitable for functionalised ketones, some quite hindered, giving access to very densely functionalised systems with up to 4 contiguous chiral centres of type **50**, although the

final aldol reaction of **49** was not always high yielding nor diastereoselective.⁸⁰ From the densely functionalized lactams **51a,b**, we found fused- β -lactones annulated to γ -lactams **52** could be formed preferentially, under standard lactonization conditions, but that spiro- β -lactone annulated to γ -lactams **53** are more difficult to form and are accessible only when the formation of the fused system is blocked and even then only under carefully optimised reaction conditions. The reversibility of the intramolecular aldol reaction was also found to be problematic (Scheme 6).^{81, 82}



This type of intramolecular aldol reaction has been shown to have value in natural product synthesis (Figure 3). Oxazolomycins **54a-d** and curromycins **54e-f**, and the close analogue, neo-oxazolomycin, all complex natural products,⁸³ have been the focus of a large amount of attention over the last decade, and a ring-forming aldol reaction has been elegantly exploited in several syntheses.^{84, 85} Our own work in the oxazolomycin area was not so much to achieve a total synthesis, but to understand something of the SAR of this compound; this work suggested that a key moiety conferring biological activity was the U-shaped central amide portion,⁸⁶ rather than the lactam unit⁸¹ which has been the focus of so much synthetic activity.^{85, 87} The intramolecular aldol has been applied to several other targets, including lactacystin **55**,^{32, 88} (–)-salinosporamide A (NPI-0052) **56**,^{89, 90} and kaitocephalin **57**.^{85, 91}

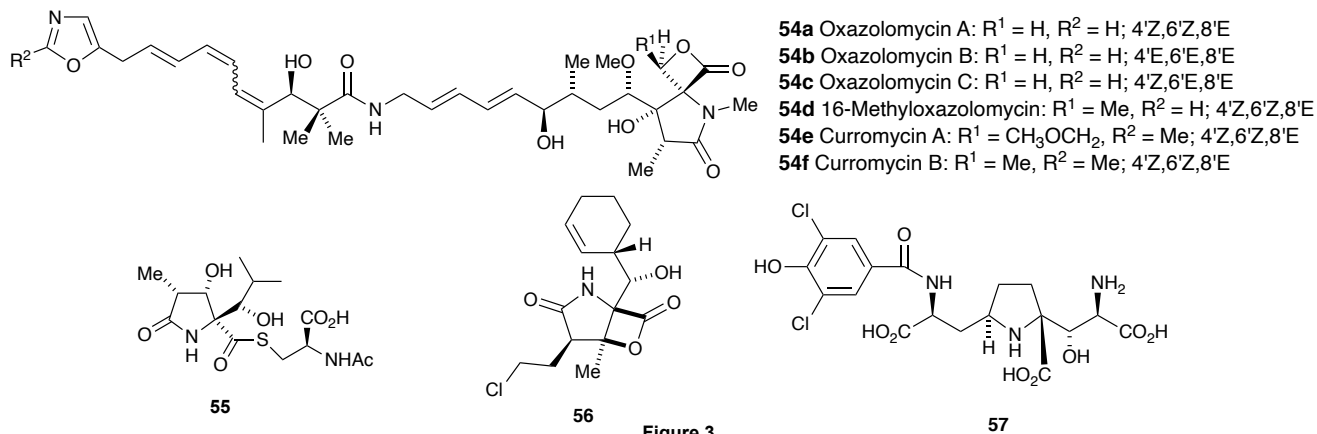
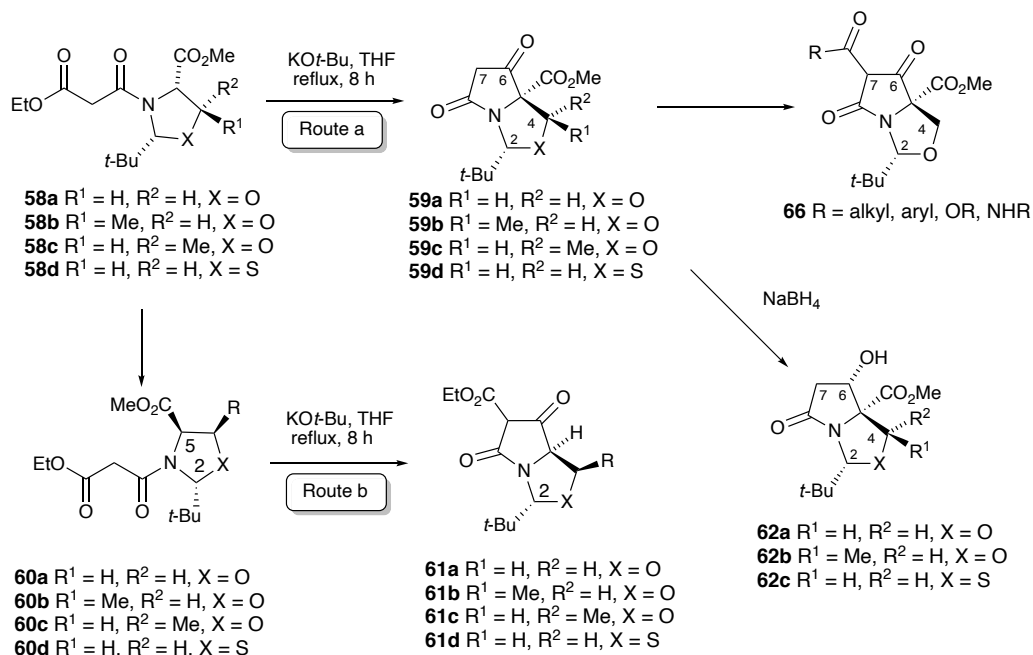


Figure 3

2. Tetramates

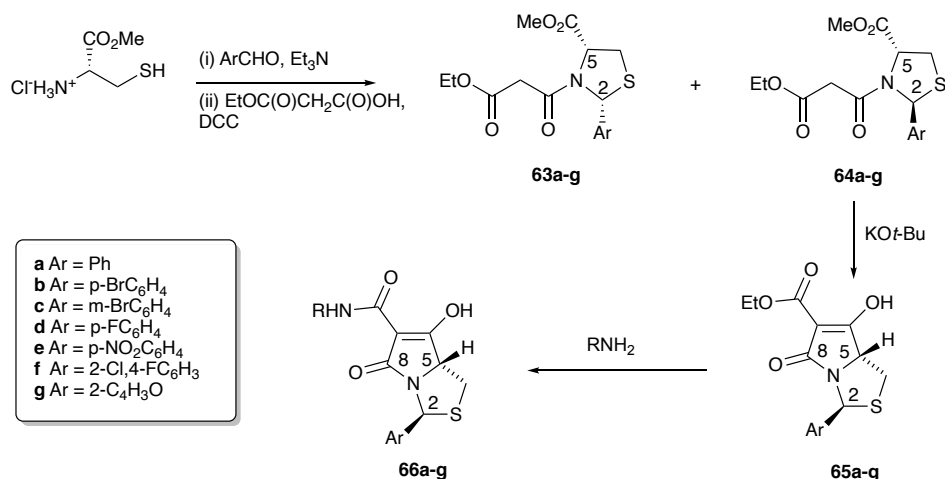
The tetramate core structural subunit occurs in a variety of natural products with a wide range of biological activity⁹² and complex bioactive tetramates continue to be discovered, examples including amycolamycin,⁹³ kibdelomycin,⁹⁴ equisetin,⁹⁵ and lajollamycin.⁹⁶ They have attracted a great deal of attention in the synthetic community,⁹⁷ with major contributions particularly from the groups of Jones,⁹⁸ Schobert^{99, 100} and Markopoulous.^{101, 102, 103}

By extending the aldol ring closure described above, we established that Dieckmann cyclisation of oxazolidine/thiazolidine templates **58a-d** derived from pivaldehyde along with serine,¹⁰⁴ threonine,⁷⁵ *allo*-threonine¹⁰⁵ or cysteine^{77, 106} readily gave enantiopure tetramates **59a-d** (Scheme 7). Although this key cyclisation is highly chemo-, diastereo- and enantioselective, it was limited to the use of pivaldehyde as the initial condensing species, since this both gives relatively stable oxazolidine/thiazolidine intermediates **58a-d** and makes for a system in which the bulky *t*-butyl group exerts a controlling steric influence in a ring-chain tautomeric equilibrium which strongly favours the ring form. Ring closure occurs from the predominantly formed *cis*-acyloxazolidines **58a-d**, in which closure from the C-5 enolate onto the ethyl ester giving **59a-d** is preferred (Scheme 7, Route a), placing the C-2 *t*-butyl and the methoxycarbonyl group on the *exo*-face (that is, less hindered convex face) of the newly generated bicyclic ring system.¹⁰⁷ An alternative mode of cyclisation, starting from the *trans*-acyloxazolidines **60a,b** (which usually arise only as a very minor intermediate by epimerisation at C-5 under the basic conditions of the cyclisation reaction) by closure of the more stabilised malonamide side chain enolate onto the C-5 ester (Scheme 7, Route b), and also placing the C-2 *t*-Bu group on the *exo*-face, generates the alternative tetramates **61a-d**, usually as minor products. Hydroxypyroglutamates **62a-c** are available by selective reduction of these tetramates, in which *endo*-hydride delivery is dictated by the bulky C-5 ester group (Scheme 7).¹⁰⁶



Scheme 7

Up to this point, we had been restricted in access to *t*-butyl substituted systems only, and this derived from the stability of the key oxazolidine intermediates **58a-d**; other aldehydes and ketones gave none of the expected oxazolidine systems by reaction with serine or threonine. Suspecting that thiazolidines would be more stable, we reacted cysteine and a range of aldehydes, and found them this time to be stable but to favour the *trans*- diastereomers **64a-g** rather than the expected *cis*-diastereomers **63a-g**.^{77, 108} Cyclisation of **64a-g** gave not the expected product from Route a (Scheme 7), but the alternative Route b (Scheme 7) leading to **65a-g** (Scheme 8), so that the entire reaction sequence was found not to be exactly comparable to the oxazolidines described above (Scheme 7); we believe that this is due principally to the reduced bulk of the aryl residue relative to the *t*-butyl group. Of interest was the observation of strong scalar cross relaxation in the NMR spectra of the thiazolidine systems.¹⁰⁹ The use of the thiazolidine core provided access to a large variety of substituted tetramates **66a-g** by ester-amide exchange.¹¹⁰



Scheme 8

A major limitation to development of this chemistry was the relative unreactivity of the enolate derived from tetramates of type **59**, and although we were able to make limited modifications by alkylation for example,¹¹¹ a significant success was achieved when we showed that C-7 acylation was possible by initial *O*-acylation followed by rearrangement, using DCC and DMAP to give **66** (Scheme 7),¹¹² along with C-7 ethoxycarbonylation and C-7 aminocarbonylation using the corresponding chloroformate and isocyanate respectively. This process proved to be highly reliable, and opened the door to the preparation of a large number of analogues, suitable for biological evaluation.^{110, 112-116} We were able to use these systems to access unusual polycyclic **67**¹¹⁷ and spirocyclic **68**¹¹⁸ systems, including the core system of isatisine **69** (Figure 4),¹¹⁹ and to apply the same concept to the elaboration of barbiturates, which had better aqueous solubility characteristics arising from their higher polarity.¹²⁰

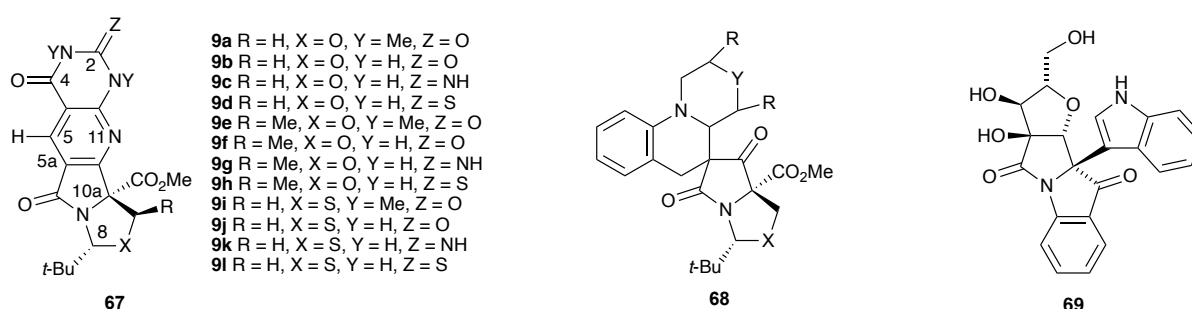
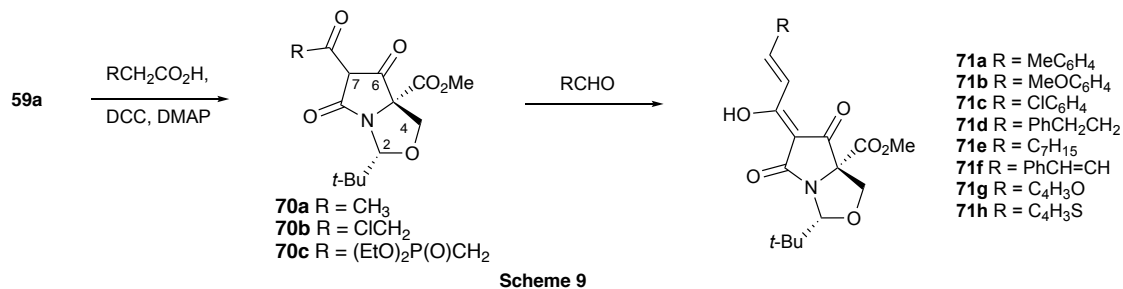
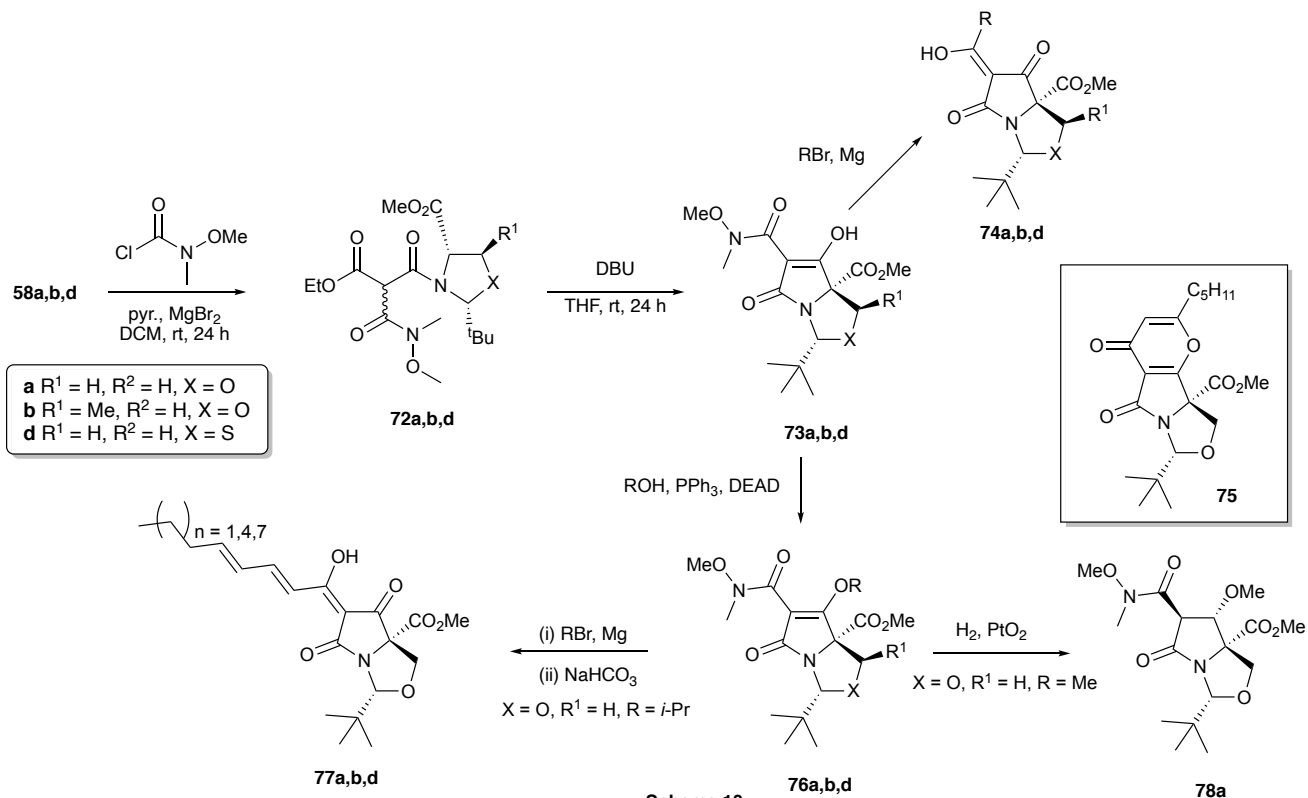


Figure 4

Another route exploiting these templates was to acetylate the tetramate **59a** to generate derivative **70a** and then to condense it with an aldehyde to give unsaturated ketone **71**, either by direct enolate formation or via the intermediate enamine (Scheme 9).¹²¹ Alternatively, conversion of the chloroacetyl derivative **70b** to phosphonate **70c** provided direct access to the alkene system of type **71**. In order to further extend the generality of the side chain manipulation, of interest was whether the Weinreb amide approach which had been so successful in the pyroglutamate series described above might also be effective with tetramates. To this end, synthesis of amides **72a,b,d** was achieved from oxazolidines/thiazolidines **58a,b,d** and their cyclisation with DBU gave tetramates **73a,b,d** very efficiently (Scheme 10). Notwithstanding the fact that this compound has every ring carbon functionalised, it was found to undergo highly selective Grignard displacement at the Weinreb amide and gave alkyl systems **74a,b,d**.¹²² However, when the Grignard was unsaturated (e.g. alkynyl Grignard), the product **74a** rapidly cyclized to give tricycle **75** within hours of formation at room temperature. To solve this, Weinreb amides **73a,b,d** could be reacted under Mitsunobu-like conditions with isopropanol to give enol ethers **76a,b,d**, enabling access to unsaturated ketones **77a,b,d** after Grignard reaction and deprotection.¹²³ The protected Weinreb amide **76a** also provided access to pyroglutamates **78a** by catalytic reduction.¹²⁴

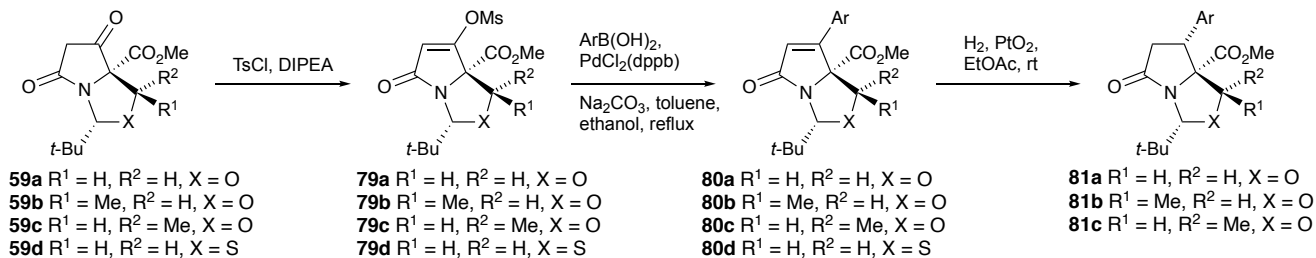


Scheme 9

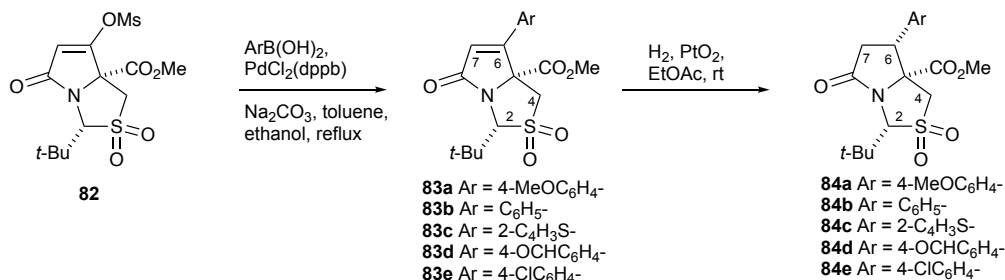


Scheme 10

With the successful conversion of tetramates to pyroglutamates by catalytic reduction, it became of interest extend this approach, and we wondered if transition metal mediated couplings on a suitable derivative might be feasible. Thus, conversion of **59a-d** to mesylates **79a-d** was effected, and Pd(0) couplings provided access to the substituted systems **80a-d**; these could be readily reduced under mild hydrogenation conditions, giving diastereoselective access to pyroglutamates **81a-d**, and bringing us full circle back to where our journey had started, with the development of approaches to functionalized pyroglutamates (Scheme 11).^{105, 125} Of interest was that this approach also permitted access to similarly functionalized sulfones **84** by conversion of mesylate **82** to enones **83a-e** and sulfones **84a-e** (Scheme 12).



Scheme 11



Scheme 12

Metal chelation

Tetramates exhibit extensive tautomeric behavior (Figure 5), and are easily capable of forming metal salts with diverse cations.¹²⁶ The metal chelating behaviour of 3-acyltetramates has been recently reviewed,^{99, 102, 126} and chelation both of natural products¹²⁷ and of simpler systems^{103, 128} has been reported and investigated in detail.¹²⁹ During the course of our work, peak broadening was a recurrent observation and especially so after column purification. We had earlier identified calcium (as well as Na, Mg, Fe and Zn) salt formation during the isolation of tetramates,^{121, 123, 130} that could be substantially removed by washing under acidic conditions, but this work highlighted the ease with which tetramates sequester metals, complicating purification, characterization and biological analysis.

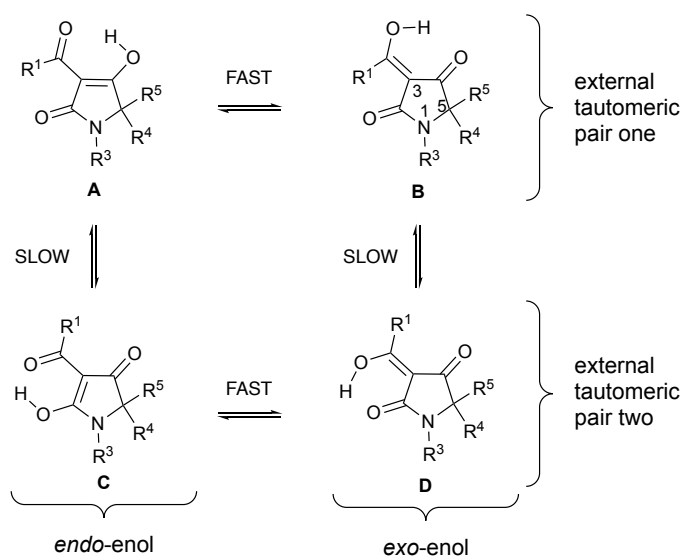


Figure 5

Biological activity

Since the parent atural products had all been reported to possess antibacterial activity, of interest was a similar examination of our compound library for which a large number of compounds were available. We established the existence of strong Gram-positive activity, along with some Gram negative activity, for various library subsets.¹¹⁵ While simple tetramates were inactive,¹³¹ 7-carboxamido ($R'=RNH$)^{110, 113, 130, 132} and 7-acyl^{114, 120} derivatives ($R'=alkyl, aryl$) **85** were particularly active, while 7-enamino derivatives¹³³ were inactive; we identified 4 regions of the bicyclic systems which were important for effective bacterial cell killing activity (Figure 6), and that at least some of the compounds bound at the known binding site of natural product inhibitors, such as streptolydigin.¹³⁴ It has recently been reported that substituted tetramic, tetronic acids and dihydropyridin-2-ones are potent inhibitors of undecaprenyl pyrophosphate synthase (UPPS),¹³⁵ and we found that some of our compounds showed dual activity against UPPS and RNAP.¹³⁰ Of interest is that the hydroxylated pyroglutamates of type **28**, **32**, and **36** showed better Gram negative activity,^{56, 57, 121-123} and broader activity was found for spiro systems⁴⁸ although alkylated and arylated pyroglutamates were fully inactive.^{105, 125} It is clear that these systems offer considerable promise for the development of antibacterial agents. Some tetramate compounds showed activity in pine wood nematode whole organism assays.¹¹⁶

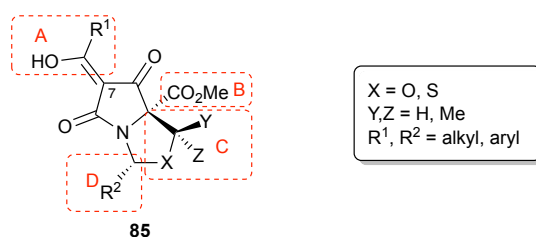


Figure 6

Conclusion

Within the drug discovery process, there has been much recent interest to address the decline in productivity and one immediate possibility is to develop heterocyclic systems with increased molecular complexity suitable for “escaping from flatland”.¹³⁶ The tetramate and pyroglutamic heterocycles described here-in provide non-planar but stereochemically well-defined skeletons, with several points of diversity, in as few as 3 synthetic steps from readily available starting materials and with favourable cheminformatic parameters (including MW, PSA, numbers of rotatable bonds, H-bond acceptors and H-bond donors). Furthermore, they have ample scope for ADMET optimisation using the Lipinski parameters, for application in fragment-based drug design,¹³⁷ in which there is significant current interest.¹³⁸ They therefore offer promise for application as core systems for library generation in the drug discovery process, in addition to any other role that they may have in a synthetic context.

Acknowledgement

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