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Ketene-S,S-Acetals As 1,3-Dipolarophiles Towards Azides. A New Synthetic Entry Into Cyclic Amino Acids‡

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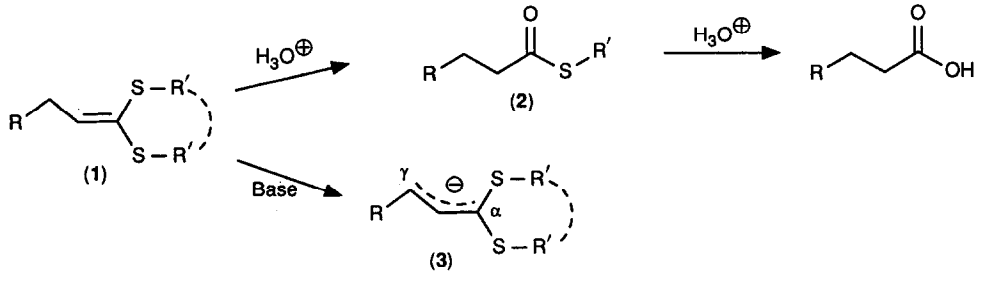
Abstract. Intramolecular azide cycloaddition reactions of ketene-S,S-acetals proceed to give a reactive imine as the initially-formed intermediate and this mechanism is supported by thermolysis of (**18**) which gave the stable imine (**22**). N-Acylation of this intermediate leads to cyclic variants of 2-amino ketene-S,S-acetals (**20**, **24**, **27**), which can be viewed as masked α-amino acids, and reduction leads to the corresponding dithiane (**21**, **25**, **29a**). Both systems have been converted to cyclic α-amino acids and the scope, in terms of the ring sizes available, and the limitations of this intramolecular cycloaddition process are discussed.

Introduction.

Ketene-S,S-acetals (**1**) represent a readily accessible and synthetically versatile class of sulfur-based reagents. In terms of oxidation level, ketene-S,S-acetals are equivalent to carboxylic acids and this equivalence may be expressed either by Hg^{II}-mediated (or another "soft" metal) or acid-mediated hydrolysis (*Scheme 1*); acyl sulfide (**2**), an intermediate in this cleavage pathway, may also be isolated. In general, however, ketene-S,S-acetals are significantly more stable than their oxygen or nitrogen-containing counterparts and release of the masked carboxyl function of (**1**) is usually more straightforward than is hydrolytic cleavage of the closely related S,S-acetals/ketals.[1]

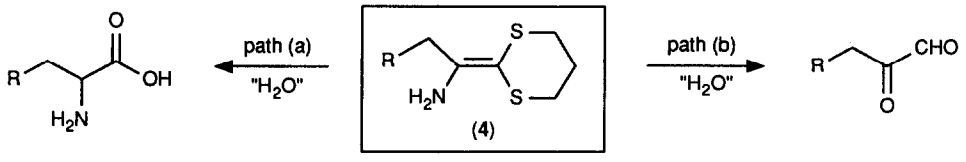


SCHEME 1

‡**It is a pleasure to dedicate this paper to Professor Charles Rees F.R.S. on the occasion of his 65th birthday.**

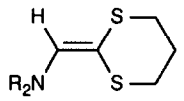
The connectivity provided by the π-bond between sulfur and the allylic position makes the corresponding allylic anions (**3**) available and these ambident nucleophiles have been used as synthetic equivalents of either acyl anions ($RCH{=}CH.CO^{\ominus}$) or homoenolates ($RHC^{\ominus}\text{-}CH_2CO_2H$), depending on how the regiochemistry (α vs γ) of electrophilic attack is controlled.[2]

The chemistry of the more highly functionalised variants of ketene-S,S-acetals has not, however, been developed to the same extent. We were particularly interested in the synthetic opportunities that might be afforded by 2-amino ketene-S,S-acetals (**4**). These systems, by analogy to (**1**), should function as masked α-amino acids (*path (a), Scheme 2*). There is an added complication here in that the amino substituent in (**4**) can also be viewed as an enamine and can lead, on hydrolysis, to an α-ketoaldehyde (*path (b), Scheme 2*). The ability to select between these two pathways is crucial and this is an area that we discuss in more detail later on in this paper.



SCHEME 2

To date, two synthetic routes to 2-amino ketene-S,S-acetals have been described, however, both approaches have limitations in terms of the range of derivatives that are made available. Seebach[3] has utilized a Peterson-type olefination of N,N-disubstituted formamides to provide (**5**) and Page[4] has described the reaction between 2-lithio-1,3-dithiane and nonenolizable nitriles which leads to the primary amino derivatives (**6**); these products often contain a significant amount of the corresponding imino tautomer.



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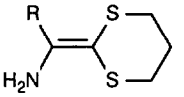
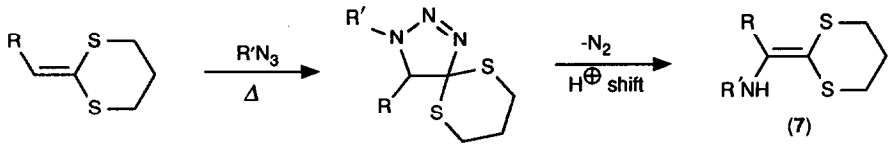


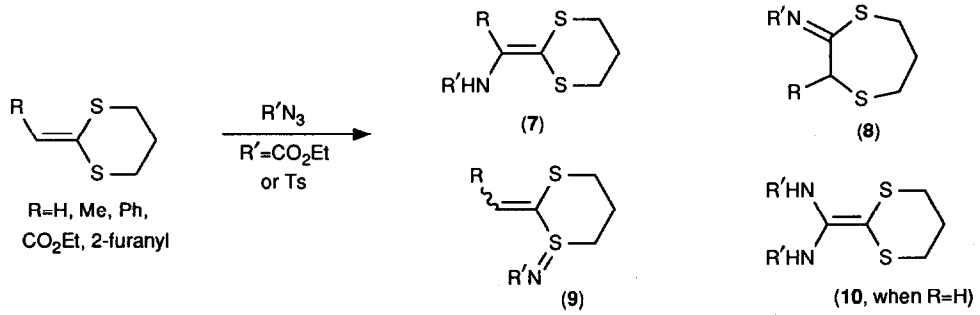
6

Both routes suffer from the basicity of the 1,3-dithianyl nucleophile but are, in other ways, quite efficient. However, the conversion of (**5**) or (**6**) to α-amino acids has not been reported and the opportunities offered by this chemistry would be made more attractive if these derivatives were generally accessible. The key question was how to introduce the amine function - simple ketene-S,S-acetals are themselves readily prepared by a variety of flexible procedures - and we were drawn to the possibility of achieving this by using the ketene-S,S-acetal as a 1,3-dipolarophile towards an organic azide (*Scheme 3*).[5] This raises another interesting and, as yet, open issue: how do ketene-S,S-acetals behave towards 1,3-dipoles? This was unknown at the outset of our programme but since that time Yamamoto has described the reactions of a simple ketene-S,S-acetal with nitrile oxides and nitrones.[6]



SCHEME 3

We initiated our study in this area by investigating a series of intermolecular azide cycloaddition reactions.[7] The results of this are summarised in *Scheme 4* and although 2-amino ketene-S,S-acetals (**7**, R′= CO_2Et) were isolated, these were often minor components and other pathways were observed to compete. These included ring-expansion [to give (**8**)], oxidation at S leading to sulfilamines (**9**) and the formation of 2:1 adducts, such as (**10**). The distribution of these products was dictated by the azide used (EtO_2CN_3 or 4-$MeC_6H_4SO_2N_3$ [TsN_3]) and the substituent (R) on the 1,3-dipolarophile.



SCHEME 4

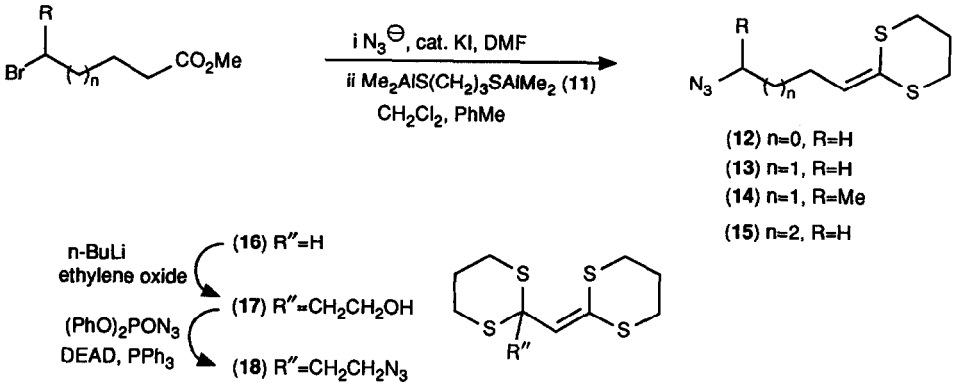
The constraints imposed by the intramolecular variant of this reaction should suppress a number of alternative pathways, such as sulfilamine formation and the production of 2:1 adducts. Alkyl (electron-rich) azides would also be expected to exhibit a different reactivity profile[8] to the more electron-deficient dipoles used in *Scheme 4* and in this paper we wish to describe the scope and synthetic potential of the intramolecular cycloaddition reactions of ketene-S,S-acetal with azides. This process leads efficiently to cyclic 2-amino ketene-S,S-acetals and the synthetic equivalence of these adducts to α-amino acids has been expressed. We have examined the range of ring sizes that are available and also studied the effect of oxidation at sulfur on dipolarophilic reactivity.

Results and Discussion.

Synthesis of ω-Azido Ketene-S,S-Acetals - Acyclic Precursors of Cyclic α-Amino Acids.

A series of simple ω-azido ketene-S,S-acetals (**12-15**) have been synthesised using the chemistry shown in *Scheme 5*, based on the use of a readily available bromoester, with the introduction of the ketene-S,S-acetal function as the final step. This was achieved, in the presence of the azide moiety, using *bis*(dimethylaluminum)propane-1,3-dithiolate (**11**) (BDP), a reagent that was originally introduced by Corey

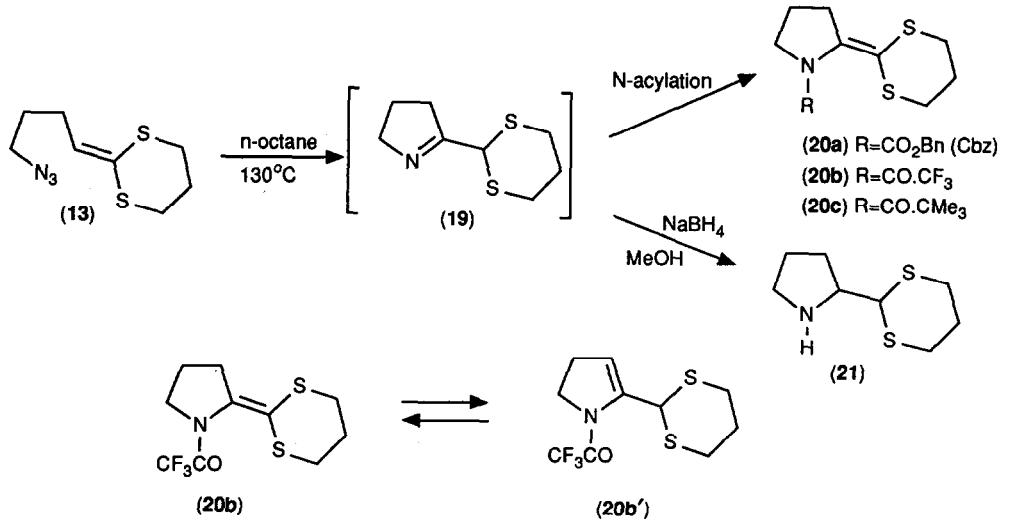
and Beames[9] for use in the protection of esters and lactones. The more highly functionalised variant (**18**) was prepared by alkylation of 2-[(1,3-dithian-2-ylidene)methyl]-1,3-dithiane (**16**)[10] with ethylene oxide to give (**17**), followed by azide displacement of the primary alcohol to give (**18**).



SCHEME 5

Scope of the Intramolecular 1,3-Dipolar Cycloaddition Process.

The butanoate derivative (**12**) was thermally stable and was recovered unchanged, even after heating in decalin at 190°C. This was not too surprising given the known thermal stability of 4-azidobut-1-ene towards intramolecular azide cycloaddition[11] and four-membered rings cannot, therefore, be prepared using this chemistry. However, efficient intramolecular 1,3-dipolar cycloaddition was observed in the pentanoate series (*Scheme 6*).



SCHEME 6

Thermolysis of (**13**) (n-octane, 126°C, 4h) gave a new product (by TLC) which has been assigned

tentatively (*see below*) as the cyclic imine tautomer (**19**). We were, however, unable to satisfactorily characterise this intermediate, but acylation (BnOCOCl, py) of the crude reaction mixture gave the N-Cbz-protected 2-amino ketene-S,S-acetal (**20a**) in 65% overall yield from (**13**). Imine (**19**) was also readily reduced ($NaBH_4$, MeOH) to give pyrrolidine (**21**) in 84% yield from (**13**).

The N-trifluoroacetyl and N-pivaloyl derivatives (**20b**) and (**20c**) were prepared by acylation of imine (**19**) with trifluoroacetic anhydride and pivaloyl chloride in 70% and 55% yields respectively. The N-trifluoroacetyl derivative was found to exist as a 4:1 mixture of (**20b**) together with the corresponding endocyclic enamine tautomer (**20b'**).

Circumstantial support for the assignment of an imine, rather than enamine structure, to intermediate (**19**) comes from thermolysis of the *bis*(dithianyl) derivative (**18**). Under the same conditions, (**18**) gave an essentially quantitative yield of imine (**22**), the structure of which was established by X-ray crystallographic analysis (*Figure 1*).

Imine (**22**) is unable to isomerise to an isomeric endocyclic enamine, though the corresponding exocyclic enamine tautomer is, in principle, accessible. Steric considerations may prevent tautomerism but the factors that control this process in these systems remain to be defined.

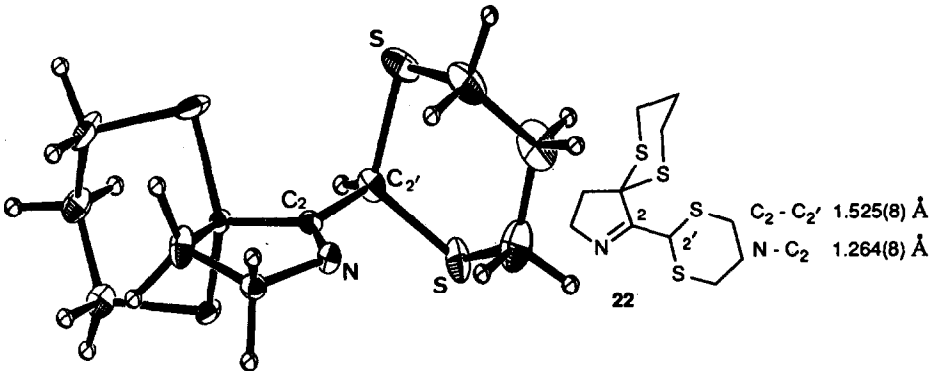
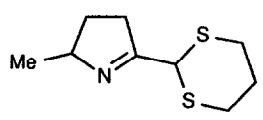


FIGURE 1. ORTEP Diagram of Imine 22

Thermolysis of the secondary azide (**14**) followed a similar course and interception of the putative imine intermediate (**23**) with either benzyl chloroformate or $NaBH_4$ gave (**24**) and (**25**) in 26% and 86% yields respectively. The low yield of (**24**) probably reflects the more hindered environment of the nitrogen nucleophile and pyrrolidine (**25**) was isolated as a 1:1 mixture of *cis*- and *trans*- diastereomers which were not separated. Cyclisation to give the piperidine ring system was also successful, although the reaction was significantly slower in this case than in the corresponding five-ring series. Thermolysis of (**15**) (n-octane, 126°C, 24h) cleanly gave a new product, assigned as (**26**) (by analogy to (**19**)), which was trapped by benzyl chloroformate to give (**27**) in 52% overall yield.

Imine (**26**) was not particularly reactive and we had to adopt a two-phase system (Et_2O/H_2O) in order to achieve this N-acylation step. Interestingly, under these conditions we also isolated the hydrolysis product (**28**) in 34% yield, a transformation which corresponds to *path (b)* in Scheme 2; none of the corresponding α-amino acid was observed. Reduction ($NaBH_4$) of imine (**26**) gave piperidine (**29a**) in 58% yield from (**15**) and the corresponding N-toluenesulfonyl (Ts) and N-*tert*-butoxycarbonyl (Boc) derivatives (**29b**) and (**29c**)

were prepared by standard methods.



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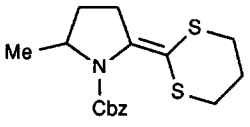

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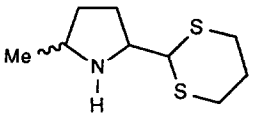

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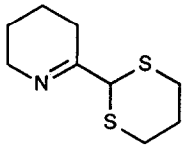

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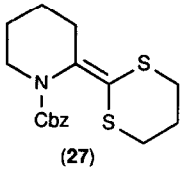

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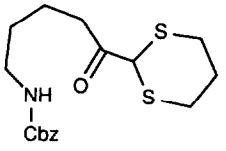

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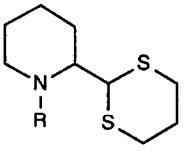
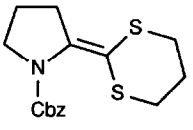


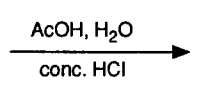
(29a) R=H
(29b) R=Ts
(29c) R=Boc

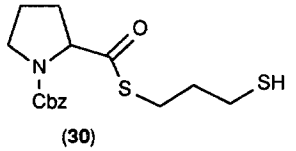
2-Amino Ketene-S,S-Acetals as Masked α-Amino Acids.

The ability to control the hydrolytic cleavage of 2-amino ketene-S,S-acetals i.e. *path (a) vs path (b)* (*Scheme 2*), was key to the success of this phase of the programme. The cleavage of (**27**) to give (**28**) under basic conditions has been noted and with this in mind we examined the use of an acid-mediated cleavage. Treatment of the N-Cbz derivative (**20a**) with 50% aqueous acetic acid gave the desired acyl sulfide (**30**) in 48% yield, together with the "enamine"-derived product (**31**) (*Scheme 7*). Use of 50% aqueous acetic acid containing a small amount of concentrated hydrochloric acid gave ONLY acyl sulfide (**30**) and this reactive ester was immediately treated with sodium methoxide to give the racemic proline derivative (**32**) in 84% overall yield from (**20a**). The reasons behind this selectivity are not yet clear but the structure of (**32**) was confirmed by independent synthesis from L-proline using standard procedures.

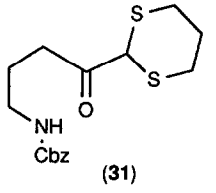


(20a)





(30)



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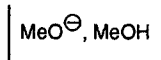
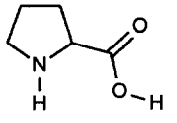
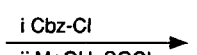
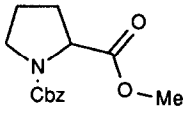






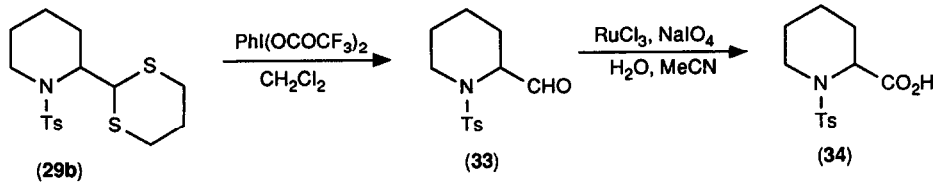


(32)

SCHEME 7

An alternative method for generating the α-amino acid function is available and this is illustrated in *Scheme 8* for the piperidine series. The thioacetal function of (**29b**) was cleaved using $PhI(OCOCF_3)_2$[12] and

the resulting aldehyde (**33**) was oxidised to give the pipecolic acid derivative (**34**) in 53% overall yield.

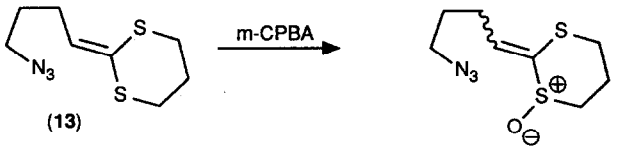


(**29b**) (**33**) (**34**)

SCHEME 8

Reactivity of Ketene-S,S-Acetal Monosulfoxides as 1,3-Dipolarophiles.

While we have established that ketene-S,S-acetals will undergo efficient intramolecular 1,3-dipolar cycloaddition with alkyl azides, we were also interested in studying the reactivity of the corresponding monosulfoxides. Oxidation at sulfur will make the π-bond more electron-deficient - the ability to tune the electronic environment of the dipolarophilic component in this way is not achievable with ketene-N,N- or ketene-O,O-acetals - which may accelerate the cycloaddition reaction and thereby enhance the scope of the chemistry. The introduction of a sulfoxide also results in the generation of a new stereocentre.[13] This has implications for stereochemical control both in a relative, as well as an absolute sense, but there are limitations to using a sulfoxide as a stereocontrol element for asymmetric synthesis which need to be evaluated.



(**13**) (**35a/b**)

4 : 1 mixture of diastereoisomers

SCHEME 9

Oxidation of (**13**) (*Scheme 9*) using mCPBA gave a 4:1 mixture (56%) of two monosulfoxides (**35a/b**) but, by using $NaIO_4$ as oxidant, only one product was obtained, albeit in 25% yield, which corresponded to the major component of the peracid-based procedure. We were, however, unable to separate or assign E/Z stereochemistry to these monosulfoxides. Thermolysis of this mixture at 80°C (cyclohexane) resulted in rapid consumption of the minor monosulfoxide *only*; the major sulfoxide isomer was stable at this temperature but, on thermolysis at 130°C, underwent extensive decomposition. However, we were unable to isolate or trap (by *in situ* N-acylation) any products resulting from the minor monosulfoxide and, at this point, it seems clear that the more easily controlled reactions involve the ketene-S,S-acetals as the dipolarophile. Although the corresponding sulfoxides are available, their reactivity will need to be the subject of a more extensive study.

In summary, the intramolecular 1,3-dipolar cycloaddition reaction between ketene-S,S-acetals and azides is an efficient method for the construction of N-based heterocycles. Retaining the functionality of the ketene-S,S-acetal allows the resulting heterocyclic products, 2-amino ketene-S,S-acetals, to be unmasked to

liberate α-amino acids. In other work we have used these intermediates as building blocks to achieve further substitution of the heterocyclic ring. This extends the scope of the chemistry described in this paper and also provides access to 3-substituted prolines in a stereoselective fashion.[14]

Finally, it is an honour to present this work in recognition of the contributions that Charles Rees has made to many of the mechanistic and synthetic aspects of heterocyclic chemistry. His intellect and enthusiasm have, and will continue to make a personal impact on us.

Acknowledgements.

We thank SERC, ICI Pharmaceuticals and Bath University for financial support. We also thank Dr. J. Ballantine and the SERC MS Service at the University of Swansea for their help with high resolution mass measurements.

Experimental.

All solvents and reagents were routinely purified prior to use by standard methods. Chromatography was carried out using silica gel Merck 9385, unless otherwise stated.

Synthesis of ω-Azido Ketene-S,S-Acetals (12-15).

Preparation and use of *bis*(dimethylaluminium)propane-1,3-dithiolate (BDP) (11)

This reagent was introduced by Corey[9] and is best prepared and used as follows: into a dried flask which has been flushed with nitrogen was added dichloromethane (20 ml) and trimethylaluminium (2.0 M in toluene, 10 ml, 20 mmol) by syringe. The reaction vessel was cooled to 0°C using an ice bath and propane-1,3-dithiol (1.0 ml, 10 mmol) added dropwise by syringe. CAUTION: care must be exercised at this stage because the reaction is exothermic and methane gas is evolved. When the addition of the dithiol was complete the ice bath was removed and the solution stirred for one hour which may result in precipitation of the reagent (depending on the ambient temperature). The carboxylate ester (10 mmol) was then added as a solution in dichloromethane (20 ml) in one portion by syringe and reaction was usually complete after stirring for 48 hours at ambient temperature. Solvent was removed by rotary evaporation and the residual oil diluted with ether (200 ml). Moist sodium sulfate was added by spatula which causes evolution of methane and precipitation of aluminium salts. The reaction was vigorous at first but became slower and was complete after 1.5-2 hours. The solution was filtered through sodium sulfate (anhydrous) and the solids washed with ether. The solvent was then removed *in vacuo* and the product ketene-S,S-acetal was purified by chromatography using silica gel (Merck 9385)

2-(3-Azidoprop-1-ylidene)-1,3-dithiane (12)

A solution of methyl 4-azidobutanoate[15] (318 mg, 2 mmol) in dichloromethane (4 ml) was added to a freshly prepared solution of BDP (2 mmol) in dichloromethane/toluene (2:1, 6 ml) at room temperature and then stirred for 2 days. The normal work-up procedure was followed by chromatography (2-10% EtOAc/petrol) gave (12) (171 mg, 42%) as a colourless oil. (Found: M^+-CH_2N_3, 145.0132. $C_6H_9S_2$ requires M, 145.0145); υ_{max} (thin film) 2070, 1570, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 2.13-2.22 (2H, m), 2.53 (2H, q, J = 7 Hz), 2.89 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 5.8 Hz), 3.31 (2H, t, J = 7 Hz), 5.90 (1H, t, J = 7.3 Hz); *m/z* (low eV E.I.) 201 (M^+, 40%), 145 (M^+-CH_2N_3, 70), 119 (100).

2-(4-Azidobut-1-ylidene)-1,3-dithiane (13)

Methyl 5-azidopentanoate. Methyl 5-bromopentanoate (10 mmol) was dissolved in DMF (10 ml) and treated with sodium azide (780 mg, 12 mmol) and potassium iodide (10 mg), then stirred for 18 hours. Water (20 ml) was added and the product extracted into petrol (3 x 25 ml). The combined organic layers were washed with water (10 ml) then dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* to yield methyl 5-azidopentanoate (1.34 g, 85% overall yield) as a colourless liquid. υ_{max} 2950, 2080, 1730, 1430 cm^{-1}; δ_H

(270 MHz; $CDCl_3$) 1.55-1.76 (4H, m), 2.34 (2H, t, *J* = 7 Hz), 3.28 (2H, t, *J* = 6.5 Hz), 3.66 (3H, s); *m/z* (C.I.) 158 (M^++H, 20%), 130 (35), 115 (40), 98 (100). This material was used without further purification and was not characterized by elemental analysis or high resolution mass determination.

To a freshly prepared solution of BDP (6 mmol) in dichloromethane/toluene (2:1, 18 ml) was added a solution of methyl 5-azidopentanoate (940 mg, 6.0 mmol) in dichloromethane (12 ml). After stirring for 3 days at room temperature the reaction mixture was quenched and, after work up using the normal procedure, the product was purified by chromatography to give (**13**) (790 mg, 61%) as a pale yellow oil. (Found: M^+-N_2, 187.0487. $C_8H_{13}NS_2$ requires M, 187.0489); υ_{max} (thin film) 2070, 1570, 1430 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.68 (2H, quintet, *J* = 7 Hz), 2.16 (2H, m), 2.31 (2H, q, *J* = 7 Hz), 2.87 (4H, m), 3.29 (2H, t, *J* = 7 Hz), 5.90 (1H, t, *J* = 7.5 Hz); *m/z* (70 eV E.I.) 187 (M^+-N_2, 25%), 159 (15), 145 (40), 119 (100), 106 (40).

2-(4-Azidopent-1-ylidene)-1,3-dithiane (14)

Methyl 5-Azidohexanoate. Cyclohexane-1,3-dione (11.2 g, 100 mmol) was hydrolysed using the known procedure[16] to give 5-oxohexanoic acid which was esterified by dissolving in dry methanol, cooling to 0°C and adding thionyl chloride to give 5-oxohexanoic acid methyl ester. This compound was reduced using sodium borohydride in dry methanol at 0°C and the product was purified by chromatography to give methyl 5-hydroxyhexanoate (6.42 g, 44%). A solution of methyl 5-hydroxyhexanoate (1.46 g, 10 mmol) in dichloromethane was cooled to 0°C and treated with tosyl chloride (1.91 g, 10 mmol) and pyridine (3.23 ml, 40 mmol). After warming to room temperature and stirring overnight the solvent was removed and the product was purified by chromatography to give the tosylate of methyl 5-hydroxyhexanoate (2.25 g, 75%); υ_{max} (thin film) 1720, 1580 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25 (3H, d, *J* = 6 Hz), 1.51-1.60 (4H, m), 2.20-2.25 (2H, m) 2.44 (3H, s), 3.64 (3H, s), 4.61 (1H, sextet, J = 6 Hz), 7.34 (2H, d, *J* = 8.0 Hz, part of AA'BB'), 7.78 (2H, d, *J* = 8.2 Hz, part of AA'BB'). This intermediate was not characterized by elemental analysis or high resolution mass determination.

The tosylate (2.15 g, 7.2 mmol) (prepared above) was dissolved in DMF (20 ml) and treated with sodium azide (2.0 g, 31 mmol). The reaction mixture was then heated at 120°C in an oil bath under reflux for 3 hours and, after cooling, water (40 ml) was added and the product was extracted with petrol (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered then concentrated *in vacuo* to give methyl 5-azidohexanoate (1.127 g, 92%) as a colourless oil. (Found: M^+, 171.1026. $C_7H_{13}N_3O_2$ requires M, 171.1007); υ_{max} (thin film) 2080, 1720, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.27 (3H, d, *J* = 6.5 Hz), 1.48-1.53 (2H, m), 1.60-1.85 (2H, m), 2.34 (2H, t, *J* = 7.5 Hz), 3.45 (1H, sextet, *J* = 6.5 Hz), 3.68 (3H, s); δ_C (68 MHz; $CDCl_3$) 19.17 (CH_3), 21.31 (CH_2), 33.41 (CH_2), 35.32 (CH_2), 51.38 (CH), 57.44 (CH_3), 173.46; *m/z* (70 eV E.I.) 171 (M^+, 10%), 139 (15), 129 (100), 11 (25).

A solution of methyl 5-azidohexanoate[17] (445 mg, 2.6 mmol) in dichloromethane (5 ml) was added to a freshly prepared solution of BDP (2.6 mmol) in toluene/dichloromethane (1:2, 5 ml) at room temperature. After stirring for 2 days the normal work-up procedure was followed and the product was purified by flash chromatography (2-6% EtOAc/petrol) to give (**14**) (380 mg, 66%) as an oil. (Found: M^+-N_2, 201.0657. $C_9H_{15}NS_2$ requires M, 201.0644); υ_{max} (thin film) 2060, 1570, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.27 (3H, d, *J* = 6.5 Hz), 1.50-1.66 (2H, m), 2.12-2.20 (2H, m), 2.31 (2H, q, *J* = 7.5 Hz), 2.86 (4H, 2 x t, *J* = 6.5 Hz), 3.47 (1H, sextet, *J* = 6.5 Hz), 5.90 (1H, t, *J* = 7.5 Hz); δ_C (68 MHz; $CDCl_3$) 19.36 (CH_3), 25.10 (CH_2), 25.95 (CH_2), 29.48 (CH_2), 30.20 (CH_2), 35.26 (CH_2), 57.34 (CH), 132.04 (CH); *m/z* (70 eV E.I.) 201 (M^+-N_2, 1%), 186 (1), 159 (2), 145 (2), 143 (2), 119 (100).

2-(5-Azidopent-1-ylidene)-1,3-dithiane (15)

A solution of methyl 6-azidohexanoate[16] (1.71 g, 10 mmol) in dichloromethane (20 ml) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane/toluene (2:1, 30 ml) and stirred at room temperature for 48 hours. The normal work-up procedure was followed by chromatography (2-4% EtOAc/petrol) which gave (**15**) (1.52 g, 67%) as a pale yellow oil; (Found: M^+-N_2, 201.0626, $C_9H_{15}NS_2$ requires M, 201.0644); υ_{max} (thin film) 2090, 1580, 1410 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.40-1.55 (2H, m), 1.57-1.75 (2H, m), 2.11-2.21 (2H, m), 2.25 (2H, q, J = 7.3 Hz), 2.84-2.88 (4H, m), 3.28 (2H, t, J = 7 Hz), 5.92 (1H, t, J = 7.4 Hz); *m/z* (C.I.) 230 (M^++H, 65%), 199 (100); (70 eV E.I.) 201 (M^+-N_2, 5%), 145 (40), 119 (100), 106 (35), 71 (50).

2-[1,3-Dithian-2-ylidene)methyl]-2-(2-azidoethyl)-1,3-dithiane (18)

The alcohol (**17**) was prepared from (**16**) according to the known procedure.[10] A solution of (**17**) (230

mg, 0.78 mmol) in dry THF (10 ml) was cooled to 0°C under an atmosphere of nitrogen then treated with triphenyl phosphine (204 mg, 0.78 mmol), diethylazodicarboxylate (136mg, 0.78 mmol) and diphenylphosphoryl azide (215 mg, 0.78 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for a further 18 hours. The solvent was removed *in vacuo* and the product was isolated following flash chromatography (2-10% EtOAc/petrol) to give (**18**) (156 mg, 63%) as a colourless oil. υ_{max} (thin film) 2070, 1550, 1420 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85-2.08 (2H, m), 2.13 (2H, quintet, J = 6.6 Hz), 2.58 (2H, t, J = 7.7 Hz), 2.77-3.04 (4H, m), 3.47 (2H, t, J = 7.7 Hz), 6.13 (1H, s); *m/z* (70 eV E.I.) 319 (M^+, 1%), 263 (20), 249 (10), 198 (20), 159 (100); *m/z* (CI) 320 (M^++H). We were unable to obtain satisfactory analytical data for this compound.

Intramolecular 1,3-Dipolar Cycloaddition Reactions.

General Procedure for Thermolysis Reactions in n-Octane: Preparation of 2-($\Delta^{1,2}$-Pyrrolidin-2-yl)-1,3-dithiane (19).

In a typical reaction, a freshly prepared sample of (**13**) was placed in a dried flask and *n*-octane (5 ml per mmol of (**13**)) was added. The solution was heated at reflux, under an atmosphere of nitrogen. After 4 hours, (**13**) was absent and a new product, assigned as imine (**19**), had formed cleanly (by TLC). The solution of (**19**) in *n*-octane was stable for several hours if air and moisture were excluded, but all attempts to isolate (**19**) were unsuccessful and resulted in the formation of a number of more polar products. The imine intermediate was then treated in a number of different ways - N-acylation or $NaBH_4$ reduction - as described below.

2-[Pyrrolidine-1-(benzyloxycarbonyl)-2-ylidene]-1,3-dithiane (20a)

The thermolysis of (**13**) (435 mg, 2.0 mmol) was carried out as above and the resulting solution of (**19**) was allowed to cool, diluted with dichloromethane (4 ml) and then cooled to 0°C using an ice bath. Pyridine (316 mg, 4.0 mmol) was added, followed by benzyl chloroformate (344 mg, 2.0 mmol). After stirring for 3 hours with two subsequent additions of benzyl chloroformate, the solvent was removed and the reaction mixture was purified by chromatography (10-15% EtOAc/petrol) to give (**20a**) (421 mg, 65%) as a colourless liquid. (Found: M^+, 321.0855. $C_{16}H_{19}NO_2S_2$ requires M, 321.0855); υ_{max} (thin film) 1680, 1600 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.85 (2H, quintet, J = 7.5 Hz), 2.10 (2H, m), 2.66 (2H, t, J = 7.5 Hz), 2.71 (2H, t, J = 5.5 Hz), 2.80 (2H, t, J = 5.5 Hz), 3.66 (2H, t, J = 7.5 Hz), 5.16 (2H, s), 7.26-7.38 (5H, m); *m/z* (70 eV E.I.) 321 (M^+, 10%), 186 (25), 120 (20), 105 (55), 91 (100).

By using similar methods, the N-trifluoroacetyl and N-pivaloyl derivatives (**20b**) and (**20c**) were prepared using trifluoroacetic anhydride and pivaloyl chloride respectively.

2-[1-(2,2,2-Trifluoroacetyl)pyrrolidin-2-ylidene]-1,3-dithiane (20b): Isolated as a 4:1 mixture of (**20b**) and (**20b'**) in 70% yield as an oil which crystallized on standing, m.p. 53-57°C. (Found: C, 42.6; H, 4.37; N, 5.04; $C_{10}H_{12}F_3NOS_2$ requires C, 42.39; H, 4.27; N, 4.94%); υ_{max} 1700, 1600, 1460 cm^{-1}; δ_H (270 MHz; $CDCl_3$) (peaks due to both isomers) 2.02 (2H, quintet, J = 6.5 Hz), 2.11-2.20 (2H, m), 2.71 (2H, t, J = 7.9 Hz), 2.84 (2H, t, J = 6.3 Hz), 2.93 (2H, t, J = 6 Hz), 3.86 (2H, t, J = 7.2 Hz); peaks due to (**20b'**): 4.11 (2H, dt, J = 1, 7.7 Hz), 5.78 (1H, d, J = 1 Hz), 5.85 (1H, dt, J = 1.1, 1.8 Hz); *m/z* (70 eV E.I.) 283 (M^+, 50%), 250 (2), 236 (2), 222 (2), 209 (8), 186 (100).

2-[1-(2,2-Dimethylpropanoyl)pyrrolidin-2-ylidene]-1,3-dithiane (20c): Isolated in 54% yield as a colourless oil which crystallized on standing, m.p. 100-101°C. (Found: C, 57.6; H, 7.92; N, 5.13; $C_{13}H_{21}NOS_2$ requires C, 57.5; H, 7.80; N, 5.16%); υ_{max} ($CHCl_3$) 1640, 1580, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.31 (9H, s), 1.89-1.97 (2H, m), 2.12-2.14 (2H, m), 2.65 (2H, t, J = 7.6 Hz), 2.77 (2H, t, J = 5.9 Hz), 2.86 (2H, t, J = 6.1 Hz), 3.80 (2H, t, J = 7.0 Hz); *m/z* (low eV E.I.) 271 (M^+, 75%), 186 (100).

2-(Pyrrolidin-2-yl)-1,3-dithiane (21)

A solution of (**13**) (444 mg, 2.07 mmol) in *n*-octane (10 ml) was heated under reflux in an atmosphere of nitrogen for 4 hours to generate (**19**). After cooling to room temperature, an equal volume of dry methanol was added and the reaction mixture was cooled to 0°C and treated with sodium borohydride (160 mg, 4 mmol). The mixture was stirred for 1h. Water was then added and the product was extracted with ether (3 x 25 ml). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was isolated by chromatography (0-60% methanol/EtOAc) to give (**21**) (329 mg, 84%) as a waxy solid which became crystalline on standing, m.p. 27-29°C (Found: C, 50.7; H, 8.10; N, 7.2; $C_8H_{15}NS_2$ requires C, 50.75; H, 7.99; N, 7.40%); υ_{max} ($CHCl_3$) 3200 (broad), 1450 cm^{-1}, δ_H (270 MHz; $CDCl_3$) 1.73-2.14 (6H, m), 2.77-3.17 (6H, m), 3.53 (1H, q, J = 7.5 Hz), 4.11 (1H, d, J = 8 Hz), 4.32 (1H, broad); δ_C (68 MHz; $CDCl_3$)

25.20 (CH_2), 25.66 (CH_2), 29.09 (CH_2), 29.16 (CH_2), 29.29 (CH_2), 46.34 (CH_2), 52.80 (CH), 60.85 (CH); *m/z* (C.I.) 190 (MH^+, 100%); (70 eV E.I.) 119 (5), 70 (100).

2-Aza-1-(1,3-dithian-2-yl)-6,10-dithiaspiro[4.5]dec-1-ene (22)

A solution of (**16**) (150 mg, 0.47 mmol) in n-octane (5 ml) was heated under reflux for 4 hours in an atmosphere of nitrogen. The product crystallized on addition of petrol and was recrystallized from dichloromethane/petrol to give (**22**) (134 mg, 98%) as a colourless crystalline solid, m.p. 123-124°C. (Found: C, 45.0; H, 5.97; N, 4.74; $C_{11}H_{17}NS_4$ requires C, 45.32; H, 5.88; N, 4.81%); υ_{max} ($CHCl_3$) 1630, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.95-2.18 (4H, m), 2.74 (2H, t, J = 6.4 Hz), 2.82-2.92 (4H, m), 3.05 (2H, ddd, J = 3.0, 11.9, 14.6 Hz), 3.23 (2H, ddd, J = 3.8, 6.8, 14.4 Hz), 4.04 (2H, t, J = 6.6 Hz), 4.99 (1H, s,); *m/z* (70 eV E.I.) 291 (M^+, 20%), 258 (25), 216 (20), 185 (100), 172 (25), 153 (30), 146 (70).

Crystal data for (22): $C_{11}H_{17}NS_4$, M = 291.36, orthorhombic, a = 13.480(3), b = 13.343(2), c = 15.496(5)Å, U = 2786.9, space group $Pbca$, Z = 4, D_c = 1.39 gcm^{-3}, μ(Mo-K_α) = 0.64 cm^{-1}, $F(000)$ = 1232. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24°$. The crystal was a strong diffractor and of the 2420 reflections which were collected, 1695 were unique with $I \geq 3\sigma I$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by conventional Direct methods and refined using the SHELX suite of programs. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions. The final residual after 9 cycles of full-matrix least squares refinement was R = 0.0650 for unit weights. The number of parameters varied was 145. Max. final shift/esd was 0.005, the average being 0.002. The max. and min. residual densities were 0.19 and -0.22 eÅ respectively. Full details of this structure determination have been deposited at the Cambridge Crystallographic Data Base.

2-[5-Methylpyrrolidine-1-(benzyloxycarbonyl)-2-ylidene]-1,3-dithiane (24)

Using a similar procedure to that described for (**20a**), thermolysis of (**14**) gave (**24**) in 26% yield (Found: M^+, 335.1029. $C_{17}H_{21}NO_2S_2$ requires M, 335.1012); υ_{max} (thin film) 1680, 1590 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.29 (3H, d, J = 6.5 Hz), 1.42-1.50 (1H, m), 2.08-2.20 (3H, m), 2.41 (1H, ddd, J = 8.5, 9.5, 15 Hz), 2.62 (1H, dt, J = 14, 6 Hz), 2.74 (1H, dt, J = 13, 4.5 Hz), 2.82-2.97 (3H, m), 4.22 (1H, sextet, J = 6 Hz), 5.07-5.40 (2H, m), 7.26-7.41 (5H, m); δ_C (68 MHz; $CDCl_3$) 21.99 (CH_3), 25.27 (CH_2), 29.52 (CH_2), 30.20 (CH_2), 30.78 (CH_2), 31.04 (CH_2), 56.63 (CH), 67.33 (CH_2), 127.89 (CH), 128.05 (CH), 128.31 (CH), 136.36 (C), 139.83 (C), 153.00 (C); *m/z* (70 eV E.I.) 335 (M^+, 10%), 244 (15), 200(20), 91 (100).

2-(5-Methylpyrrolidin-2-yl)-1,3-dithiane (25)

Using a similar procedure to that described for (**21**), thermolysis of (**14**) followed by treatment of the crude product with $NaBH_4$, gave (**25**) in 81% yield as a mixture of *cis* and *trans* isomers(Found : M^+-dithianyl, 84.0816. $C_5H_{10}N$ requires M, 84.0813), υ_{max} (thin film) 3300 (broad), 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.17/1.18 (2 x 3H, d, J = 6.5, 6 Hz), 1.28-1.37 (1H, m), 1.77-2.13 (5H, m), 2.74 (1H, broad), 2.78-2.92 (4H, m), 3.20/3.32 (2 x 1H, m), 3.41/3.59 (2 x 1H, q, J = 7.5 Hz), 4.02/4.06 (2 x 1H, d, J = 7.5 Hz); m/z (70 eV E.I.) 119 (5%), 84 (100); m/z (CI) 204 (M^++H).

2-[Piperidine-1-(benzyloxycarbonyl)-2-ylidene]-1,3-dithiane (27) and N-(Benzyloxycarbonyl)-5-(1,3-dithian-2-yl)-5-oxopentylamine (28)

Thermolysis of (**15**) was carried out in n-octane for 24 hours. N-Acylation under the usual conditions failed and a two-phase procedure was used. The crude reaction mixture was cooled in ice and treated with ether (10 ml), water (10 ml), potassium carbonate (660 mg, 4.74 mmol) and benzyl chloroformate (490 mg, 2.84 mmol). After stirring for 3 hours, the thermolysis product was absent and two new products had formed. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by chromatography (EtOAc/petrol) to give (**27**) in 52% yield as an oil followed by (**28**) in 34% yield as a white, amorphous solid.

Data for (**27**): (Found: M^+, 335.1030, $C_{17}H_{21}NO_2S_2$ requires M, 335.1013); υ_{max} (thin film) 1670, 1580, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.50-1.70 (4H, m), 1.75-1.85 (2H, m), 2.00-2.15 (2H, m), 2.61-3.10 (6H, m), 5.15 (2H, s), 7.26-7.40 (5H, m); *m/z* (low eV E.I.) 335 (M^+, 100%), 220 (15), 200(15), 106 (10), 100 (10).

Data for **28**: m.p. 51-52°C. (Found: C, 58.0; H, 6.58; N, 3.89%; $C_{17}H_{23}NO_3S_2$ requires C, 57.76; H, 6.56; N, 3.96%); υ_{max} ($CHCl_3$) 3350, 1680, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.49-1.57 (2H, m), 1.61-1.70 (2H,

m), 1.94-2.14 (2H, m), 2.54-2.62 (2H, ddd, J = 3.4, 5.3, 13.9 Hz), 2.65 (2H, t, J = 7 Hz), 3.17-3.27 (2H, ddd, J = 3.4, 10.0, 13.8 Hz), 3.22 (2H, t, J = 6.6 Hz), 4.19 (1H, s), 4.83 (1H, s, broad), 5.09 (2H, s), 7.30-7.36 (5H, m); *m/z* (70 eV E.I.) 353 (M^+, 2%), 335 (1), 262 (10), 245 (3), 205 (3), 149 (6), 119 (100).

2-(Piperidin-2-yl)-1,3-dithiane (29a)

$NaBH_4$ reduction of the putative imine intermediate (**27**) (resulting from thermolysis of (**15**)) gave (**29a**) in 58% yield as an oil. (Found: C, 53.1; H, 8.7; N, 6.9; $C_9H_{17}NS_2$ requires C, 53.20; H, 8.37; N, 6.90%); υ_{max} (thin film) 3300, 1430 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30-1.44 (3H, m), 1.55-1.63 (1H, m), 1.80-1.99 (3H, m), 2.05-2.18 (2H, m), 2.64 (1H, dt, J = 2.9, 11.8 Hz), 2.76-2.96 (5H, m), 3.09-3.14 (1H, m), 4.00 (1H, d, J = 6.6 Hz); δ_C (68 MHz; $CDCl_3$) 24.62 (CH_2), 26.11 (CH_2), 26.21 (CH_2), 29.55 (CH_2), 29.81 (CH_2), 30.42 (CH_2), 47.06 (CH_2), 53.22 (CH), 59.36 (CH); *m/z* (C.I.) 204 ($M+H^+$, 60%), 149 (5), 84 (100).

2-[1-(4-Methylbenzenesulfonyl)piperidin-2-yl]-1,3-dithiane (29b)

A solution of (**29a**) (471 mg, 2.32 mmol) was dissolved in dichloromethane (10 ml) under an atmosphere of nitrogen, cooled in ice and treated with tosyl chloride (443 mg, 2.32 mmol), pyridine (275 mg, 3.48 mmol) and DMAP (5 mg), then stirred by 0°C for 12 hours. The solvent was removed *in vacuo* and the product was purified by chromatography (EtOAc/petrol) to give (**29b**) (503 mg, 61%) as a colourless crystalline solid m.p. 111-112°C (MeOH) (Found: C, 53.8; H, 6.64; N, 3.93, $C_{16}H_{23}NO_2S_3$ requires C, 53.75; H, 6.48; N, 3.92%); υ_{max} ($CHCl_3$) 1600, 1470, 1340, 1160 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.15-1.35 (1H, m), 1.36-1.55 (4H, m), 1.86-1.99 (1H, m), 2.00-2.12 (2H, m), 2.42 (3H, s), 2.68-2.83 (2H, m), 2.86-3.06 (3H, m), 3.73 (1H, m), 4.32-4.37 (2H, m), 7.29 (2H, d, J = 8.3 Hz, part of AA'BB'), 7.79 (2H, d, J = 8.3 Hz, part of AA'BB'); *m/z* (C.I.) 358 (MH^+, 85%), 252 (10), 238 (100), 213 (15).

2-[Piperidine-1-(*tert*-butoxycarbonyl)-2-yl]-1,3-dithiane (29c)

Amine (**29a**) in dichloromethane was treated with di-*tert*-butyldicarbonate and triethylamine under standard conditions to give, after aqueous workup, (**29c**) in 73% yield as a colourless solid. m.p. 94-96°C (petrol); (Found: C, 55.2; H, 8.45; N, 4.56; $C_{14}H_{25}NO_2S_2$ requires C, 55.44; H, 8.30, N, 4.62%); υ_{max} ($CHCl_3$) 1680, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.47 (9H, s), 1.40-1.65 (5H, m), 1.90-2.20 (3H, m), 2.60-3.15 (5H, broad), 3.90-4.65 (3H, broad); *m/z* (C.I.) 304 ($M+H^+$, 6%), 288 (3), 248 (40), 204 (65), 184 (65), 128 (100).

Hydrolysis of 2-Amino Ketene-S,S-Acetals to give Cyclic Amino Acids.

Methyl N-(Benzyloxycarbonyl)prolinate (32)

A solution of (**20a**) (111 mg, 0.34 mmol) in a mixture of acetic acid (2 ml) and concentrated hydrochloric acid (4 drops) was heated under reflux for 5 minutes. The product was extracted with petrol (4 x 5 ml) and the combined organic layers were dried (Na_2SO_4), filtered and then concentrated *in vacuo*. The crude residue was dissolved in dry methanol (2 ml) and treated with a freshly prepared solution of sodium methoxide (excess) in methanol at room temperature. After 30 minutes water (2 ml) was added and the product was extracted with EtOAc (3 x 5 ml). The extracts were dried (Na_2SO_4), filtered and concentrated and the product isolated following chromatography (10-15% EtOAc/petrol) to yield (**32**) (78 mg, 84%) as a colourless oil. A sample of (**32**) was also prepared by treating N-(Cbz) proline with thionyl chloride in methanol using a literature procedure. Spectroscopic data for products obtained from both routes were identical and in agreement with those reported previously.[18]

N-(Benzyloxycarbonyl)proline S-(3-mercaptopropyl) ester (30)

A solution of (**20a**) (189 mg, 0.587 mmol) in a mixture of glacial acetic acid (2 ml) and concentrated hydrochloric acid (4 drops) was heated under reflux for 5 minutes. The reaction mixture was diluted with water (5 ml) and the product extracted with EtOAc (3 x 10 ml) and the combined organic extracts were dried (Na_2SO_4), filtered and then concentrated. The product was isolated by chromatography to give acyl sulfide (**30**) (114 mg, 58%) as a colourless liquid. υ_{max} (thin film) 2500, 1680, 1400 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.34/1.39 (1H, 2 x t, J = 8 Hz), 1.77-1.89 (2H, 2 x quintet, J = 7 Hz), 1.90-2.20 (4H, m), 2.47/2.57 (2H, 2 x q, J = 8 Hz), 2.91-2.98 (2H, 2 x t, J = 7 Hz), 3.45-3.70 (2H, m), 4.45/4.55 (1H, 2 x dd, J = 3, 8 Hz), 5.05-5.20 (2H, m), 7.27-7.36 (5H, m); *m/z* (C.I.) 340 (MH^+, 6%), 322 (1), 296 (35), 232 (5), 204 (55), 160 (30), 91 (100). Acyl sulfide (**30**) was not characterized by elemental analysis or high resolution mass determination. Duplication of signals in ^1H NMR is due to amide resonance.

N-(Benzyloxycarbonyl)-4-(1,3-dithian-2-yl)-4-oxobutanylamine (31)

KeteneS,S-acetal (**20a**) (473 mg, 1.47 mmol) was dissolved in a mixture of acetic acid (2 ml) and water (2 ml) and the solution was heated under reflux for 1 hour. Water (5 ml) was added and the products were extracted with EtOAc (3 x 10 ml) and the combined organic extracts were dried ($MgSO_4$), filtered then concentrated *in vacuo*. Purification by chromatography (10-25% EtOAc/petrol) gave (**30**) (239 mg, 48%) (*see above*), followed by (**31**) (41 mg, 8%) as a colourless oil.
Data for (**31**): υ_{max} (thin film) 3350, 1680, 1500 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.84 (2H, quintet, J = 7 Hz), 1.97-2.07 (2H, m), 2.5 (2H, ddd, J = 3, 5.5, 14 Hz), 2.69 (2H, t, J = 7 Hz), 3.14-3.25 (4H, m), 4.19 (1H, s), 4.95 (1H, broad), 5.09 (2H, s), 7.26-7.34 (5H, m); *m/z* (C.I.) 340 (MH^+, 25%), 322 (5), 296 (25), 248 (10), 222 (10), 204 (45), 160 925), 119 930), 91 (100). Ketone **31** was not characterized by elemental analysis or high resolution mass determination.

1-(4-Methylbenzenesulfonyl)piperidine-2-carboxaldehyde (33)

A solution of (**29b**) (230 mg, 0.64 mmol) was dissolved in dichloromethane (10 ml) and treated with *bis*(trifluoroacetoxy)iodobenzene (305 mg, 0.71 mmol). After 5 minutes at room temperature, water (5 ml) was added and the product was extracted with dichloromethane (2 x 10 ml). The combined organic extracts were dried ($NaSO_4$), filtered, concentrated *in vacuo* and the product was purified by chromatography (15-30% EtOAc/petrol) to give (**33**) (169 mg, 74% corrected yield based on NMR which showed 20% unreacted (**29b**)); υ_{max} (thin film) 1730, 1600, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.30-1.60 (6H, m), 2.44 (3H, s), 3.22 (1H, ddd, J = 3.0, 8.8, 12.6 Hz), 3.37 (1H, ddt, J = 1.5, 5.3, 13 Hz), 4.06 (1H, t, J = 5.0 Hz), 7.33 (2H, d, J = 8.2 Hz, part of AA'BB'), 7.69 (2H, d, J = 8.2 Hz, part of AA'BB'), 9.56 (1H, d, J = 0.5 Hz); *m/z* 268 (MH^+, 80%), 238 (100), 155 (30), 91 (60). Aldehyde (**33**) was not characterized by elemental analysis or high resolution mass determination. A previous report of (**33**) contained no analytical data.[19]

1-(4-Methylbenzenesulfonyl)pipecolic acid (34)

A solution of (**33**) (149 mg (containing 20% (**29b**)), 0.42 mmol) was dissolved in a mixture of water, acetonitrile and tetrachloromethane (3:2:2, 2 ml total volume) and treated with sodium periodate (360 mg, 1.67 mmol) and ruthenium trichloride (2 mg). The reaction mixture was stirred rapidly for 18 hours then the product was extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated *in vacuo* and the product was isolated by chromatography (0-40% methanol/EtOAc) to give (**34**) (85 mg, 72%) as a crystalline solid.
A sample of (**34**) was also prepared by dissolving pipecolic acid (1.29 g, 10 mmol) and sodium hydroxide (800 mg, 20 mmol) in ether (10 ml) and water (10 ml), adding tosyl chloride (1.91 g, 10 mmol) and stirring vigorously for 3 hours. The organic layer was then removed and the aqueous layer was acidified to congo red with 2N hydrochloric acid, causing precipitation of (**34**) (2.15 g, 76%) which was recrystallized from EtOAc/petrol to give plates, m.p. 100-101°C; (Found: C, 54.9; H, 6.07; N, 4.88, $C_{13}H_{17}NO_4S$ requires C, 55.10; H, 6.05; N, 4.94%); υ_{max} ($CHCl_3$) 2900, 2500-3200 (broad), 1720, 1600, 1450 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.25-1.55 (2H, m), 1.60-1.80 (3H, m), 2.1-2.2 (1H, m), 2.42 (3H, s), 3.19 (1H, dt, J = 2.5, 12.8 Hz), 3.75 (1H, d, broad, J = 12.4 Hz), 4.78 (1H, d, J = 5.1 Hz), 7.28 (2H, d, J = 8.3 Hz, part of AA'BB'), 7.69 (2H, d, J = 8.3 Hz, part of AA'BB'); *m/z* (70 eV E.I.) 238 (M^+-CO_2H, 100%); (C.I.) 284 (MH^+, 25%), 238 (100), 155 (15), 91 (35). A previous report of (**34**) gave analytical data only for the dicyclohexylamine salt.[20] This derivative was prepared starting from both (**34**) and had m.p. 181-184°C and from commercially available pipecolic acid and had m.p. 186-188°C (lit.,[20] 166-168°C).

E and Z-2-(4-Azidobut-1-ylidene)-1,3-dithiane-1-oxide (35a/b)

A solution of (**13**) (880 mg, 4.1 mmol) in CH_2Cl_2 (12 ml) was cooled to -20 °C and treated dropwise with a solution of *m*-chloroperbenzoic acid (710 mg, 4.1 mmol) in CH_2Cl_2 (8 ml). The progress of the reaction was carefully monitored by TLC and, when complete, water (20 ml) was added and the mixture was extracted with EtOAc (4 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purifed by chromatography (EtOAc/$CHCl_3$) to give sulfoxides (**35a/b**) (530 mg, 56%, 4:1 mixture of E/Z isomers which were not assigned) as a pale yellow oil. υ_{max} (thin film) 2090, 1700, 1050 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.70-1.80 (2H, m), 2.45-2.90 (8H, m), 3.35 (2H, t, J = 7 Hz), 6.48 (1H, t, J = 7 Hz, minor isomer), 6.66 (1H, t, J = 7 Hz, major isomer); *m/z* (C.I.) 232 (M^++1). These products were unstable and we were unable to obtain satisfactory elemental analysis/high resolution mass data.

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