2-Amino Ketene *S,S*-Acetals as α-Amino Acid Homoenolate Equivalents. Synthesis of 3-Substituted Prolines and Molecular Structure of 2-(*N*-Pivaloylpyrrolidin-2-ylidene)-1,3-dithiane

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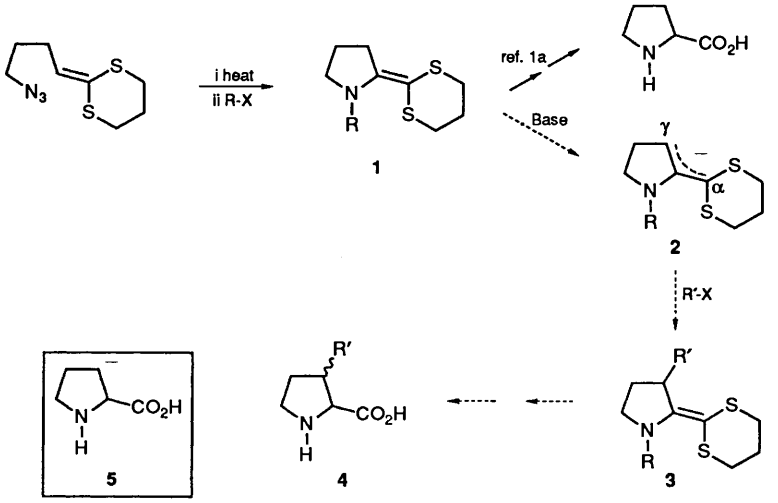
Allylic deprotonation of the heterocyclic 2-amino ketene *S,S*-acetal **8a**, followed by regioselective γ-alkylation reaction of the resulting organolithium **10** (a proline homoenolate equivalent) with electrophiles, leads to adduct **11**. Controlled hydrolytic cleavage of **11** gives a series of 3-substituted prolines, including the conformationally-constrained aspartate and glutamate derivatives, **14e** and **14f** respectively. The bicyclic thiolactam **18** has been prepared in an attempt to provide an asymmetric variant of organolithium **10** but efforts to generate the requisite ketene *N,S*-acetal **19** were unsuccessful. Extension of the ketene *S,S*-acetal chemistry to other ring sizes has been examined within the context of substituted azetidine-2-carboxylates. Condensation of the protected amino ester **20** with $AlMe_3$–$HS(CH_2)_3SH$ was complicated, however, by the reactivity of the four-membered ring and led to the ring-opened adduct **24**, with none of the required ketene *S,S*-acetal **22** being observed.

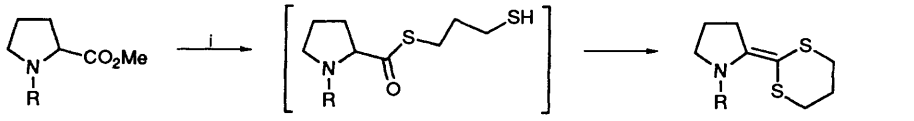
We recently described a new approach to the synthesis of five- and six-membered ring cyclic amino acids based on the reactivity of a ketene *S,S*-acetal as a functionalised 1,3-dipolarophile towards azides.[1] The products **1** of these intramolecular cycloaddition processes may be viewed as heterocyclic variants of 2-amino ketene *S,S*-acetals.[2] Since simple ketene *S,S*-acetals are themselves recognised as synthetic equivalents of carboxylic acids,[3] we were able, by, for example, carrying out a controlled hydrolysis, to convert cycloadducts **1** into heterocyclic α-amino acids. This is illustrated in Scheme 1 for proline, but this chemistry was also applied successfully to the synthesis of hydroxylated prolines[1a,c] and to the corresponding six-membered ring, pipecolic acid. The cycloaddition process, however, failed to give a four-membered ring analogue of **1**, the precursor of azetidine-2-carboxylic acid.[1b]

The ketene *S,S*-acetals **1** also provide a potentially flexible vehicle for further manipulation of the core heterocyclic structure. In particular, we were attracted by the possibility of carrying out an allylic deprotonation of **1** and allowing the resulting sulfur-stabilised carbanion **2** to react with electrophiles.[4] This latter species is an ambident nucleophile, capable of reaction *via* the α-site (adjacent to sulfur) or the γ-site (remote to sulfur) and, under most circumstances α-reactivity would be expected to predominate (see below).[3,4] However, alkylation of **2** at the γ-site to give **3** would, if achievable, offer the advantage that the ketene *S,S*-acetal, and consequently a masked carboxylate, remains intact. Release of the carboxylate function would then lead to the 3-substituted cyclic α-amino acid **4**. Use of anion **2**, in this γ-selective fashion, then becomes synthetically equivalent to using a homoenolate,[5] based on heterocycle **5** (see Scheme 1).

The fate of allylic anion **2** in its reactivity towards electrophiles is not easy to predict. Allylic anions derived from simple ketene *S,S*-acetals have been thoroughly studied and, while most work has focused on exploiting α-reactivity, we[6] and others[7] have demonstrated that high levels of γ-selectivity can also be attained. This is achieved by an appropriate choice of substituents on sulfur (bulky residues sterically encumber the α-site and favour reaction at the γ-centre),[6,7a] the nature of the metal-ion component (Cu shows a higher γ:α ratio than does Li)[7b] and by incorporation of an anion-stabilising residue at the γ-site.[6,7c] The influence of a heteroatom at the β-site of an allylic anion of this type has not, however, been examined but would be expected, based on the nitrogen lone pair–π-bond inter-



Scheme 1

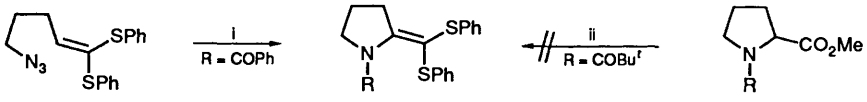


6a R = $COBu^t$
6b R = CO_2CH_2Ph
6c R = $COCF_3$
6d R = SO_2Tol

7a R = $COBu^t$
7b R = CO_2CH_2Ph
7c R = $COCF_3$
7d R = SO_2Tol

8a R = $COBu^t$ 40%
8b R = CO_2CH_2Ph 35%
8c R = $COCF_3$ 17%

Scheme 2 *Reagents and conditions:* i, $Me_2AlS(CH_2)_3SAlMe_2$ (BDP), CH_2Cl_2, PhMe, room temperature (up to 7 d) or reflux (up to 15 h)



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Scheme 3 *Reagents and conditions:* i, octane, 126 °C, then PhCOCl (38%); ii, $(PhS)_3Al$, CH_2Cl_2, PhMe, reflux

action, to have a substantial influence on α/γ reactivity and regioselectivity.

In this paper we describe the realisation of our objective, the generation of an equivalent of homoenolate **5**, and illustrate this methodology by the synthesis of a series of 3-substituted prolines. We also describe a preliminary attempt to develop the asymmetric variant of homoenolate **5** by an extension of the concept of 'self-reproduction of chirality.'[8] The limitations of this chemistry, in terms of its applicability to four-membered rings are also defined.

Results and Discussion

3-Substituted prolines are of interest as conformationally-constrained variants of the more common α-amino acids (see **14e** and **14f** below) and such systems have potential as probes for establishing the bioactive conformations of peptides.[9] Synthetic activity in this area is significant but most of the methods developed to date for the synthesis of 3-substituted prolines are based on the use of acyclic precursors, rather than on direct manipulation of the proline nucleus itself.[9e,10]

Our original synthesis of the heterocyclic amino ketene *S,S*-acetals (*e.g.* **1**) relied on an intramolecular 1,3-dipolarcycloaddition reaction.[1a,b] While this chemistry is suitable for the synthesis of more complex derivatives, in order to develop the chemistry of allylic anion **3** we required more direct access to **1**, preferably from proline itself. Esters are known to react with bis(dimethylaluminium)propane-1,3-dithiolate (BDP) (prepared from propane-1,3-dithiol and trimethylaluminium) to give ketene *S,S*-acetals directly.[11] This transformation had not previously been applied to suitably protected α-amino acids, but a series of *N*-substituted prolinates **6** were successfully treated with BDP to give the corresponding ketene *S,S*-acetals **8** (Scheme 2). The modest yields obtained most probably reflect the hindered environment associated with an α,α-disubstituted ester. Reaction proceeds *via* the corresponding thioester **7**, which can be isolated. However, completion of the sequence shown in Scheme 2 required either long reaction times or heating which is in marked contrast to the conditions required to convert α-mono substituted esters to ketene *S,S*-acetals.*

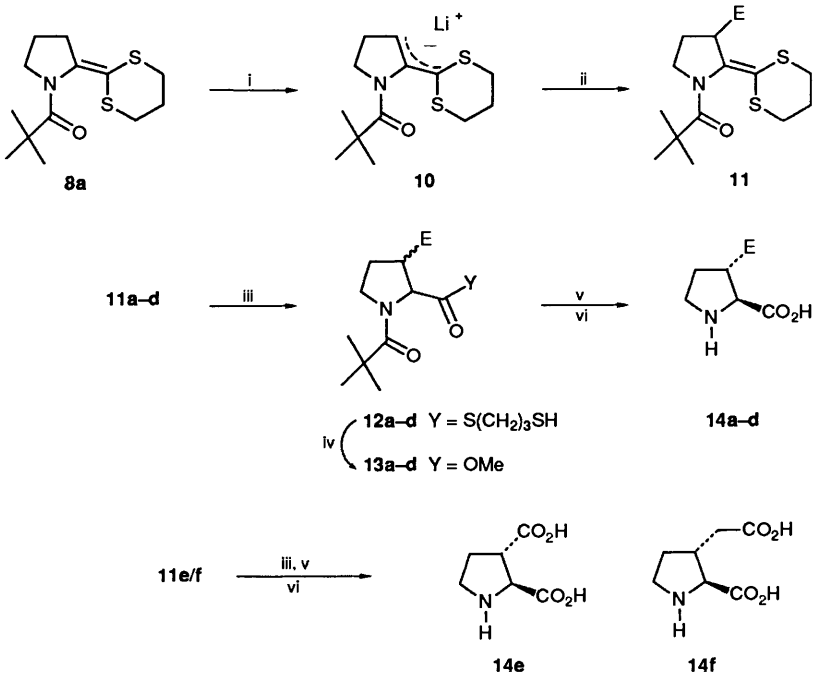
The *N*-pivaloyl derivative **8a** was selected over **8b** and **8c** for further study for a number of reasons. Previous work had demonstrated that γ-selectivity in the reactions of allylic anions derived from ketene *S,S*-acetals was enhanced by the presence of bulky substituents on sulfur; SPh being better than the 1,3-dithianyl residue.[7] We were able to prepare the SPh derivative **9** (R = COPh) but only by the use of the intramolecular azide cycloaddition-based chemistry; the hindered nature of $(PhS)_3Al$[12] and the prolinate component both contributed to make the more direct approach unworkable (Scheme 3). The *N*-pivaloyl moiety should, however, provide the α-site with a demanding steric environment (see below) and **8a**, which is available on a synthetically useful scale, is crystalline and possesses good chemical stability.

Allylic deprotonation of **8a** was carried out using lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and the resulting organolithium **10** was treated with a series of electrophiles to give, after work-up, the γ-alkylated adducts **11** in moderate to good isolated yields (Scheme 4). Adducts **11** were then converted into the corresponding 3-substituted prolines by one of two methods. The alkylated adducts **11a–d** were treated with $BF_3{\cdot}Et_2O$ in CH_2Cl_2–EtOAc to give, after an aqueous quench, thioesters **12**. Isolation was most conveniently conducted by reaction of the crude product with sodium methoxide in methanol. Except for **12a**, this gave consistently better yields than direct hydrolysis. The resulting methyl esters **13** were then cleaved under basic conditions and the *N*-pivaloyl residue was removed using aqueous trifluoroacetic acid either at room temperature (2 d) or at reflux (2 h). The fully deprotected 3-substituted prolines **14** were then isolated following ion exchange chromatography. The ester-containing adducts **11e** and **11f** were cleaved using $BF_3{\cdot}Et_2O$, to give **12e** and **12f** respectively, followed by sequential treatment with aqueous sodium hydroxide and aqueous trifluoroacetic acid. The results of this aspect of the study are shown in Scheme 4 and Table 1.†

The fully deprotected amino acids **14e** and **14f**[13] were of interest as conformationally constrained variants of aspartic and glutamic acid respectively. There is also a close structural resemblance between the excitatory amino acid, kainic acid, and **14f**, with the latter being known as a ligand for the kainate and related receptors.[14]

* Attempts to convert the *N*-tosyl proline derivative **6d** into the corresponding ketene *S,S*-acetal were unsuccessful with only a low (11%) yield of the corresponding thioester **7d** being isolated. A Peterson-type olefination of *N*-tosylpiperidin-2-one using 2-lithio-2-(trimethylsilyl)-1,3-dithiane also failed, with only aldol-type products being observed.

† In some cases, both the *cis*- and *trans*-isomers of **14** were observed though the *trans*-isomer, which is generally thermodynamically more stable,[10i] was assumed to be the major product and stereochemical assignment of the final amino acid products **14** were based on the literature data. *cis*/*trans* Stereochemical assignments of intermediates **12** and **13** were not carried out except for the methyl ester **13d**, which was shown to have *trans*-configuration by ^1H NMR (NOE).



Scheme 4 *Reagents and conditions:* i, LDA, THF, −78 to 0 °C; ii, Electrophile (E^+), see Table 1; iii, BF_3•Et_2O, EtOAc, CH_2Cl_2 then 5% aqueous K_2CO_3; iv, MeO^-, MeOH; v, 2 mol dm^{-3} NaOH, reflux; vi, CF_3CO_2H/H_2O (4:1), room temp. or reflux, then Dowex 50 × 8–10

Table 1

Electrophile	11	12	14
MeI	**11a** (50%)	**12a** (75%)	**14a** (96%)[c] R = Me
$PhCH_2Br$	**11b** (86%)	**12b** (88%)	**14b** (48%)[d] R = CH_2Ph
$CH_3(CH_2)_2I$	**11c** (72%)	**12c** (81%)	**14c** (60%)[d] R = $(CH_2)_2CH_3$
CH_2=$CHCH_2Br$	**11d** (66%)	**12d** (88%)	
$ClCO_2Me$	**11e** (85%)	**12e** (38%)	**14e** (73%)[c] R = CO_2H
$BrCH_2CO_2Et$	**11f** (64%)	**12f** (46%)	**14f** (74%)[c] R = CH_2CO_2H
HCHO	**11g** (82%) R = CH_2OH[b]		
PhCHO	**11h** (55%) R = PhCH(OH)[b]		

[a] This adduct was converted into **13d** (92% yield from **12d**) but was not carried through to **14d**. The *trans*-configuration of **13d** was established by ^1H NMR spectroscopy (see Experimental section). [b] Deprotection of **11g** and **11h** to produce the corresponding 3-substituted proline was not successful (see text). [c] Yield from **12**. [d] Yield from methyl ester **13**.

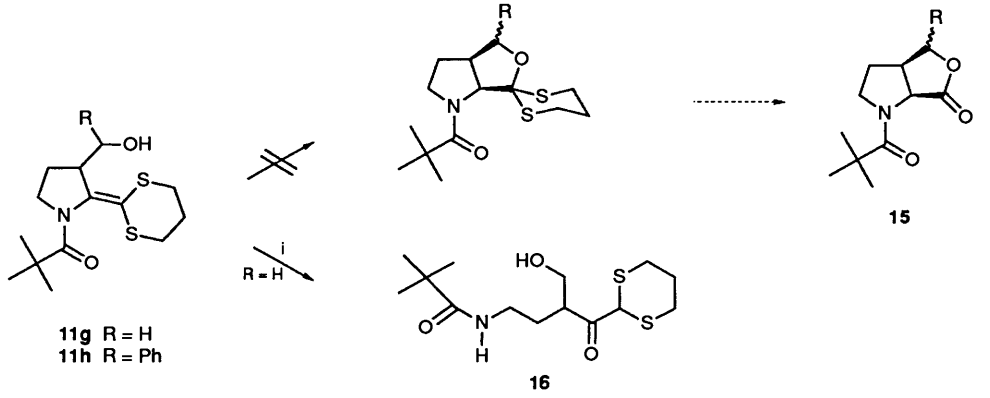
The aldehyde adducts **11g** and **11h** could not be cleaved successfully even though cyclisation of the hydroxy function, under acidic conditions, to give **15** was predicted to be facile. In the event, we were unable to achieve cyclisation of **11g** under a variety of conditions, and when Hg^{II}-mediated hydrolysis was examined, only the ring-opened ketone **16** was obtained (Scheme 5). This corresponds to an alternative mode of cleavage of 2-amino ketene *S,S*-acetals and has been observed previously.[1b]

The factors that control α- *vs.* γ-selectivity in the reaction of anion **10** with electrophiles are still not yet clear. The high degree of γ-selectivity observed for both 'soft' (*e.g.* HCHO, PhCHO) and 'hard' (*e.g.* $ClCO_2Me$) electrophiles was surprising; the γ-site is usually regarded as 'soft' and the α-site as 'hard' in terms of the incoming electrophile.[4a–e] Complexation involving the carbonyl residue can be excluded here, though this interaction might be important in acyclic derivatives related to **10**, but the dominant influence is presumed to reside in the nitrogen lone pair–π-bond interaction. With this in mind we have established the structure of amide **8** by X-ray crystallographic analysis [Fig. 1(*a*)/(*b*)].

The amide carbonyl does not appear to be perturbed [ν_{max}-($CHCl_3$)/cm^{-1} 1640], but the molecule cannot readily accommodate a planar amide unit. Nitrogen shows marked pyramidalisation and the carbonyl function is twisted significantly. Fig. 1(*b*) shows an alternative view of **8** through the C-5–C-8–C-9 plane. The nitrogen and oxygen atoms lie 0.24 and 0.55 Å above and below this plane respectively. Further studies are required to determine more precisely the involvement of nitrogen lone pair with the adjacent π-system, but the ability of a β-heteroatom substituent to modify regioselectivity in this way opens up a number of interesting possibilities that merit further study.

The chemistry shown in Schemes 2 and 4 does result in loss of chirality from proline and, consequently, the formation of racemic products following alkylation. We have explored one possible solution to the problem of generating an asymmetric variant of anion **10**, based on an extension of the concept of 'self-reproduction of chirality'. This has already been shown to be an efficient and enantioselective entry to α,α-disubstituted prolines[8b,c] and we have opted to adapt the chemistry described above to use a more readily accessible ketene *N,S*-acetal **19** (rather than a ketene *S,S*-acetal) as a masked carboxy function (Scheme 6). The temporary aminal stereocentre in **19** is then available to control the facial selectivity in the subsequent alkylation step and, although this centre is relatively remote to C-3 of proline, facial discrimination should still be feasible.

Condensation of proline *N*-methylamide[16] with pivalaldehyde gave the bicyclic imidazolidinone **17** as a single diastereoisomer in 46% yield and reaction of **17** with Lawesson's



Scheme 5 *Reagents and conditions:* i, $HgCl_2$, H_2O, MeCN, room temp. (56%)

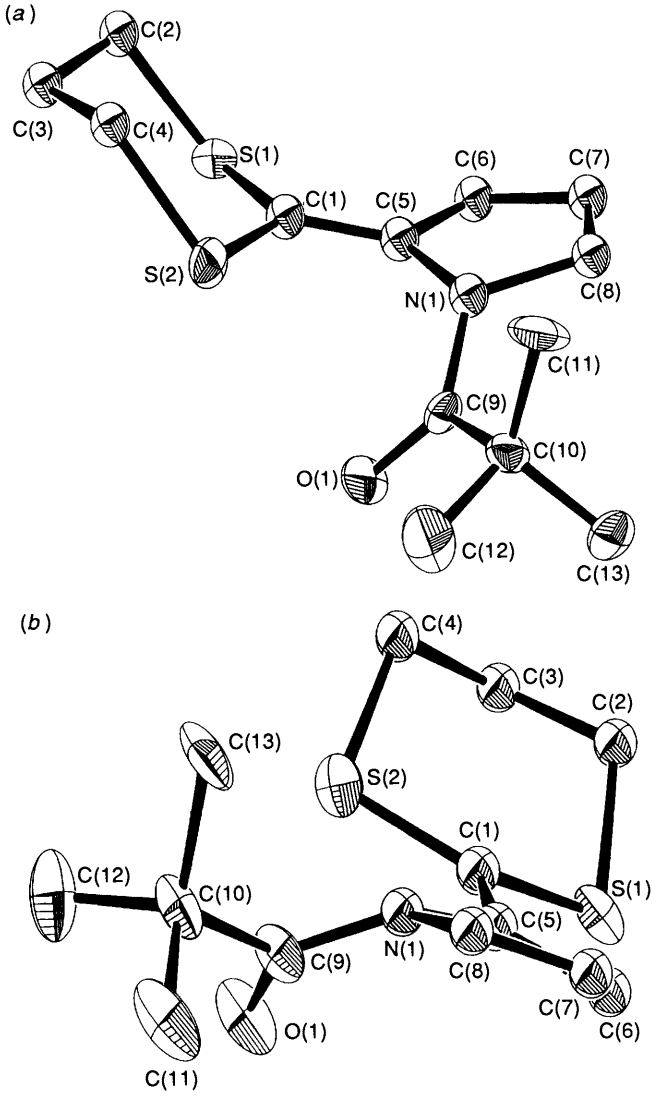


Fig. 1 (*a*) ORTEP plot of **8a** showing labelling scheme used; (*b*) ORTEP view of **8a** through C-5–C-8–C-9 plane

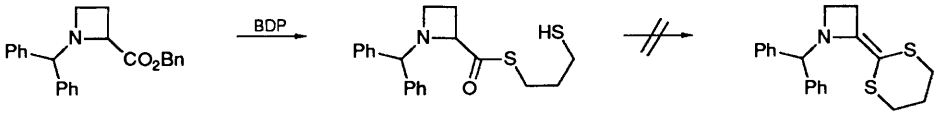
reagent[17] gave the corresponding thioamide **18** as a crystalline solid in 48% yield. However, we were unable to achieve a selective *S*-methylation of **18** in order to generate **19** under a wide variety of conditions. In addition, thioamide **18** was surprisingly resistant to enolization (as judged by D_2O quench) with a range of alkyllithium and lithium amide bases, conditions which were successfully used to deprotonate amide **17**. Direct methylation of **18** (using MeI or $MeOSO_2CF_3$) in the presence of a weak base ($EtNPr^i_2$) gave products resulting from alkylation of the pyrrolidine amine function and we were also unsuccessful in achieving an *S*-methylation of **18** using diazomethane in the presence of silica gel.

The chemistry shown in Schemes 2 and 4 does not appear to undergo direct extrapolation into the asymmetric series but this chemistry should, nevertheless, be applicable to the manipulation of other ring sizes. There are a number of versatile and efficient syntheses available for ring-substituted pipecolic acids[18] but 3-substituted azetidine-2-carboxylates, and methods for their synthesis, are almost unknown.[19] Focusing on systems of this type was also a challenge within the context of our earlier work since we had been unsuccessful in generating the four-membered ring analogue of **1** by intramolecular azide cycloaddition.[1b]

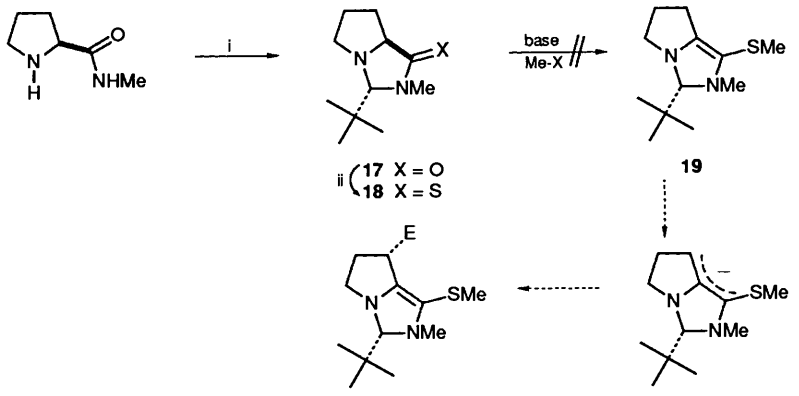
Racemic azetidine-2-carboxylic acid was protected using standard methods to give the *N*-pivaloyl derivative **20** in 97% overall yield (Scheme 7). Reaction of **20** with BDP proceeded cleanly (as judged by TLC) to give initially the thioester **21**; this unstable product was isolated in 38% yield in one experiment. Longer reaction times would normally be required in order to convert **21** into the desired ketene *S,S*-acetal **22**, but in this case the reactivity of the azetidine ring intervened. After 28 h at room temperature or alternatively 5 h at reflux, following the formation of **21**, the only product that could be isolated (in 24% yield) was assigned as the ring-cleaved amide **24** [ν_{max}/cm^{-1} (thin film) 3340 (NH) and 2520 (SH); δ_H(270 MHz; $CDCl_3$) 1.40 (1 H, t, *J* 8 Hz, SH) and 7.95 (1 H, s, NH)]. We suggest that this product arises by fragmentation of the intermediate alkoxide **23** which involves a 1,2-migration of sulfur[21] followed by addition of a second mole of BDP and dehydration.*

In summary, heterocyclic analogues of 2-amino ketene *S,S*-acetals provide an unusual spectrum of reactivity that allows, in the case of the five-membered ring, for the generation of an

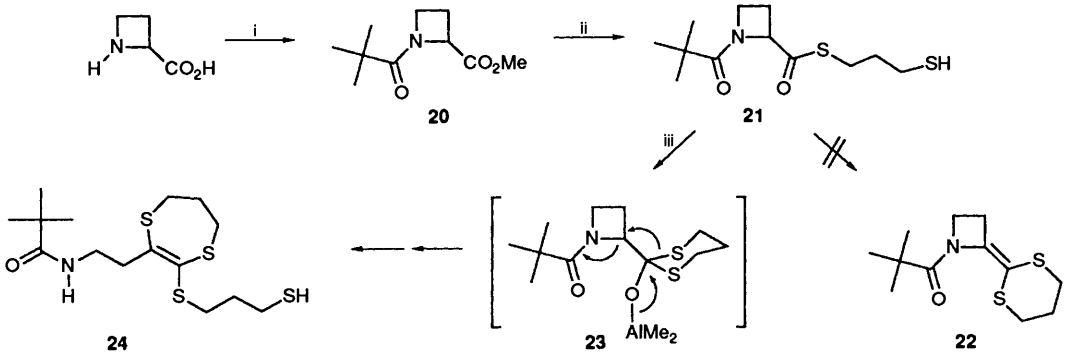
* The amide function present in **23** is obviously capable of interacting with an aluminium species, thus enhancing its ability to act as a leaving group. We have also examined this reaction sequence with the *N*-alkyl derivative **25**.[20] Although the thioester **26** could be isolated in 56% yield, no evidence was available for the formation of the corresponding ketene *S,S*-acetal.



25 **26**



Scheme 6 *Reagents and conditions:* i, Bu^{t}CHO, H$^+$, PhMe (46%); ii, (4-MeOC$_6$H$_4$)$_2$P$_2$S$_4$, CH$_2$Cl$_2$ (48%)



Scheme 7 *Reagents and conditions:* i, MeOH, SOCl$_2$, then Bu^{t}COCl, py (97%); ii, BDP, CH$_2$Cl$_2$, PhMe, 20 h (38% isolated yield); iii, from **20**: as ii, then reflux, 5 h (24%)

equivalent of a proline homoenolate. Direct extension of this chemistry to provide enantiomerically pure 3-substituted prolines was not successful and alternative solutions to this problem must be sought. We have not yet extended this chemistry to encompass pipecolic acid derivatives, but the methodology is limited, in the case of azetidine-2-carboxylates, by the reactivity associated with the four-membered ring.

Experimental

General experimental and spectroscopic methods have been described previously.[1c]

Preparation and Use of Bis(dimethylaluminium)propane-1,3-dithiolate (BDP): General Procedure for the Preparation of Ketene S,S-Acetals **8**.—This reagent was introduced by Corey and is best prepared and used as follows: into a dried flask which had been flushed with nitrogen was added dichloromethane (1 cm^3 mmol^{-1}) and trimethylaluminium (2.0 mol dm^{-3} in toluene; 2 equiv.) by syringe. The reaction vessel was cooled to 0 °C using an ice bath and propane-1,3-dithiol (1 equiv.) added dropwise by syringe. *CAUTION*: care must be excercised 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 1 h which may result in precipitation of the reagent (depending on the ambient temperature). The carboxylate ester **6** was then added as a solution in dichloromethane (1 cm^3 mmol^{-1}) in one portion by syringe. The intermediate thioester **7** was formed cleanly within several hours but conversion into the corresponding ketene *S,S*-acetal required a longer period. Reaction was usually complete after stirring for up to 7 d at ambient temperature or between 10–15 h at reflux after complete formation of the intermediate thioester was observed by TLC. Solvent was then removed by rotary evaporation and the residual oil diluted with ether. Moist sodium sulfate was added by spatula causing evolution of methane and precipitation of aluminium salts. The reaction was vigorous at first but became slower and was complete after 1.5–2 h. The solution was filtered through sodium sulfate (anhydrous) and the solids washed well with ether. The solvent was then removed under reduced pressure and the product ketene *S,S*-acetal **8** was purified by chromatography. The major by-product of this reaction was the corresponding thioester **7**. Thioesters **7** were isolated following chromatography and, where available, spectral data (IR, ^{1}H NMR and mass spectra) for these intermediates are presented.

2-(N-*Pivaloylpyrrolidin-2-ylidene*)-1,3-*dithiane* **8a**. A solution of methyl *N*-pivaloylprolinate **6a** (2.13 g, 10 mmol) in dichloromethane (20 cm^3) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane–toluene (2:1, 30 cm^3). The reaction mixture was stirred at room temp. for 7 d and, following work-up, chromatography (ethyl acetate–light petroleum) gave the *title compound* **8a** (1.1 g, 40%) as an oil that crystallized with time, m.p. 101–102 °C (MeOH) (Found: C, 57.6; H, 7.9; N, 5.15. C$_{13}$H$_{21}$NOS$_2$ requires C, 57.5; H, 7.80; N, 5.16%); ν_{max}/cm^{-1} 2900, 2840, 1640, 1580 and 1450; δ_H 1.31 (9 H, s), 1.89–1.97 (2 H, m), 2.12–2.14 (2 H, m), 2.65 (2 H, t, *J* 7.5), 2.77 (2 H, t, *J* 6), 2.86 (2 H, t, *J* 6) and 3.80 (2 H, t, *J* 7); *m/z* (low eV E.I.) 271 (M$^+$, 75%) and 186 (100).

Crystal data for compound **8a**. A crystal of approximate dimensions 0.25 × 0.25 × 0.3 mm was used for data collection. C$_{13}$H$_{21}$ONS$_2$, *M* = 271.4, monoclinic, *a* = 7.642(2), *b* = 11.333(2), *c* = 16.845(2) Å, *γ* = 89.34(2)°, *U* = 1458.7 Å^3, space group $P2_1/n$, (unique axis c), *Z* = 4, D_c = 1.13 gcm^{-3}, *μ*(Mo-K*α*) = 3.04 cm^{-1}, *F*(000) = 584. Data were measured at room temp. on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 24°$. 2478 reflections were collected of which 1129 were unique and observed with $I \leq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects and also for absorption.[15a] The structure was solved by Direct methods and

Table 2 Fractional atomic coordinates for **8a**

Atom	*x*	*y*	*z*
S(1)	0.2092(5)	0.7791(2)	0.4822(1)
S(2)	0.5401(4)	0.8325(2)	0.3880(1)
O(1)	0.3913(13)	0.8310(5)	0.2318(4)
C(9)	0.3727(16)	0.9386(8)	0.2334(5)
C(10)	0.4699(18)	1.0159(8)	0.1715(5)
C(11)	0.3548(21)	1.0410(9)	0.1011(6)
C(12)	0.6256(20)	0.9457(11)	0.1423(7)
C(13)	0.5394(20)	1.1314(9)	0.2081(7)
N(1)	0.2807(11)	0.9923(6)	0.2931(4)
C(1)	0.3206(14)	0.8601(7)	0.4074(5)
C(2)	0.3580(15)	0.7951(8)	0.5647(6)
C(3)	0.5368(17)	0.7534(9)	0.5487(6)
C(4)	0.6358(16)	0.8346(8)	0.4865(6)
C(5)	0.2149(14)	0.9287(7)	0.3607(5)
C(6)	0.0329(16)	0.9629(8)	0.3730(6)
C(7)	0.0145(27)	1.0726(14)	0.3263(10)
C(8)	0.1514(17)	1.0930(9)	0.2769(6)

refined using the SHELX[15b,c] suite of programs. In the final least squares cycles the S-1, S-2, O-1 and C-9—13 atoms were allowed to vibrate anisotropically. The remaining carbon atoms were treated isotropically. Hydrogens were included at calculated positions. Final residuals after nine cycles of full-matrix least squares refinement were $R = 0.0894$ for unit weights. The total number of parameters varied was 109. Max. final shift/esd was 0.004, the average being 0.001. The max. and min. residual densities were 0.27 and -0.18 eÅ^{-3} respectively. Non-hydrogen atom coordinates are given in Table 2. Isotropic thermal parameters, bond distances and angles and tables of anisotropic temperature factors and hydrogen atom positions are available as supplementary data.* The asymmetric unit is shown in Fig. 1(*a*)/(*b*), along with the labelling scheme used.

Data for S-(3-*mercaptopropyl*) N-*pivaloylpyrrolidine*-2-*carbothioate* **7a**: (Found: $M^+ + H$, 290.1248. $C_{13}H_{24}NO_2S_2$ requires *M*, 290.1248); ν_{max}/cm^{-1} 3000, 2570, 1700 and 1640; δ_H 1.29 (9 H, s), 1.40 (1 H, t, *J* 8), 1.87 (2 H, quintet, *J* 7), 1.85–1.99 (2 H, m), 2.01–2.17 (2 H, m), 2.56 (2 H, m), 2.98 (2 H, t, *J* 7), 3.70–3.85 (2 H, m) and 4.71 (1 H, dd, *J* 3.5, 8); *m*/*z* (C.I.) 290 ($M^+ + H$, 5%).

2-(N-*Benzyloxycarbonylpyrrolidin*-2-*ylidene*)-1,3-*dithiane* **8b**. A solution of freshly prepared BDP (4 mmol) in dichloromethane–toluene (2:1, 12 cm^3) was treated with a solution of methyl *N*-Cbz prolinate **6b** (1.40 g, 4 mmol) in dichloromethane (8 cm^3). After stirring for 5 d at room temp., the normal work-up procedure was followed by chromatography (10–25% ethyl acetate in light petroleum) to yield the *title compound* **8b** (450 mg, 35%) as an oil (Found: M^+, 321.0855. $C_{16}H_{19}NO_2S_2$ requires *M*, 321.0855); ν_{max}/cm^{-1} 1680 and 1600; δ_H 1.85 (2 H, quintet, *J* 7.5), 2.10 (2 H, m), 2.66 (2 H, t, *J* 7.5), 2.71 (2 H, t, *J* 5.5), 2.80 (2 H, t, *J* 5.5), 3.66 (2 H, t, *J* 7.5), 5.16 (2 H, s) and 7.26–7.38 (5 H, m); *m*/*z* (70 eV E.I.) 321 (M^+, 10%). Data for *S*-(3-mercaptopropyl) N-benzyloxycarbonylpyrrolidine-2-carbothioate **7b** has been described previously.[1c]

2-[N-(2,2,2-*Trifluoroacetyl*)*pyrrolidin*-2-*ylidene*]-1,3-*dithiane* **8c**. A solution of methyl *N*-(2,2,2-trifluoroacetyl)prolinate **6c** (2.25 g, 10 mmol) in dichloromethane (20 cm^3) was added to a freshly prepared solution of BDP (10 mmol) in dichloromethane–toluene (2:1, 30 cm^3). After being stirred for 2 d at room temp. the reaction mixture was heated under reflux for 10 h. Normal work-up, followed by chromatography (10–15% ethyl acetate in light petroleum) gave the *title compound* **8c** (488 mg, 17%) as a colourless oil which crystallised with time, m.p. 58–62 °C (Found: C, 42.6; H, 4.35; N, 5.05. $C_{10}H_{12}F_3NOS_2$ requires C, 42.39; H, 4.27; N, 4.94%); ν_{max}/cm^{-1} 1700, 1600 and 1460; δ_H 2.02 (2 H, quintet, *J* 6.5), 2.11–2.20 (2 H, m), 2.71 (2 H, t, *J* 8), 2.84 (2 H, t, *J* 6), 2.93 (2 H, t, *J* 6) and 3.86 (2 H, t, *J* 7); *m*/*z* (70 eV E.I.) 283 (M^+, 50%).

Data for S-(3-*mercaptopropyl*) N-(2,2,2-*trifluoroacetyl*)*pyrrolidine*-2-*carbothioate* **7c**: ν_{max}/cm^{-1} 2570 and 1710; δ_H 1.40 (1 H, t, *J* 8), 1.89 (2 H, quintet, *J* 7), 1.97–2.34 (4 H, m), 2.57 (2 H, q, *J* 7), 3.03 (2 H, t, *J* 7), 3.63–3.92 (2 H, m) and 4.74 (1 H, dd, *J* 3, 8); *m*/*z* (70 eV E.I.) 301 (M^+, 2%).

General Procedure for Deprotonation–Alkylation of **8a**.—A solution of LDA (1.2 mmol) in THF (3 cm^3) under an atmosphere of nitrogen was cooled to -78 °C and treated with a solution of **8a** (271 mg, 1 mmol) in THF (5 cm^3), which was added dropwise by syringe. The reaction mixture was allowed to warm to 0 °C over 30 min and then stirred for an additional 90 min with the temperature kept between -20 and 0 °C. The pale yellow solution was then cooled to -78 °C and a solution of the electrophile (1–2 equiv.) in THF (3 cm^3) was added. The reaction mixture was allowed to warm to room temp. then stirred for 2–3 h. Water (5 cm^3) was then added and the product extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the product was isolated following purification by chromatography (ethyl acetate–light petroleum). The yields of adducts are shown in Table 1 and spectroscopic and analytical data for each is displayed below.

2-(N-*Pivaloyl*-3-*methylpyrrolidin*-2-*ylidene*)-1,3-*dithiane* **11a**. Isolated as an oil which crystallised with time, m.p. 75–77 °C (Found: C, 58.7; H, 8.3; N, 4.9. $C_{14}H_{23}NOS_2$ requires C, 58.90; H, 8.1; N, 4.91%); ν_{max}/cm^{-1} 1630, 1600 and 1440; δ_H 1.07 (3 H, d, *J* 7), 1.32 (9 H, s), 1.92 (1 H, quintet, *J* 7), 2.02–2.20 (3 H, m), 2.63–2.97 (4 H, m), 3.28 (1 H, d of quintet, *J* 1.5, 7) and 3.70–3.94 (2 H, m); *m*/*z* (low eV E.I.) 285 (M^+, 100%).

2-(3-*Benzyl*-N-*pivaloylpyrrolidin*-2-*ylidene*)-1,3-*dithiane* **11b**. Isolated as a colourless liquid (Found: C, 66.1; H, 7.85; N, 3.65. $C_{20}H_{27}NOS_2$ requires C, 66.44; H, 7.53; N, 3.87%); ν_{max}/cm^{-1} 1660 and 1600; δ_H 1.32 (9 H, s), 1.78–1.88 (1 H, ddd, *J* 2, 7.5, 13), 1.87–1.98 (1 H, m), 2.02–2.16 (2 H, m), 2.42 (1 H, dd, *J* 9, 13.5), 2.69 (2 H tt, *J* 4, 14), 2.82–2.90 (2 H, m), 2.90 (1 H, dd, *J* 6, 13.5), 3.45 (1 H, ddt, *J* 2, 6.5, 8.5), 3.75 (1 H, dt, *J* 4, 9.5), 3.84 (1 H, dt, *J* 8.5, 12) and 7.15–7.32 (5 H, m); *m*/*z* (70 eV E.I.) 361 (M^+, 40%).

2-(N-*Pivaloyl*-3-*propylpyrrolidin*-2-*ylidene*)-1,3-*dithiane* **11c**. Isolated as a crystalline solid, m.p. 93–94 °C (Found: C, 61.3; H, 8.8; N, 4.45. $C_{16}H_{27}NOS_2$ requires C, 61.29; H, 8.68; N, 4.47%); ν_{max}/cm^{-1} 1660, 1600 and 1470; δ_H 0.89 (3 H, t, *J* 7), 1.31 (9 H, s), 1.20–1.50 (4 H, m), 1.73 (1 H, dddd, *J* 2, 3.5, 7.5, 12.5), 1.99 (1 H, ddt, *J* 8, 9.5, 12.5), 2.08–2.18 (2 H, m), 2.65 (1 H, dt, *J* 4, 13.5), 2.76 (1 H, dt, *J* 5, 13), 2.82–2.97 (2 H, m), 3.15–3.24 (1 H, m), 3.71 (1 H, dt, *J* 3.5, 9.5) and 3.87 (1 H, dt, *J* 8, 10); *m*/*z* (low eV E.I.) 313 (M^+, 100%).

2-(3-*Allyl*-N-*pivaloylpyrrolidin*-2-*ylidene*)-1,3-*dithiane* **11d**.—Isolated as a colourless solid, m.p. 80–82 °C (Found: C, 61.6; H, 8.4; N, 4.45. $C_{16}H_{25}NOS_2$ requires C, 61.69; H, 8.09; N, 4.50%); ν_{max}/cm^{-1} 1660 and 1600; δ_H 1.31 (9 H, s), 1.80 (1 H, dddd, *J* 2.5, 4, 8, 12), 1.95–2.18 (4 H, m), 2.24–2.33 (1 H, m), 2.66 (1 H, dt, *J* 4.5, 13.5), 2.77 (1 H, dt, *J* 5, 13), 2.83–2.97 (2 H, m), 3.27 (1 H, ddt, *J* 2, 5, 8), 3.70 (1 H, dt, *J* 4, 10), 3.86 (1 H, dt, *J* 8, 10), 5.00–5.06 (2 H, m) and 5.73 (1 H, ddt, *J* 7, 10, 17); *m*/*z* (low eV E.I.) 311 (M^+, 100%).

2-[3-(*Methoxycarbonyl*)-N-*pivaloylpyrrolidin*-2-*ylidene*]-1,3-*dithiane* **11e**. Isolated as a colourless solid, m.p. 123–125.5 °C (Found: C, 54.7; H, 7.15; N, 4.25. $C_{15}H_{23}NO_3S_2$ requires C, 54.68; H, 7.04; N, 4.25%); ν_{max}/cm^{-1} 1740, 1630 and 1600; δ_H

* For details of the Cambridge Crystallographic Data deposition Scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

1.31 (9 H, s), 2.06–2.30 (4 H, m), 2.69–2.96 (4 H, m), 3.68 (3 H, s), 3.82 (1 H, dt, *J* 3, 10), 3.99 (1 H, dt, *J* 8, 10) and 4.04 (1 H, dd, *J* 2, 8.5); *m/z* (70 eV E.I.) 329 (M^+, 25%).

2-[3-(*Ethoxycarbonylmethyl*)-N-*pivaloylpyrrolidin*-2-*ylidene*]-1,3-*dithiane* **11f**. Isolated as a colourless oil (Found: M^+, 357.13994. $C_{17}H_{27}NO_3S_2$ requires *M*, 357.143 24); ν_{max}/cm^{-1} 1740 and 1660; δ_H 1.26 (3 H, t, *J* 7), 1.31 (9 H, s), 1.78–1.86 (1 H, m), 2.04–2.23 (4 H, m), 2.65–2.93 (5 H, m), 3.54–3.65 (1 H, m), 3.72 (1 H, dt, *J* 4.5, 10), 3.89 (1 H, dt, *J* 7.5, 10) and 4.09–4.16 (2 H, m); *m/z* (low eV E.I.) 357 (M^+, 100%).

2-[3-(*Hydroxymethyl*)-N-*pivaloylpyrrolidin*-2-*ylidene*]-1,3-*dithiane* **11g**. Isolated as a colourless oil: ν_{max}/cm^{-1} 3200–3600, 1670 and 1600; δ_H 1.31 (9 H, s), 1.95–2.20 (4 H, m), 2.65–2.95 (4 H, m) and 3.35–4.70 (5 H, m); *m/z* (low eV E.I.) 301 (M^+, 100%), 216 (65), 57 (30) and 45 (50). We were unable to obtain a satisfactory high resolution mass determination (70 eV) for **11g**.

2-[N-*Pivaloyl*-3-(α-*hydroxybenzyl*)*pyrrolidin*-2-*ylidene*]-1,3-*dithiane* **11h**. Isolated as a colourless solid, m.p. 47–50 °C (Found: C, 63.5; H, 7.3; N, 3.7. $C_{20}H_{27}NO_2S_2$ requires C, 63.6; H, 7.21; N, 3.71%); ν_{max}/cm^{-1} 3300–3500br 1630 and 1570; δ_H 1.29 (9 H, s), 1.80–2.30 (4 H, m), 2.60–2.75 (3 H, m), 2.82–2.98 (2 H, m), 3.54 (1 H, dt, *J* 2.5, 7.5), 3.65–3.80 (2 H, m), 4.42 (1 H, d, *J* 7) and 7.25–7.40 (5 H, m); *m/z* (C.I.) 378 (M^+ + H, 50%).

General Procedure for Hydrolysis of **11a–d** *and* **11e–f** *to* **13a–d** *and* **12e–f**, *respectively*.—A solution of the ketene *S,S*-acetal **11** (1 mmol) in dichloromethane (10 mmol, 0.65 cm^3) under an atmosphere of nitrogen was cooled to −30 °C. Boron trifluoride–diethyl ether (10 mmol, 1.23 cm^3) was added by syringe, followed by ethyl acetate (2 mmol, 0.975 cm^3). The reaction mixture was allowed to warm to room temp. over 30 min then stirred for an additional 2–3 h. The reaction was then quenched with 5% aqueous potassium carbonate (5 cm^3), the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 cm^3). The combined organic layers were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue was purified by chromatography (ethyl acetate–light petroleum) to give the corresponding thioesters **12**. The thioesters were not characterised by elemental analysis or high resolution mass determination but appropriate IR, ^1H NMR and mass spectral data are presented below.

Thioesters **12a–d** were directly converted into the corresponding methyl esters **13a–d** using the following general procedure. A solution of the thioester (1 mmol) in dry methanol (2 cm^3) was cooled to 0 °C under an atmosphere of nitrogen and then treated with a freshly prepared solution of sodium methoxide (5 equiv.) in methanol (2 cm^3). After stirring at 0 °C for 2–3 h, water (5 cm^3) was added and the product was extracted with ethyl acetate (3 × 5 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the product was purified by chromatography (ethyl acetate–light petroleum) to give the corresponding methyl esters **13a–d**.

S-(3-*Mercaptopropyl*) 3-*methyl*-N-*pivaloylpyrrolidine*-2-*carbothioate* **12a**. Isolated as an oil which ^1H NMR spectroscopy revealed to be a 7:3 mixture of diastereoisomers; ν_{max}/cm^{-1} 1700 and 1640; δ_H 1.18 (3 H, d, *J* 6.5), 1.28 (9 H, s), 1.40 (1 H, t, *J* 8), 1.87 (2 H, quintet, *J* 7), 1.80–2.00 (1 H, m), 2.08–2.25 (2 H, m), 2.57 (2 H, q, *J* 8), 2.98 (2 H, t, *J* 7), 3.64–3.95 (2 H, m), 4.25 (0.7 H, d, *J* 6) and 4.67–4.73 (0.3 H, m); *m/z* (C.I.) 304 (M^+ + H, 5%). This intermediate was also directly converted into **14a** without formation of **13a** (see below).

Methyl 3-*methyl*-N-*pivaloylprolinate* **13a**. Isolated as a colourless oil in 51% yield from **12a** which ^1H NMR spectroscopy indicated to be a single diastereoisomer (Found: M^+, 227.1520. $C_{12}H_{21}NO_3$ requires *M*, 227.1521); ν_{max}/cm^{-1} 1750 and 1630; δ_H 1.16 (3 H, d, *J* 6.5), 1.26 (9 H, s), 1.55–1.75 (1 H, m), 2.06–2.26 (2 H, m), 3.62–3.73 (1 H, m), 3.73 (3 H, s), 3.87 (1 H, ddd, *J* 4.5, 7, 9.5) and 4.02 (1 H, d, *J* 6); *m/z* (low eV E.I.) 277 (M^+, 30%).

S-(3-*Mercaptopropyl*) 3-*benzyl*-N-*pivaloylpyrrolidine*-2-*carbothioate* **12b**. Isolated as a colourless oil which ^1H NMR spectroscopy revealed to be a 13:1 mixture of diastereoisomers; ν_{max}/cm^{-1} 2550, 1700 and 1640; δ_H 1.28 (9 H, s), 1.40 (1 H, t, *J* 8), 1.55–1.75 (2 H, m), 1.88 (2 H, quintet, *J* 7), 2.03 (1 H, m), 2.55–2.64 (3 H, m), 2.96–3.13 (3 H, m), 3.69 (1 H, dt, *J* 7, 10), 3.87 (1 H, ddd, *J* 5, 7, 10), 4.60 (0.93 H, d, *J* 5.5), 4.90 (0.07 H, *J* 2) and 7.15–7.36 (5 H, m); *m/z* (C.I.) 380 (M^+ + H, 5%).

Methyl 3-*benzyl*-N-*pivaloylprolinate* **13b**. Isolated as a colourless oil in 79% yield from **12b** which ^1H NMR spectroscopy revealed to be a single diastereoisomer (Found: M^+, 303.185 38. $C_{18}H_{25}NO_3$ requires *M*, 303.183 44); ν_{max}/cm^{-1} 1760 and 1640; δ_H 1.26 (9 H, s), 1.60–1.78 (1 H, m), 1.98–2.10 (1 H, m), 2.39–2.51 (1 H, m), 2.62 (1 H, dd, *J* 9, 14), 2.97 (1 H, dd, *J* 5, 14), 3.63–3.76 (1 H, m), 3.69 (3 H, s), 3.84 (1 H, ddd, *J* 5, 7, 10), 4.25 (1 H, d, *J* 6) and 7.16–7.33 (5 H, m); *m/z* (low eV E.I.) 303 (M^+, 15%).

S-(3-*Mercaptopropyl*) N-*pivaloyl*-3-*propylpyrrolidine*-2-*carbothioate* **12c**. Isolated as a colourless oil which ^1H NMR spectroscopy revealed to be a mixture of diastereoisomers (ratio >20:1); ν_{max}/cm^{-1} 2550, 1700 and 1640; δ_H(major component) 0.93 (3 H, t, *J* 7), 1.29 (9 H, s), 1.30–1.40 (2 H, m), 1.39 (1 H, t, *J* 8), 1.55–1.70 (3 H, m), 1.87 (2 H, quintet, *J* 7), 2.03–2.30 (2 H, m), 2.57 (2 H, dt, *J* 7, 8), 2.97 (2 H, t, *J* 7), 3.87 (1 H, dt, *J* 7, 10), 3.85–3.95 (1 H, m) and 4.34 (1 H, d, *J* 5.5); *m/z* (C.I.) 332 (M^+ + H, 5%).

Methyl N-*pivaloyl*-3-*propylprolinate* **13c**. Isolated as a colourless oil in 69% yield from **12c** which ^1H NMR spectroscopy revealed to be a single diastereoisomer (Found: M^+, 255.1821. $C_{14}H_{25}NO_3$ requires *M*, 255.1834); ν_{max}/cm^{-1} 1760 and 1650; δ_H 0.92 (3 H, t, *J* 7.5), 1.26 (9 H, s), 1.32–1.44 (2 H, m), 1.53–1.69 (3 H, m), 2.05–2.22 (2 H, m), 3.63–3.74 (1 H, m), 3.73 (3 H, s), 3.85 (1 H, ddd, *J* 4, 7.5, 10) and 4.13 (1 H, d, *J* 5); *m/z* (70 eV E.I.) 255 (M^+, 5%).

S-(3-*Mercaptopropyl*) 3-*allyl*-N-*pivaloylpyrrolidine*-2-*carbothioate* **12d**. Isolated as a colourless oil which ^1H NMR spectroscopy revealed to be a 10:1 mixture of diastereoisomers; ν_{max}/cm^{-1} 2550, 1720 and 1640; δ_H 1.28 (9 H, s), 1.40 (1 H, t, *J* 8), 1.60–1.75 (2 H, m), 1.87 (2 H, quintet, *J* 7), 2.04–2.29 (2 H, m), 2.35–2.45 (1 H, m), 2.57 (2 H, q, *J* 7.5), 2.98 (2 H, t, *J* 7), 3.65–3.77 (1 H, m), 3.82–3.91 (1 H, m), 4.42 (0.9 H, d, *J* 3), 4.82 (0.1 H, d, *J* 2), 5.00–5.15 (2 H, m) and 5.71–5.85 (1 H, m); *m/z* (C.I.) 330 (M^+ + H, 4%).

Methyl 3-*allyl*-N-*pivaloylprolinate* **13d**. Isolated as a colourless oil in 92% yield from **12d** which ^1H NMR spectroscopy revealed to be a single diastereoisomer (Found: M^+, 253.169 14. $C_{14}H_{23}NO_3$ requires *M*, 253.167 79); ν_{max}/cm^{-1} 1760 and 1640; δ_H 1.26 (9 H, s), 1.65–1.75 (1 H, m), 2.06–2.26 (3 H, m), 2.30–2.43 (1 H, m), 3.67–3.88 (1 H, m), 3.73 (3 H, s), 3.79–3.88 (1 H, m), 4.19 (1 H, d, *J* 3), 5.06–5.12 (2 H, m) and 5.77 (1 H, ddt, *J* 7, 10.5, 17); *m/z* (low eV E.I.) 253 (M^+, 7%).

^1H COSY showed that the signal at δ 2.30–2.43 is due to an allylic proton. Irradiation at δ 2.37 showed NOE enhancements at δ 4.19 (11%), δ 5.10 (3%) and δ 5.77 (9%).

S-(3-*Mercaptopropyl*)-3-(*methoxycarbonyl*)-N-*pivaloylpyrrolidine*-2-*carbothioate* **12e**. Prepared using the general procedure described above and isolated as an oil which ^1H NMR spectroscopy revealed to be a single diastereoisomer; ν_{max}/cm^{-1} 2550, 1750, 1700 and 1630; δ_H 1.28 (9 H, s), 1.39 (1 H, t, *J* 8), 1.88 (2 H, quintet, *J* 7), 2.29 (1 H, q, *J* 6.5), 2.57 (2 H, dt, *J* 7, 8), 2.97–3.03 (3 H, m), 3.75 (3 H, s), 3.81–3.92 (2 H, m) and 5.05 (1 H, d, *J* 3.5); *m/z* (C.I.) 348 (M^+ + H, 10%).

S-(3-*Mercaptopropyl*) 3-(*ethoxycarbonylmethyl*)-N-*pivaloylpyrrolidine*-2-*carbothioate* **12f**. Prepared using the general procedure described above and isolated as an oil which ^1H NMR

spectroscopy revealed to be a single diastereoisomer; ν_{max}/cm^{-1} 2550, 1740, 1680 and 1640; δ_H 1.27 (3 H, t, *J* 7), 1.28 (9 H, s), 1.40 (1 H, t, *J* 8), 1.65–1.77 (2 H, m), 1.88 (2 H, quintet, *J* 7), 2.28–2.39 (2 H, m), 2.57 (2 H, q, *J* 7), 2.67–2.74 (1 H, m), 2.98 (2 H, t, *J* 7), 3.74 (1 H, d, t, *J* 7, 10), 3.85–3.96 (1 H, m), 4.16 (2 H, q, *J* 7) and 4.38 (1 H, d, *J* 7); *m/z* (C.I.) 376 ($M^+ + H$, 5%).

General Procedure for Hydrolysis of **13a–c** *to give* 3-*Substituted Prolines* **14a–c**.—A solution of **13** (0.2 mmol) in trifluoroacetic acid–water (4:1) (2 cm^3) was either stirred at room temp. for 2 d or heated at reflux for 2 h. The solvent was then removed under reduced pressure and the product purified by ion exchange chromatography (DOWEX 50 × 8–10, water then 2 mol dm^{-3} aqueous pyridine) to give the free amino acid **14**. For details of further purification and characterisation see below.

(±)-3-*Methylproline* **14a**.Isolated in 96% yield from **12a** (by direct hydrolysis using aqueous sodium hydroxide followed by aqueous TFA) as a 10:1 mixture of *trans* and *cis* isomers, m.p. 205–208 °C. Recrystallization from ethanol–ether gave a 30:1 mixture, m.p. 218–223 °C (lit.,[10b] 240–248 °C [for pure *trans*]); $\delta_H(D_2O)$ 1.22 (3 H, d, *J* 7), 1.67 (1 H, dq, *J* 8.5, 13), 2.13–2.25 (1 H, m), 2.31–2.47 (1 H, m), 3.32–3.47 (2 H, m) and 3.59 (1 H, d, *J* 8); peaks due to minor *cis* isomer: 0.99 (d, *J* 7.5) and 4.06 (d, *J* 7.5).

(±)-3-*Benzylproline* **14b**. Isolated in 48% yield from **12b** as colourless needles, m.p. 251–253 °C (ethanol–ether) (Found: C, 69.2; H, 7.35; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.37; N, 6.82%); ν_{max}/cm^{-1} 3300–3600br and 1610; $\delta_H(D_2O)$ 1.80 (1 H, dq, *J* 7, 14), 1.96 (1 H, dq, *J* 7, 14), 2.65–2.74 (2 H, m), 3.09–3.19 (1 H, m), 3.30–3.45 (2 H, m), 3.80 (1 H, d, *J* 6) and 7.31–7.40 (5 H, m); *m/z* (70 eV E.I.) 205 (M^+, 10%). We were unable to obtain satisfactory elemental analysis of this product.

(±)-3-*Propylproline* **14c**. Isolated as a glass in 61% yield from **12c**: $\delta_H(D_2O)$ 0.89 (3 H, t, *J* 7), 1.27–1.48 (3 H, m), 1.62–1.79 (2 H, m), 2.17–2.28 (1 H, m), 2.33–2.46 (1 H, m), 3.30–3.47 (2 H, m) and 3.79 (1 H, d, *J* 7). Amino acid **14c** was dissolved in 2 mol dm^{-3} hydrochloric acid (1 cm^3) and the resulting solution evaporated under reduced pressure to give the hydrochloride salt of **14c** as a colourless crystalline solid, m.p. 138.5–140.5 °C [lit.,[10i] 131–133 °C (for *cis*/*trans* mixture)]; $\delta_H(D_2O)$ 0.90 (3 H, t, *J* 7), 1.28–1.49 (3 H, m), 1.65–1.80 (2 H, m), 2.20–2.32 (1 H, m), 2.41–2.53 (1 H, m), 3.31–3.51 (2 H, m) and 3.94 (1 H, d, *J* 7.5).

(±)-*Pyrrolidine*-2,3-*dicarboxylic acid* **14e**. Isolated in 73% yield from **12e** as a glass which ^1H NMR spectroscopy revealed to be a 26:1 mixture of diastereoisomers (Found: $M^+ + H$, 160.0610. $C_6H_{10}NO_4$ requires *M*, 160.0610); $\delta_H(D_2O)$ 2.17–2.24 (2 H, m), 3.30 (1 H, dt, *J* 5, 8), 3.37–3.52 (2 H, m) and 4.45 (1 H, d, *J* 5); peak due to minor diastereoisomer: 4.30 (d, *J* 6); *m/z* (C.I.) 160 ($M^+ + H$, 100%). We were not able to crystallise either **14e** or the corresponding hydrochloride salt.

(±)-*Pyrrolidine*-3-*carboxymethyl*-2-*carboxylic acid* **14f**. Isolated in 74% yield from **12f** as a glass which ^1H NMR spectroscopy revealed to be a 14:1 mixture of diastereoisomers (Found: $M^+ + H$, 174.0766. $C_7H_{12}NO_4$ requires *M*, 174.0766); $\delta_H(D_2O)$ 1.82 (1 H, dq, *J* 8, 13), 2.28–2.40 (1 H, m), 2.59 (1 H, dd, *J* 8.5, 15.5), 2.67–2.81 (1 H, m), 2.87 (1 H, dd, *J* 4.5, 15.5), 3.34–3.51 (2 H, m) and 3.86 (1 H, d, *J* 8); peak due to minor diastereoisomer; 4.48 (d, *J* 5.5); *m/z* (C.I.) 174 ($M^+ + H$, 100%).

Synthesis of N-*Benzoyl*-2-[*bis*(*phenylthio*)*methylene*]*pyrrolidine* **9** (R = COPh).—Aluminium tris(phenylthiolate) (20 mmol) was prepared by heating a mixture of trimethylaluminium (2 mol dm^{-3} in toluene; 10 cm^3, 20 mmol) and thiophenol (6 cm^3, 60 mmol) in dry toluene (30 cm^3) for 48 h under an atmosphere of nitrogen. To this reagent was added a solution of δ-valerolactone (2 g, 20 mmol) in toluene (10 cm^3) and the solution was heated under reflux for 3 d. 15% Aqueous sodium hydroxide (100 cm^3) was added cautiously and the mixture was extracted with ethyl acetate (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the residue purified by chromatography (20–50% ethyl acetate in light petroleum) to give 2,2-*bis*(*phenylthio*)*tetrahydropyran* (1.5 g, 25%) as an oil (Found: M^+, 302.0794. $C_{17}H_{18}OS_2$ requires *M*, 302.0796); ν_{max}/cm^{-1} 3300–3500br and 1570; δ_H 1.47 (2 H, quintet, *J* 5), 1.73–1.85 (2 H, m), 2.26–2.38 (2 H, m), 4.05 (2 H, t, *J* 5.5) and 7.15–7.65 (10 H, m); *m/z* (low eV E.I.) 302 (M^+, 50%). ^1H NMR spectroscopy indicates the ring-closed isomer rather than the acyclic ω-hydroxy ketene *S*,*S*-acetal.

5-*Azido*-1,1-*bis*(*phenylthio*)*pent*-1-*ene*. The above phenylthio adduct (1.5 g, 5 mmol) was dissolved in THF (30 cm^3), cooled to 0 °C and treated with triphenylphosphine (1.31 g, 5 mmol), diethyl azodicarboxylate (870 mg, 5 mmol) followed by a solution of diphenylphosphoryl azide (1.39 g, 5 mmol) in THF (10 cm^3). After warming to room temp. and stirring for 12 h the solvent was removed under reduced pressure and the product was isolated following purification by chromatography (ethyl acetate–light petroleum) to give 5-*azido*-1,1- *bis*(*phenylthio*)-*pent*-1-*ene* (1.3 g, 78%) as a colourless oil (Found: $M^+ - N_2$, 299.0792 $C_{17}H_{17}NS_2$ requires *M*, 299.0801); ν_{max}/cm^{-1} 2070 and 1570; δ_H 1.72 (2 H, quintet, *J* 7), 2.52 (2 H, q, *J* 7), 3.29 (2 H, t, *J* 7), 6.26 (1 H, t, *J* 7) and 7.06–7.64 (10 H, m); *m/z* (70 eV E.I.) 299 ($M^+ - N_2$, 1%).

2-[*Bis*(*phenylthio*)*methylene*]*pyrrolidine*. A solution of 5-azido-1,1-bis(phenylthio)pent-1-ene (825 mg, 2.52 mmol) in octane (10 cm^3) was heated under reflux for 6 h. The solvents were then removed under reduced pressure and the product purified by chromatography (ethyl acetate–light petroleum) to give 2-[*bis*(*phenylthio*)*methylene*]*pyrrolidine* (497 mg, 66%) as an oil (Found: M^+, 299.0781. $C_{17}H_{17}NS_2$ requires *M*, 299.0801); ν_{max}/cm^{-1} 3380, 1570 and 1450; δ_H 2.09 (2 H, quintet, *J* 7), 2.89 (2 H, t, *J* 8), 3.49 (2 H, t, *J* 7), 5.57 (1 H, br) and 7.05–7.28 (10 H, m); *m/z* (low eV E.I.) 299 (M^+, 100%).

N-*Benzoyl*-2-[*bis*(*phenylthio*)*methylene*]*pyrrolidine* **9** (R = COPh). A solution of 2-[bis(phenylthio)methylene]pyrrolidine (200 mg, 0.67 mmol) in dichloromethane (5 cm^3) was cooled to 0 °C and treated with pyridine (79 mg, 1 mmol), benzoyl chloride (104 mg, 0.74 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (5 mg). After warming to room temp. and stirring for 12 h, the solvent was removed under reduced pressure and the product was isolated following purification by chromatography (ethyl acetate–light petroleum) to give N-*benzoyl*-2-[*bis*(*phenylthio*)*methylene*]*pyrrolidine* (155 mg, 57%) as an oil (Found: $M^+ + H$, 404.1145. $C_{24}H_{22}NOS_2$ requires *M*, 404.1141); ν_{max}/cm^{-1} 1650 and 1570; δ_H 1.99 (2 H, quintet, *J* 7.5), 2.99 (2 H, t, *J* 8), 3.83 (2 H, t, *J* 7) and 7.12–7.62 (15 H, m); *m/z* (C.I.) 404 ($M^+ + H$, 30%).

2-[2-(*Hydroxymethyl*)-4-(N-*pivaloylamino*)*butanoyl*]-1,3-*dithiane* **16**.—A solution of **11g** (133 mg, 0.44 mmol) in aqueous acetonitrile (1:4, 10 cm^3) was treated with mercury(II) chloride (463 mg, 1.7 mmol). After stirring for 9 h at room temp. the mixture was extracted with dichloromethane–light petroleum (1:1, 10 cm^3). The organic layer was washed with water (1 cm^3) then brine (1 cm^3), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography (60–80% ethyl acetate in light petroleum) to give the *title compound* **16** (77 mg, 56%) as colourless needles, m.p. 125 °C (CH_2Cl_2–light petroleum) (Found: C, 52.4; H, 8.0; N, 4.25. $C_{14}H_{25}NO_3S_2$ requires C, 52.63; N, 7.89; N, 4.38%); ν_{max}/cm^{-1} 3400, 1710, 1620 and 1550; δ_H 1.28 (9 H, s), 1.75–1.97 (2 H, m), 2.00–2.18 (2 H, m), 2.29 (1 H, t, *J* 5.5), 2.54–2.64 (2 H, m), 3.05–3.20 (3 H, m), 3.25–3.45 (2 H, m), 3.78–3.85 (2 H, m), 4.42 (1 H, s) and 6.00 (1 H, s, br); *m/z* (70 eV E.I.) 319 (M^+, 2%).

(2S,5S)-2-tert-*Butyl*-3-*methyl*-1,3-*diazabicyclo*[3.3.0]*octan*-4-*one* **17**.—Pivalaldehyde (1.98 g, 2.5 cm^3, 23 mmol) was added to a solution of proline *N*-methylamide[15] (1.02 g, 8 mmol) in toluene (25 cm^3) containing CF_3CO_2H (3 drops) and the resulting mixture was heated at reflux (water separation) for 14 h. The solvents were removed under reduced pressure and the residual oil partitioned between CH_2Cl_2 (20 cm^3) and saturated aqueous $NaHCO_3$ (10 cm^3). The aqueous layer was further extracted with CH_2Cl_2 (10 cm^3) and the combined extracts were washed with water, brine and dried (Na_2SO_4). After filtration the solvent was removed under reduced pressure and the residue purified by chromatography (ethyl acetate–light petroleum to give the *title compound* **17** (720 mg, 46%) as a yellow oil, $[\alpha]_D^{22}$ −35.7 (*c* 1.07, $CHCl_3$) (Found: $M^+ + H$, 197.1654. $C_{11}H_{21}N_2O$ requires *M*, 197.1654); ν_{max}/cm^{-1} 1680 and 1455; δ_H 0.93 (9 H, s), 1.67–1.90 (3 H, m), 2.14–2.02 (1 H, m), 2.45–2.54 (1 H, m), 2.91 (3 H, s), 3.12–3.19 (1 H, m), 3.59 (1 H, s) and 3.72 (1 H, dd, *J* 9, 6); *m/z* (C.I.) 197 ($M^+ + H$).

(2S,5S)-2-tert-*Butyl*-3-*methyl*-1,3-*diazabicyclo*[3.3.0]*octane*-4-*thione* **18**.—Lawesson's reagent (2.0 g, 5 mmol) was added to a solution of lactam **17** in CH_2Cl_2 (15 cm^3) and stirred under an atmosphere of nitrogen for 20 h. The solution was concentrated under reduced pressure and purification by chromatography (ethyl acetate–light petroleum, 1:9) gave *thioamide* **18** (1.05 g, 48%) as colourless crystals, m.p. 82–83 °C (light petroleum), $[\alpha]_D^{22}$ −3.3 (*c* 0.82, $CHCl_3$) (Found: C, 62.2; H, 9.65; N, 13.1. $C_{11}H_{20}N_2S$ requires C, 62.22; H, 9.49; N, 13.19%); ν_{max}/cm^{-1} 1500 and 1295; δ_H 0.99 (9 H, s), 1.65–1.80 (2 H, m), 2.03–2.16 (1 H, m), 2.26–2.39 (1 H, m), 2.49 (1 H, dd, *J* 15.5, 7), 3.20–3.25 (1 H, m), 3.29 (3 H, m), 4.07 (1 H, s) and 4.16–4.21 (1 H, m); *m/z* (70 eV E.I.) 212 (M^+).

Methyl N-*Pivaloylazetidine*-2-*carboxylate* **20**.—A solution of azetidine-2-carboxylic acid (950 mg, 9.4 mmol) in methanol (22 cm^3) was cooled to 0 °C and thionyl chloride (1.71 cm^3, 23.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temp. and then stirred for 24 h. The solvent was evaporated under reduced pressure to give a yellow oil. The resulting residue was dissolved in dichloromethane (20 cm^3), cooled to 0 °C and pivaloyl chloride (1.27 cm^3, 10.3 mmol) and pyridine (1.52 cm^3, 18.8 mmol) were added dropwise. The reaction mixture was allowed to warm to room temp. and stirred for 20 h. Hydrochloric acid (2 mol dm^{-3}, 25 cm^3) was added and the aqueous phase extracted with dichloromethane (2 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure and the product purified by chromatography (ethyl acetate–light petroleum) to give the *title compound* **20** (1.81 g, 97%) as a colourless oil (Found: M^+, 199.1193. $C_{10}H_{17}NO_3$ requires *M*, 199.1208); ν_{max}(film)/cm^{-1} 1720 and 1600; δ_H 1.20 (9 H, s), 2.12–2.25 (1 H, m), 2.48–2.64 (1 H, m), 3.78 (3 H, s), 4.25–4.40 (1 H, m), 4.40–4.55 (1 H, m) and 4.65–4.80 (1 H, m); *m/z* (70 eV E.I.) 199 (M^+, 17%).

S-(3-*Mercaptopropyl*) N-*Pivaloylazetidine*-2-*carbothioate* **21**.—A solution of trimethylaluminium (2.0 mol dm^{-3} in toluene, 1.5 cm^3, 3 mmol) in dichloromethane (3 cm^3) was cooled to 0 °C under nitrogen and propane-1,3-dithiol (0.15 cm^3, 1.5 mmol) was added dropwise; addition was exothermic and methane was evolved. The resulting suspension was allowed to warm to room temp. and then stirred for 1 h. A solution of ester **20** (300 mg, 1.5 mmol) in dichloromethane (10 cm^3) was added and the reaction mixture stirred at room temp. for 20 h. The solvent was evaporated under reduced pressure and the residual oil diluted with diethyl ether (30 cm^3). An excess of moist sodium sulfate was added (vigorous evolution of methane) and, after stirring at room temp. for 2 h, the suspension was filtered through anhydrous sodium sulfate and the solids washed well with diethyl ether. The solvent was removed under reduced pressure and the product isolated following chromatography (ethyl acetate–light petroleum) to give the title compound **21** (150 mg, 38%) as a colourless oil; ν_{max}(film)/cm^{-1} 2500, 1670 and 1625; δ_H(400 MHz; $CDCl_3$) 1.23 (9 H, s), 1.42 (1 H, t, *J* 7.5), 1.92 (2 H, m), 2.12–2.23 (1 H, m), 2.60 (2 H, q, *J* 7.5), 2.60–2.70 (1 H, m), 3.03 (2 H, t, *J* 7.5), 4.26–4.38 (1 H, m), 4.38–4.50 (1 H, m) and 4.80–4.92 (1 H, m); *m/z* (C.I) 276 ($M^+ + H$, 100%). This intermediate was not characterised further.

3-{3-[2-(N-*Pivaloylamino*)*ethyl*]-1,4-*dithiepin*-2-*ylthio*}*propane*-1-*thiol* **24**.—The procedure described above was repeated and, after stirring at room temp. for 20 h, the reaction mixture was heated under reflux for 5 h. Following the same work-up procedure as for **21**, purification by chromatography (ethyl acetate–light petroleum) gave the *title compound* **24** (160 mg, 24%) as a colourless oil (Found: M^+, 365.0957. $C_{15}H_{27}NOS_4$ requires *M*, 365.0976); ν_{max}(film)/cm^{-1} 3340, 2520, 1660 and 1580; δ_H 1.25 (9 H, s), 1.40 (1 H, t, *J* 8), 1.90 (2 H, m, *J* 8), 2.12–2.24 (2 H, m), 2.60–2.73 (6 H, m), 2.82–2.92 (4 H, m), 3.24 (2 H, dd, *J* 7, 0.5) and 7.95 (1 H, s); δ_C(68 MHz; $CDCl_3$) 23.4 (CH_2), 25.4 (CH_2), 27.5 (CH_3), 29.9 (CH_2), 30.0 (CH_2), 30.3 (CH_2), 31.0 (CH_2), 31.1 (CH_2), 33.3 (CH_2), 40.0 (C), 110.9 (C), 140.4 (C) and 176.0 (C); *m/z* (low eV E.I.) 365 (M^+, 14%).

S-(3-*Mercaptopropyl*) N-(*Diphenylmethyl*)*azetidine*-2-*carbothioate* **26**.—A solution of trimethylaluminium (2.0 mol dm^{-3} in toleune, 0.5 cm^3, 1.0 mmol) in dichloromethane (1 cm^3) was cooled to 0 °C under nitrogen, and propane-1,3-dithiol (0.05 cm^3, 0.5 mmol) was added dropwise. The reaction mixture was then stirred at room temp. for 1 h. A solution of ester **25**[19] (180 mg, 0.5 mmol) in dichloromethane (1 cm^3) was then added, and the reaction mixture stirred at room temp. for 48 h. Following the same work-up procedure described for **21**, the product was isolated by chromatography (ethyl acetate–light petroleum) to give the *title compound* **26** (95 mg, 56%) as a colourless oil. ν_{max}/cm^{-1} 2500 and 1655; δ_H 1.35 (1 H, t, *J* 7.5), 1.69 (2 H, m), 1.91 (1 H, p, *J* 7), 2.38–2.47 (1 H, m), 2.53–2.85 (4 H, m), 2.96 (1 H, q, *J* 8), 3.50 (1 H, dt, *J* 4, 8), 3.93–4.00 (1 H, t, *J* 8), 4.56 (1 H, s) and 7.15–7.40 (10 H, m); *m/z* (C.I.) 3.58 ($M^+ + H$, 27%). This product was not characterised further.

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