Ketene *S,S*-Acetals as 1,3-Dipolarophiles: Application to the Synthesis of Polyhydroxylated Pyrrolidines

William O. Moss,[a] Robert H. Bradbury,[b] Neil J. Hales[b] and Timothy Gallagher*[,a]
[a] *School of Chemistry, Bath University, Bath, BA2 7AY, UK*
[b] *ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, SK10 4TG, UK*

Two approaches to the synthesis of the hydroxylated pyrrolidines **3** and **4**, based on exploiting the reactivity of a ketene *S,S*-acetal as a 1,3-dipolarophile, are described. Both routes utilize a carbohydrate starting material and the strategy based on D-erythrose was successfully concluded. The use of D-ribose, although not successful in terms of the synthetic objectives, does serve to probe the scope and limitations of ketene *S,S*-acetals as highly functionalised dipolarophiles.

The synthesis of polyhydroxylated nitrogen-based heterocycles has attracted a great deal of interest over recent years. This is due primarily to the ability of these molecules, the 'aza-sugars', to inhibit the action of a range of glycosidases, the enzymes involved in the process of 'trimming' cell-surface oligosaccharides.[1] Important members of this class include deoxynorjirimycin[2] (piperidine), castanospermine[3] and swainsonine[4] (indolizidines) and, more recently, the alexines[5] (pyrrolizidines). Structurally less complex variants have also been of interest and finding alternative synthetic routes to these molecules can offer new opportunities and structures that are currently not available from the naturally occurring alkaloids. In this paper we describe a new and enantiospecific strategy directed towards hydroxylated pyrrolidines, based on exploiting the use of a ketene *S,S*-acetal **1** as a 1,3-dipolarophile, in an intramolecular fashion.[6]

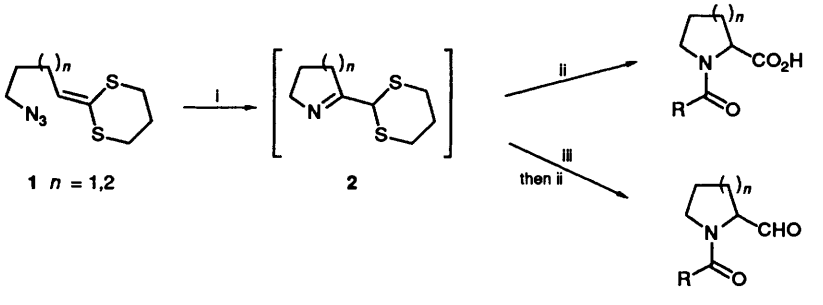
We have recently described the use of this highly functionalised dipolarophile as a vehicle for the synthesis of heterocyclic α-amino acids and aldehydes, using an azide as the 1,3-dipole component (Scheme 1).[6b,d] This reaction appears to proceed *via* the imine **2** and this intermediate may be trapped either by acylation on nitrogen or by reduction using $NaBH_4$. The overall reaction sequence, which can be used to generate 5- and 6-membered rings, may then be extended to provide access to either the carboxylic acid (a cyclic α-amino acid) or the corresponding aldehyde by unmasking the functionality contained in either a ketene *S,S*-acetal or an *S,S*-acetal respectively.

We were interested in probing the synthetic scope of this cycloaddition process and chose to focus our effort on the synthesis of two hydroxylated pyrrolidine derivatives (2*S*,3*S*,4*R*)-3,4-dihydroxyproline **3** and (2*R*,3*S*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol **4**, which have both attracted interest in terms of their potential as glycosidase inhibitors.[7] These two structurally related heterocycles contain a level of functionality and stereochemical complexity that represents a significant challenge to the strategy that we intended to examine. The proline derivative **3** was first synthesised from 3,4-dehydroproline[8] but, more recently, was prepared in enantiomerically pure form from D-glucose by Fleet.[7b,c] The C-2 epimer of **3** has also been synthesised by Fleet and unambiguously characterised by X-ray crystallographic analysis.[7d] This latter study was of particular value because our strategy would require that the stereocentre at C-2 be set following the establishment of the pyrrolidine ring and the possibility of epimerization at this centre was a legitimate concern. (2*R*,3*S*,4*R*)-2-(Hydroxymethyl)pyrrolidine-3,4-diol **4**, also synthesised by Fleet and co-workers, has been shown to be an inhibitor of coffee bean α-galactosidase.[7a–c]

The general approaches to the synthesis of **3** and **4** that are described in this paper are outlined below and both utilise a carbohydrate starting material to provide the two hydroxy-bearing stereocentres.

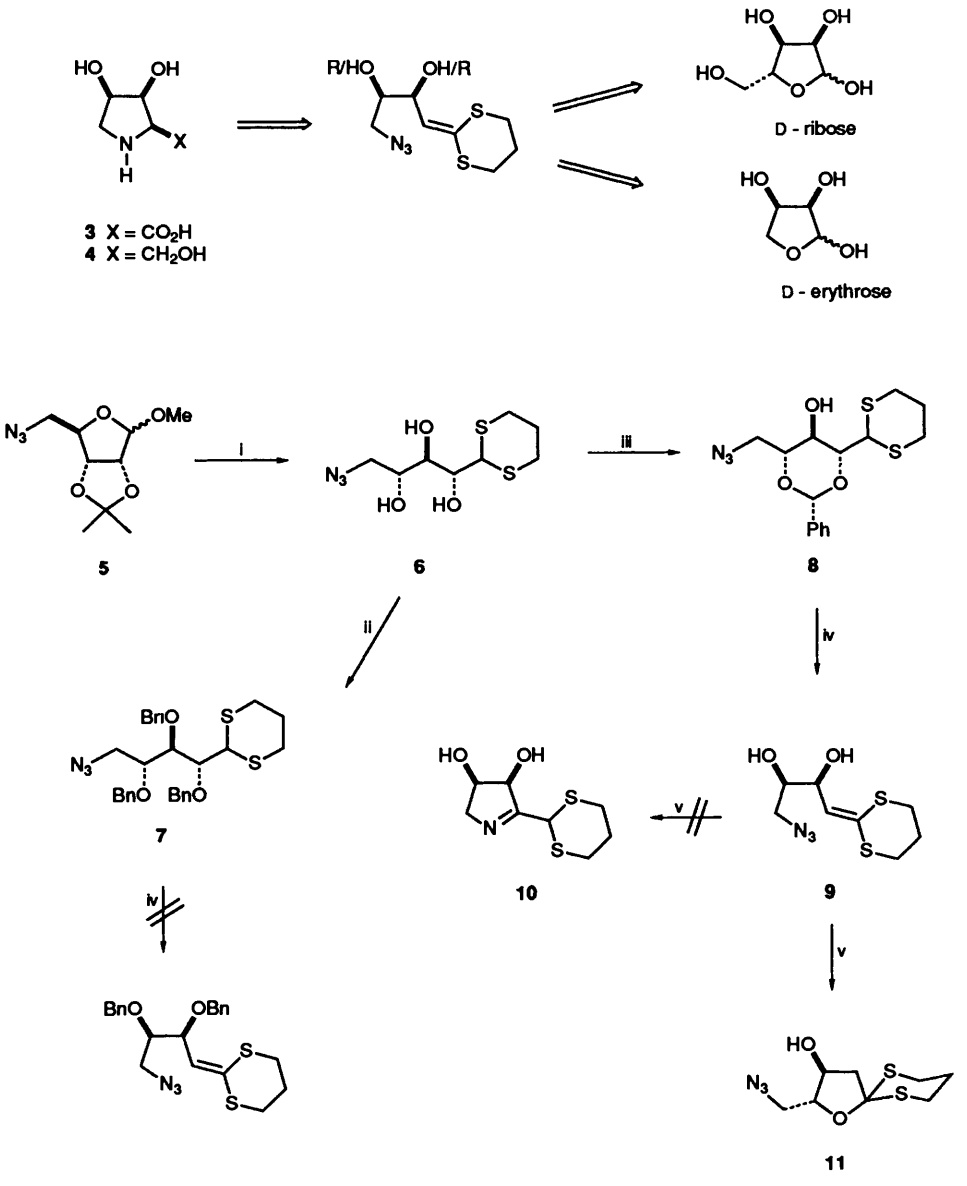
The chemistry based on the use of D-ribose is shown in Scheme 2. This was ultimately not successful but this aspect of the study does serve to illustrate certain of the limitations associated with the more general reactivity of ketene *S,S*-acetals.[9] Reaction of the azide **5**[10] with propane-1,3-dithiol under acidic conditions gave the acyclic triol **6** which was then benzylated to give **7** (65%) or treated with benzaldehyde dimethyl acetal to give **8** (93%). The acetal **8** was a single diastereoisomer and has been assigned the all-equatorial configuration based on ^1H NMR.

Our intention was to introduce the ketene *S,S*-acetal by metallation at C-2 of the dithianyl moiety in order to trigger a β-elimination. All attempts to achieve this in the tris(*O*-benzyl) series (based on **7**) failed, however, lithiation of the acetal **8** with lithium diisopropylamide (2 equiv.) and fragmentation with loss of PhCHO proceeded smoothly and the ketene *S,S*-acetal **9** was isolated in 73% yield. This intermediate was, however, unstable and this can be attributed to the presence of the free diol function. Thermolysis of **9**, under conditions that we have used previously, gave none of the desired cycloadduct



1 *n* = 1,2 2

Scheme 1 *Reagents and conditions:* i, octane, 126 °C; ii, RCOCl then H_3O^+; iii, $NaBH_4$



Scheme 2 *Reagents and conditions:* i, $HS(CH_2)_3SH$, H^+ (75%); ii, NaH, BnBr, THF (65%); iii, $PhCH(OMe)_2$, H^+ (93%); iv, lithium diisopropylamide (2 equiv.), THF (73%); v, octane, 126 °C (21%)

10 and the only product observed, in 21% yield, was the cyclic dithioortho ester **11**. This corresponds to an acid-catalysed hydration of the ketene *S,S*-acetal and this process, which is facile for systems leading to five and six-membered rings, could not be suppressed by employing alternative thermolysis conditions or diol protection (using Me_2SiCl_2, carbonyldiimidazole or acetyl chloride).

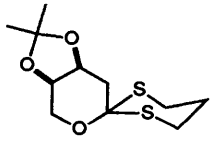
Our second and more successful synthetic study was based on the use of 2,3-*O*-isopropylideneerythrose **12** and is shown in Scheme 3. Peterson olefination[11] of **12** served to generate the ketene *S,S*-acetal **13**† directly which was converted into the desired azide **14** in 66% overall yield.

Thermolysis of **14** was carried out at 126 °C and the intermediate imine **15**, which was not isolated or characterised, was reduced *in situ* to give, after N-protection, the all-*cis* trisubstituted pyrrolidine **16**. We were unable to *N*-acylate the imine **15** directly, presumably because the deactivating influence of the acetonide function, but direct reduction of this intermediate provided an efficient mechanism for stereocontrol at C-2, based on the bias afforded by the [3.3.0]bicyclic skeleton.

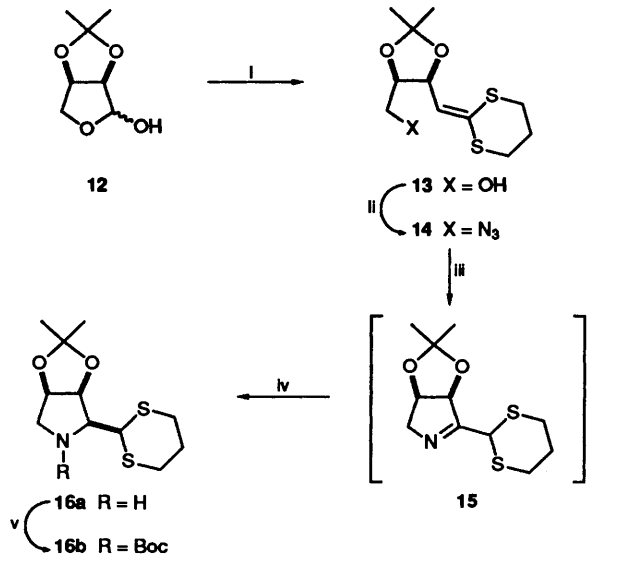
The other complication that we encountered in this aspect of the program relates to the conversion of the primary alcohol **13** into the azide **14**. Our initial attempts used a sequence based on tosylation followed by azide displacement (Scheme 4). This displacement reaction, which would be expected to be more difficult due to the presence of the adjacent heteroatoms, did give the azide **14**, but as a 1:1 mixture with the isomeric azido ketene *S,S*-acetal **17**.

These isomers could not be separated, but under the usual thermolysis conditions (octane, 126 °C), **14** was consumed and **17** was recovered unchanged in 31% overall yield from **13**. The

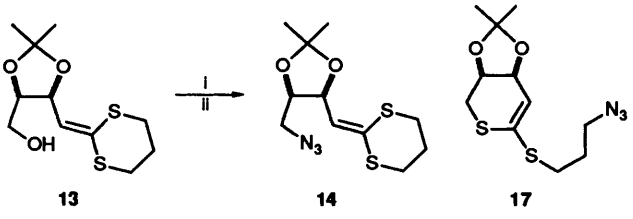
† The diol **13** in $CDCl_3$ underwent, with time, a clean acid-catalysed cyclisation to give the ring-closed addition product **13a**.



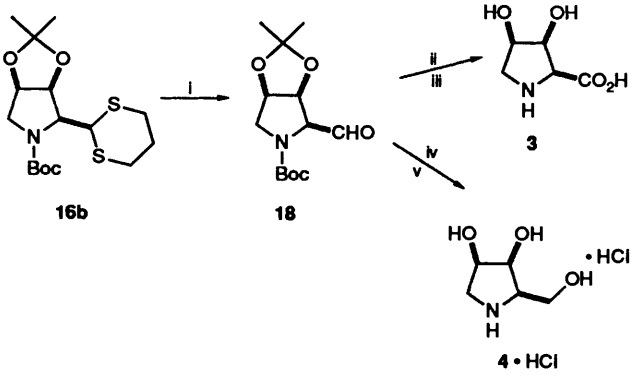
13a



Scheme 3 *Reagents and conditions:* i, 2-lithio-2-trimethylsilyl-1,3-dithiane, THF; ii, $(PhO)_2PON_3$, EtO_2CNNCO_2Et, PPh_3 (65% from **12**); iii, octane, 126 °C; iv, $NaBH_4$, MeOH; v, $Bu^tCO_2{\cdot}O{\cdot}CO_2Bu^t$ [$(Boc)_2O$], CH_2Cl_2 (56% from **14**)



Scheme 4 *Reagents and conditions:* i, $MeC_6H_4SO_2Cl$, py, then NaN_3, DMF, 120 °C, 20 min; ii, octane, 126 °C, 4 h (31% yield of **17** from **13**) [**14** removed by thermolysis]



Scheme 5 *Reagents and conditions:* i, $Tl(OCOCF_3)_3$, Et_2O, H_2O (94%); ii, $RuCl_3$, $NaIO_4$, CCl_4, MeCN; iii, CF_3CO_2H, then CF_3CO_2H, MeOH, followed by Dowex 50 H^+ (44% from **18**); iv, $NaBH_4$, MeOH; v, HCl–H_2O (30% from **18**)

azide **17** clearly arises by participation of sulfur during the displacement reaction, but it is important to note that this can be prevented using the more reactive Mitsunobu-type conditions[12] shown in Scheme 3.

The final phase of the synthetic study is shown in Scheme 5. Cleavage of the dithianyl moiety of **16** was examined under a wide variety of conditions without success. The use of PhI-$(O_2CCF_3)_2$, a reagent that was recently introduced by Stork[13] for thioacetal cleavage and which had been successfully used in our earlier work, failed in this case. We were, however, able to isolate the target aldehyde **18** in 41% yield using *N*-chlorosuccinimide (in the presence of $AgNO_3$)[14] but the efficiency of this step was increased dramatically (to 93% yield) when $Tl(O_2CCF_3)_3$[15] was used to carry out deprotection. It appears that the problems encountered in this step are most likely associated with the instability of the aldehyde under the reaction conditions used. The advantage of the thallium-mediated process was that the rate of hydrolysis was rapid and this allowed the product to be isolated and purified quickly. This is not, in a more general sense, the reagent of choice but we did not re-examine or optimise alternative procedures. Oxidation[16] of the aldehyde **18** was straightforward and removal of the two acid-labile protecting groups followed by purification by ion-exchange chromatography gave (2*S*,3*S*,4*R*)-3,4-dihydroxy proline **3** in 15.5% overall yield from 2,3-*O*-isopropylideneerythrose. Alternatively, reduction of the aldehyde **18** using $NaBH_4$ followed by deprotection gave the triol **4** (as the corresponding hydrochloride salt) in 10% overall yield from 2,3-*O*-isopropylideneerythrose.

We were able to make direct spectroscopic comparisons with data for **3** and **4** that were kindly supplied by Dr. George Fleet and this also served to exclude the possibility that epimerization at C-2 had occurred during either cleavage of the thioacetal **16** or oxidation of the aldehyde **18**.

In summary, the use of ketene *S*,*S*-acetals can be extended to provide access to highly functionalised nitrogen heterocycles in a stereochemically defined manner. There are certain problems associated with the reactivity of the sulfur-containing 1,3-dipolarophile but these limitations can be overcome and use made of the functionality that is available in this synthetically flexible moiety.

Experimental

General.—IR spectra were recorded using a Perkin-Elmer 1310 grating spectrophotometer using either $CHCl_3$ (for solids) or thin films (liquids). Routine mass spectra from electron ionisation (EI, 70 eV), chemical ionisation (CI, isobutane) and high resolution accurate mass determination were recorded with a VG Analytical 7070E instrument with a VG2000 data system. High resolution mass measurement under CI conditions were carried out at the SERC MS Service Centre at Swansea. ^1H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were recorded in $CDCl_3$ on a JEOL GNM GX FT 270 spectrometer; *J* values in Hz. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Unless otherwise stated, chromatography was carried out using silica gel Merck 9385. LP refers to light petroleum (b.p. 60–80 °C).

2-[(1R,SR,3R)-4-*Azido*-1,2,3-*trihydroxybutyl*]-1,3-*dithiane* **6**.—A solution of the azide **5**[10] (6.3 g, 27.5 mmol) in dichloromethane (50 cm^3) was treated with propane-1,3-dithiol (6.0 cm^3, 60.5 mmol) and toluene-*p*-sulfonic acid (100 mg). After being stirred for 24 h, the reaction mixture was concentrated to an oil and the product was purified by chromatography (60–120 mesh silica, 10–100% ethyl acetate in petrol) to give the title compound **6** (5.64 g, 75%) as a colourless crystalline solid, m.p. 121–122 °C (ethyl acetate–LP) (Found: M^+, 265.0544. $C_8H_{15}N_3O_3S_2$ requires *M*, 265.0552); ν_{max}/cm^{-1} 3500–3100br, 2070 and 1450; δ_H 1.67–1.86 (2 H, m), 2.69–2.76 (2 H, m), 2.78–2.97 (2 H, m), 3.21 (1 H, dd, *J* 3, 13), 3.32 (1 H, dd, *J* 8, 13), 3.60–3.66 (2 H, m), 3.83–3.88 (1 H, m), 4.37 (1 H, d, *J* 2), 5.06 (1 H, d, *J* 6), 5.19 (1 H, d, *J* 6) and 5.40 (1 H, d, *J* 5.5) (intensity of peaks at 5.06, 5.19, 5.40 reduced by D_2O shake); *m*/*z* (70 eV EI) 265 (M^+, 1%), 149 (60), 119 (40) and 43 (100).

2-[(1R,2R,3R)-4-*Azido*-1,2,3-*tribenzyloxybutyl*]-1,3-*dithiane* **7**.—A solution of the triol **6** (450 mg, 1.70 mmol) in dry THF

(10 cm^3) was cooled to −20 °C under N_2 and treated with sodium hydride (290 mg, 7.65 mmol) and tetrabutylammonium iodide (5 mg). The mixture was stirred for 10 min, after which a solution of benzyl bromide (1.02 g, 6 mmol) in dry THF (5 cm^3) was added dropwise to it by syringe. It was then allowed to warm to room temperature and stirred overnight. Water (5 cm^3) was added to the mixture cautiously and the product was extracted with ethyl acetate (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the product was isolated following chromatography (15% ethyl acetate in LP) to give the title compound **7** (590 mg, 65%) as a colourless oil; ν_{max}/cm^{-1} 2080 and 1600; δ_H 1.85–1.97 (1 H, m), 2.02–2.11 (1 H, m), 2.59–2.86 (4 H, m), 3.24 (1 H, dd, *J* 3, 13), 3.47 (1 H, dd, *J* 7.5, 13), 3.74 (1 H, dd, *J* 4, 6), 3.91 (1 H, dt, *J* 3, 6), 4.01 (1 H, dd, *J* 3.5, 6), 4.47 (1 H, d, *J* 4.5), 4.60–4.95 (6 H, m) and 7.27–7.36 (15 H, m); *m/z* (CI) 508 ($M^+ + H - N_2$ 70%). The azide **7** was not characterised by elemental analysis or high resolution mass determination.

(2R,4R,5R,6R)-4-*Azidomethyl*-6-(1,3-*dithian*-2-*yl*)-2-*phenyl*-1,3-*dioxan*-5-*ol* **8**.—A solution of the triol **6** (1.53 g, 5.76 mmol) in dichloromethane (20 cm^3) was treated with benzaldehyde dimethoxyacetal (3 cm^3) and toluene-*p*-sulfonic acid (5 mg). After being stirred at room temperature for 30 min, the reaction mixture was neutralised with triethylamine and the solvent was removed under reduced pressure. The product was isolated following chromatography (20–30% ethyl acetate–LP) to give the title compound **8** (1.89 g, 94%) as a colourless oil which crystallised with time, m.p. 118–119 °C (Found: C, 51.0; H, 5.46; N, 11.8. $C_{15}H_{19}N_3O_3S_2$ requires C, 50.97; H, 5.42; N, 11.89%); ν_{max}/cm^{-1} 3400, 2080 and 1450; δ_H 1.95–2.17 (2 H, m), 2.70–2.85 (3 H, m), 2.95–3.10 (2 H, m), 3.55 (1 H, dd, *J* 5.5, 13), 3.65 (1 H, dd, *J* 3, 13), 3.91 (1 H, ddd, *J* 3, 5.5, 9), 3.94 (1 H, t, *J* 8.5), 4.02 (1 H, dd, *J* 4, 8.5), 4.29 (1 H, d, *J* 4), 5.65 (1 H, s), 7.33–7.56 (5 H, m); *m/z* (low eV EI) 353 (M^+, 20%), 307 (5) and 119 (100).

2-[(2S,3R)-4-*Azido*-2,3-*dihydroxybutylidene*]-1,3-*dithiane* **9**.—A solution of the azide **8** (529 mg, 1.5 mmol) in dry THF (10 cm^3) was added dropwise to a freshly prepared solution of LDA (3.36 mmol) in THF (10 cm^3) at −78 °C under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature and was then quenched with water (10 cm^3) and the product was extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the product was purified by chromatography (30–50% ethyl acetate in LP) to give the title compound **9** (264 mg, 73%) as a colourless oil (Found: M^+, 247.0432. $C_8H_{13}N_3O_2S_2$ requires *M*, 247.0448); ν_{max}/cm^{-1} 3200–3500br, 2080 and 1570; δ_H 1.61 (1 H, br), 2.17 (2 H, quint, *J* 6), 2.41 (1 H, br), 2.85–3.05 (4 H, m), 3.37 (1 H, dd, *J* 4, 13), 3.43 (1 H, dd, *J* 7, 13), 3.78–3.87 (1 H, m), 4.71 (1 H, dd, *J* 4.5, 8.5) and 5.89 (1 H, d, *J* 8.5); *m/z* (70 eV EI), 247 (M^+, 5%).

(2R,3S)-2-*Hydroxymethyl*-1-*oxa*-6,10-*dithiaspiro*[4.5]*decan*-3-*ol* **11**.—The diol **9** (265 mg, 1.07 mmol) was dissolved in dichloromethane (0.5 cm^3), and the solution was then diluted with octane (3 cm^3) and heated under reflux (bath temp. 140 °C) for 3 h. This led to the formation (TLC) of a less polar product which was isolated following chromatography (ethyl acetate–LP) to give the title compound **11** (55 mg, 21%) as an oil (Found: M^+, 247.0442. $C_8H_{13}N_3O_2S_2$ requires *M*, 247.0448); ν_{max}/cm^{-1} 3300–3500, 2080 and 1420; δ_H 1.92–2.07 (1 H, m), 2.13–2.23 (1 H, m), 2.31 (1 H, dd, *J* 3.5, 14.5), 2.35 (1 H, br), 2.54 (1 H, dd, *J* 7, 14.5), 2.70–2.82 (2 H, m), 3.38–3.56 (4 H, m) and 4.21–4.33 (2 H, m); *m/z* (low eV EI) 247 (M^+, 100%).

(4S,5R)-4-(1,3-*Dithian*-2-*ylidenemethyl*)-5-*hydroxymethyl*-2,2-*dimethyl*-1,3-*dioxolane* **13**.—A solution of 2-trimethylsilyl-1,3-dithiane (1.39 g, 7.22 mmol) in dry THF (15 cm^3), was cooled to −60 °C under nitrogen and treated with butyllithium (1.6 mol dm^{-3} in hexanes; 4.5 cm^3, 7.22 mmol) which was added dropwise by syringe. The resulting solution was allowed to warm to 0 °C and then re-cooled to −78 °C when a solution of 2,3-*O*-isopropylideneerythrose (525 mg, 3.28 mmol) in THF (10 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temperature, when saturated brine (10 cm^3) was added and the product extracted with ethyl acetate (3 × 15 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography (25–60% ethyl acetate in LP) to give the title compound **13** (659 mg, 77%) as an oil (Found: M^+, 262.0685. $C_{11}H_{18}O_3S_2$ requires *M*, 262.0697); ν_{max}/cm^{-1} 3300–3500, 1570 and 1400; δ_H 1.34 (3 H, s), 1.53 (3 H, s), 1.87–2.18 (2 H, m), 2.04 (1 H, dd, *J* 4, 14), 2.24 (1 H, dd, *J* 6.5, 14), 2.56–2.66 (2 H, m), 3.08 (1 H, ddd, *J* 3, 12.5, 14), 3.39 (1 H, ddd, *J* 3, 12.5, 14), 4.03–4.16 (3 H, m) and 4.41 (1 H, dt, *J* 5.5, 6); *m/z* (low eV EI) 262 (M^+, 100).

Cyclisation of the ketene *S,S*-acetal **13** took place when a solution in $CDCl_3$ was set aside overnight to give **13a**: δ_H 1.34 (3 H, s), 1.52 (3 H, s), 2.31–1.92 (4 H, m), 2.70–2.54 (2 H, m), 3.09 (1 H, m), 3.40 (1 H, m), 4.20–4.02 (3 H, m) and 4.42 (1 H, m). This product was not characterised further.

(4S,5R)-4-*Azidomethyl*-5-(1,3-*dithian*-2-*ylidenemethyl*)-2,2-*dimethyl*-1,3-*dioxolane* **14**.—A solution of the alcohol **13** (658 mg, 2.51 mmol) in dry THF (5 cm^3) was treated with diethyl azodicarboxylate (457 mg, 2.51 mmol), triphenylphosphine (687 mg, 2.51 mmol) and then a solution of diphenylphosphoryl azide (721 mg, 2.51 mmol) in THF (5 cm^3) at 0 °C. After the mixture had been stirred for 1 h, the solvent was removed under reduced pressure and the product was isolated following chromatography (15% ethyl acetate in LP) to give the title compound **14** (613 mg, 85%) as an oil; ν_{max}/cm^{-1} 1570 and 1470; δ_H 1.39 (3 H, s), 1.52 (3 H, s), 2.11–2.21 (2 H, m), 2.76–3.06 (4 H, m), 3.16 (1 H, dd, *J* 4, 13), 3.26 (1 H, dd, *J* 7.5, 13), 4.30 (1 H, dt, *J* 4, 7.5), 5.19 (1 H, dd, *J* 6.5, 8.5) and 5.86 (1 H, d, *J* 8.5); the azide **14** was not characterised by elemental analysis or high resolution mass determination.

(1R,5S,6S)-6-(1,3-*Dithian*-2-*yl*)-3,3-*dimethyl*-2,4-*dioxa*-7-*azabicyclo*[3.3.0]*octane* **16a**.—A solution of the azide **14** (3.07 g, 10.7 mmol) in octane (30 cm^3) was heated at reflux for 4 h under an atmosphere of nitrogen. The solution was allowed to cool to room temperature, when it was cooled in ice and diluted with dry methanol (30 cm^3) and sodium borohydride (890 mg, 21.4 mmol) was added to it. After 30 min the mixture was diluted with water and the product was extracted with ether (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by chromatography (methanol–ethyl acetate) to give the title compound **16a** (1.69 g, 61%) which crystallised with time, m.p. 101–102 °C (Found: C, 50.4; H, 7.4; N, 5.1. $C_{11}H_{19}NO_2S_2$ requires C, 50.52; H, 7.32; N, 5.36%); ν_{max}/cm^{-1} 1450, 1360, 1190 and 1050; δ_H 1.34 (3 H, s), 1.49 (3 H, s), 1.87–2.06 (1 H, m), 2.07–2.17 (1 H, m), 2.43 (1 H, br), 2.66 (1 H, dd, *J* 4, 13), 2.79–2.96 (4 H, m), 3.12 (1 H, d, *J* 13), 4.27 (1 H, d, *J* 10.5) and 4.67–4.71 (3 H, m) (irradiation of the peak at δ 1.49 gave NOE enhancements at δ 1.34, 3.12 and 4.27); *m/z* (CI) 262 (M^+ + H, 35%).

tert-*Butyl*(1R,5S,6S)-6-(1,3-*Dithian*-2-*yl*)-3,3-*dimethyl*-2,4-*dioxa*-7-*azabicyclo*[3.3.0]*octane*-7-*carboxylate* **16b**.—A solution of the pyrrolidine **16a** (400 mg, 1.6 mmol) in dichloromethane (10 cm^3) was treated with a solution of di-*tert*-butyl dicarbonate

(350 mg, 1.6 mmol) in dichloromethane (3 cm^3) and triethylamine (1.5 cm^3). After 12 h, the solvent was removed under reduced pressure and the product was purified by chromatography (15% ethyl acetate in LP) to give the title compound **16b** (489 mg, 91%) which crystallized with time, m.p. 118.5–119.5 °C (hexane) (Found: C, 53.4; H, 7.66; N, 3.82. $C_{16}H_{27}NO_4S_2$ requires C, 53.15; H, 7.52; N, 3.87%); ν_{max}/cm^{-1} 1670, 1450 and 1400; δ_H 1.37 (3 H, s), 1.48 (9 H, s), 1.56 (3 H, s), 2.00 (2 H, quint, *J* 5.5), 2.55–2.77 (2 H, m), 2.92–3.15 (2 H, m), 3.11 (1 H, dd, *J* 5.5, 12), 4.09 (1 H, dd, *J* 8, 12), 4.20 (1 H, br), 4.45 (1 H, br), 4.75 (1 H, dt, *J* 7, 12.5), 4.87 (1 H, t, *J* 7); *m/z* (low eV EI) 361 (M^+, 30%), 305 (50) and 242 (100).

(1R,5S,6S)-tert-*Butyl* 6-*Formyl*-3,3-*dimethyl*-2,4-*dioxa*-7-*azabicyclo*[3.3.0]*octane*-7-*carboxylate* **18**.—A solution of the carbamate **16b** (383 mg, 1.06 mmol) in moist ether (10 cm^3) was treated with thallium(III) trifluoroacetate (630 mg, 1.17 mmol) and stirred at room temperature for 12 h. Water (10 cm^3) was then added to it and the product was extracted with ethyl acetate (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated under reduced pressure and the product was purified immediately by chromatography (40% ethyl acetate in LP) to give the title compound **18** (269 mg, 93%) as an oil which decomposed with time (Found: M^+ − CHO, 242.1401. $C_{12}H_{20}NO_4$ requires *M*, 242.1391); ν_{max}/cm^{-1} 3500br, 1700 and 1360; δ_H 1.30 (3 H, s), 1.43 (9 H, s), 1.49 (3 H, s), 3.60 (1 H, br), 3.75 (1 H, br), 4.10 (1 H br), 4.82 (1 H, dt, *J* 2, 6), 4.99 (1 H, t, *J* 6), and 9.44 (1 H, s); *m/z* (CI) 272 (M^+ + H, 2), 256 (10), 242 (30), 216 (95), 200 (25), 186 (55), 172 (60) and 142 (100). The aldehyde **18** was used in the next step immediately.

(2S,3S,4R)-3,4-*Dihydroxyproline Trifluoroacetic Acid Salt* **3**·CF_3CO_2H.—7-tert-*Butyl* 6-*Hydrogen* (1R,5S,6S)-3,3-*Dimethyl*-2,4-*dioxa*-7-*azabicyclo*[3.3.0]*octane*-6,7-*dicarboxylate*. The aldehyde **18** (252 mg, 0.093 mmol) was dissolved in a mixture of water (3 cm^3), carbon tetrachloride (2 cm^3) and acetonitrile (2 cm^3) and sodium periodate (80 mg, 0.36 mmol) and ruthenium trichloride (2 mg) were added to the solution. The reaction mixture was then stirred rapidly for 6 h. The product was extracted with dichloromethane (3 × 10 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was purified by chromatography (0–20% methanol in ethyl acetate) to give the carbamate (19 mg, 71%) (Found: M^+ − Bu^{t}OCO, 186.0768. $C_8H_{12}NO_4$ requires *M*, 186.0765); ν_{max}/cm^{-1} 3000–3500, 1680 and 1370; δ_H 1.33 (3 H, s), 1.43 (9 H, s), 1.47 (3 H, s), 3.67–3.80 (2 H, m), 4.51 (1 H, d, *J* 7), 4.84 (1 H, dt, *J* 4, 6), 4.99 (1 H, dd, *J* 6.5, 7), CO_2H not observed; *m/z* (CI) 288 (M^+ + H, 1%).

(1R,5S,6S)-3,3-*Dimethyl*-2, 4-*dioxa*-7-*azabicyclo*[3.3.0]*octane*-6-*carboxylic acid trifluoroacetic acid salt*. A solution of the above carbamate (19 mg, 0.07 mmol) in TFA (1 cm^3) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure to give the *N*-protected amino acid (TFA salt) as a glass which was used without further purification; δ_H(270 MHz, D_2O) 1.36 (3 H, s), 1.48 (3 H, s), 1.39 (1 H, dd, *J* 4, 13), 3.63 (1 H, d, *J* 13), 4.47 (1 H, d, *J* 5), 5.11 (1 H, dd, *J* 4, 6) and 5.21 (1 H, t, *J* 6).

The amino acid prepared above was dissolved in a mixture of TFA and methanol (10:1; 2 cm^3) and the solution stirred at room temperature for 5 days. The solvent was removed under reduced pressure to give **3**·CF_3CO_2H (11 mg, 62% overall yield for both deprotection steps) as a glass; δ_H(270 MHz, D_2O) 3.36 (1 H, dd, *J* 7.9, 8.2), 3.60 (1 H, dd, *J* 7.7, 12), 4.52 (2 H, m) and 1 H was obscured by HOD peak.

(2*S*,3*S*,4*R*)-3,4-Dihydroxyproline **3** was then obtained by chromatography using Dowex 50 H^+ as described in the literature [7c] and its structure was confirmed by comparison of the spectroscopic data (^1H and ^{13}C NMR) obtained for this material with those supplied by Dr. G. W. J. Fleet.

(2R,3S,4R)-2-(*Hydroxymethyl*)*pyrrolidine*-3,4-*diol Hydrochloride* **4**.—A solution of the aldehyde **18** (41 mg, 0.15 mmol) in dry methanol (1 cm^3) was cooled to 0 °C and sodium borohydride (20 mg, 0.31 mmol) was added to it. After 5 min, water (2 cm^3) was added and the product was extracted with ether (3 × 15 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and then concentrated under reduced pressure and the product was purified by chromatography (30–50% ethyl acetate in LP) to give the corresponding *N*-Boc acetonide-protected diol (15 mg, 37%); δ_H 1.33 (3 H, s), 1.47 (9 H, s), 1.50 (3 H, s), 3.55 (2 H, m), 3.85 (4 H, m), 4.70 (1 H, br) and 4.80 (1 H, br). The above product was dissolved in water (1 cm^3) and 2 mol dm^{-3} HCl (1 drop), and the solution stirred for 12 h at room temperature. The solvent was then removed under reduced pressure to give **4** the title compound (as the hydrochloride salt; 7.5 mg, 81%, 30% from **18**) which crystallized with time, m.p. 156–157 °C (lit.,[7c] 159–161 °C). The identity of the salt **4** was confirmed by comparison of its spectroscopic data (^1H and ^{13}C NMR) obtained for this material with those supplied by Dr. G. W. J. Fleet.

(1S,6S)-3-(3-*Azidopropylthio*)-8,8-*dimethyl*-7,9-*dioxa*-4-*thiabicyclo*[4.3.0]*non*-2-*ene* **17**.—A solution of compound **13** (698 mg, 2.66 mmol) in dichloromethane (10 cm^3) was cooled to 0 °C and treated with pyridine (2 cm^3, 25 mmol) and tosyl chloride (508 mg, 2.66 mmol). After 20 h at room temperature, two products had formed (TLC). The solvent was removed under reduced pressure and the residue was purified by chromatography (ethyl acetate–LP) to give the corresponding tosylate (756 mg, 68%) which crystallized with time, m.p. 54–55 °C; ν_{max}/cm^{-1} 2970, 1570 and 1350; δ_H 1.33 (3 H, s), 1.36 (3 H, s), 2.12–2.21 (2 H, m), 2.45 (3 H, s), 2.78–3.05 (4 H, m), 3.87 (1 H, dd, *J* 6.5, 10), 3.98 (1 H, dd, *J* 4.5, 10), 4.32 (1 H, dt, *J* 4.5, 6.5), 5.16 (1 H, dd, *J* 6.5, 8.5), 5.71 (1 H, d, *J* 8.5), 7.27 (2 H, d, *J* 8, part of AA′BB′) and 7.82 (2 H, d, *J* 8, part of AA′BB′).

A solution of the above tosylate (592 mg, 1.42 mmol) in DMF (4 cm^3) was treated with sodium azide (500 mg, 8 mmol), and heated at 120 °C for 20 min. The reaction mixture was then cooled and the products were isolated following chromatography (ethyl acetate–LP) to give a 1:1 mixture of compounds **14** and **17** (328 mg, 81%) as an oil. Thermolysis of this mixture (76 mg, 0.265 mmol) in octane for 4 h, under the conditions described above, resulted in cyclisation of **14**, and **17** (35 mg, 46%) was recovered unchanged following chromatography (ethyl acetate–LP). Data for the azide **17**: ν_{max}/cm^{-1} 2080, 1570 and 1360; δ_H 1.38 (3 H, s), 1.47 (3 H, s), 1.82–1.95 (2 H, m), 2.60–2.86 (3 H, m), 3.05 (1 H, ddd, *J* 6, 7, 13), 3.42 (2 H, t, *J* 6.5), 4.26 (1 H, ddd, *J* 4.5, 6, 11), 4.48 (1 H, dd, *J* 4.5, 6) and 6.20 (1 H, d, *J* 5); *m/z* (CI) 288 (M^+ + H, 20%). The azide **17** was not characterised by elemental analysis or high resolution mass determination.

Acknowledgements

We thank ICI Pharmaceuticals and SERC fo the provision of a CASE Award, Bath University for additional financial support, and Drs. George Fleet and Nigel Ramsden for their help in the characterisation of compounds **3** and **4**. Dr. J. Ballantine and the SERC Mass Spectrometry Service (University College Swansea) are thanked for high resolution CI measurements.

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Paper 2/02034C
Received 21*st April* 1992
Accepted 12*th May* 1992