'Hidden' Axial Chirality as a Stereodirecting Element in Reactions Involving Enol(ate) Intermediates. Part 1.[1] Cyclisation Reactions of Methyl (4*R*)-3-(2-Diazo-3-oxobutanoyl)thiazolidine-4-carboxylate and Related Compounds

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Methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)thiazolidine-4-carboxylate **1b** underwent cyclisation, under a variety of basic conditions, to give methyl (6*S*)-2-oxo-8-thia-1,4,5-triazabicyclo[4.3.0]non-3-ene-6-carboxylate **2a** in an enantiopure state. The absolute configuration of compound **2a** was deduced by X-ray crystallography. Similar stereoselective cyclisations, proceeding with retention of configuration, were observed with methyl (4*R*)-3-[diazo(methoxycarbonyl)acetyl]thiazolidine-4-carboxylate **1g** (to give compound **5a**), methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-2,2-dimethylthiazolidine-4-carboxylate **20a** (to give compound **21a**) and methyl (2*R*,4*R*)-3-(2-diazo-3-oxobutanoyl)-2-methylthiazolidine-4-carboxylate **22a** (to give compound **24**). An X-ray crystallographic analysis of compound **22a** revealed that the amide and diazo ketone units, although individually near planar, were twisted from each other by 35°; it was notable that the amide linkage adopted the (*Z*)-geometry required for the cyclisation reaction whereas the diazo moiety was incorrectly aligned. It is suggested that the cyclisation reactions proceed by way of planar enol(ate) intermediates, *e.g.* **6a**, which possess axial chirality.

In connection with other work, we required the diazoacetyl thiazolidine **1a**. Since the deacetylation of α-acetyl-α-diazo carbonyl compounds under basic conditions is well established,[2] we expected that compound **1a** would be accessible from the acetyldiazoacetylthiazolidine **1b**. As a consequence of examining the deacetylation reaction, we encountered a novel cyclisation with an unprecedented stereochemical outcome. We now report on our findings which, we believe, have important implications in stereoselective synthesis.

The thiazolidine **1c**,[3] prepared in 66% yield by treatment of L-cysteine hydrochloride with aqueous formaldehyde followed by subjection of the product to the action of hot methanolic hydrogen chloride and neutralisation, underwent reaction with diketene and triethylamine in boiling dichloromethane to give the acetylacetylthiazolidine **1d** in *ca.* 78% yield. In the presence of *p*-carboxybenzenesulfonazide (*p*-CBSA), triethylamine and acetonitrile,[4] compound **1d** was converted into the acetyldiazoacetylthiazolidine **1b** (*ca.* 76% yield after chromatography).

On the basis of ^{1}H NMR spectroscopy, the product of the reaction of the thiazolidine **1c** with diketene existed in deuteriochloroform at ambient temperature as a 7:3 mixture of the keto and enol tautomers **1d** and **1e**; in turn, the keto tautomer was present as a 5:2 mixture of rotamers and the enol tautomer as a 4:1 mixture of rotamers (arising from restricted rotation about the amide bond). There was no evidence for restricted rotation about the amide bond of compound **1b** under corresponding conditions.

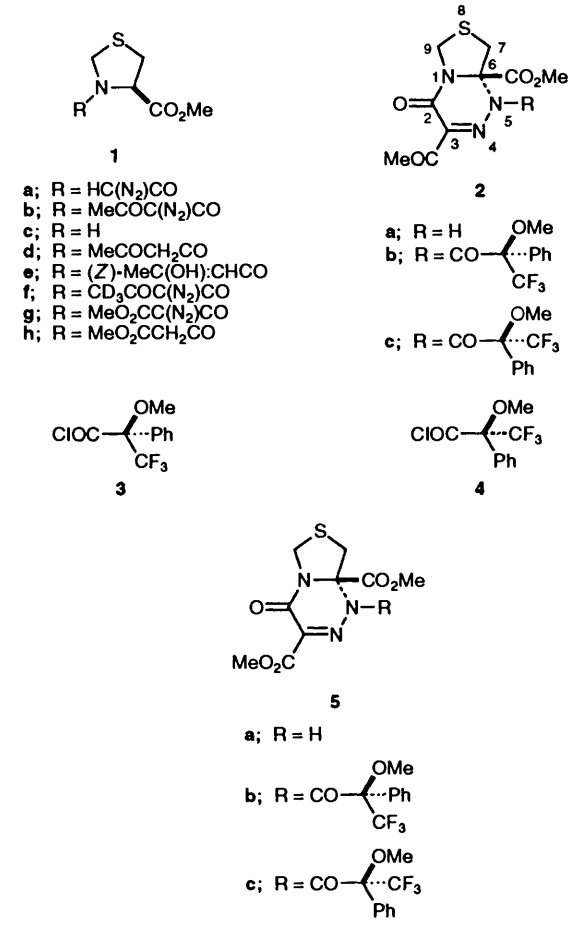
When the acetyldiazoacetylthiazolidine **1b** was treated with methanolic sodium methoxide and the concentrate subjected to chromatography, the desired diazoacetylthiazolidine **1a** was isolated in *ca.* 37% yield as a slightly impure and somewhat unstable yellow oil. Compound **1a**, which was optically active {$[\alpha]_D$ −101 (CH_2Cl_2)}, featured a strong IR absorption at 2120 cm^{-1} for the diazo group; its ^{1}H NMR spectrum incorporated a one-proton singlet at δ 4.96 ($CDCl_3$) for the diazoacetyl hydrogen atom. A second material {$[\alpha]_D$ −289 (MeOH)}, designated compound **A**, was isolated in 35% yield after recrystallisation.

A mixture of the aforementioned compounds was also produced when the acetyldiazoacetylthiazolidine **1b** was treated with triethylamine in methanol; after chromatography, the diazoacetylthiazolidine **1a** was obtained in 62% yield and compound **A** in 35% yield. The use of pyrrolidine in acetonitrile at ambient temperature provided the diazoacetylthiazolidine **1a** in 55% yield and compound **A** in 43% yield; under refluxing conditions, only compound **A** was isolated (59% yield). Sodium hydroxide in aqueous dioxane also effected the transformation of the acetyldiazoacetylthiazolidine **1b** into compound **A** (59% yield). The best conditions devised for the preparation of compound **A** involved the addition of triethylamine to a boiling solution of the acetyldiazoacetylthiazolidine **1b** in methanol; after treatment with charcoal and recrystallisation, compound **A** was isolated in 65% yield. The optical rotations of compound **A** isolated in the aforecited experiments were in good agreement with that of the original sample.

Elemental analysis established that compound **A** was isomeric with the acetyldiazoacetylthiazolidine **1b** and spectroscopic considerations left little doubt that it possessed the structure **2a**. Thus, absorptions were present at 3220, 1745, 1680 and 1640 cm^{-1} in the IR spectrum (KBr) and at 225 (ε 7500), 257 (4100) and 311 nm (4800) in the UV spectrum (EtOH). As well as featuring two singlets at δ 2.40 and 3.78 for the acetyl and methoxy groups, the ^{1}H NMR spectrum ($CDCl_3$) displayed an AB quartet (*J* 12 Hz) centred at δ 3.50 for the 7-methylene group, two doublets (*J* 10 Hz) at δ 4.58 and 5.03 for the 9-methylene group, and a broad singlet at δ 7.70 (exchangeable with D_2O) for the 5-hydrogen atom.

Since it displayed a consistent optical rotation {$[\alpha]_D$ − 283 to −289 (MeOH)} when generated under a variety of conditions, the bicycle **2a** was considered to be enantiomerically pure. This notion was substantiated by treating the material with the (*S*)- and (*R*)-acid chlorides **3** and **4**[5] in dichloromethane in the presence of pyridine; in each case, only one diastereoisomeric amide was detected in the crude product by ^{1}H NMR spectroscopy. Following chromatographic purification, the amide **2b** was isolated in 42% yield from the reaction involving the (*S*)-acid chloride **3** and the amide **2c** was obtained in 53% yield from the reaction involving the (*R*)-acid chloride **4**.

The absolute configuration of compound **2a** was deduced by



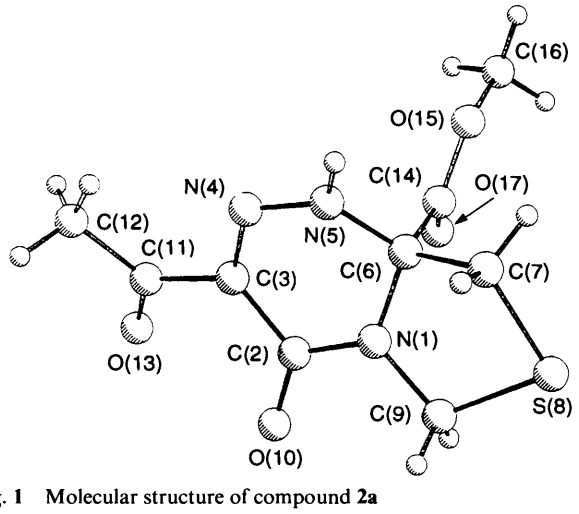
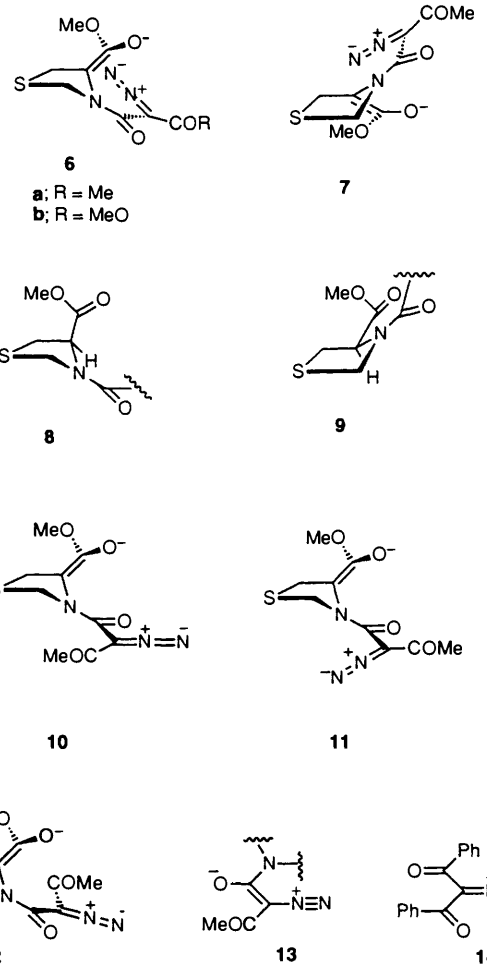


Fig. 1 Molecular structure of compound **2a**

X-ray crystallography. The molecular structure (see Experimental section for crystal data and other information) is shown in Fig. 1 together with its crystallographic labelling. Clearly, the bicycle **2a**, possessed the (*S*)-configuration at position 6. In consequence, the stereostructures of the Mosher amides **2b** and **2c** were defined.

Evidently, the **1b**→**2a** transformation had proceeded with retention of configuration. The basic conditions required for the cyclisation suggest that an ester enolate (or enol) intermediate intervenes. Classically, such species are planar and, in the absence of other chiral features, they react with electrophiles to give racemic products.[6] However, the enolate **6a**, required for the cyclisation reaction, possesses axial chirality and a sizeable energy barrier is likely to separate it from its enantiomer **7**. We suggest, therefore, that intramolecular trapping of the enolate **6a** by the highly electrophilic diazo function occurs more rapidly than racemisation. An interesting consequence of this interpretation is that there is a marked kinetic preference for the thiazolidine **1b** to undergo



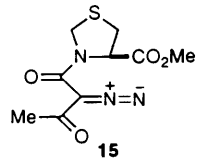
deprotonation to give the enolate **6a** rather than its enantiomer **7**. Presumably, this is attributable to the greater ease in attaining the geometry **8** compared with the geometry **9** (in which a severe $A^{1,3}$ interaction[7] exists between the acyl substituent and the methoxycarbonyl group) required for the deprotonation reactions.

In the hope of providing support for the intermediacy of the enolate **6a**, the reaction of the thiazolidine **1b** with triethylamine in perdeuteriomethanol was monitored by NMR spectroscopy. There was no evidence for deuterium incorporation at position 4 of the starting material, although complete exchange of the acetyl hydrogen atoms did occur to give compound **1f**. Evidently, the enolate **6a** undergoes cyclisation faster than reprotonation. Moreover, it seems unlikely that the enolates **10** and **11**, which also possess axial chirality, are generated. Thus, it would be necessary to invoke that the isomerisation **10**→**6a** and **11**→**6a** (which involve rotations about an amide-like bond) would be fast compared with enolate protonation. It is possible that the enolate **12**, which also possesses axial chirality, intervenes. Again, however, it would be necessary to postulate that the **12**→**6a** isomerisation is fast compared with enolate protonation.

As already mentioned, there was evidence for restricted rotation at room temperature in the case of the acetylacetylthiazolidine **1d** but not in the case of the acetyldiazoacetylthiazolidine **1b**. The barrier to rotation about the amide bond would be

expected to be lower in the latter case than in the former because of a contribution of type **13**. Indeed, when the NMR spectrum of compound **1b** in deuteriochloroform was recorded at −60 °C, there was evidence for the presence of three rotameric forms in the ratio of 50:32:18.

In the case of dibenzoyldiazomethane, the geometry **14** is preferred in the crystal state in which the carbonyl groups bear an *anti*-type relationship.[8] However, whereas the torsion angle between the carbonyl function *syn* to the diazo moiety is small (*ca.* 10°) that involving the *anti*-carbonyl group is significant (*ca.* 37°). Assuming that a similar geometry prevails in the case of the acetyldiazoacetylthiazolidine **1b**, then the conformers **15**–**18** are contenders for the three observed rotamers.



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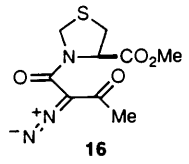

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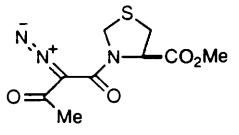

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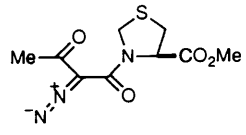

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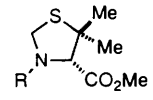

19

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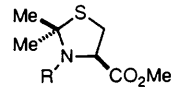
b; R = H
c; R = $MeCOCH_2CO$
d; R = (*Z*)-MeC(OH):CHCO



20

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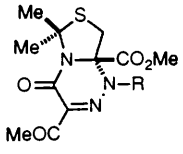
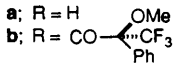
b; R = H
c; R = $MeCOCH_2CO$
d; R = (*Z*)-MeC(OH):CHCO



21

a; R = H
b; R = CO– 

Irrespective of the precise conformational situation, it is clear that compound **1b** is represented by at least three rapidly equilibrating rotamers under conditions similar to those required for the cyclisation reaction. We suggest, therefore, that there is a kinetic preference for the rotamer **15** to undergo the deprotonation reaction to give the enolate **6a**.

To define the scope of the cyclisation reaction, it was decided to prepare a series of modified diazoacetylthiazolidines and to examine their behaviour under basic conditions. Hopefully, a crystalline diazo precursor would emerge, which, through X-ray analysis, would reveal the geometry of the diazoacetamide linkage.

The synthesis of the diazo(methoxycarbonyl)acetylthiazolidine **1g** was undertaken to determine the effect of the reduced electrophilicity of the diazo moiety. Thus, treatment of the thiazolidine **1c** with methyl malonyl chloride, triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane gave the methoxycarbonylacetylthiazolidine **1h** (isolated as a syrup in 91% yield after chromatography). Under diazo-transfer conditions, compound **1h** was converted into the diazo derivative **1g** in *ca.* 67% yield. On the basis of ^1H NMR spectroscopy, compound **1h** was present in deuteriochloroform at room temperature as a 2:1 mixture of rotamers; there was no evidence for restricted rotation in the case of compound **1g** under comparable conditions.

When heated in methanol with triethylamine, the diazo(methoxycarbonyl)acetylthiazolidine **1g** was transformed into the bicycle **5a** (*ca.* 28% yield after crystallisation), identified by its spectroscopic properties. Like its relative **2a**, compound **5a** displayed a large negative optical rotation {$[\alpha]_D$ −282 (CH_2Cl_2)}. Moreover, it reacted with the (*S*)-acid chloride **3** to give the amide **5b** (56 % yield after chromatography) and with the (*R*)-acid chloride **4** to give the amide **5c** (77% yield after chromatography); in each case, the products were single diastereoisomers by ^1H NMR spectroscopy.

These results left little doubt that the bicycle **5a** was enantiomerically pure. They also revealed that the diazo(methoxycarbonyl) acetyl function serves as an effective intramolecular trap for the presumed enolate intermediate **6b**.

The effect of dimethyl substitution at position 5 of the thiazolidine ring was probed by preparing the acetyldiazoacetyl(dimethyl)thiazolidine **19a**. Thus, the dimethylthiazolidine **19b**[9a] (obtained in 33% overall yield by treatment of D-penicillamine with aqueous formaldehyde and subjection of the product to the action of hot methanolic hydrogen chloride and neutralisation), underwent reaction with diketene and triethylamine in boiling dichloromethane to give mainly compound **19c** in quantitative yield. Under diazo-transfer conditions, the last-cited material was transformed into the acetyldiazoacetyl(dimethyl)thiazolidine **19a** (94% yield).

By ^1H NMR spectroscopy, the product of the reaction of the dimethylthiazolidine **19b** with diketene existed in deuteriochloroform at ambient temperature as a 7:3 mixture of the keto and enol tautomers **19c** and **19d**; in turn, the keto tautomer was present as a 4:1 mixture of rotamers and the enol tautomer as a 5:1 mixture of rotamers. There was no evidence for restricted rotation about the amide bond in the case of the acetyldiazoacetyl(dimethyl)thiazolidine **19a**.

The desired bicyclic product was not formed when the acetyldiazoacetyl(dimethyl)thiazolidine **19a** was heated in methanol in the presence of triethylamine.

To determine the effect of dimethyl substitution at position 2 of the thiazolidine ring, the synthesis of compound **20a** was undertaken. When L-cysteine was subjected to the action of hot methanolic hydrogen chloride and the product heated with acetone, the dimethylthiazolidine **20b*** was isolated in 41% yield after neutralisation. Compound **20b** underwent reaction with diketene to give the acetylacetylthiazolidine **20c** in *ca.* 95% yield. Under diazo-transfer conditions, the last-cited material was transformed into the diazo derivative **20a** (35% yield after chromatography).

On the basis of ^1H NMR spectroscopy, the product of the reaction of the thiazolidine **20b** with diketene existed in deuteriochloroform at ambient temperature as a 4:1 mixture of the keto and enol tautomers **20c** and **20d**. However, in contrast to their relatives **1d** and **1e** and **19c** and **19d**, these tautomers showed little evidence for the presence of rotameric forms. Like its relatives **1b** and **19a**, the acetyldiazoacetylthiazolidine **20a** showed no evidence for restricted rotation about the amide bond in deuteriochloroform at ambient temperature.

* For a synthesis of the hydrochloride salt of this compound, see ref. 9*b*.

In hot methanol containing triethylamine, the diazo derivative **20a** was transformed into the bicycle **21a** (31% yield after chromatography). On the basis of its large negative optical rotation $\{[\alpha]_D -191\ (CH_2Cl_2)\}$ and its reaction with the (*R*)-acid chloride **4** to give the Mosher amide **21b** as a single diastereoisomer in 61% yield, the bicycle **21a** was considered to be enantiomerically pure. Evidently, the cyclisation reaction tolerates dimethyl substitution at position 2 of the thiazolidine ring.

In the examples considered to date, the thiazolidine ring of the cyclisation precursor has incorporated one stereogenic centre—that at position 4. To determine whether it would be possible to override the inherent tendency for cyclisation to occur with complete retention of configuration, it was decided to introduce asymmetry at position 2 of the thiazolidine ring. The synthesis of the acetyldiazoacetyl(methyl)thiazolidine **22a** and/or **23a** was, therefore, examined.

A 3:2 mixture of the methylthiazolidines **22b** and **23b**, prepared in 55% yield by treatment of L-cysteine hydrochloride with acetaldehyde in water followed by subjection of the product to the action of hot methanolic hydrogen chloride and neutralisation, underwent reaction with diketene and triethylamine in boiling dichloromethane to give the acetylacetyl derivative **22c** in *ca.* 98% yield. Under diazo-transfer conditions, the last-cited material was transformed into the acetyldiazoacetyl(methyl)thiazolidine **22a** (*ca.* 34% yield after crystallisation), whose stereostructure was established by X-ray crystallography.

The molecular structure of compound **22a** (see Experimental section for crystal data and other information) is shown in Fig.2 together with its crystallographic labelling.

On the basis of ^{1}H NMR spectroscopy, the product of the reaction of the mixture of the thiazolidines **22b** and **23b** with diketene appeared to be mainly one diastereoisomer although it existed in deutereriochloroform as a 3:1 mixture of keto and enol tautomers; in turn, the keto tautomer was present as a 4:3 mixture of rotamers and the enol tautomer as a 4:1 mixture of rotamers. From the X-ray analysis, we infer that the keto and enol tautomers possesses the stereostructures **22c** and **22d**. Seemingly, the thiazolidines **22b** and **23b** equilibrate under the acetoacetylation conditions and there is a kinetic preference for the diastereoisomer **22b** to react with diketene.

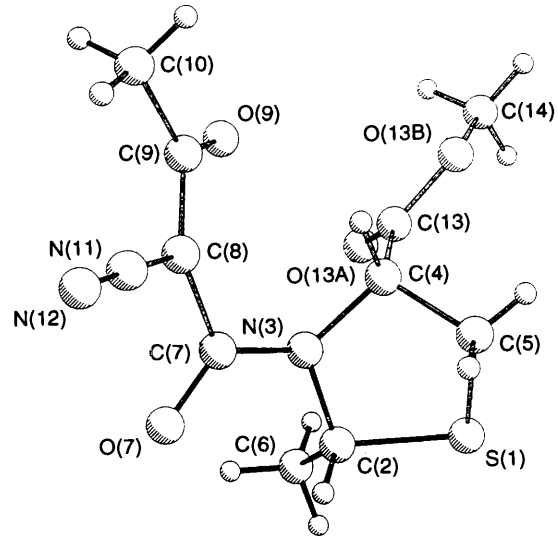


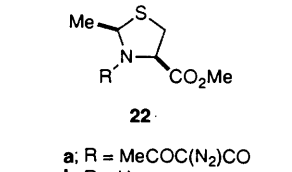
Fig. 2 Molecular structure of compound **22a**

In hot methanol containing triethylamine, the acetyldiazoacetylthiazolidine **22a** was transformed into the bicycle **24** (*ca.* 69% yield); there was no evidence for a second diastereoisomer in the crude product. The high negative optical rotation $\{[\alpha]_D -221\ (CH_2Cl_2)\}$ displayed by the bicycle left little doubt that it possessed the stereostructure **24**.

As well as establishing that compound **22a** possessed the (2*R*)-stereochemistry, the X-ray analysis revealed that the amide and diazo ketone units, although individually near planar, were twisted from each other by 35°. It was notable that the amide linkage adopted the (*Z*)-geometry required for the cyclisation reaction whereas the diazo ketone moiety (in which the diazo and carbonyl groups were *anti*) was incorrectly aligned. Of the four rotamers **15**–**18** discussed earlier, the rotamer **16** shows the closest approximation to the geometry adopted by compound **22a** in the crystal state.

The aforecited findings are of interest in a number of respects. Thus, although there is precedent for the intermolecular addition of *C*-nucleophiles to the diazo function of α-diazo carbonyl compounds,[10] we are aware of only one example of the intramolecular variant.[11] The results also provide a dramatic illustration of the powerful stereodirecting effect that can be achieved in the trapping of thiazolidine ester enolates possessing 'self-assembled' axial chirality. This stereoinduction principle has not been widely recognised although Seebach and Wasmuth[12] noted that it provided a possible explanation for the observation that the alkylation of di(*tert*-butyl) *N*-formyl-L-asparate led to a mixture of C(2)- and C(3)-alkylated materials in which the former products were optically active (e.e.s *ca.* 60%). Finally, the results imply that there is a greater kinetic acidity for the C(4)-hydrogen atom of thiazolidines of type **25** with the (*Z*)-geometry of the amide bond than in thiazolidines of type **26** in which the amide bond adopts the (*E*)-geometry.

Following our preliminary communication of this work, Fuji and co-workers[13] have reported that the ketone **27** was converted into alkylated products of type **28** (with e.e.s of 48–67%) in the presence of potassium hydride, alkyl halides and 18-crown-6. They postulate that an enolate with axial chirality is involved as an intermediate.



22

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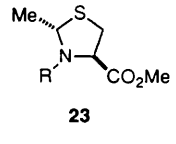
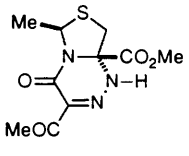
b; R = H
c; R = $MeCOCH_2CO$
d; R = (*Z*)-MeC(OH):CHCO



23

a; R = $MeCOC(N_2)CO$
b; R = H



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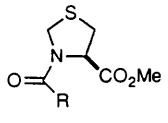

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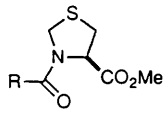

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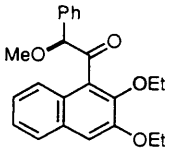

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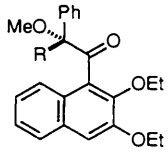

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Experimental

Dry solvents/reagents, referred to in the ensuing experiments,

were prepared as follows: pyridine (after distillation from NaOH pellets) and acetonitrile were stored over 4 Å molecular sieves; dichloromethane was allowed to stand over calcium chloride granules; methanol was distilled from magnesium turnings and iodine.

TLC was performed using plastic sheets coated with silica gel (Merck Kieselgel 60); the sheets were initially examined under UV light (Mineralight UVG2-58 lamp) and developed with iodine vapour. Column chromatography was effected under pressure (*ca.* 10 psi*) using either Merck Kieselgel H Type 60 or Crossfield Sorbsil C60 flash silica. Evaporations were conducted under reduced pressure (using a water-pump or an oil-pump) with a Buchi rotary evaporator. M.p.s were determined using a Buchi 512 melting point apparatus. Optical rotations, measured at *ca.* 20 °C using either a Thorn Automation Type 243 or an Optical Activity 1000 polarimeter, are given in 10^{-1} deg cm^2 g^{-1}. IR Spectra were recorded using a Perkin-Elmer 783 spectrometer. A Perkin-Elmer Lambda 15 was used to determine UV spectra; extinction coefficients (ε) are presented in cm^2 $mmol^{-1}$. ^1H NMR spectra were measured at 300 MHz using a Bruker AC 300; *J* values and separations are given in Hz. A Kratos MS45 spectrometer was used to obtain EI and CI mass spectra (NH_3 as the carrier gas); FAB mass spectra (*p*-$NO_2C_6H_4CH_2OH$ as matrix) were measured using either a Kratos Concept IS spectrometer or a VG ZAB-E spectrometer. Elemental analyses were performed with a Carlo-Erba Model 1106 analyser.

Preparation of Methyl (4R)-3-(3-*Oxobutanoyl*)*thiazolidine*-4-*carboxylate* **1d** (*With K. J. Jankowski*).—37% Aqueous formaldehyde (22 cm^3, 0.29 mol) was added to a solution of L-cysteine hydrochloride (38.8 g, 0.246 mol) in water (100 cm^3). After 20 h, the solution was concentrated and the residue was dried [by addition of toluene and re-evaporation (× 3)]. The product was dissolved in methanol (200 cm^3) which had been saturated with hydrogen chloride and the solution was heated under reflux for 6 h. Evaporation of the solvent left a residue which was partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic phase left methyl (4*R*)-thiazolidine-4-carboxylate **1c**[3] (24.0 g, 66%) as a colourless oil; δ(300 MHz; $CDCl_3$) 2.40 (1 H, br s, NH), 2.88 and 3.26 (each 1 H, dd, *J* 10 and 7, 5-H_2), 3.78 (3 H, s, MeO_2C), 3.86 (1 H, t, *J* 7, 4-H) and 4.12 and 4.38 (each 1 H, d, *J* 9, 2-H_2) (addition of D_2O caused the signal at δ 2.40 to disappear).

Diketene (5.45 cm^3, 70.7 mmol) and triethylamine (6 drops) were added to a solution of the thiazolidine **1c** (10.3 g, 70.0 mmol) in dry dichloromethane (50 cm^3). After having been heated under reflux for 12 h, the mixture was washed with dilute hydrochloric acid followed by brine. Evaporation of the dried ($MgSO_4$) organic layer left an orange oil (12.6 g, *ca.* 78%) which was predominantly the title compound **1d**. A sample, after purification by silica gel column chromatography [hexanes–EtOAc (2:5) as eluent] and crystallisation (from CH_2Cl_2–hexanes), was obtained as dull-white crystals which existed in deuteriochloroform as a 7:3 mixture of the *title compound* **1d** (as a 5:2 mixture of rotamers) and *methyl* (4R)-3-[(Z)-3-*hydroxybut*-2-*enoyl*]*thiazolidine*-4-*carboxylate* **1e** (as a 4:1 mixture of rotamers); m.p. 40–41 °C; $[\alpha]_D$ −119 (1.2% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 1740 (ester C=O), 1720 (ketone C=O) and 1650 (amide C=O); λ_{max}(EtOH)/nm 203 (ε 5100) and 257 (9800); δ(300 MHz; $CDCl_3$) 1.94 [0.9 H, s, 0.3 × *Me*C(OH)], 2.26 and 2.86 (0.6 and 1.5 H, each s, 0.7 × MeCO), 3.15–3.39 (2 H, m, 5-H_2), 3.48 and 3.55 [0.4 and 1 H, AB q (*J* 15, separation of inner lines 12) and s, 0.7 × $MeCOCH_2$], 3.73 and 3.76 (2.1 and 0.9 H, each s, MeO_2C), 4.45–4.60 and 4.72 [1.8 and 0.2 H, m and d (*J* 10), 2-H_2], 4.86 (0.3 H, dd, *J* 6 and 2, 0.3 × 4-H), 5.05–5.11 [1 H, m, 0.7 × 4-H and 0.3 × MeC(OH):C*H*] and 13.94 and 14.12 [0.24 and 0.06 H, each br s, 0.3 × MeC(O*H*)]; *m/z* (CI) 232 (MH^+, 100%) (Found: C, 46.5; H, 5.4; N, 5.8; S, 13.9. $C_9H_{13}NO_4S$ requires C, 46.75; H, 5.65; N, 6.05; S, 13.85%).

Preparation of Methyl (4R)-3-(2-*Diazo*-3-*oxobutanoyl*)-*thiazolidine*-4-*carboxylate* **1b** (*With K. J. Jankowski*).—Dry triethylamine (21 cm^3, 158 mmol) and *p*-CBSA (14.3 g, 62.9 mmol) were added to a stirred solution of the crude oxobutanoyl derivative **1d** (9.60 g, *ca.* 41.5 mmol) in dry acetonitrile (320 cm^3). After 2 h, the mixture was concentrated and dichloromethane was added to the residue which was filtered. The filtrate was washed with dilute hydrochloric acid followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. Subjection of the residue to silica gel column chromatography [hexanes–EtOAc (2:5) as eluent] gave the *title compound* **1b** (8.10 g, *ca.* 76%) as a yellow syrup; $[\alpha]_D$ −243 (1.2% in $CHCl_3$); ν_{max}(film)/cm^{-1} 2110 (C=N^+=N^-), 1750 (ester C=O) and 1650br (diazo ketone and diazo amide C=O); λ_{max}(EtOH)/nm 230 (ε14800); δ(300 MHz; $CDCl_3$) (at 292 K) 2.35 (3 H, s, MeCO), 3.23 and 3.33 [each 1 H, dd (*J* 12 and 5) and dd (*J* 12 and 7), 5-H_2], 3.75 (3 H, s, MeO_2C), 4.57 and 4.62 (each 1 H, d, *J* 10, 2-H_2) and 5.15 (1 H, dd, *J* 7 and 5, 4-H); (at 268 K) 2.35 (3 H, br s, MeCO), 3.20 and 3.33 [each 1 H, br s and dd (*J* 12 and 7), 5-H_2], 3.75 (3 H, s, MeO_2C), 4.58 (2 H, br s, 2-H_2) and 5.03 (1 H, br s, 4-H); (at 258 K) 2.32sh and 2.37 (together 3 H, each br s, MeCO), 3.18 and 3.33 [each 1 H, br s and dd (*J* 12 and 7), 5-H_2], 3.75 (3 H, s, MeO_2C), 4.55 (2 H, br s, 2-H_2) and 4.83 and 5.00 (together 1 H, each br s, 4-H); (at 246 K) 2.30, 2.32 and 2.41 (0.6, 1.05 and 1.35 H, each s, MeCO), 3.13–3.22 and 3.28–3.40 (together 2 H, each m, 5-H_2), 3.84, 3.86 and 3.87 (1.05, 1.35 and 0.6 H, each s, MeO_2C), 4.54 and 4.63 [together 2 H, br s and d (*J* 9), 2-H_2] and 4.87–5.05 (1 H, m, 4-H); (at 239 K) 2.30, 2.32 and 2.41 (0.6, 1.05 and 1.35 H, each s, MeCO), 3.20–3.30 and 3.38–3.50 (0.8 and 1.2 H, each m, 5-H_2), 3.84, 3.86 and 3.87 (1.05, 1.35 and 0.6 H, each s, MeO_2C), 4.60–4.75 (2 H, m, 2-H_2) and 4.95–5.10 (1 H, m, 4-H); *m/z* (CI) 275 [$M(NH_4)^+$, 41%], 258 (MH^+, 99), 232 (100) and 146 (90) (Found: C, 42.0; H, 4.4; N, 16.0; S, 12.1. $C_9H_{11}N_3O_4S$ requires C, 42.0; H, 4.30; N, 16.35; S, 12.45%).

Reaction of the Diazo Compound **1b** *with Basic Methanol.*—(*a*) Methanolic sodium methoxide (*ca.* 0.1 mol dm^{-3}; 1 cm^3) was added in drops to a stirred ice-cooled solution of the diazo compound **1b** (0.100 g, 0.39 mmol) in dry methanol (2 cm^3). After 5 min, the bright yellow solution was concentrated and the residue was subjected to silica gel column chromatography [hexanes–EtOAc (1:2) as eluent] to give two fractions.

The first-eluted material (0.031 g, *ca.* 37%), isolated as a slightly impure and somewhat unstable yellow oil, was identified as methyl (4*R*)-3-diazoacetylthiazolidine-4-carboxylate **1a**; $[\alpha]_D$ −101 (1% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2120 (C=N^+=N^-), 1730 (ester C=O) and 1600 (diazo amide C=O); λ_{max}(EtOH)/nm 203 (ε 6500); δ(300 MHz; $CDCl_3$) 3.19–3.30 (2 H, s, 5-H_2), 3.75 (3 H, s, MeO_2C), 4.38 and 4.4 [each 1 H, d (separation 7.5) and br s, 2-H_2], 4.96 (1 H, s, $COCHN_2$) and 5.0 (1 H, br s, 4-H); δ(300 MHz; CD_3COCD_3) 3.19 and 3.34 [each 1 H, br d (separation 11) and dd (*J* 11 and 7), 5-H_2], 3.99 (3 H, s, MeO_2C), 4.37 and 4.6 [each 1 H, d (*J* 8) and br s, 2-H_2], 5.0 (1 H, br s, 4-H) and 5.60 (1 H, s, $COCHN_2$); *m/z* (FAB) 216 (MH^+, 100%).

The second-eluted material was crystallised from ethanol to give the bicyclononene **2a** (0.035 g, 35%) {m.p. 174–176 °C; $[\alpha]_D$ −289 (0.5% in MeOH)}, identified by its 300 MHz ^1H NMR spectrum.

* 1 psi = *ca.* 6.895 × 10^3 Pa.

(*b*) Triethylamine (0.33 cm^3, 2.37 mmol) was added to a stirred solution of the diazo compound **1b** (0.200 g, 0.78 mmol) in dry methanol (2 cm^3). After 12 h, the mixture was concentrated and the residue was fractionated by silica gel column chromatography [hexanes–EtOAc (1:2) as eluent] to give two fractions.

The first-eluted material (0.104 g, 62%), isolated as a yellow oil, was identified as the diazoacetyl derivative **1a** on the basis of its 300 MHz ^1H NMR spectrum.

The second-eluted material was crystallised from ethanol to give the bicyclononene **2a** (0.070 g, 35%) {m.p. 175–176 °C; $[\alpha]_D$ −286 (0.55% in MeOH)}, identified by its 300 MHz ^1H NMR spectrum.

Reaction of the Diazo Compound **1b** *with Pyrrolidine.*—(*a*) Pyrrolidine (0.11 cm^3, 1.3 mmol) was added to a stirred solution of the diazo compound **1b** (0.110 g, 0.43 mmol) in dry acetonitrile (5 cm^3). After 12 h, the mixture was concentrated and the residue was subjected to silica gel column chromatography [hexanes–EtOAc (1:2) as eluent] to give two fractions.

The first-eluted material (0.051 g, 55%), isolated as a yellow oil, was identified as the diazoacetyl derivative **1a** on the basis of its 300 MHz ^1H NMR spectrum.

The second-eluted material was crystallised from ethanol to give the bicyclononene **2a** (0.047 g, 43%) {m.p. 175–176 °C; $[\alpha]_D$ −289 (0.55% in MeOH)}, identified by its 300 MHz ^1H NMR spectrum.

(*b*) Pyrrolidine (0.08 cm^3, 0.96 mmol) was added to a boiling solution of the diazo compound **1b** (0.090 g, 0.35 mmol) in dry acetonitrile (5 cm^3). Evaporation after 3 h and purification of the product as above gave the bicyclononene **2a** (0.053 g, 59%) {m.p. 175–176 °C; $[\alpha]_D$ −283 (0.5% in MeOH)}, identified by its 300 MHz ^1H NMR spectrum.

Reaction of the Diazo Compound **1b** *with Sodium Hydroxide.*—Sodium hydroxide (0.5 mol dm^{-3}; 1 cm^3, 0.5 mmol) was added to a stirred solution of the diazo compound **1b** (0.100 g, 0.39 mmol) in dioxane (2 cm^3). Evaporation after 12 h, subjection of the residue to silica gel column chromatography [hexanes–EtOAc (1:2) as eluent] and crystallisation of the chromatographed product from ethanol gave the bicyclononene **2a** (0.059 g, 59%) {m.p. 176–177 °C; $[\alpha]_D$ −288 (0.5% in MeOH)}, identified by its 300 MHz ^1H NMR spectrum.

Preparation of Methyl (6R)-3-*Acetyl*-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **2a**.—Triethylamine (4.0 cm^3, 28.7 mmol) was added to a boiling solution of the diazo compound **1b** (2.47 g, 9.6 mmol) in dry methanol (40 cm^3). After 2 h, the mixture was concentrated and dichloromethane was added to the residue. The resultant brown solid was filtered off, dissolved in hot methanol and treated with charcoal. Filtration, evaporation of the filtrate and recrystallisation of the residue from ethanol gave the *title compound* **2a** (1.60 g, 65%); m.p. 172–174 °C; $[\alpha]_D$ −289 (0.5% in MeOH); ν_{max}(KBr)/cm^{-1} 3220 (NH), 1745 (ester C=O) and 1680 and 1640 (amide and ketone C=O and C=N); λ_{max}(EtOH)/nm 225 (ε 7500), 257 (4100) and 311 (4800); δ(300 MHz; CD_3COCD_3) 2.39 (3 H, s, MeCO), 3.73 and 3.91 (each 1 H, d, *J* 12, 7-H_2), 3.91 (3 H, s, MeO_2C), 4.63 and 5.15 (each 1 H, d, *J* 10, 9-H_2) and 10.1 (1 H, br s, 5-H) (addition of D_2O caused the signal at δ 10.1 to disappear); δ(300 MHz; $CDCl_3$) 2.40 (3 H, s, MeCO), 3.43 and 3.58 (each 1 H, d, *J* 12, 7-H_2), 3.78 (3 H, s, MeO), 4.58 and 5.03 (each 1 H, d, *J* 10, 9-H_2) and 7.70 (1 H, br s, 5-H) (addition of D_2O caused the signal at δ 7.70 to disappear); *m*/*z* (FAB) 258 (MH^+, 100%) (Found: C, 42.3; H, 4.5; N, 16.3; S, 12.3. $C_9H_{11}N_3O_4S$ requires C, 42.0; H, 4.30; N, 16.35; S, 12.45%).

Crystal Data for Compound **2a**.—$C_9H_{11}N_3O_4S$, *M*, 257.26. Orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.6145(7), b = 8.2671(8), c = 20.637(2) Å, V = 1129(1) $Å^3$, Z = 4, D_c = 1.51 g cm^{-3}, μ(Mo-Kα) 2.43 cm^{-1}, λ = 0.71069 Å. Crystal dimensions: 0.4 × 0.15 × 0.04 mm.

Data collection and processing. Intensity data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo-Kα radiation using ω–2θ scans to a maximum 2θ value of 48 deg, ω scan width = 0.75 + 0.35 tan θ and scan speed ranging from 0.4 to 5 deg min^{-1} according to the intensity gathered in a pre-scan; 3796 reflections were measured of which 1664 were unique (R_{int} = 0.02) and of those 1406 were considered observed [$F \geq 3\sigma(F)$]. Three intensity standards measured repeatedly during data collection showed no decline. Lorentz, polarisation and absorption (max., min. transmission 0.99, 0.96) corrections were applied.

Structure analysis and refinement. TREF routines in SHELX-85[14] were used to solve the structure; all non-hydrogen atoms were refined anisotropically and hydrogen atoms were subjected to isotropic refinements.[15] A multiplier (η) of the anomalous scattering component was also refined[16] and converged to a value of 1.3(3), thus confirming the absolute configuration assignment. Final agreement factors based on *F* with 199 parameters refining were R = 0.041 and R_w = 0.037 [w = 1.505 60/[$\sigma^2(F_o)$ + 0.000 18F_o^2]. Scattering factors were taken from 'International Tables for X-Ray Crystallography'.[17] All calculations were carried out on the University of Manchester Computing Centre Amdahl 5760 computer. The molecule and its atomic labelling, plotted using the PLUTO program,[18] are shown in Fig. 1. Full parameters of the analysis have been deposited at the Cambridge Crystallographic Data Centre.*

Preparation of Methyl (6S)-3-*Acetyl*-5-[(R)-α-*methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **2b**.—The acid chloride **3**[5] (0.580 g, 2.3 mmol) followed by dry pyridine (2.5 cm^3) were added to a stirred suspension of the bicyclononene **2a** (0.296 g, 1.15 mmol) in dry dichloromethane (5 cm^3). A solution resulted which, after 15 h, was diluted with dichloromethane and washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and brine. Evaporation of the dried ($MgSO_4$) organic phase left a syrup (0.315 g) which was predominantly the title compound **2b** by 300 MHz ^1H NMR spectroscopy (there was no evidence for the presence of a diastereoisomeric amide). Subjection of the material to silica gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* **2b** (0.227 g, 42%) as an amorphous solid; $[\alpha]_D$ −99 (1.2% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1760 (ester C=O), 1720 (amide and ketone C=O) and 1675 (amide C=O and C=N); λ_{max}(EtOH)/nm 206 (ε 14 400) and 258 (8000); δ(300 MHz; $CDCl_3$) 1.73 (3 H, s, MeCO), 3.62 (3 H, q, *J* 1.5, MeO), 3.66 and 4.48 (each 1 H, d, *J* 12.5, 7-H_2), 3.77 (3 H, s, MeO_2C), 4.41 and 4.99 (each 1 H, d, *J* 10, 9-H_2) and 7.28–7.32 and 7.39–7.42 (3 and 2 H, each m, Ph); *m*/*z* (FAB) 474 (MH^+, 50%) and 189 (100) (Found: C, 47.9; H, 3.9; F, 12.4; N, 8.7; S, 7.1. $C_{19}H_{18}F_3N_3O_6S$ requires C, 48.2; H, 3.85; F, 12.05; N, 8.90; S, 6.75%).

Preparation of Methyl (6S)-3-*Acetyl*-5-[(S)-α-*methoxy*-α-*trifluoromethyl*)*phenylacetyl*]-2-*oxo*-8-*thia*-1,4,5-*triaza-bicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **2c**.—The bicyclononene **2a** (0.243, g, 0.94 mmol) was treated with the acid chloride **4**[5] in the manner described in the previous experiment. Work-up and purification as before gave the *title compound* **2c**

* For full details of the C.C.D.C. deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

(0.236 g, 53%) as an amorphous solid; $[\alpha]_D$ −310 (0.76% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1755 (ester C=O), 1720 (amide and ketone C=O) and 1675 (amide C=O and C=N); δ(300 MHz; $CDCl_3$) 2.04 (3 H, s, MeCO), 3.66 and 4.54. (each 1 H, d, *J* 12, 9-H_2), 3.72 (3 H, q, *J* 1.5, MeO), 3.84 (3 H, s, MeO_2C), 4.38 and 5.11 (each 1 H, d, *J* 10, 2-H_2) and 7.41–7.45 (5 H, m, Ph); *m/z* (FAB) 474 (MH^+, 40%) and 189 (100) (Found: C, 48.1; H, 3.7; F, 12.0; N, 8.6; S, 7.2. $C_{19}H_{18}F_3N_3O_6S$ requires C, 48.2; H, 3.85; F, 12.05; N, 8.90; S, 6.75%).

Reaction of the Diazo Compound **1b** *with Triethylamine in Perdeuteriomethanol.*—Triethylamine (0.41 cm^3, 2.90 mmol) was added to a solution of the diazo compound **1b** (0.257, g, 1.0 mmol) in perdeuteriomethanol (1 cm^3) and the reaction was monitored by 300 MHz ^{1}H NMR spectroscopy. After 3.75 h at room temp., mainly a 1 : 1 mixture of compounds **1f** and **2a** was present. Thus, the 3-proton singlet at δ 2.26 had disappeared whereas the 1-proton double doublets at δ 3.45 and 3.60, the 3-proton singlet at δ 3.95, the 1-proton doublets at δ 4.86 and 4.97 and the 1-proton double doublet at δ 5.30 had reduced to about a half of their original intensity. About 60% transesterification had occurred in the product **2a** on the basis of the height of the methyl ester signal at δ 3.93 and the appearance of a methanol signal at δ 3.50. After 5 h at room temp. and 14 h at −20 °C, *ca.* 25% of compound **1f** was still present; there was no evidence that any exchange of the 4-hydrogen atom had occurred.

Preparation of Methyl (4R)-3-(*Methoxycarbonylacetyl*)-*thiazolidine-4-carboxylate* **1h**.—Methyl malonyl chloride (7.00 g, 5.13 mmol), dry triethylamine (7.15 cm^3, 5.25 mmol) and a few crystals of DMAP were added to a stirred solution of the thiazolidine **1c** (5.70 g, 3.87 mmol) in dry dichloromethane (30 cm^3). After 15 min, the mixture was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and brine. Evaporation of the dried ($MgSO_4$) organic phase and subjection of the residue to silica gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* **1h** (8.70 g, 91%) as a colourless syrup which existed in deuteriochloroform as a 2 : 1 mixture of rotamers; $[\alpha]_D$ −120 (1.1% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 1745 (ester C=O) and 1660 (amide C=O); λ_{max}(EtOH)/nm 203 (ε 7300) and 245 (900); δ(300 MHz; $CDCl_3$) 3.23 and 3.31 [each 0.66 H, dd (*J* 12 and 4) and dd (*J* 12 and 7), 5-H_2 of major rotamer], 3.35–3.58 (2.66 H, m, $COCH_2CO_2Me$ and 5-H_2 of minor rotamer), 3.74, 3.75 and 3.80 (1, 4 and 1 H, each s, 2 × MeO_2C), 4.52 and 4.79 (each 0.33 H, d, *J* 9, 2-H_2 of minor rotamer), 4.60 and 4.64 (each 0.66 H, d, *J* 8, 2-H_2 of major rotamer) and 4.92 and 5.13 [0.33 and 0.66 H, dd (*J* 7 and 2) and dd (*J* 7 and 4), 4-H]; *m/z* (EI) 247 (M^+, 12%), 161 (43) and 88 (100) (Found: C, 43.7; H, 5.2; N, 5.5; S, 12.6. $C_9H_{13}NO_5S$ requires C, 43.7; H, 5.30; N, 5.65; S, 12.95%).

Preparation of Methyl (4R)-3-[*Diazo*(*methoxycarbonyl*)]-*acetyl*]*thiazolidine-4-carboxylate* **1g**.—*p*-CBSA (10.1 g, 4.45 mmol) was added in portions over 15 min to a stirred solution of the methoxycarbonylacetyl derivative **1h** (8.70 g, 3.52 mmol) and dry triethylamine (15.3 cm^3, 112 mmol) in dry acetonitrile (100 cm^3). After 12 h, the mixture was concentrated and dichloromethane was added to the residue which was filtered. The filtrate was washed with dilute hydrochloric acid followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated to leave a syrup (6.40 g, *ca.* 67%) which was predominantly the *title compound* **1g**. A sample, after purification by silica gel column chromatography [hexanes–EtOAc (2:1) as eluent], was obtained as a yellow syrup; $[\alpha]_D$ −201 (1% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2140 ($C{=}N^+{=}N^-$), 1750 (ester C=O), 1720 (diazo ester C=O) and 1630 (diazo amide C=O); λ_{max}(EtOH)/nm 204 (ε 11 000) and 254 (8000); δ(300 MHz; $CDCl_3$) 3.24 and 3.30 [each 1 H, dd (*J* 12 and 5) and dd (*J* 12 and 7), 5-H_2], 3.79 and 3.81 (each 3 H, s, 2 × MeO_2C), 4.67 and 4.74 (each 1 H, d and br d, separation 10, 2-H_2) and 5.19 (1 H, dd, *J* 7 and 5, 4-H); *m/z* (EI) 146 (100%) (Found: C, 39.5; H, 4.2; N, 15.3. $C_9H_{11}N_3O_5S$ requires C, 39.55; H, 4.05; N, 15.40%).

Preparation of Dimethyl (6R)-2-*Oxo*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-5-*ene*-3,6-*dicarboxylate* **5a**.—A mixture of the crude diazo compound **1g** (6.00 g, *ca.* 22 mmol), triethylamine (6.3 cm^3, 46 mmol) and dry methanol (125 cm^3) was heated under reflux for 2 h. Evaporation and crystallisation of the residue from methanol gave the *title compound* **5a** (1.70 g, *ca.* 28%); m.p. 171–173 °C; $[\alpha]_D$ −282 (0.8% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3220 (NH), 1745 and 1715 (ester C=O) and 1640 (amide C=O); λ_{max}(EtOH)/nm 204 (ε 9100), 254 (3100) and 313 (3000); δ(300 MHz; $CDCl_3$) 3.47 and 3.63 (each 1 H, d, *J* 11.5, 7-H_2), 3.83 and 3.89 (each 3 H, s, 2 × MeO_2C), 4.64 and 5.03 (each 1 H, d, *J* 9.5, 9-H_2) and 7.95 (1 H, br s, 5-H); *m/z* (FAB) 272 [$(M - H)^+$, 100%] (Found: C, 39.7; H, 4.1; N, 15.4; S, 11.8. $C_9H_{11}N_3O_5S$ requires C, 39.55; H, 4.05; N, 15.40; S, 11.75%).

Preparation of Dimethyl (6S)-5-[(R)-α-*Methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*-[4.3.0]*non*-3-*ene*-3,6-*dicarboxylate* **5b**.—The bicyclononene **5a** (0.239 g, 0.87 mmol) was treated with the (*S*)-acid chloride **3**[5] in the manner described for compound **2a**. Work-up and purification as before gave the *title compound* **5b** (0.240 g, 56%). After crystallisation from dichloromethane–light petroleum, the sample showed m.p. 118 °C; $[\alpha]_D$ −78 (0.3% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1750 (ester C=O), 1730 (ester and amide C=O) and 1690 (amide C=O and C=N); λ_{max}(EtOH)/nm 203 (ε 15 500) and 257 (9000); δ (300 MHz; $CDCl_3$) 3.67 (3 H, q, *J* 1.5, MeO), 3.68 and 4.54 (each 1 H, d, *J* 12.5, 7-H_2), 3.69 and 3.81 (each 3 H, s, 2 × MeO_2C), 4.46 and 5.01 (each 1 H, d, *J* 10, 9-H_2) and 7.32–7.36 and 7.43–7.45 (3 and 2 H, each m, Ph); *m/z* (FAB) 490 (MH^+, 40%) and 189 (100) (Found: C, 46.3; H, 3.4; N, 8.6; S, 7.0. $C_{19}H_{18}F_3N_3O_7S$ requires C, 46.65; H, 3.70; N, 8.60; S, 6.55%).

Preparation of Dimethyl (6S)-5-[(S)-α-*Methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*-[4.3.0]*non*-3-*ene*-3,6-*dicarboxylate* **5c**.—The bicyclononene **5a** (0.131 g, 0.48 mmol) was treated with the (*R*)-acid chloride **4**[5] in the manner described for compound **2a**. Work-up and purification as before gave the *title compound* **5c** (0.180 g, 77%) as an amorphous solid; $[\alpha]_D$ −196 (0.45% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1755 (ester C=O), 1725 (ester and amide C=O) and 1685 (amide C=O and C=N); λ_{max}(EtOH)/nm 205 (ε 12 000) and 248 (7900); δ(300 MHz; $CDCl_3$) 3.54 and 4.53 (each 1 H, d, *J* 12, 7-H_2), 3.68 (3 H, q, *J* 1, MeO), 3.79 and 3.84 (each 3 H, s, 2 × MeO_2C), 4.36 and 5.06 (each 1 H, d, *J* 10, 9-H_2) and 7.33–7.37 and 7.42–7.44 (3 and 2 H, each m, Ph); *m/z* (FAB) 490 (MH^+, 50%) and 189 (100) (Found: C, 46.9; H, 4.0; N, 8.5; S, 6.2. $C_{19}H_{18}F_3N_3O_7S$ requires C, 46.65; H, 3.70; N, 8.60; S, 6.55%).

Preparation of Methyl (4S)-5,5-*Dimethyl*-3-(3-*oxobutanoyl*)*thiazolidine*-4-*carboxylate* **19c**.—A mixture of D-penicillamine (2.40 g, 16 mmol), water (15 cm^3) and 37% aqueous formaldehyde (15 cm^3) was stirred for 2 days. Evaporation left a white solid which was dried (*in vacuo*; P_2O_5). Hydrogen chloride was bubbled for *ca.* 10 min into a suspension of the solid in methanol (100 cm^3) and the mixture was heated under reflux for 3.5 days. Evaporation left an oil which was partitioned between dichloromethane and aqueous sodium hydrogen carbonate. The organic phase was dried ($MgSO_4$)and

concentrated and the oily residue was dissolved in light petroleum. After having been left in a freezer overnight, the solution deposited crystals of methyl (4*S*)-5,5-dimethylthiazolidine-4-carboxylate **19b**[9a] (0.940 g, 33%); m.p. 36 °C; $[\alpha]_D$ + 74 (0.8% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3340 (NH) and 1740 (ester C=O); λ_{max}(EtOH)/nm 205 (ε 1100); δ(300 MHz; $CDCl_3$) 1.21 and 1.66 (each 3 H, s, 5-Me_2), 3.0 (1 H, br s, 3-H), 3.51 (1 H, s, 4-H), 3.78 (3 H, s, MeO) and 4.22 and 4.34 (each 1 H, d, *J* 10, 2-H_2) (Found: C, 48.0; H, 7.8; N, 8.1; S, 18.7. $C_7H_{13}NO_2S$ requires C, 48.0; H, 7.50; N, 8.00; S, 18.30%).

A mixture of the thiazolidine **19b** (0.750 g, 4.28 mmol), diketene (0.37 cm^3, 4.76 mmol) and triethylamine (5 drops) in dry dichloromethane (25 cm^3) was heated under reflux for 15 h. The cooled solution was washed with dilute hydrochloric acid and brine, dried ($MgSO_4$) and concentrated to leave a colourless oil (1.10 g, 100%) in a slightly impure state which existed in deuteriochloroform as a 7:3 mixture of the title compound **19c** (as a 4:1 mixture of rotamers) and methyl (4*S*)-5,5-dimethyl-3-[(*Z*)-3-hydroxybut-2-enoyl]thiazolidine-4-carboxylate **19d** (as a 5:1 mixture of rotamers); $[\alpha]_D$ + 124 (0.5% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 1750 (ester C=O), 1720 (ketone C=O) and 1650 (amide C=O); λ_{max}(EtOH)/nm 203 (ε 6600) and 256 (4300); δ(300 MHz; $CDCl_3$) *inter alia* 1.40, 1.41, 1.56 and 1.58 (*ca.* 1.68, 1.32, 1.32 and 1.68 H, each s, 4-Me_2), 1.92 and 1.96 [*ca.* 0.15 and 0.75 H, each s, 0.3 × *Me*C(OH)], 2.27 and 2.29 (*ca.* 0.42 and 1.68 H, each s, 0.7 × MeCO), 3.39 and 3.56 [*ca.* 0.28 and 1.12 H, AB q (*J* 15, separation of inner lines 12) and s, 0.7 × MeCOC*H*$_2$], 3.56, 3.75 and 3.76 (*ca.* 0.57, 1.68 and 0.75 H, each s, MeO_2C), 4.21, 4.31, 4.54 and 4.55 (0.05, 0.14, 0.56 and 0.25 H, each s, 4-H), 4.61–4.87 (2 H, m, 2-H_2), 5.07 [0.3 H, s, 0.3 × MeC(OH):C*H*] and 13.92 and 14.23 [0.25 and 0.05 H, each s, 0.3 × MeC(O*H*)]; *m*/*z* (FAB; *m*-NBA) 260 (MH^+, 100%).

Preparation of Methyl (4S)-3-(2-*Diazo*-3-*oxobutanoyl*)-5,5-*dimethylthiazolidine*-4-*carboxylate* **19a**.—*p*-CBSA (2.90 g, 12.8 mmol) followed by triethylamine (3.74 cm^3, 26.8 mmol) were added to a stirred solution of the oxobutanoyl derivative **19c** (2.55 g, 9.85 mmol) in dry acetonitrile (50 cm^3). After 1 h, the mixture was filtered and the filtrate was concentrated. Subjection of the residue to silica gel column chromatography [hexanes–EtOAc (1:1) as eluent] gave the *title compound* **19a** (2.66 g, 94%) as a chromatographically homogeneous yellow oil; $[\alpha]_D$ + 179 (0.5% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2120 (C=N^+=N^-), 1750 (ester C=O) and 1650br (diazo amide and diazo ketone C=O); λ_{max}(EtOH)/nm 204 (ε 10 500), 226 (13 400) and 307 (3700); δ(300 MHz; $CDCl_3$) 1.38 and 1.58 (each 3 H, s, 5-Me_2), 2.32 (3 H, s, MeCO), 3.72 (3 H, s, MeO_2C), 4.50 (1 H, s, 4-H) and 4.57 and 4.73 (each 1 H, br d and d, *J* 9, 2-H_2); *m*/*z* (FAB) 286 (MH^+, 60%) and 55 (100).

Preparation of Methyl (4R)-2,2-*Dimethyl*-3-(3-*oxobutanoyl*)*thiazolidine*-4-*carboxylate* **20c**.—An ice-cooled suspension of L-cysteine (10.0 g, 82.5 mmol) in methanol (350 cm^3) was saturated with hydrogen chloride; the mixture was then heated under reflux for 1.5 h. Evaporation of the cooled solution left a residue which was heated with acetone (150 cm^3) overnight. The product obtained after evaporation was partitioned between dichloromethane and aqueous sodium hydrogen carbonate. After having been washed with water (× 3), the organic phase was dried ($MgSO_4$) and concentrated to leave methyl (4*R*)-2,2-dimethylthiazolidine-4-carboxylate **20b** (6.00 g, 41%) as a pale-yellow oil; δ(300 MHz; $CDCl_3$) 1.47 and 1.65 (each 3 H, s, 2-Me_2), 2.4 (1 H, br s, 3-H), 2.97 and 3.37 [each 1 H, dd (*J* 10.5 and 9) and dd (*J* 10.5 and 7), 5-H_2], 3.73 (3 H, s, MeO) and 4.03 (1 H, dd, *J* 9 and 7, 4-H).

A mixture of the thiazolidine **20b** (6.00 g, 34 mmol), diketene (2.86 cm^3, 37.1 mmol) and dry triethylamine (0.25 cm^3) in dry dichloromethane (150 cm^3) was heated under reflux overnight. The cooled solution was washed with dilute hydrochloric acid and brine, dried ($MgSO_4$) and concentrated to leave the title compound **20c** (8.40 g, *ca.* 95%) as a yellow oil. A sample, purified by silica gel column chromatography (light petroleum–EtOAc; gradient elution), existed in deuteriochloroform as a 4:1 mixture of the *title compound* **20c** and *methyl* (4R)-3-[(Z)-3-*hydroxybut*-2-*enoyl*]-2,2-*dimethylthiazolidine*-4-*carboxylate* **20d**; $[\alpha]_D$ −69 (0.38% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 1750 (ester C=O), 1730 (ketone C=O) and 1650 (amide C=O); ν_{max}(EtOH)/nm 203 (ε 6600) and 255 (3300); δ(300 MHz; $CDCl_3$) 1.78, 1.82, 1.85 and 1.87 (2.4, 2.4, 0.6 and 0.6 H, each s, 2-Me_2), 2.22 [3 H, s, MeCO and *Me*C(OH)], 3.24 (2 H, d, separation 3.5, 5-H_2), 3.36 (1.6 H, AB q, *J* 15, separation of inner lines 21, 0.8 × COC*H*$_2$COMe), 3.74 (3 H, s, MeO), 4.64 [0.2 H, br s, 0.2 × MeC(OH):C*H*], 4.72–4.76 and 4.79 [0.2 and 0.8 H, br m and t (separation 3.5), 4-H] and 14.15 [0.2 H, br s, MeC(O*H*):CH]; *m*/*z* (FAB) 260 (MH^+, 100%) (Found: C, 51.2; H, 6.5; N, 5.5; S, 12.0. $C_{11}H_{17}NO_4S$ requires C, 50.95; H, 6.60; N, 5.40; S, 12.35%).

Preparation of Methyl (4R)-3-(2-*Diazo*-3-*oxobutanoyl*)-2,2-*dimethylthiazolidine*-4-*carboxylate* **20a**.—*p*-CBSA (4.62 g, 20.3 mmol) was added in portions over 15 min to a stirred solution of the acetonyl derivative **20c** (4.20 g, *ca.* 16.2 mmol) and dry triethylamine (6.72 cm^3, 48.2 mmol) in dry acetonitrile (125 cm^3). A precipitate was deposited which, after 1 h, was removed by filtration. The filtrate was diluted with three times its volume of water and extracted with dichloromethane (× 3). After having been washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and brine, the organic layer was dried ($MgSO_4$) and evaporated to leave an orange oil (2.9 g). Subjection of the material to silica gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* **20a** (1.60 g, 35%) as a bright-yellow oil; $[\alpha]_D$ −324 (0.28% in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2120 C=N^+=N^-), 1750 (ester C=O) and 1650br (diazo amide and diazo ketone C=O); λ_{max}(EtOH)/nm 236 (ε 12 200); δ(300 MHz; $CDCl_3$) 1.77 and 1.84 (each 3 H, s, 2-Me_2), 2.21 (3 H, s, MeCO), 3.24 and 3.30 [each 1 H, dd (*J* 12 and 3.5) and dd (*J* 12 and 6), 5-H_2], 3.72 (3 H, s, MeO) and 4.92 (1 H, dd, *J* 6 and 3.5, 4-H); *m*/*z* (FAB) 286 (MH^+, 12%), 147 (50) and 73 (100) (Found: C, 46.2; H, 5.4; N, 14.4; S, 10.8. $C_{11}H_{15}N_3O_4S$ requires C, 46.3; H, 5.30; N, 14.75; S, 11.25%).

Preparation of Methyl (6S)-3-*Acetyl*-9,9-*dimethyl*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **21a**.—A solution of the crude diazo derivative **20a** (1.10 g, *ca.* 13.9 mmol) and dry triethylamine (1.48 cm^3, 10.9 mmol) in dry methanol (25 cm^3) was heated under reflux for 4 h. Evaporation and subjection of the residue to silica gel column chromatography (light petroleum–EtOAc; gradient elution) gave the *title compound* **21a** (0.340 g, *ca.* 31%) as an off-white solid. After recrystallisation from dichloromethane–diethyl ether, the sample showed m.p. 143–145 °C; $[\alpha]_D$ −191 (0.7% in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3200 (NH), 1750 (ester C=O), 1690 (amide and ketone C=O) and 1640 (C=N); λ_{max} (EtOH)/nm 201 (ε 6300), 224 (7000), 257 (4000) and 312 (4800); δ(300 MHz; $CDCl_3$) 1.91 and 2.01 (each 3 H, s, 9-Me_2), 2.42 (3 H, s, MeCO), 3.43 and 3.56 (each 1 H, d, *J* 11, 7-H_2), 3.82 (3 H, s, MeO_2C) and 7.45 (1 H, br s, NH); *m*/*z* (FAB) 286 (MH^+, 100) (Found: C, 46.6; H, 5.5; N, 14.7; S, 11.5. $C_{11}H_{15}N_3O_4S$ requires C, 46.3; H, 5.30; N, 14.75; S, 11.25%).

Preparation of Methyl (6S)-3-*Acetyl*-5-[(S)-α-*methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]-9,9-*dimethyl*-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **21b**.—The bicyclononene **21a** (0.038 g, 0.13 mmol) was treated with the (*R*)-

acid chloride **4**[5] in the manner described for compound **2a**. Work-up and purification as before gave the *title compound* **21b** (0.041 g, 61%) as a solid; $[\alpha]_D$ −344 (0.9% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1755 (ester C=O), 1720 (amide and ketone C=O) and 1670 (amide C=O and C=N); λ_{max}(EtOH)/nm 202 (ε 16 100) and 259 (7500); δ(300 MHz; $CDCl_3$) 1.80 and 1.94 (each 3 H, s, 9-Me_2), 1.99 (3 H, s, MeCO), 3.64 (3 H, q, *J* 1, MeO), 3.81 (3 H, s, MeO_2C), 3.86 and 4.52 (each 1 H, d, *J* 13, 7-H_2) and 7.35–7.37 and 7.42–7.44 (3 and 2 H, each m, Ph); *m/z* (FAB) 502 (MH^+, 80%) and 189 ($C_9H_8F_3O^+$, 100) (Found: C, 50.2; H, 4.6; F, 11.5; N, 8.6; S, 6.6. $C_{21}H_{22}F_3N_3O_6S$ requires C, 50.3; H, 4.40; F, 11.35; N, 8.40; S, 6.40%).

Preparation of Methyl (2R,4R)-3-(2-*Diazo*-2-*oxobutanoyl*)-2-*methylthiazolidine*-4-*carboxylate* **22a**.—Acetaldehyde (10.6 cm^3, 0.12 mol) was added to a solution of L-cysteine hydrochloride (38.8 g, 0.246 mol) in water (100 cm^3). After 14 h, the solution was concentrated and the residue dried [by addition of toluene and re-evaporation (× 3)]. The product was dissolved in methanol (200 cm^3) which had been saturated with hydrogen chloride and the solution was heated under reflux for 6 h. Evaporation of the solvent left a residue which was partitioned between dichloromethane and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic phase left a 3:2 mixture of methyl (2*R*,4*R*)-2-methylthiazolidine-4-carboxylate **22b** and its (2*S*,4*R*)-diastereoisomer **23b** (21.4 g, 55%) as a clear oil; δ(300 MHz; $CDCl_3$) 1.44 and 1.54 (1.2 and 1.8 H, each d, *J* 6, 2-Me), 2.2 (1 H, br s, 3-H), 2.87, 3.05 and 3.23–3.31 [0.6, 0.4 and 1 H, dd (*J* 10 and 9), dd (*J* 10 and 6) and m, 5-H_2], 3.71 and 3.73 (1.2 and 1.8 H, each s, MeO), 3.78 and 4.04 [0.6 and 0.4 H, dd (*J* 9 and 7) and dd (*J* 7 and 5), 4-H] and 4.51 and 4.71 (0.6 and 0.4 H, each q, *J* 6, 2-H).

Diketene (4.62 cm^3, 59.9 mmol) and triethylamine (5.5 cm^3, 39.5 mmol) were added to a solution of the thiazolidines **22b** and **23b** (6.44 g, 40 mmol) in dry dichloromethane (100 cm^3). After having been heated under reflux for 14 h, the mixture was washed with dilute hydrochloric acid followed by brine. Evaporation of the dried ($MgSO_4$) organic phase gave an orange oil (9.6 g, *ca.* 98%) which was considered to be mainly a 3:1 mixture of methyl (2*R*,4*R*)-2-methyl-3-(3-oxobutanoyl)-thiazolidine-4-carboxylate **22c** (as a 4:3 mixture of rotamers) and methyl (2*R*,4*R*)-3-[(*Z*)-3-hydroxybut-2-enoyl]-2-methylthiazolidine-4-carboxylate **22d** (as a 4:1 mixture of rotamers); δ(300 MHz; $CDCl_3$) *inter alia* 1.55, 1.62 and 1.64 (*ca.* 0.9, 1.35 and 1.75 H, each d, *J* 6, 2-Me), 1.96 [*ca.* 0.75 H, s, 0.25 × *Me*C(OH)], 2.27 and 2.30 (*ca.* 0.9 and 1.35 H, each s, 0.75 × MeCO), 3.24–3.44 (2 H, m, 5-H_2), 3.49 and 3.55 [0.6 and 0.9 H, d (separation 6) and s, 0.75 × MeCOC*H*$_2$], 3.76, 3.77 and 3.79 (*ca.* 1.35, 0.75 and 0.9 H, each s, MeO_2C), 4.70 and 4.81 [*ca.* 0.05 and 0.2 H, br s and dd (*J* 6.5 and 3), 0.25 × 4-H], 4.93–5.17 [*ca.* 1.75 H, m, 0.75 × 4-H, 0.25 × MeC(OH):C*H* and 0.75 × 2-H], 5.41 and 5.54 [*ca.* 0.20 and 0.05 H, q (*J* 6) and br s, 0.25 × 2-H] and 13.95 and 14.23 [*ca.* 0.20 and 0.05 H, each br s, MeC(O*H*)].

p-CBSA (2.45 g, 11 mmol) was added in portions over 15 min to a stirred solution of the crude oxobutanoyl derivative **22c** (2.45 g, 10 mmol) and dry triethylamine (3.86 cm^3, 27.7 mmol) in dry acetonitrile (20 cm^3). After 12 h, the mixture was concentrated and dichloromethane was added to the residue which was filtered. The filtrate was washed with dilute hydrochloric acid followed by aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated. The residue was dissolved in hot methanol and the solution was treated with charcoal and filtered. Evaporation and recrystallisation of the residue from dichloromethane–hexanes gave the *title compound* **22a** (0.900 g, *ca.* 34%) as a yellow solid; m.p. 94–95 °C; $[\alpha]_D$ −2.5 (1.1% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2130 (C=N$^+$=N$^-$), 1755 (ester C=O), 1645 (diazo ketone C=O) and 1620 (diazo amide C=O); λ_{max} (EtOH)/nm 229 (ε 13 000); δ(300 MHz; $CDCl_3$) 1.64 (3 H, d, *J* 6, 2-Me), 2.36 (3 H, s, MeCO), 3.31 and 3.38 [each 1 H, dd (*J* 12 and 6.5) and dd (*J* 12 and 4), 5-H_2], 3.81 (3 H, s, MeO_2C), 4.97 (1 H, dd, *J* 6.5 and 4, 4-H) and 5.43 (1 H, q, *J* 6, 2-H); *m/z* (FAB) 272 (MH^+, 100%) (Found: C, 44.5; H, 5.0; N, 15.6; S, 11.9. $C_{10}H_{13}N_3O_4S$ requires C, 44.25; H, 4.85; N, 15.50; S, 11.80%).

Crystal Data for Compound **22a**.—$C_{10}H_{13}N_3O_4S$, *M*, 271.29. Orthorhombic, space group $P2_12_12_1$ (No. 19), a = 14.822(8), b = 15.602(9), c = 5.543(5) Å, V = 1282(2) Å^3, Z = 4, D_c = 1.406 g cm^{-3}, μ(Mo–Kα) = 2.51 cm^{-1}, λ = 0.710 69 Å. Crystal dimensions: 0.2 × 0.1 × 0.06 mm.

Data collection and processing. Intensity data were collected on a Rigaku AFC6S diffractometer with graphite-monochromated Mo–Kα radiation using ω–2θ scans to a maximum of 2θ value of 48 deg, ω scan width = 1.15 + 0.30 tan θ and scan speed of 2 deg min^{-1} with a maximum of 3 re-scans for weak reflections [$I < 10\sigma(I)$]; 926 unique reflections were collected of which 735 were considered observed [$I > 2\sigma(I)$]. Three intensity standards measured repeatedly during data collection showed no decline. Lorentz and polarisation corrections were applied but absorption effects were ignored.

Structure analysis and refinement. TREF routines in SHELX-86[14] were used to solve the structure. Sulfur and some of the non-hydrogen atoms were subjected to anisotropic refinement; the remaining atoms were refined isotropically except for the methyl hydrogen atoms which were constrained to chemically reasonable positions. Final agreement factors based on F with 114 parameters refining were R = 0.060 and R_w = 0.068 [w = $1/\sigma^2$ (F_o)]. Scattering factors were taken from 'International Tables for X-Ray Crystallography'.[17] All calculations were performed on a Digital Vax station 3520 using the TEXSAN crystallographic software package. The molecule with its atomic labelling, plotted using the PLUTO program,[18] is shown in Fig. 2. Full parameters of the analysis have been deposited at the Cambridge Crystallographic Data Centre.*

Preparation of Methyl (6S,9R)-9-*Methyl*-2-*oxo*-8-*thia*-1,4,5-*triazabicyclo*[4.3.0]*non*-3-*ene*-6-*carboxylate* **24**.—A mixture of the diazo compound **22a** (0.450 g, 1.66 mmol), triethylamine (0.47 cm^3, 3.4 mmol) and methanol (10 cm^3) was heated under reflux for 2 h. Evaporation left a residue which was partitioned between ethyl acetate and dilute hydrochloric acid. After having been washed with brine, the organic phase was dried ($MgSO_4$) and concentrated to leave the *title compound* **24** (0.312 g, 69%) as a pale-brown solid. After recrystallisation from methanol–diethyl ether, a sample showed m.p. 153–154 °C; $[\alpha]_D$ −221 (0.68% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3200 (NH), 1745 and 1740 (ester C=O), 1680 (amide and ketone C=O) and 1640 (C=N); λ_{max}(EtOH)/nm 201 (ε 8200), 225 (8200) and 311 (5600); δ(300 MHz; $CDCl_3$) 1.73 (3 H, d, *J* 6.5, 9-Me), 2.43 (3 H, s, MeCO), 3.46 and 3.75 (each 1 H, d and br d, *J* 12, 7-H_2), 5.61 (1 H, q, *J* 6.5, 9-H) and 8.02 (1 H, br s, 5-H) (addition of D_2O caused the signal at δ 8.02 to disappear and that at δ 3.75 to sharpen); *m/z* (FAB) 272 (MH^+, 100%) (Found: C, 44.0; H, 4.5; N, 15.2; S, 11.4. $C_{10}H_{13}N_3O_4S$ requires C, 44.25; H, 4.85; N, 15.50; S, 11.80%).

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* For full details of the C.C.D.C. deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

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