‘Hidden’ axial chirality as a stereodirecting element in reactions involving enol(ate) intermediates. Part 2.† Cyclisation reactions of methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-1,1-dioxo-1λ^6,3- (and 1-oxo-1λ^4,3-) thiazolidine-4-carboxylates

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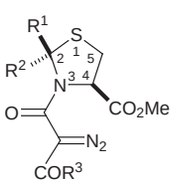
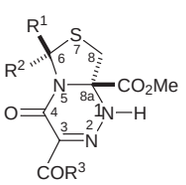
Methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-1,1-dioxo-1λ^6,3-thiazolidine-4-carboxylate **14** undergoes a base-induced cyclisation to give methyl (8a*S*)-3-acetyl-4,7,7-trioxo-1,4,6,7,8,8a-hexahydro-7λ^6-[1,3]thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylate **15** in a state of high enantiomeric purity. Similar stereoselective cyclisations, proceeding with retention of configuration, are observed with methyl (1*R*,4*R*)- and (1*S*,4*R*)-3-(2-diazo-3-oxobutanoyl)-1-oxo-1λ^4,3-thiazolidine-4-carboxylates **25** and **27** to give compounds **33** and **34**. It is suggested that the cyclisation reactions proceed by way of planar ester enol(ate) intermediates which possess axial chirality, *e.g.* **35**.

The bicyclic sulfone **15** and the bicyclic sulfoxides **33** and **34** are also produced by oxidation of methyl (8a*S*)-3-acetyl-4-oxo-1,4,8,8a-tetrahydro[1,3]thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylate **5** with *m*-chloroperoxybenzoic acid (in DMF in the case of the sulfone **15** and in $CHCl_3$ in the case of the sulfoxides **33** and **34**). The use of the oxidant in methanol or of hydrogen peroxide in formic acid leads to an oxidative deacetylation to give methyl (8a*S*)-3,4,7,7-tetraoxoperhydro-7λ^6-[1,3]thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylate **17**, the structure of which is established by an X-ray crystallographic analysis. The analysis reveals an interesting packing arrangement of the molecules in the crystal, attributable to an intermolecular H-bonding network. In particular, intermolecular H-bonding between the ester carbonyl oxygen atom and the amino hydrogen atom at position 1 provides a possible explanation for the shift of the ester carbonyl absorption to 1680 cm^{-1} in the solid-state IR spectrum of compound **17**.

Introduction

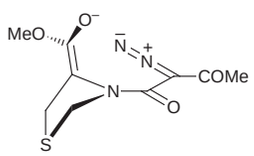
Recently, we showed[1] that the diazo ester **1** underwent a base-induced cyclisation to give the bicyclic compound **5**‡ in a state of high enantiomeric purity. Similar stereoselective cyclisations, proceeding with retention of configuration, were observed with compounds **2**–**4** to give the corresponding products **6**–**8**.





1	R^1 = H, R^2 = H, R^3 = Me	**5**
2	R^1 = H, R^2 = H, R^3 = OMe	**6**
3	R^1 = Me, R^2 = Me, R^3 = Me	**7**
4	R^1 = Me, R^2 = H, R^3 = Me	**8**

We postulated that the reactions proceeded by way of planar ester enolate (or enol) intermediates which possessed axial chirality. For example, the species **9** was considered to be involved in the **1**→**5** cyclisation. The marked kinetic preference for the diazo ester **1** to undergo deprotonation to give the enolate **9** rather than its enantiomer **10** was attributed to the greater ease in attaining the geometry **11** compared with the geometry **12** (in which a severe $A^{1,3}$ interaction exists between the *N*-acyl substituent and the CO_2Me group) required for the deprotonation reactions.



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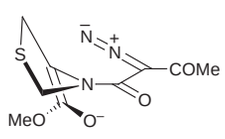

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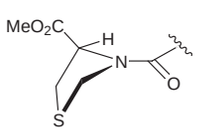

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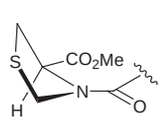

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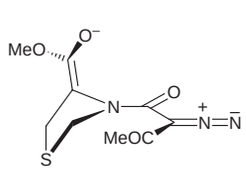

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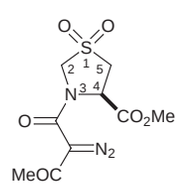


14

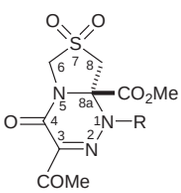
When the **1**→**5** cyclisation was performed with triethylamine in perdeuteriomethanol, there was no evidence for deuterium incorporation at position 4 of the starting material (although complete exchange of the acetyl methyl protons did occur). Evidently, the enolate **9** underwent cyclisation faster than reprotonation. Moreover, it seemed unlikely that an enolate akin to **13** (which also possesses axial chirality) was generated, implying that the 4-proton of the diazo ester **1** was more acidic when the (*Z*)-rotameric geometry of the amide was adopted.

† For Part 1, see ref. 1.
‡ Earlier, compound **5** and related bicycles were named using an extension of the von Baeyer system. However as they are examples of ‘*ortho*-fused’ heterocycles, they may also be designated using the fusion principle. The fusion nomenclature is used in this paper.

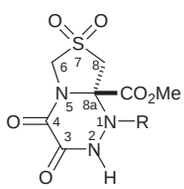
Compared with their thiazolidine relatives, 3-acyl-1,1-dioxo-1λ⁶,3-thiazolidine-4-carboxylates are expected to possess more acidic 4-protons and to undergo β-elimination reactions more readily.[2] Accordingly, it was of interest to examine the behaviour of the diazo ester sulfone **14** under basic conditions. The findings of this study are the subject of this paper.

Results and discussion

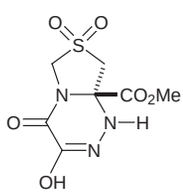
The thiazolidine dioxide **14**, prepared in 56% yield by oxidation of the thiazolidine **1** with *m*-chloroperoxybenzoic acid in ethyl acetate, underwent reaction with triethylamine in methanol under reflux to give the bicyclic sulfone **15** in 86% yield. Since the specific rotation of the product **15** {$[\alpha]_D$ −245 (MeOH)} was quite similar to that of the bicyclic sulfide **5** {$[\alpha]_D$ −289 (MeOH)},[1] it was inferred that the cyclisation reaction had again occurred with retention of configuration.



15 R = H
16 R = COMe



17 R = H
18 R = COMe



19

To corroborate this inference, efforts were made to derive the bicyclic sulfone **15** by oxidation of the bicyclic sulfide **5**. The use of *m*-chloroperoxybenzoic acid in DMF provided the required sulfone **15** {$[\alpha]_D$ −265 (MeOH)} in 28% yield after two crystallisations. Clearly, little loss of stereochemical integrity had occurred during the breakage of the C(4)–H bond of the reactant **14** and the formation of the N(1)–C(8a) bond of the product **15**.

When methanol was used in place of DMF in the aforecited reaction, the sulfone **15** was only the minor component of a 69:31 mixture. The major product, designated compound **A**, was isolated in a pure state by fractional crystallisation albeit in only 16% yield. Compound **A** could be obtained more efficiently by treatment of the bicyclic sulfide **5** or the bicyclic sulfone **15** with hydrogen peroxide and formic acid; the yield was 44% in the former instance and 62% in the latter.

Elemental analysis and mass spectrometry established that compound **A** possessed the molecular formula, $C_7H_9N_3O_6S$. The structure **17** was strongly supported by NMR spectroscopy; in particular, the ^{13}C NMR spectrum (CD_3SOCD_3) showed the presence of two amide-type carbonyl groups at δ 159.0 and 161.2 and the ^1H NMR spectrum featured two exchangeable protons at δ 6.94 and 10.25. Surprisingly, the IR spectrum (recorded in the solid state) lacked a typical saturated ester carbonyl absorption (expected at ~1750 cm^{-1}); it featured two carbonyl-region absorptions at 1680 (attributed to the ester carbonyl group) and at 1630 cm^{-1} (ascribed to the cyclic amide carbonyl groups). Moreover, the UV spectrum featured an absorption maximum at 226 nm (ε 6100), consistent with the presence of conjugation and possibly indicative of the structure **19**.

Compound **A** was shown to possess the structure **17** on the basis of a single crystal X-ray crystallographic analysis. The molecular structure of the two chemically identical molecules present in the asymmetric unit is shown in Fig. 1, together with their crystallographic labelling. As Fig. 2 reveals, the molecules pack in an interesting manner which is attributed to an intermolecular H-bonding network (Table 1). The amidic hydrogen atoms and carbonyl oxygen atoms are involved in H-bonding to one another [N(2)–H to O(13) and N(12)–H to O(4)], linking the molecules into infinite spiral columns (4 molecules per turn), generated by the crystallographic screw axis. The

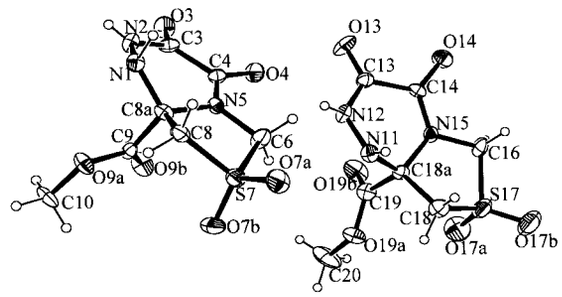


Fig. 1 Molecular structure of compound **17** (showing the asymmetric unit).

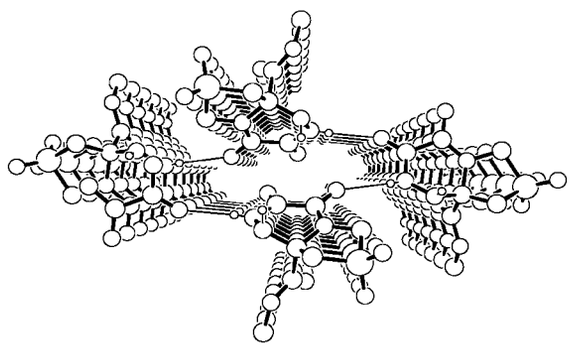


Fig. 2 Crystal packing of compound **17**.

Table 1 Intermolecular H-bonding in compound **17**

D–H	*d*(D–H)	*d*(H···A)	∠DHA	*d*(D···A)	A
N(1)–H	0.97(7)	2.49(7)	140(5)	3.30(1)	O(3)[a]
N(1)–H	0.97(7)	2.51(7)	134(5)	3.27(1)	O(4)[b]
N(2)–H	0.74(8)	2.11(8)	176(10)	2.84(1)	O(13)[b]
N(11)–H	0.78(12)	2.39(11)	123(10)	2.88(1)	O(14)[c]
N(11)–H	0.78(12)	2.50(12)	147(11)	3.19(1)	O(19b)[a]
N(12)–H	0.67(16)	2.25(16)	171(20)	2.91(1)	O(4)

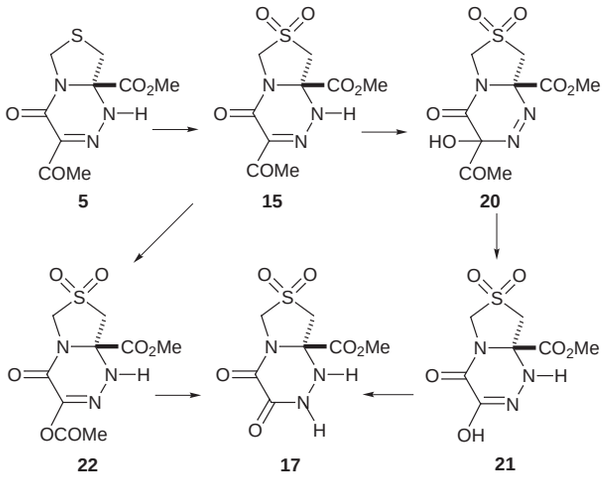
Where D = donor atom, A = acceptor atom, *d* = distance in Å, ∠ = angle in degrees, [a] denotes [x, $y-1$, z], [b] denotes [$-x+1$, $y-1/2$, $-z+2$] and [c] denotes [$-x+1$, $y-1/2$, $-z+1$].

columnar structure is further reinforced by H-bonding between the amino hydrogen atoms and carbonyl oxygen atoms [N(1)–H to O(3) and N(11)–H to O(19b)]. Both amino hydrogen atoms are bifurcated with N(1)–H linking across the column to O(4) and N(11)–H joining adjacent columns *via* O(14). The intermolecular H-bonding between N(11)–H and the ester carbonyl oxygen atom [O(19b)] in one of the stacks of the asymmetric unit may, in part, explain the IR spectral shift of the ester carbonyl absorption alluded to earlier.

To provide further support for the intermolecular H-bonding hypothesis, compound **17** was treated with acetic anhydride and pyridine. The resultant *N*-acetyl derivative **18**, isolated in 45% yield, showed a relatively normal ester carbonyl absorption at 1760 cm^{-1} in the solid state (the amide carbonyl absorptions at 1740 and 1720 cm^{-1} were also notably shifted in comparison with those of the precursor **17**). It also displayed a UV absorption maximum at 262 nm (ε 6300). Presumably, the UV absorptions of compounds **17** and **18** are associated with the presence of their amidic 3,4-dicarbonyl units.

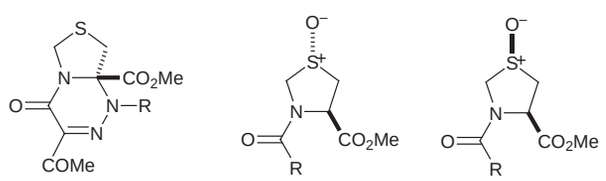
Possible routes to compound **17** from the bicyclic sulfide **5** are suggested in Scheme 1. Initial oxidation at the sulfur atom affords the sulfone **15**, which may then undergo hydroxylation at position 3 to give the species **20** or a Baeyer–Villiger type reaction to furnish the species **22**; deacetylation of the species **20** or **22** may then lead to the product **17** (by way of **21** in the former case).

In the hope of shedding some light on the reaction sequence, it was decided to examine the oxidation of the *N*-acetyl deriv-



Scheme 1

ative **16**. Clearly, an intermediate akin to the species **20** would be inaccessible in this instance. Under acetylation conditions [Ac_2O, pyridine and 4-dimethylaminopyridine (DMAP)], compound **5** was converted into the *N*-acetyl derivative **23** in 60% yield after 15 h and into the *N*-(acetyloxy)vinyl derivative **24** (tentative regiostructure) in 53% yield after 7 days. Compound **23** underwent oxidation with *m*-chloroperoxybenzoic acid in ethyl acetate to give the sulfone **16** in 64% yield. No reaction occurred when the sulfone **16** was treated with hydrogen peroxide and formic acid. This finding suggests that a Baeyer–Villiger type reaction is unlikely to be involved in the **15**→**17** transformation.



23 R = COMe
24 R = C(:CH_2)OCOMe
25 R = C(:N_2)COMe
26 R = Me
27 R = C(:N_2)COMe
28 R = Me

Returning to the stereoselective cyclisation reaction, it was decided to extend the study to the thiazolidine oxides **25** and **27**. Whilst, of course, the sulfinyl groups would be expected to contribute opposing stereodirecting effects on the cyclisation reaction, it would be instructive to determine if the 'mismatched' case could upset the axial chirality induction.

Oxidation of the thiazolidine **1** with *m*-chloroperoxybenzoic acid in ethyl acetate provided a 65:35 mixture of the thiazolidine oxides **25** and **27** in 90% yield. The use of magnesium monoperoxyphthalate in THF furnished an 88:12 mixture of the sulfoxides **25** and **27** in 82% yield; crystallisation of the mixture afforded the major sulfoxide **25** in 25% yield.

Nachtergaele and Anteunis have assigned[3] the stereochemistries of the thiazolidine oxides **26** and **28** on the basis of coupling constant values and aromatic solvent-induced shift (ASIS) studies. They found that the *trans* sulfoxide **26** adopted the conformation **29** in which the 4-methoxycarbonyl group was placed between the 5-protons (lying closer to 5-Hβ), whereas the *cis* sulfoxide **28** preferred the geometry **31** with the 4-proton located between the 5-protons (lying closer to 5-Hα). In compound **26**, the 2- and 5-protons *anti* to the sulfinyl oxygen atom (*i.e.* Hβ in **29**) also experienced a larger Δ ASIS [$\delta(CDCl_3) - \delta(C_6D_6)$] than those *syn* to the sulfinyl oxygen atom (*i.e.* Hα in **29**).

As Table 2 shows, the coupling constants of the ring protons of our major thiazolidine oxide **25** were very close to those of the *trans* sulfoxide **26**; similarly, there was a good match between the values of our minor thiazolidine oxide **27** and those of the *cis* sulfoxide **28**. These findings provided strong support for our stereochemical assignments and indicated that compound **25** adopted the conformation **30** and that compound **27** took up the geometry **32**.

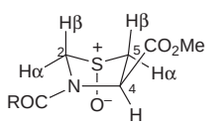
Table 2 Coupling constants (in Hz) of the ring protons of the thiazolidine oxides **25**–**28** (in $CDCl_3$)

Compound	$J_{2\alpha,2\beta}$	$J_{2\alpha,5\alpha}$	$J_{4,5\alpha}$	$J_{4,5\beta}$	$J_{5\alpha,5\beta}$
25	12	2.5	7.5	9.5	14
27	12	0	8	2	14
26[a]	12.2	2.5	7.8	9.0	14.2
28[a]	11.4	0	8.4	2.4	13.8

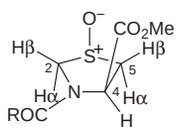
[a] Only the values for the major rotameric forms are quoted from ref. 3.

Table 3 Chemical shifts of the 2- and 5-protons of compound **25**

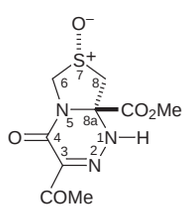
Solvent	2-Hα	2-Hβ	5-Hα	5-Hβ
$CDCl_3$	4.70	4.48	3.53	3.02
C_6D_6	4.13	3.83	2.81	2.00
Δ	0.57	0.65	0.72	1.02



29 R = Me
30 R = C(:N_2)COMe



31 R = Me
32 R = C(:N_2)COMe



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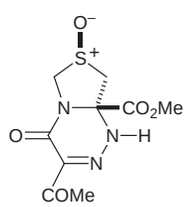


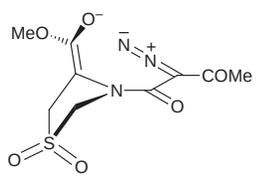
34

Although the aforecited findings suggested that the cyclisation reaction occurred with retention of configuration at the stereocentre adjacent to the methoxycarbonyl group, it was appropriate to establish the enantiomeric purity of the bicyclic sulfoxides **33** and **34**. Attempts to reduce the mixture to the bicyclic sulfide **5**, using phosphorus tribromide in DMF[4] or sodium iodide in the presence of trifluoroacetic anhydride,[5] were unproductive. However, the mixture reacted with *m*-chloroperoxybenzoic acid in methanol to give a 20:80 mixture of compounds **15** and **17**, from which the major product **17** was isolated by fractional crystallisation in 26% yield. The specific rotation of the product {$[\alpha]_D$ −214 (MeOH)} was very close to that of the material obtained earlier by oxidation of the bicyclic sulfide **5**. Clearly, the enantiomeric purities of the bicyclic sulfoxides **33** and **34** were high.

Having established the stereostructures of the bicyclic sulfoxides **33** and **34**, it was appropriate to define the stereoselectivity of sulfoxidation reactions of the bicyclic sulfide **5**. When treated with *m*-chloroperoxybenzoic acid in ethyl acetate, the bicyclic sulfide **5** gave rise to a 33:67 mixture of the bicyclic

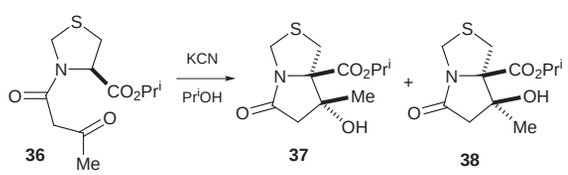
sulfoxides **33** and **34** (inseparable by column chromatography) in 89% yield. The use of chloroform as the solvent led to the production of a 17:83 mixture of the sulfoxides **33** and **34**, from which it was possible to isolate the major sulfoxide **34** in 46% yield (by virtue of its insolubility in $CHCl_3$). Clearly, although there is a solvent influence, the oxidant delivers its oxygen atom preferentially to the *exo*-orientated lone pair of the sulfur atom of the bicycle **5**.

The aforecited findings provide further notable illustrations of the powerful stereodirecting effect that can be achieved using the principle of self-induction of axial chirality. It is striking that the thiazolidine ester enolate **35**, which we invoke as an intermediate in the formation of the bicyclic sulfone **15**, shows little tendency to β-eliminate [presumably, because the enolate double bond and the C(5)–S(1) bond adopt a near-parallel arrangement]. It is also significant that both the (1*R*)-thiazolidine oxide **25** and the (1*S*)-thiazolidine oxide **27** undergo the cyclisation reaction, to give the bicyclic sulfoxides **33** and **34**, with a high degree of stereoretention. Seemingly, the axial chirality stereodirecting effect overrides any 'mismatching' influence.



35

Recently, Fuji and his co-workers have reported[6] examples of intermolecular α-alkylations of *N*-alkoxycarbonyl-*N*-methylphenylalanine esters that proceed with up to 82% ee. In reactions induced by lithium 2,2,6,6-tetramethylpiperidide in THF at −78 °C, they favoured the involvement of a *C*-lithiated intermediate formed with retention of configuration. We have also observed[7] that the thiazolidine **36** underwent an intramolecular aldol reaction (in Pr^iOH containing KCN) to give the bicycles **37** and **38** (Scheme 2) with ees of 99%; axially chiral enolates were invoked as reaction intermediates.



Scheme 2

Experimental

Pyridine was dried by distillation from sodium hydroxide pellets and left over 4 Å molecular sieves. Light petroleum refers to that fraction boiling in the range 40–60 °C.

TLC was performed on Merck Kieselgel 60 silica gel plastic sheets; the sheets were initially examined under UV light (Mineralight UVG2-58 lamp) and developed with either iodine vapour or conc. aq. potassium permanganate. Column chromatography was effected, under positive pressure from a compressed air line, employing Crossfield Sorbsil C60 flash silica.

Evaporations were conducted under reduced pressure (using a water-pump or an oil-pump) at ≤40 °C with a Buchi rotary evaporator. Mps were determined with a Buchi 512 melting point apparatus. Optical rotations, given in 10^{-1} deg cm^2 g^{-1}, were measured at ~20 °C using a Thorn Automation Type 243 or an Optical Activity 1000 polarimeter. Elemental analyses were performed with a Carlo-Erba Model 1106 analyser. A Perkin-Elmer Lambda 15 spectrometer was used to determine UV spectra; extinction coefficients (ε) are presented in cm^2 $mmol^{-1}$. IR Spectra were recorded using a Perkin-Elmer 783 spectrometer. NMR Spectra were measured using a Bruker AC 300 [with distortionless enhancement by polarisation transfer (DEPT) editing for ^{13}C spectra]; *J* values and separations are given in Hz. FAB Mass spectra (*m*-$NO_2C_6H_4CH_2OH$ as matrix) were measured using a VG 7AB-E spectrometer; EI and CI (NH_3 as carrier gas) spectra were recorded on a Kratos MS 45 instrument.

Methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-1,1-dioxo-1λ⁶-3-thiazolidine-4-carboxylate 14

m-Chloroperoxybenzoic acid (~80% purity, 2.33 g, ~10.8 mmol) was added in portions over 5 min to a stirred solution of the thiazolidine **1**[1] (1.30 g, 5.05 mmol) in ethyl acetate (20 cm^3). Evaporation after 15 h and subjection of the product to column chromatography [light petroleum–EtOAc (2:1) as eluent] gave the *title compound* **14** (1.26 g, 86%) as a yellow foam; $[\alpha]_D$ −229 (*c* 0.8, CH_2Cl_2); λ_{max} (EtOH)/nm 231 (ε 15 000); ν_{max} (film)/cm^{-1} 2130 (C=N_2), 1750 (ester C=O) and 1660br (amide and diazo ketone C=O); δ_H (300 MHz; $CDCl_3$) 2.40 (3 H, s, MeCO), 3.53 and 3.61 [each 1 H, dd (*J* 5 and 14) and dd (*J* 8.5 and 14), 5-H_2], 3.83 (3 H, s, MeO), 4.55 and 4.62 [each 1 H, br d (separation 12), 2-H_2] and 5.51 (1 H, dd, *J* 5 and 8.5, 4′-H); *m*/*z* (EI) 290 (MH^+, 100%).

Methyl (8a*S*)-3-acetyl-4,7,7-trioxo-1,4,6,7,8,8a-hexahydro-7λ⁶-[1,3]thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylate 15

Method (*a*). Triethylamine (0.66 g, 6.5 mmol) was added to a solution of the diazo compound **14** (0.620 g, 2.15 mmol) in methanol (25 cm^3) under reflux. After 1 h the mixture was treated with charcoal and filtered through Celite. The filtrate was concentrated and the residue partitioned between ethyl acetate and dilute hydrochloric acid. Evaporation and crystallisation of the material from ethanol gave the *title compound* **15** (0.280 g, 45%); mp 170–171 °C; $[\alpha]_D$ −245 (*c* 0.7, MeOH) (Found: C, 37.1; H, 3.6; N, 14.3; S, 11.0. $C_9H_{11}N_3O_6S$ requires C, 37.4; H, 3.8; N, 14.5; S, 11.1%); λ_{max} (EtOH)/nm 223 (ε 10 600), 263 (6500) and 311 (6700); ν_{max} (KBr)/cm^{-1} 3280 (N–H), 1755 (ester C=O), 1720 (acetyl C=O) and 1680 (amide C=O); δ_H (300 MHz; CD_3SOCD_3) 2.28 (3 H, s, MeCO), 3.76 (3 H, s, MeO), 4.03 and 4.34 [each 1 H, dd (*J* 2 and 14) and d (*J* 14), 8-H_2], 4.50 and 5.28 [each 1 H, d (*J* 12) and dd (*J* 2 and 12), 6-H_2] and 11.3 (1 H, br s, 1-NH); *m*/*z* (EI) 290 (MH^+, 2%) and 60 (100).

Method (*b*). A mixture of the bicycle **5**[1] (0.510 g, 1.98 mmol), *m*-chloroperoxybenzoic acid (~80% purity, 1.30 g, ~6.0 mmol) and DMF (50 cm^3) was stirred overnight. Evaporation and crystallisation of the residue from propan-2-ol gave a product (0.310 g), which was mainly the sulfone **15**. Crystallisation of the material from ethanol gave the sulfone **15** (0.160 g, 28%); mp 172–173 °C; $[\alpha]_D$ −265 (*c* 0.5, MeOH). The ^1H NMR spectrum of the sample matched that of the product obtained in (*a*).

Methyl (8a*S*)-3,4,7,7-tetraoxoperhydro-7λ⁶-[1,3]thiazolo[4,3-*c*]-[1,2,4]triazine-8a-carboxylate 17

Method (*a*). A mixture of the bicycle **5** (0.102 g, 0.40 mmol), *m*-chloroperoxybenzoic acid (~80% purity; 0.320 g, ~1.6 mmol) and methanol (5 cm^3) was stirred for 3 days. Evaporation and subjection of the residue to column chromatography [EtOAc–hexanes (2:1) as eluent] gave a 69:31 mixture of compounds **17** and **15** [the ratio was estimated by NMR spectroscopy (CD_3SOCD_3) from the integrals of the singlets at δ 10.3 (attributed to the 1-NH of **17**) and 11.3 (ascribed to the 1-NH of **15**)]. Crystallisation of the mixture from methanol–diethyl ether gave the *title compound* **17** (0.020 g, 16%); $[\alpha]_D$ −200 (*c* 0.5, MeOH). The ^1H NMR spectrum of the sample matched that of the material prepared in (*b*).

Method (*b*). Aq. hydrogen peroxide (30 wt%; 12.2 cm^3, 108 mmol) was added to a stirred solution of the bicycle **5** (0.810 g, 3.08 mmol) in formic acid (96%; 75 cm^3) at 0–5 °C. After 15 h the mixture was concentrated and the residue crystallised from ethanol to give the *title compound* **17** (0.364 g, 44%); mp 228–229 °C; $[\alpha]_D$ −192 (*c* 0.4, MeCN) and −210 (*c* 0.5, MeOH) (Found: C, 32.1; H, 3.7; N, 15.7; S, 12.1. $C_7H_9N_3O_6S$ requires C, 32.0; H, 3.5; N, 16.0; S, 12.2%); λ_{max} (EtOH)/nm 226 (ε 6100); ν_{max} (KBr)/cm^{-1} 3300 and 3220 (N–H), 1680 (ester C=O) and 1630 (amide C=O); δ_H (300 MHz; CD_3SOCD_3) 3.78 (3 H, s, MeO), 3.84 and 4.23 (each 1 H, d, *J* 14, 8-H_2), 4.62 and 5.14 (each 1 H, d, *J* 12.5, 6-H_2), and 6.94 and 10.25 (each 1 H, s, 1- and 2-NH) (addition of D_2O caused the signals at δ 6.94 and 10.25 to disappear); δ_C (75 MHz; CD_3SOCD_3) 58.20 (CH_3O), 58.80 (8-CH_2), 66.98 (6-CH_2), 82.48 (8a-C), 159.0 and 161.2 (3- and 4-CO) and 171.5 (ester CO); *m*/*z* (FAB) 264 (MH^+, 100%).

Crystal data for compound 17. $C_7H_9N_3O_6S$, $M = 263.22$. Colourless needle, dimensions: 0.40 × 0.15 × 0.15 mm. Monoclinic, $a = 13.322(5)$, $b = 6.274(2)$, $c = 13.281(5)$ Å, $\beta = 107.90(2)°$, $V = 1056(1)$ Å^3. Space group $P2_1$(no. 4), $Z = 4$, $D_c = 1.655$ g cm^{-3}, $F(000)$ 544, μ(Mo-Kα) = 3.15 cm^{-1}.

Data collection and processing. Intensity data were collected on a Rigaku AFC6S diffractometer with Mo-Kα radiation ($\lambda = 0.71069$ Å) using the ω scans to a maximum 2θ value of 50.0° with a scan rate of 4.0° min^{-1} (3 rescans) and a scan width of $(1.22 + 0.30 \tan \theta)°$; 2079 reflections were measured of which 2064 were unique ($R_{int} = 0.057$). An empirical absorption correction based on azimuthal scans of several reflections was applied, which resulted in transmission factors ranging from 0.81 to 1.00. Data were corrected for Lorentz and polarisation effects. A correction for secondary extinction was applied (coefficient = 0.68705×10^{-6}).

Structure analysis and refinement. The structure was solved by direct methods;[8] non-hydrogen atoms were refined anisotropically and hydrogen atoms were subjected to isotropic refinements. The final cycle of full-matrix least-squares refinement was based on 1056 observed reflections [$I > 2.00\sigma(I)$] and 321 variable parameters and converged with $R = 0.042$ and $R_w = 0.044$. Neutral atom scattering factors were taken from Cromer and Waber.[9] Anomalous dispersion effects were included in F_{calc};[10] the values of $\Delta f'$ and $\Delta f''$ were those of Cromer.[11] All calculations were performed with TEXSAN crystallographic software package of Molecular Structure Corporation. The asymmetric unit with its atomic labelling is shown in Fig. 1.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/301. See http://www.rsc.org/suppdata/p1/1999/1067/ for crystallographic files in .cif format.

Method (*c*). Aq. hydrogen peroxide (30 wt%; 1.7 cm^3, 15 mmol) was added to a stirred solution of the sulfone **15** (0.120 g, 0.42 mmol) in formic acid (96%; 10 cm^3) at 0–5 °C. After 15 h the mixture was concentrated and the residue crystallised from ethanol to give compound **17** (0.068 g, 62%). The ^{1}H NMR spectrum of the sample matched that of the product obtained in (*b*).

Method (*d*). A 63 : 37 mixture of the bicyclic sulfoxides **33** and **34** (obtained from the reaction of a 65 : 35 mixture of the thiazolidine oxides **25** and **27** with Et_3N in MeOH) (0.500 g, 1.83 mmol) in methanol (20 cm^3) was stirred with *m*-chloroperoxybenzoic acid (~80%, 1.18 g, ~5.5 mmol) for 48 h. Evaporation and subjection of the product to column chromatography [hexanes–EtOAc (1 : 2) as eluent] led to the isolation of a white solid (0.420 g) that was mainly a 20 : 80 mixture of compounds **15** and **17** [the ratio was estimated by NMR spectroscopy (CD_3SOCD_3) from the relative intensities of the signals at δ 5.16 (attributed to a 6-H of **17**) and at δ 5.29 (attributed to a 6-H of **15**)]. Fractional crystallisation of the mixture from methanol–diethyl ether gave compound **17** (0.127 g, 26%), $[\alpha]_D$ −214 (*c* 0.5, MeOH). The ^{1}H NMR spectrum of the sample matched that of the product obtained in (*b*).

Methyl (8a*S*)-1-acetyl-3,4,7,7-tetraoxoperhydro-7λ^6-[1,3]-thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylate 18

A mixture of compound **17** (0.310 g, 1.18 mmol), dry pyridine (12.5 cm^3) and acetic anhydride (12.5 cm^3) was stirred overnight. Evaporation left a red foam which was treated with dichloromethane (25 cm^3) to give an off-white solid and a yellow solution. The filtered material (0.163 g, 45%) was identified as the *title compound* **18**; mp 166–168 °C; $[\alpha]_D$ −212 (*c* 0.5, MeCN) (Found: C, 35.1; H, 3.5; N, 13.5; S, 10.7. $C_9H_{11}N_3O_7S$ requires C, 35.4; H, 3.6; N, 13.8; S, 10.5%); λ_{max} (EtOH)/nm 203 (ε 5000) and 262 (6300); ν_{max} (KBr)/cm^{-1} 3280 (N–H), 1760 (ester C=O), and 1740 and 1720 (amide C=O); δ_H (300 MHz; CD_3SOCD_3) 2.39 (3 H, s, MeCO), 3.86 (3 H, s, MeO), 4.15 and 4.39 [each 1 H, dd (*J* 2 and 14) and d (*J* 14), 8-H_2], 4.75 and 5.38 [each 1 H, d (*J* 13) and dd (*J* 2 and 13), 6-H_2] and 7.62 (1 H, s, 2-NH); *m*/*z* (FAB) 611 (M_2H^+, 6%), 306 (MH^+, 90) and 264 (100).

Acetylation reactions of the bicycle 5

Method (*a*). The bicycle **5** (0.257 g, 1.0 mmol) was added under an atmosphere of argon to a stirred mixture of dry pyridine (5 cm^3) and acetic anhydride (5 cm^3) containing a few crystals of DMAP. Evaporation after 15 h left an oil which was dissolved in ethyl acetate; the solution was washed with dilute hydrochloric acid followed by water, dried ($MgSO_4$) and concentrated. Subjection of the residue to column chromatography [hexanes–EtOAc (1 : 1) as eluent] gave *methyl (8a*S*)-1,3-diacetyl-4-oxo-1,4,8,8a-tetrahydro[1,3]thiazolo[4,3-c][1,2,4]triazine-8a-carboxylate* **23** (0.180 g, 60%) as a chromatographically homogeneous, colourless oil; $[\alpha]_D$ −173 (*c* 0.9, CH_2Cl_2) (Found: C, 44.5; H, 4.4; N, 13.7; S, 11.0. $C_{11}H_{13}N_3O_5S$ requires C, 44.2; H, 4.4; N, 14.0; S, 10.7%); λ_{max} (EtOH)/nm 202 (ε 8700) and 259 (8900); ν_{max} (KBr)/cm^{-1} 1755 (ester C=O), 1720 (acetyl C=O) and 1675 (amide C=O); δ_H (300 MHz; $CDCl_3$) 2.48 and 2.51 (each 3 H, s, 2 × MeCO), 3.63 and 4.43 (each 1 H, d, *J* 12.5, 8-H_2), 3.79 (3 H, s, MeO), and 4.39 and 5.10 (each 1 H, d, *J* 10, 6-H_2); *m*/*z* (FAB) 300 (MH^+, 100%) and 258 (65).

Method (*b*). The aforecited reaction was repeated but left for 7 days. Work-up as before and subjection of the product to column chromatography (hexanes–EtOAc; gradient elution) gave *methyl (8aS)-3-acetyl-1-[1-(acetyloxy)vinyl]-4-oxo-1,4,8,8a-tetrahydro[1,3]thiazolo[4,3-c][1,2,4]triazine-8a-carboxylate* **24** (0.180 g, 53%) as a colourless oil. After crystallisation from dichloromethane–hexanes, the sample showed: mp 82–83 °C; $[\alpha]_D$ −258 (*c* 0.86, CH_2Cl_2) (Found: C, 45.8; H, 4.4; N, 12.0; S, 9.3. $C_{13}H_{15}N_3O_6S$ requires C, 45.8; H, 4.4; N, 12.3; S, 9.4%); λ_{max} (EtOH)/nm 210 (ε 10 900), 244 (9100) and 315 (6200); ν_{max} (KBr)/cm^{-1} 1765 and 1750 (ester C=O), 1715 (acetyl C=O) and 1680 (amide C=O); δ_H (300 MHz; $CDCl_3$) 2.21 and 2.34 (each 3 H, s, 2 × MeCO), 3.66 and 4.44 (each 1 H, d, *J* 12.5, 8-H_2), 3.80 (3 H, s, MeO), 4.49 and 4.98 (each 1 H, d, *J* 10, 6-H_2), and 5.51 and 6.51 (each 1 H, d, *J* 1.5, C:CH_2); *m*/*z* (FAB) 342 (MH^+, 80%) and 300 (100).

Methyl (8a*S*)-1,3-diacetyl-4,7,7-trioxo-1,4,6,7,8,8a-hexahydro-7λ^6-[1,3]thiazolo[4,3-*c*][1,2,4]thiazine-8a-carboxylate 16

A mixture of compound **23** (0.170 g, 0.57 mmol), *m*-chloro-

peroxybenzoic acid (~80% purity; 0.404 g, ~1.9 mmol) and ethyl acetate (20 cm^3) was stirred overnight. Evaporation and subjection of the residue to column chromatography [EtOAc–light petroleum (2:1) as eluent] gave the *title compound* **16** (0.120 g, 64%). After crystallisation from ethyl acetate–light petroleum, the sample showed: mp 159–161 °C; $[\alpha]_D$ −60 (*c* 0.4, CH_2Cl_2) (Found: C, 39.5; H, 3.9; N, 12.4; S, 9.2. $C_{11}H_{13}N_3O_7S$ requires C, 39.9; H, 4.0; N, 12.7; S, 9.7%); λ_{max} (EtOH)/nm 207 (ε 6700), 254 (9100) and 296 (3800); ν_{max} (KBr)/cm^{-1} 1750 (ester C=O), 1720 (acetyl C=O) and 1685 (amide C=O); δ_H (300 MHz; CD_3SOCD_3) 2.46 (6 H, s, 2 × MeCO), 3.68 and 4.42 [each 1 H, dd (*J* 2 and 14) and d (*J* 14), 8-H_2], 3.83 (3 H, s, MeO), and 4.10 and 5.23 [each 1 H, d (*J* 12.5) and dd (*J* 2 and 12.5), 6-H_2]; *m*/*z* (CI) 349 (MNH_4^+, 44%), 332 (MH^+, 57) and 144 (100).

Methyl (1*R*,4*R*)- and (1*S*,4*R*)-3-(2-diazo-3-oxobutanoyl)-1-oxo-1λ⁴,3-thiazolidine-4-carboxylates 25 and 27

Method (*a*). A mixture of the thiazolidine **1** (1.00 g, 3.9 mmol), *m*-chloroperoxybenzoic acid (~80% purity; 0.870 g, ~4 mmol) and ethyl acetate (50 cm^3) was stirred for 1 h. Evaporation and subjection of the residue to column chromatography [EtOAc–MeOH (9:1) as eluent] gave a 65:35 mixture of the *title compounds* **25** and **27** (0.956 g, 90%) as a foam; λ_{max} (EtOH)/nm 229 (ε 16 400); ν_{max} (film)/cm^{-1} 2120 (C=N_2), 1750 (ester C=O) and 1650br (amide and diazo ketone C=O); δ_H (300 MHz; $CDCl_3$) 2.38 and 2.39 (1.05 and 1.95 H, each s, MeCO), 3.02, 3.27, 3.53 and 3.56 [0.65, 0.35, 0.65 and 0.35 H, dd (*J* 9.5 and 14), dd (*J* 8 and 13.5), ddd (*J* 2.5, 7 and 14) and br dd (*J* 2 and 14), 5-H_2], 3.82 (3 H, s, MeO), 4.48, 4.70 and 5.13 [1, 0.65 and 0.33 H, br d (separation 13), very br d (separation 12) and d (*J* 12), 2-H_2], and 5.43 and 5.63 [0.35 and 0.65 H, dd (*J* 2 and 8) and dd (*J* 7.5 and 9.5), 4-H]; *m*/*z* (FAB) 274 (MH^+, 100%).

Method (*b*). A mixture of the thiazolidine **1** (0.640 g, 2.49 mmol), magnesium monoperoxyphthalate (~80% purity; 0.780 g, ~1.3 mmol) and THF (75 cm^3) was stirred for 3.5 h. Evaporation and subjection of the residue to column chromatography (Me_2CO as eluent) gave an 88:12 mixture of the sulfoxides **25** and **27** (0.560 g, 82%). Crystallisation of the material from ethyl acetate–light petroleum gave the *(1R,4R)-title compound* **25** (0.170 g, 25%); mp 136–137 °C; $[\alpha]_D$ −50 (*c* 0.5, EtOAc) (Found: C, 39.5; H, 4.1; N, 15.3; S, 11.3. $C_9H_{11}N_3O_5S$ requires C, 39.6, H, 4.1; N, 15.4; S, 11.7%); λ_{max} (EtOH)/nm 231 (ε 16 700) and 353 (600); ν_{max} (KBr)/cm^{-1} 2110 (C=N_2), 1750 (ester C=O) and 1640br (amide and diazo ketone C=O); δ_H (300 MHz; $CDCl_3$) 2.39 (3 H, s, MeCO), 3.02 and 3.53 [each 1 H, dd (*J* 9.5 and 14) and ddd (*J* 2.5, 7 and 14), 5-H_2], 3.82 (3 H, s, MeO), 4.48 and 4.70 [each 1 H, br d (*J* 12) and very br d (separation 12), 2-H_2], and 5.63 (1 H, dd, *J* 7.5 and 9.5, 4-H) [irradiation at δ 4.70 caused the ddd at δ 3.53 to collapse to a dd (*J* 7 and 14) and the d at δ 4.48 to collapse to a s]; δ_H (300 MHz; C_6D_6) 1.7 (3 H, br s, MeCO), 2.00 and 2.81 [each 1 H, dd (*J* 10 and 14) and ddd (*J* 2.5, 7 and 14), 5-H_2], 3.35 (3 H, s, MeO), 3.83 and 4.13 (each 1 H, br s, 2-H_2) and 5.80 (1 H, dd, *J* 7.5 and 10, 4-H) [irradiation at δ 4.13 caused the ddd at δ 2.81 to collapse to a dd (*J* 7 and 14)]; *m*/*z* (FAB) 274 (MH^+, 100%) and 146 (70).

Methyl (7*R*,8a*S*)- and (7*S*,8a*S*)-3-acetyl-4,7-dioxo-1,4,6,7,8,8a-hexahydro-7λ⁴-[1,3]thiazolo[4,3-*c*][1,2,4]triazine-8a-carboxylates 33 and 34

Method (*a*). Triethylamine (0.23 cm^3, 1.65 mmol) was added to a solution of a 65:35 mixture of the sulfoxides **25** and **27** (0.151 g, 0.55 mmol) in methanol (3 cm^3) under reflux. Evaporation after 1 h and subjection of the product to column chromatography [EtOAc–MeOH (9:1) as eluent] gave a 63:37 mixture of the title compounds **33** and **34** (0.100 g, 66%) [the ratio was estimated by NMR spectroscopy (CD_3SOCD_3) from the integrals of the d (*J* 12.5) at δ 5.20 (attributed to a 6-H of **34**) and of the dd (*J* 3 and 12.5) at δ 5.52 (ascribed to a 6-H of **33**)].

Method (*b*). The aforecited reaction was repeated using the sulfoxide **25** (0.139 g, 0.51 mmol). Work-up and purification as before gave the *(7R,8aS)-title compound* **33** (0.085 g, 61%). After crystallisation from ethanol, the sample showed: mp 72–75 °C; $[\alpha]_D$ +137 (*c* 0.5, MeOH) (Found: C, 39.6; H, 4.0; N, 15.5; S, 11.7. $C_9H_{11}N_3O_5S$ requires C, 39.6; H, 4.1; N, 15.4; S, 11.7%); λ_{max} (EtOH)/nm 202 (ε 10 100), 230 (7600) and 279 (12 300); ν_{max} (KBr)/cm^{-1} 3200br (N–H), 1750 (ester C=O), 1680 (amide and acetyl C=O) and 1635 (C=N); δ_H (300 MHz; CD_3SOCD_3) 2.38 (3 H, s, MeCO), 3.80 and 3.94 [each 1 H, dd (*J* 2 and 15) and d (*J* 15), 8-H_2], 3.82 (3 H, s, MeO), and 4.31 and 5.52 [each 1 H, d (*J* 12.5) and dd (*J* 3 and 12.5), 6-H_2]; *m*/*z* (FAB) 274 (MH^+, 100%).

Method (*c*). A mixture of the bicycle **5** (0.430 g, 1.67 mmol), *m*-chloroperoxybenzoic acid (~80% purity; 0.360 g, ~1.7 mmol) and chloroform (40 cm^3) was stirred for 1 h. Evaporation left a 17:83 mixture of the (7*R*,8a*S*)- and (7*S*,8a*S*)-title compounds **33** and **34** by NMR spectroscopy. Addition of chloroform to the mixture and filtration gave the *(7S,8aS)-title compound* **34** (0.212 g, 46%). A sample, crystallised from acetic acid, showed: mp 194 °C; $[\alpha]_D$ +5 (*c* 0.45, MeOH) and −121 (*c* 0.4, MeCN) (Found: C, 39.5; H, 4.0; N, 15.5; S, 12.1%); λ_{max} (EtOH)/nm 223 (ε 8700) and 315 (5300); ν_{max} (KBr)/cm^{-1} 3180br (N–H), 1750 (ester C=O), 1675 (amide and acetyl C=O) and 1630 (C=N); δ_H (300 MHz; CD_3SOCD_3) 2.37 (3 H, s, MeCO), 3.77 and 4.14 [each 1 H, d, *J* 13.5, 8-H_2], 3.79 (3 H, s, MeO), 4.47 and 5.21 (each 1 H, d, *J* 13, 6-H_2) and 11.3 (1 H, br s, 1-NH); *m*/*z* (FAB) 274 (MH^+, 100%).

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