A Cyclisation Reaction of Methyl (4*R*)-3-(2-Diazo-3-oxobutanoyl)thiazolidine-4-carboxylate which proceeds with Retention of Configuration, probably *via* a Planar Ester Enolate Intermediate possessing Axial Chirality

Brian Beagley,[a] Michael J. Betts,[b] Robin G. Pritchard,[a] Anthony Schofield,[a] Richard J. Stoodley*[a] and Shaheen Vohra[a]

[a] *Department of Chemistry, UMIST, P.O. Box 88, Manchester M60 1QD, UK*
[b] *Chemistry I Department, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

Under basic conditions, the title compound **1b** is converted into methyl (6*S*)-3-acetyl-2-oxo-8-thia-1,4,5-triazabicyclo[4.3.0]non-3-ene-6-carboxylate **4a**, the absolute configuration of which is established by X-ray crystallography.

In connection with other work, we needed the diazoacetyl thiazolidine **1a**. Since the deacetylation of α-acetyl-α-diazo carbonyl compounds is well established,[1] we expected that compound **1a** would be accessible from the acetyldiazoacetyl thiazolidine **1b**. We now report on a cyclisation reaction, remarkable for its stereochemical outcome, in which compound **1b** was found to undergo during efforts to bring about the deacetylation.

The thiazolidine **2**[2] reacted with diketene and triethylamine in boiling dichloromethane to give the acetoacetyl derivative **1c** (84% yield after chromatography), m.p. 40–41 °C, $[\alpha]_D^{20}$ −119° (CH_2Cl_2). Under diazo-transfer conditions ($HO_2CC_6H_4SO_2N_3$-*p*, Et_3N, MeCN),[3] the last-cited material was transformed into the diazo derivative **1b** (94% yield after chromatography), $[\alpha]_D^{20}$ −243° ($CHCl_3$). On the basis of 300 MHz ^1H NMR spectroscopy, compound **1c** existed in deuteriochloroform at ambient temperature as a 2:1 mixture of rotamers; there was no evidence for restricted rotation in compound **1b** under corresponding conditions.

When compound **1b** was treated with methanolic sodium methoxide and the mixture partitioned between chloroform and water, the desired diazo amide **1a**, $[\alpha]_D^{20}$ −101° (CH_2Cl_2), was isolated as a yellow oil in 36% yield after evaporation of the organic phase. Concentration of the aqueous layer and recrystallisation of the residue from methanol gave a white solid, m.p. 175–177 °C, $[\alpha]_D^{20}$ −299° (MeOH), in 55% yield. Elemental analysis established that the product was an isomer of the starting material and spectroscopic considerations left little doubt that it possessed the structure **3a**. Thus, absorption 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 three-proton singlets at δ 2.43 and 3.94 for the acetyl and methoxy groups, the 300 MHz ^1H NMR spectrum (CD_3COCD_3) displayed an AB quartet (*J* 12 Hz) centred at δ 3.86 for the 7-methylene group, two one-proton doublets (*J* 10 Hz) at δ 4.66 and 5.17 for the 9-methylene group, and a broad one-proton singlet (exchangeable with D_2O) at δ 10.1 for the NH group.

Triethylamine in methanol (at ambient temperature or under reflux), pyrrolidine in boiling acetonitrile and sodium hydroxide in aqueous dioxane were also effective in inducing the **1b** → **3a** transformation (in yields ranging from 45 to 68%); moreover, in each case, the product showed a high negative optical rotation {$[\alpha]_D^{20}$ −283 to −288° (MeOH)}.

That compound **3a** was enantiomerically pure was indicated by its reaction with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[4]† in dichloromethane in the presence of triethylamine and 4-dimethylaminopyridine. The crude product contained the amide **3b** as a single diastereoisomer on the basis of 300 MHz ^1H and 84.6 MHz ^{19}F NMR spectroscopy.

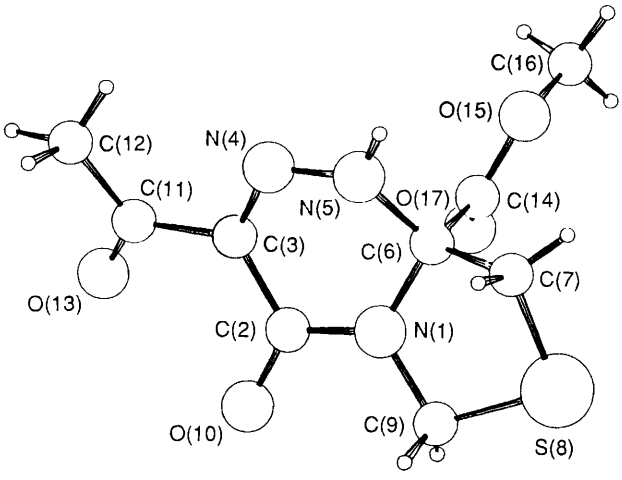
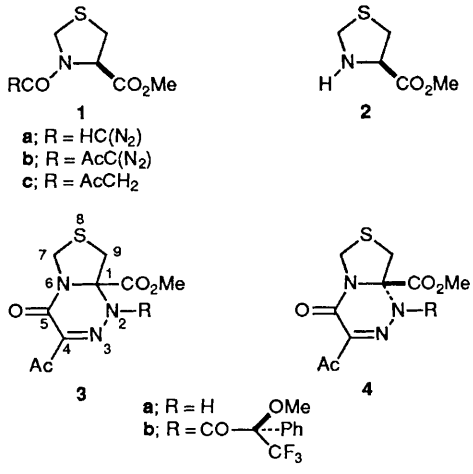
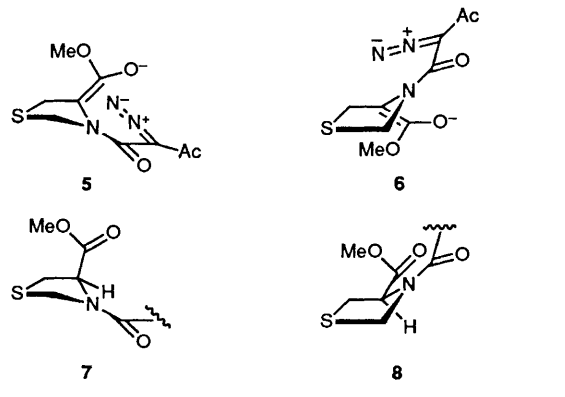


Fig. 1. X-Ray structure of compound **4a**





† It should be noted that this acid chloride is prepared from (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

The absolute configuration of compound **3a** was deduced by X-ray crystallography.‡ The molecular structure, shown in Fig. 1, revealed that the material, *i.e.* **4a**, possessed the (*S*)-configuration at position 6. In consequence, the Mosher amide possessed the stereostructure **4b**.

Clearly, the **1b** → **4a** transformation had proceded with retention of configuration. The 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.[5] However, the enolate **5**, required for the cyclisation reaction, possesses axial chirality¶ and a sizeable energy barrier would be expected to separate it from its enantiomer **6**. We suggest, therefore, that intramolecular trapping of the enolate **5** 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 compound **1b** to undergo deprotonation to give the enolate **5** rather than its enantiomer **6**.** Presumably, this is attributable to the greater ease in attaining the geometry **7** compared with the geometry **8** (in which a severe $A^{1,3}$ interaction[6] exists between the acyl substituent and the methoxycarbonyl group).

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‡ *Crystal data:* $C_9H_{11}N_3OS$, M = 257.26, orthorhombic, a = 6.6145(7), b = 8.2671(8), c = 20.637(2) Å, U = 1128.5 Å^3, space group $P2_12_12_1$, Z = 4.0, D_c = 1.51 Mg m^{-3}, μ = 0.243 mm^{-1}. An Enraf-Nonius CAD-4 diffractometer, employing graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) in the ω–2θ scan mode, was used to record 3796 reflections ($0 \leqslant \theta \leqslant 24°$). Lorentz–polarisation and absorption corrections were applied. The structure was solved by direct methods using the SHELX-86 program (G. M. Sheldrick, in *Crystallographic Computing 3*, Oxford University Press, 1985, pp. 175–189) and refined by block-matrix least-squares procedures (G. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, 1976) {modified to perform absolute configuration refinement (D. Rogers, *Acta Crystallogr., Sect. A*, 1981, **37**, 734) [η = 1.3(3)]} to final residuals R = 0.041 and R_w = 0.037 for 1406 observed reflections with $F \geqslant 3\sigma(F)$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Data Centre. See Notice to Authors, Issue No. 1.

§ There was no evidence for deuterium exchange at position 4 of the starting thiazolidine **1b** when the reaction was conducted in *O*-deuteriomethanol containing triethylamine.

¶ D. Seebach and D. Wasmuth (*Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 971) have reported that the alkylation of di-t-butyl *N*-formyl-L-aspartate led to a mixture of C(2)- and C(3)-alkylated products and that the former products were optically active; they recognised that one possible explanation for this observation was that an enolate intermediate with axial chirality intervened.

‖ There is precedent for the intermolecular addition of *C*-nucleophiles to the diazo function of α-diazo carbonyl compounds (L. Wolff, *Leibigs Ann. Chem.*, 1902, **325**, 129; L. Wolff and K. Lindenhayn, *Ber. deut. chem. Ges.*, 1903, **36**, 4126; L. Canonica and C. Tedechi, *Gazz. Chim. Ital.*, 1954, **84**, 175; T. Severin, *Angew. Chem.*, 1958, **70**, 745; N. Takamura and S. Yamada, *Chem. Pharm. Bull.*, 1976, **24**, 800).

** The s-*trans* relationship of the diazo and amide carbonyl groups is not essential providing the barrier for the s-*cis* → s-*trans* conversion is low. However, it seems necessary to invoke that deprotonation of the thiazolidine **1b** occurs by way of the rotamer in which the amide bond possesses the (*Z*)-geometry.