Stereoselective intramolecular aldol reactions of (4*R*)-3-(3-oxobutanoyl)-1,3-thiazolidine-4-carboxylates believed to be directed by 'self-induced' axial chirality

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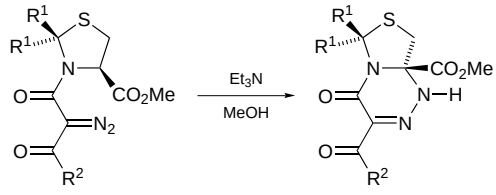
Essentially complete retention of configuration accompanies the base-induced aldol reaction of the thiazolidinecarboxylate 6c to give the fused heterocycles 7c and 8c and their retroaldol–acylation reactions to give the bicycle 9c.

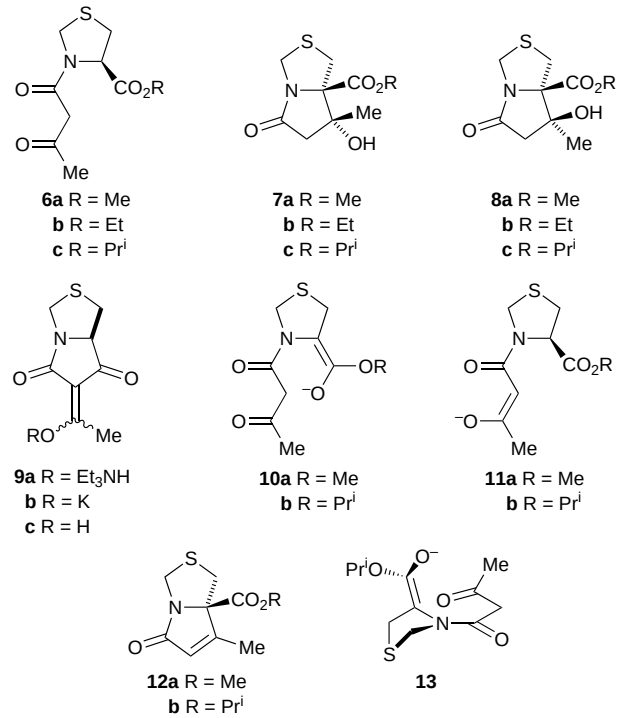
Recently we showed[1] that the diazo esters **1a–c** underwent cyclisations under basic conditions to give the bicyclic compounds **2a–c** in a state of high enantiomeric purity (Scheme 1). We postulated that the reactions proceeded by way of planar ester enolate (or enol) intermediates that possessed axial chirality. For example, the species **3** (arbitrary enolate geometry) was considered to be involved in the **1a** → **2a** cyclisation. The marked kinetic preference for the diazo ester **1a** to undergo deprotonation to give the enolate **3** rather than its enantiomer was attributed to the greater ease in attaining the geometry **4** compared with the geometry **5** (in which a severe $A^{1,2}$ interaction exists between the *N*-acyl substituent and the CO_2Me group) required for the deprotonation reactions.



Scheme 1

Whilst the aforecited findings were of significant mechanistic interest in that they exemplified a new stereoinduction principle, they were of limited synthetic impact because a C–N bond had been generated at the expense of a C–H bond at the thiazolidine stereocentre. Obviously, the ability to develop a C–C bond would notably enhance the technology, particularly because of the high interest in enantiopure α-*C*-substituted α-amino acids.[2] We now report studies that have led to the achievement of this objective.

Seeking to prepare the bicycle **7a** and/or **8a**, the acetoacetyl thiazolidine **6a**[1] was treated with NEt_3 (300 mol%) in MeOH for 17 h. Subjection of the product to silica gel column chromatography led to the isolation of two fractions. The first fraction (10% yield), $[\alpha]_D$ −85 (*c* 0.34, CH_2Cl_2) was identified as a 75 : 25 mixture of the desired aldol products **7a** and **8a**.‡§ The second fraction was considered to be the triethylammonium salt **9a**;§ treatment of an ethereal solution of the material with potassium 2-ethylhexanoate (in BuOH–Et_2O) gave the potassium salt **9b**‡ (66% yield), mp 251–252 °C, $[\alpha]_D$ −116 (*c* 0.39, H_2O). When resubjected to the cyclisation conditions, the aldol products **7a** and **8a** were unaffected, establishing that the thiazolidine **6a** underwent two competing cyclisations by way of the enolates **10a** and **11a** (arbitrary enolate geometries).



A study of the behaviour of the thiazolidine **6a** towards a variety of base/solvent combinations revealed that KCN (150 mol%) in MeOH was the most effective in promoting the desired cyclisation reactions, giving the results shown in Table 1. A simple work-up¶ provided a 76 : 24 mixture of the aldol products **7a** and **8a** in 32% yield {after chromatography, 29% yield; $[\alpha]_D$ −88 (*c* 0.25, CH_2Cl_2)}.

The slow step in the **6a** → **9b** transformation is likely to involve an intramolecular reaction of the intermediate **11a** in which the enolate adds to the ester carbonyl group. Hoping to dampen this reaction, the ethyl ester **6b**,‡‖ $[\alpha]_D$ −123 (*c* 0.41, CH_2Cl_2), and the isopropyl ester **6c**,‡‖ $[\alpha]_D$ −128 (*c* 0.59, CH_2Cl_2), were prepared. The outcomes of their cyclisation

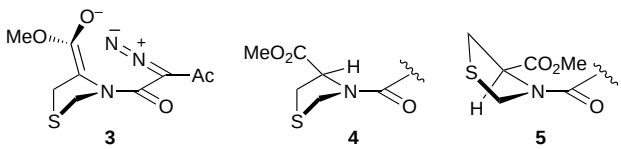


Table 1 Cyclisation reactions of thiazolidines of type **6**

Reactant	R	Conditions	*t*/h	Products	Ratio[a]
6a	Me	KCN–MeOH	2	**7a**,**8a**,**9b**	27 : 9 : 64
6b	Et	KCN–EtOH	4	**7b**,**8b**,**9b**	39 : 20 : 41
6c	Pr^i	KCN–MeOH	2	**7c**,**8c**,**9b**	69 : 23 : 8

[a] Determined by 300 MHz ^{1}H NMR spectroscopic analysis.

reactions are shown in Table 1. Work-ups provided a 72 : 28 mixture of the aldol products **7b** and **8b**‡ (47% yield after chromatography), mp 91–93 °C, $[\alpha]_D$ −98 (*c* 0.38, CH_2Cl_2), and a 72 : 28 mixture of the aldol products **7c** and **8c**‡ (68% yield after chromatography), mp 85–87 °C, $[\alpha]_D$ −95 (*c* 0.29, CH_2Cl_2). Clearly, the desired intramolecular aldol reactions became more favourable as the size of the ester group increased.

The similar optical rotations of the comparable mixtures of the aldol products **7a**/**8a**, **7b**/**8b** and **7c**/**8c** suggested common enantiomeric purities. This was substantiated by a chemical correlation involving the mixtures **7a**/**8a** and **7c**/**8c**. Thus, sequential treatment of the former mixture with Ac_2O–perchloric acid and DBU in CH_2Cl_2 gave the alkene **12a**,‡ mp 73–74 °C, $[\alpha]_D$ +228 (*c* 0.33, CH_2Cl_2). A similar sequence performed on the **7c**/**8c** mixture afforded the alkene **12b**,‡ mp 124–126 °C, $[\alpha]_D$ +215 (*c* 0.41, CH_2Cl_2), which was converted into the methyl ester **12a**, $[\alpha]_D$ +221 (*c* 0.27, CH_2Cl_2), under transesterification conditions (KCN in MeOH). On the basis of HPLC analysis,** compounds **7c** and **8c** were shown to have ees of 99%. It is concluded, therefore, that the aldol products **7a**–**c** and **8a**–**c** are essentially enantiopure.

It remained to establish that the intramolecular aldol reactions had occurred with retention of configuration at the thiazolidine stereocentre. Crystallisation of a 72 : 28 mixture of compounds **7c** and **8c** from hot water provided the major diastereomer, mp 104 °C, $[\alpha]_D$ −108 (*c* 0.33, CH_2Cl_2), which was shown to possess the absolute stereochemistry **7c** by X-ray crystallography†† (Fig. 1). Clearly, the C–H bond adjacent to the alkoxycarbonyl group had been replaced by a C–C bond with retention of configuration. Moreover, there was a kinetic preference to generate the aldol product **7c** over its diastereomer **8c** (and, similarly, of aldols **7a**,**b** over their diastereomers **8a**,**b**).

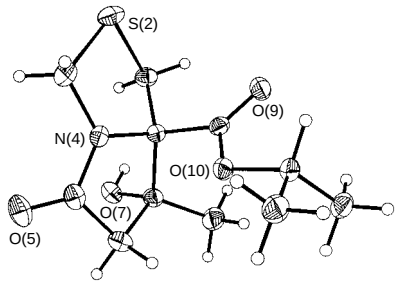


Fig. 1 Molecular structure of compound **7c**

Although stable to the cyclisation conditions, compounds **7c** and **8c** did react with KCN in refluxing MeOH to give mainly the potassium salt **9b**.‡‡ Acidification of an aqueous solution of the salt with Amberlite IR–120 (H^+) ion-exchange resin and subjection of the residue obtained after evaporation to silica gel column chromatography gave the enol **9c**‡ (82% yield), mp 142 °C, $[\alpha]_D$ −89 (*c* 0.51, CH_2Cl_2), as a 72 : 28 mixture of diastereomers, with an ee of 99%.** Evidently, under more forcing conditions, the aldol reaction can be reversed and the enolate intermediates **10a** and **10b** can be reprotonated with essentially complete retention of configuration to regenerate the thiazolidines **6a** and **6c**. Subsequent production of the enolates **11a** and **11b** then leads, by intramolecular acylation reactions, to the salt **9b** with no loss of stereochemical integrity.

As before,[1] we suggest that the stereochemical memory of the enolate **10b** can be accounted for by postulating its generation in an axially chiral form, *e.g.* **13**.

Recently, Fuji reported[3] examples of intermolecular 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.

The aforecited results are of note in a number of respects. The finding that C–C bonds can be constructed stereoselectively considerably extends the scope of self-induced axial chirality as a stereocontrol element in synthesis.§§ Compounds **7a**–**c**, **8a**–**c** and **12a**,**b** are interesting classes of essentially enantiopure fused heterocycles; by appropriate manipulation they should be convertible into α-*C*-substituted 4-thiaprolines and 5-oxoprolines. Finally, the discovery that the kinetic cyclisation products **7c** and **8c** of the thiazolidine **6c** can be converted into the thermodynamic cyclisation product **9b** provides a striking illustration of stereoretentive protonation accompanying the retroaldol reaction.

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Notes and References

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‡ The product displayed analytical and spectral properties that supported its assigned structure.

§ For analogous cyclisations on an oxazolidine framework, see ref. 4.

¶ After evaporation of the solvent, the product was partitioned between CH_2Cl_2 and brine; evaporation of the dried ($MgSO_4$) organic phase gave the aldol products **7a** and **8a** in a near-pure state.

‖ Compounds **6b** and **6c** were prepared from L-cysteine hydrochloride (in respective overall yields of 40 and 31%) by routes similar to that employed in the synthesis of compound **6a** (see ref. 1).

** The enantiomers were separated on a Chiralpak AD column, using hexanes–propan-2-ol (9 : 1) as eluent (flow rate: 0.5 cm^3 min^{-1}) in the cases of **7c**/*ent*-**7c** and **8c**/*ent*-**8c** and hexanes–ethanol (85 : 15) as eluent (flow rate: 0.7 cm^3 min^{-1}) in the case of **9c**/*ent*-**9c**.

†† *Crystal data* for **7c**: $C_{11}H_{17}NO_4S$, M = 259.32, orthorhombic, space group $P2_12_12_1$, a = 6.4154(15), b = 13.321(4), c = 14.961(5) Å, U = 1278.5(6) Å^3, Z = 4, D_c = 1.347 g cm^{-1}, μ = 0.256 mm^{-1} (Mo–Kα, λ = 0.71073 Å), F(000) = 552, T = 123(1) K. Siemens SMART CCD area-detector diffractometer, crystal size 0.18 × 0.20 × 0.60 mm, θ_{max} 29.15°, 14263 reflections measured, 3181 unique (R_{int} = 0.0419). Structure solution by direct methods, full-matrix least-squares refinement on F^2 with weighting $w^{-1} = \sigma^2(F_o^2) + (0.0676P)^2$, where $P = (F_o^2 + 2F_c^2)/3$, anisotropic displacement parameters, riding hydrogen atoms, no absorption correction, absolute structure parameter = −0.02(7). Final $Rw = \{\Sigma[w(F_o^2–F_c^2)^2]/\Sigma[w(F_o^2)^2]^{\frac{1}{2}}\}$ = 0.1002 for all data, conventional R = 0.0376 on F values of 2872 reflections with $I > 2\sigma(I)$, S = 1/073 for all data and 154 parameters. Final difference map between +0.31 and −0.44 e Å^{-3}, Programs: Siemens SMART and SAINT control and integration software, SHELXTL (G. M. Sheldrick, University of Gottingen, Germany). CCDC 182/717.

‡‡ Some transesterification, leading to compounds **7a** and **8a**, occurred during the course of this transformation.

§§ For a summary of asymmetric inductions directed by non-biaryl atropisomers, see ref. 5.

1 B. Beagley, M. J. Betts, R. G. Pritchard, A. Schofield, R. J. Stoodley and S. Vohra, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1761.
2 T. Wirth, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 225.
3 T. Kawabata, T. Wirth, K. Yahiro, H. Suzuki and K. Fuji, *J. Am. Chem. Soc.*, 1994, **116**, 10 809.
4 M. D. Andrews, A. G. Brewster and M. G. Moloney, *Synlett*, 1996, 612.
5 J. Clayden, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 949.

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