# Synthetic Study of the Highly Potent and Selective Anti-platelet Activating Factor Thiazolidin-4-one Agents and Related Compounds[1]

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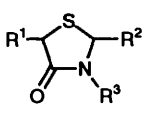
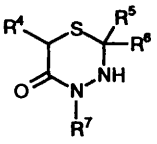
Stereoselective cyclo-condensation of α-sulfanylcarboxylic acids (or esters) **6** with *N*-methylarylimines **7** afforded the title compounds, 2-arylthiazolidin-4-ones, some of which exhibit highly potent anti-PAF activity. The reaction without added catalyst gave predominantly *cis* products, however, when titanium(IV) isopropoxide was added as catalyst *trans* products were predominantly formed. Allylation of 3-methyl-2-(3-pyridyl)thiazolidin-4-one **22** with allyl bromide using lithium amides gave the *trans*-5-allyl-2-(3-pyridyl)thiazolidin-4-one **23** with good selectivity. To study the stereostructure–activity relationship, the four optically active isomers of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one **4** and 5-(4-chlorophenyl)-3-methyl-2-(3-pyridyl)thiazolidin-4-one **5** were synthesized. The absolute configurations of compounds **4** and **5** were determined by X-ray analyses and $^1$H NMR measurements. Epimerization of the 5-position of compounds **4** and **5** was found to be effected by bases with high regioselectivity (>99%), which was checked by a cross-over experiment using several optically active compounds.

Since the discovery[2] of the platelet activating factor (PAF), a number of investigations have been devoted to developing it for the medical applications.[3] In addition, increasing interest has centred on anti-PAF active agents (PAF antagonist), and research in these areas is currently one of the most challenging problems in pharmacology. As part of our continuing programme in search of biologically active sulfur and nitrogen containing heterocycles,[1,4a,4b] we have attempted to synthesize several thiazolidin-4-ones **1** and perhydro-1,3,4-thiadiazin-5-ones **2**[4c] and evaluate their various biological activities.



**1**



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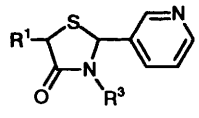

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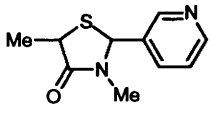

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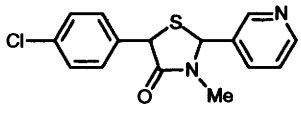


**5**

As a result of our efforts, we found highly potent PAF antagonistic activity in several 2-(3-pyridyl)thiazolidin-4-ones **3**. This novel class of anti-PAF agents, such as SM-10661 [the hydrochloride of the (+)-*cis*-isomer of **4**][1,5] and PR-1115 **5**, which is the original lead compound of a series of anti-PAF active thiazolidin-4-ones, despite their simple structure, exhibit high and selective antihypersensitive activity both *in vitro* and *in vivo*. Also noteworthy is their oral activities derived from their solubility in water.

We report here the details of a synthetic study of compounds **4** and **5** which includes (i) reactivity and relative stereoselectivity (*cis*:*trans*)† in the construction of thiazolidin-4-ones **1** ($R^2$ = Ar) and **3** through a cyclo-condensation reaction; (ii) relative stereoselectivity in the allylation of the 5-position of the thiazolidin-4-one **22**; (iii) syntheses of four optically active isomers of the two representative compounds, **4** and **5**, to clarify the stereostructure–activity relationship; and (iv) regioselective epimerization of the 5-position of the thiazolidin-4-ones **4** and **5** promoted by bases.

## Results and Discussion

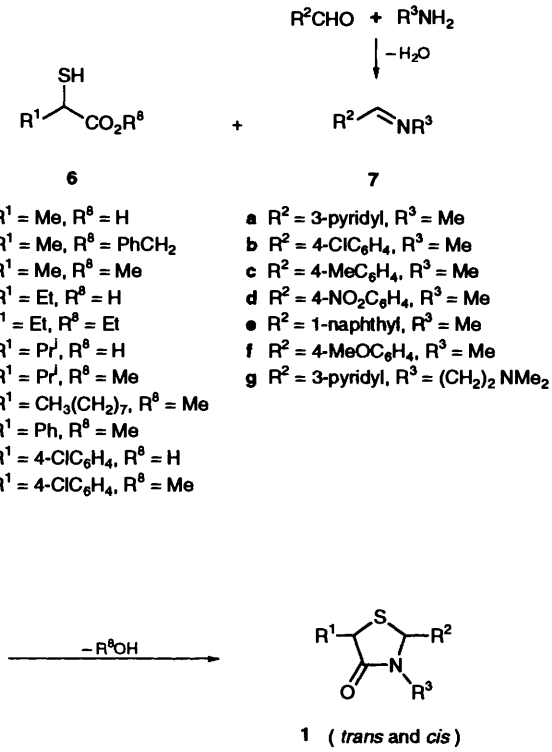
*I Cyclo-condensation of α-Sulfanylcarboxylic Acids (or their Esters) **6** with N-Methylarylimines **7**: their Reactivity and Relative Stereoselectivity* (cis:trans).—The syntheses of 2-arylthiazolidin-4-ones **1** ($R^2$ = Ar) have been prepared by the condensation of α-sulfanylcarboxylic acids **6** ($R^8$ = H) with primary amines ($R^3NH_2$) and aldehydes (ArCHO) or with the corresponding Schiff bases **7** ($R^2$ = Ar) (Scheme 1).[6] The cyclo-condensation reactions were usually carried out in refluxing benzene or toluene with azeotropic removal of water. However, little information was obtained concerning the reaction conditions and the stereoselectivity (*cis*:*trans*). To clarify these points, we first examined the reaction 2-sulfanylpropionic acid **6a** or its benzyl ester **6b** with three *N*-methylarylimines **7a**, **7b** and **7c** under various conditions as shown in Table 1. Thus, 2-sulfanylpropionic acid **6a** reacted with imines **7a**–**7c** even at 0 °C–room temperature in toluene, dichloromethane and ether solvents (Table 1, entries 1, 3 and 6–10), whereas the reaction of benzyl 2-sulfanylpropionate **6b** with imines **7a** and **7b** required elevated temperatures (entries 11–13). The higher reactivity of the acid **6a** compared with the ester **6b** could be accounted for by intermolecular activation of the imine nitrogen by the

† *cis* and *trans* are used throughout this paper to designate the relative positions of the substituents in the 2- and 5-positions of the thiazolidin-4-ones.

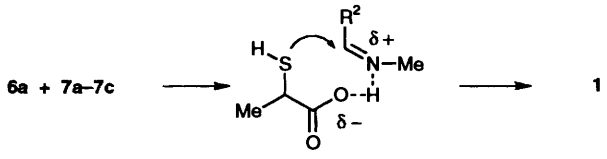
**Table 1** Cyclo-condensation between 2-sulfanylpropionic acid (or esters) **6a–6c** and imines **7a–7c**[a]

| | | | Conditions | | | | Product | |
|---|---|---|---|---|---|---|---|---|
| Entry | 6 | 7 | Solvent | $T$/°C | $t$/h | Additive | *cis*:*trans*[b] | Yield (%) |
| 1 | a | a | Toluene | R.t.[c] | 5 | — | 4:1 | 77 |
| 2 | a | a | Toluene | 120 | 2 | — | 3:1 | 88 |
| 3 | a | a | $CH_2Cl_2$ | R.t. | 5 | — | 4:1 | 78 |
| 4 | a | a | $C_2H_4Cl_2$[d] | 80 | 5 | — | 4:1 | 76 |
| 5 | a | a | $C_2H_4Cl_2$ | 80 | 5 | MS 4 Å[e] | 4:1 | 66 |
| 6 | a | a | THF | R.t. | 5 | — | 5.5:1 | 77 |
| 7 | a | a | THF | 0 | 10 | — | 6:1 | 75 |
| 8 | a | a | DME[f] | 0 | 10 | — | 6:1 | 74 |
| 9 | a | b | $CH_2Cl_2$ | R.t. | 5 | — | 4:1 | 79 |
| 10 | a | c | $CH_2Cl_2$ | R.t. | 5 | — | 8:1 | 87 |
| 11 | b | a | $CH_2Cl_2$ | R.t. | 5 | — | — | Trace |
| 12 | b | b | $CH_2Cl_2$ | R.t. | 5 | — | — | Trace |
| 13 | b | a | Toluene | 100 | 5 | — | 2:1 | 68 |
| 14 | a | b | $CH_2Cl_2$ | R.t. | 5 | $Et_3N$ | 6:1 | 21 |
| 15 | b | a | $CH_2Cl_2$ | R.t. | 48 | $Et_3N$ | 6:1 | 40 |
| 16 | a | a | $CH_2Cl_2$ | R.t. | 10 | $B(OMe)_3$ | 3:1 | 30 |
| 17 | a | a | $CH_2Cl_2$ | R.t. | 10 | $Al(OPr^i)_3$ | — | Trace |
| 18 | a | a | $CH_2Cl_2$ | R.t. | 10 | $Ti(OPr^i)_4$ | 0.8:1 | 15 |
| 19 | b | a | $CH_2Cl_2$ | R.t. | 2 | $Ti(OPr^i)_4$ | 0.25:1 | 77 |
| 20 | c | a | $CH_2Cl_2$ | R.t. | 20 | $Ti(OPr^i)_4$–MS 4 Å[g] | 0.40:1 | 58 |

[a] Molar ratio of **6**:**7**:additive = 1:1:1. [b] Ratios of *cis*:*trans* were determined by integration of the resonance of the 3-methyl protons in the $^1H$ NMR spectra. [c] R.t. = room temperature. [d] 1,2-Dichloroethane. [e] Molecular sieves 4 Å (0.5 g mmol$^{-1}$ of **6a**). [f] 1,2-Dimethoxyethane. [g] $Ti(OPr^i)_4$ (10 mol% *vs.* **6c**) and molecular sieves 4 Å (0.5 g mmol$^{-1}$ of **6c**) were used.



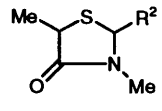

**Scheme 1**



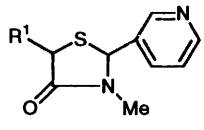

**Scheme 2**

accessible carboxylic group of **6a** (Scheme 2).‡ This push–pull mechanism is supported by the retarding effect of the presence of triethylamine on the reaction with acid **6a** (entry 14). In contrast, triethylamine slightly accelerated the reaction of the ester **6b**, where the thiolate anion of **6b** was thought to act as the nucleophile towards the imine **7a** (entry 15). Although the imine **7a** has a 3-pyridyl amine function in the molecule, the lower reactivity was similar to that of **7b** (entries 11 and 12).

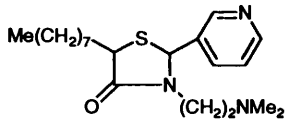
As has been reported,[8] stereoselectivity of the reactions of 2-sulfanylpropionic acid **6a** with imines **7a**, **7b** and **7c** to give the corresponding 2-aryl-3,5-dimethylthiazolidin-4-ones **4**, **8** and **9**




**8** $R^2$ = 4-$ClC_6H_4$
**9** $R^2$ = 4-$MeC_6H_4$
**10** $R^2$ = 4-$NO_2C_6H_4$
**11** $R^2$ = 1-naphthyl
**12** $R^2$ = 4-$MeOC_6H_4$



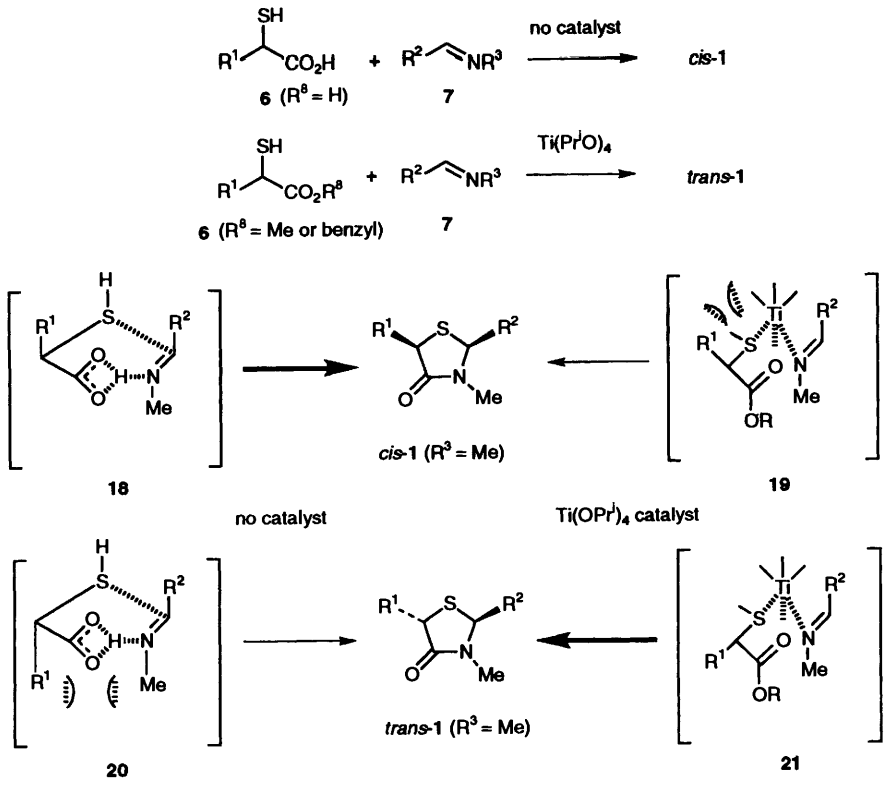

**13** $R^1$ = Et
**14** $R^1$ = $Pr^i$
**15** $R^1$ = $Me(CH_2)_7$
**16** $R^1$ = Ph




**17**

was found to be generally *cis*-dominated (*cis*:*trans* = 3:1–4:1) (entries 1–5). This tendency was enhanced up to 6:1 (*cis*:*trans*) using ether solvents such as tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) (entries 6–8). As for the imines **7**, *N*-(4-methylbenzylidene)methylamine **7c** showed relatively higher *cis* selectivity in the reaction with 2-sulfanylpropionic acid **6a** (entry 10). These results may be explained by the difference nature of the imines **7** employed.

‡ A similar phenomenon was seen in the addition of thiols to *N*-benzylideneanthranilic acid, where intramolecular activation of the imino group by the carboxylic group of benzalanthranilic acid is assumed to contribute to the high reactivity.[7]




Scheme 3

**Table 2** Stereoselectivity of the reaction between various α-sulfanylcarboxylic acids (or esters) **6** and imines **7**[a]

| Entry | 6 | 7 | Product | Method[b] | *cis*:*trans* | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **b** | **b** | **8** | A | 1:4[c] | 81 |
| 2 | **b** | **c** | **9** | A | 1:4[c] | 78 |
| 3 | **b** | **d** | **10** | A | 1:4[c] | 55 |
| 4 | **b** | **e** | **11** | A | 1:9.0[d] | 72 |
| 5 | **b** | **f** | **12** | A | 1:3[c] | 62 |
| 6 | **d** | **a** | **13** | B | 3.7:1[d] | 77 |
| 7 | **e** | **a** | **13** | A | 1:7.3[d] | 74 |
| 8 | **f** | **a** | **14** | B | 3.0:1[d] | 73 |
| 9 | **g** | **a** | **14** | A | 1:13[d] | 72 |
| 10 | **h** | **a** | **15** | A | 1:12[d] | 66 |
| 11 | **i** | **a** | **16** | A | 1:20[d] | 75 |
| 12 | **j** | **a** | **5** | B | 3.0:1[d] | 77 |
| 13 | **k** | **a** | **5** | A | 1:20[d] | 68 |
| 14 | **h** | **g** | **17** | A | 1:3[e] | 68 |

[a] Molar ratio of **6**:**7**:[$Ti(OPr^i)_4$] = 1:1:[1]. [b] Method A: using an equimolar amount of $Ti(OPr^i)_4$ in $CH_2Cl_2$ at room temperature for 10–24 h. Method B: in $CH_2Cl_2$ at room temperature for 10–24 h. [c] Ratios of *cis*:*trans* were determined by the integration of the resonance of the 3-methyl protons in the $^1H$ NMR spectra. [d] Ratios of *cis*:*trans* were determined by HPLC analysis. [e] Ratios of *cis*:*trans* were determined by the integration of the *N*,*N*-dimethyl resonance of the protons in the $^1H$ NMR spectra.

From the standpoint of the anti-PAF biological activity, the *trans*-2-(3-pyridyl)thiazolidin-4-ones are more important than the *cis*-isomers except for the 5-methyl analogue **4**. To effect *trans* selectivity, the addition of metal alkoxides such as aluminium isopropoxide, trimethylborate and titanium(IV) isopropoxide to the present reaction system was next attempted. Titanium(IV) isopropoxide was slightly effective (*cis*:*trans* = 0.8:1) in the reaction of 2-sulfanylpropionic acid **6a** with imine **7a**, although the yield was decreased (entry 18). Encouraged by the result, we applied the same conditions to the reaction of benzyl 2-sulfanylpropionate **6a**, and found that the addition of titanium(IV) isopropoxide not only accelerated the reaction but also contributed to relatively high *trans* selectivity (*cis*:*trans* = 0.25:1) (entry 19). Of note is that even using only a catalytic amount (10 mol% *vs.* **6c**) of titanium(IV) isopropoxide was effective with methyl 2-sulfanylpropionate **6c** in the presence of 4 Å molecular sieves (entry 21).§ Higher *trans* selectivity was observed in the new $Ti(OPr^i)_4$-promoted reaction (method A) using several other esters of α-sulfanylcarboxylic acids **6** as shown in Table 2 and Scheme 3. Reactions of *N*-(arylmethylidene)methylamines **7b**, **7c** and **7d** gave similar results (entries 1–3) and higher *trans* selectivity (*cis*:*trans* = 1:9.0) was shown in the case of *N*-(1-naphthylmethylidene)methylamine **7e** (entry 4). As for the esters **6**, the steric bulkiness of the $R^1$ group apparently affected the *trans*-selectivity which was enhanced up to *cis*:*trans* = 1:20, when the esters **6i** and **6k** bearing an aryl group as $R^1$ were employed (entries 7, 9–11 and 13). Finally, this reaction is sufficiently mild as to be applicable to the synthesis of optically active thiazolidin-4-ones using the available esters of **6c** and **6k** with little observable racemization (details are described in section III).

The assignment of the relative configuration (*cis* and *trans*) relied on the reported $^1H$ NMR analysis[8] and on our unequivocal determination by X-ray analyses of (2*S*,5*R*)-(−)-*cis*-**4**, (2*S*,5*S*)-(−)-*trans*-**5** and (2*R*,5*S*)-(+)-**5** stereoisomers.

The sharp contrast between the stereoselectivities of two alternative methods can be accounted for by the following plausible reaction mechanism as illustrated in Scheme 3. Steric repulsion of the $R^1$ group of acids **6** and the methyl group of the *E*-imines[9] **7** in the two metal-free transition states **18** and **20** would more preferentially lead to the *cis*-thiazolidin-4-ones (*cis*-**1**, $R^3$ = Me) than the *trans* isomers. In contrast, when $Ti(OPr^i)_4$ was present in this system, steric hindrance between the titanium(IV) ligands and the $R^1$ group of **6** would be more

§ Molecular sieves (4 Å) were used to trap the methanol by-product of the reaction. The effect on yield and stereoselectivity needs to be examined more extensively.

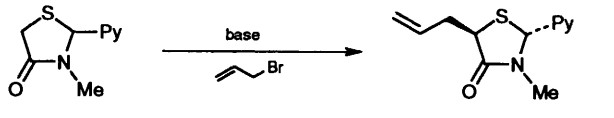
**Table 3** Allylation of 3-methyl-2-(3-pyridyl)thiazolidin-4-ones **22** with allyl bromide[a]

| Entry | Base | Solvent | T/°C | t/h | *cis*:*trans*[b] | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | LDA[c] | THF | 0 | 1 | 1:6.4 | 53 |
| 2 | LDA | THF | −78–0 | 2 | 1:8.4 | 58 |
| 3 | LDA | THF–HMPA (5:1) | −78–0 | 2 | 1:5.5 | 63 |
| 4 | KDA[d] | THF | 0 | 1 | 1:1.1 | 55 |
| 5 | LHMDS[e] | THF | 0 | 1 | 1:5.8 | 60 |
| 6 | LHMDS | THF | −78–room temp. | 2 | 1:6.7 | 66 |

[a] Molar ratio of **22**:base:allyl bromide = 1:1.1:1.1. [b] Ratios of *cis*:*trans* were determined by HPLC analysis. [c] Lithium diisopropylamide. [d] Potassium diisopropylamide (*tert*-BuOK–LDA). [e] Lithium hexamethyldisilazide.

influential than that between the methyl group of **7** and the $R^1$ group. Accordingly, the titanium(IV)-coordinated transition state **21** rather than **19** would predominantly lead to the *trans* diastereoisomer (*trans*-**1**, $R^3$ = Me). The dual course of the thiazolidin-4-one formation would proceed through a kinetically controlled process, since the *trans*- to *cis*-ratios of thiazolidin-4-one **1** ($R^3$ = Me) under thermodynamic equilibrium conditions were closer to one (details are described in section IV).

*II Allylation of the 5-Position of 3-Methyl-2-(3-pyridyl)-thiazolidin-4-one* **22**.—Allylation of the 5-position of 3-methyl-2-(3-pyridyl)thiazolidin-4-one **22** is the basis of an alternative reaction for the preparation of a series of 5-alkyl substituted 3-methyl-2-(3-pyridyl)thiazolidin-4-ones. To study the basic scope of the reactivity and stereoselectivity (*cis*:*trans*), we examined the allylation of **22** with allyl bromide to give 5-allyl-3-methyl-2-(3-pyridyl)thiazolidin-4-one **23** using several bases (Scheme 4). Among the bases, such as potassium *tert*-butoxide,




**22** **23** (*trans*)

**Scheme 4**

sodium hydride, potassium hydride and alkali amides examined, lithium diisopropylamide (LDA), potassium diisopropylamide (KDA) and lithium hexamethyldisilazide (LHMDSA) gave good resulting yields as shown in Table 3.

As for the stereoselectivity (*cis*:*trans*), employing lithium amides (LDA and LHMDSA) was found to give mostly *trans*-(*cis*:*trans* = 1:5.8–8.4) products of **23** (Table 3, entries 1–3, 5 and 6). The use of hexamethylphosphoramide (HMPA) as a co-solvent did not affect the stereoselectivity (entry 3). When KDA was used, the ratio of the *trans*-isomer was significantly decreased (entry 4). These results suggest that the allylation mediated by LDA or LHMDSA proceeded in a kinetically controlled manner, but in contrast, was mediated by KDA in a thermodynamically controlled manner, since the reaction with KDA and the use of HMPA also contribute to the liberation of the anion of **22** and/or **23** from the corresponding counter cation. This speculation is in agreement with the results of the base-catalysed epimerization of the 5-position of **3** as described in section IV.

*III Syntheses of the Four Optically Active Isomers of Thiazolidin-4-ones* **4** *and* **5**.—In order to investigate the stereostructure–activity relationship of the binding modes to the PAF receptor,[1] we planned to synthesize the four isomers of both 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one **4** and 5-(4-chlorophenyl)-3-methyl-2-(3-pyridyl)thiazolidin-4-one **5**, which are known to show high and selective anti-PAF activities in their racemic forms.

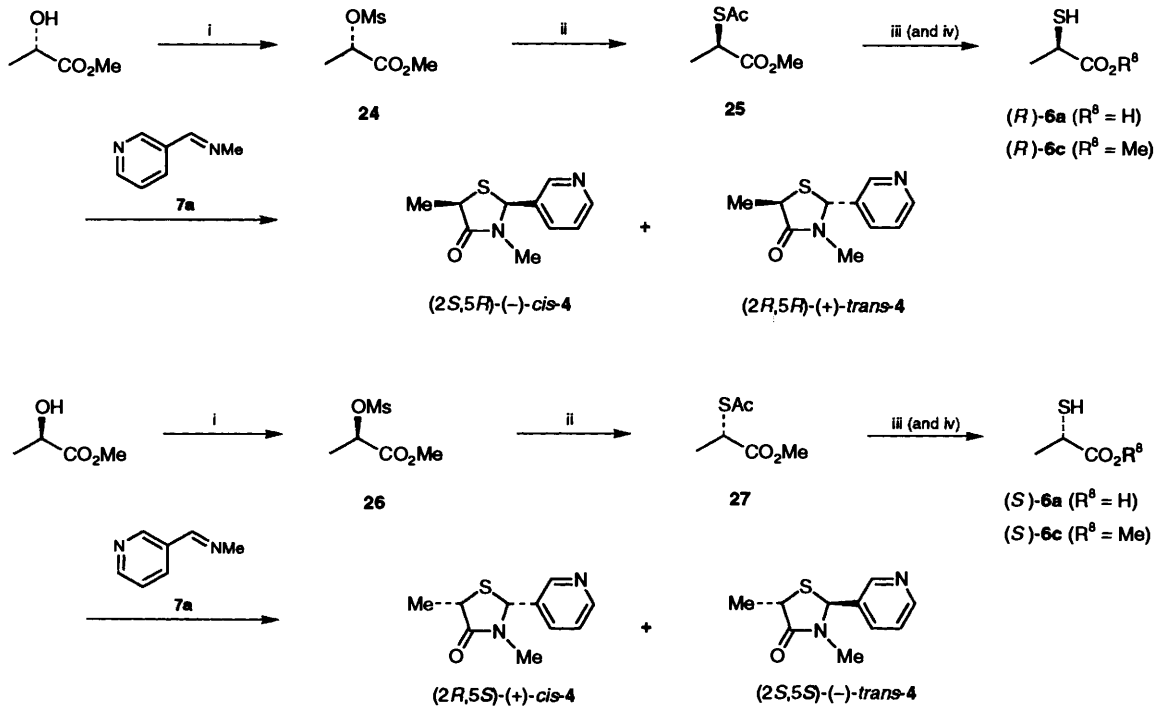
(*a*) *The four stereoisomers of 3,5-dimethyl-2-(3-pyridyl)-thiazolidin-4-one* **4**. The synthetic route towards the four stereoisomers of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one **4** is outlined in Scheme 5. (*R*)-2-Sulfanylpropionic acid (*R*)-**6a** ($[\alpha]_D^{25}$ +51.5) and (*S*)-2-sulfanylpropionic acid (*S*)-**6a** ($[\alpha]_D^{24}$ −50.9) were prepared from (*S*)- and (*R*)-methyl lactate, respectively, in three steps by the known method.[10,11] The loss of optical purity of 2-sulfanylpropionic acid (*R*)-**6a** (90% ee) and (*S*)-**6a** (89% ee) based on the reported optical rotations was assumed to be due to the incomplete $S_N2$-inversion of the acetylthiolate anion towards methanesulfonates **24** and **26** or the ease of racemization of the esters **25** and **27**.[11] We used sodium thioacetate in DMF for the $S_N2$ reaction, but the optical purity of **25** or **27** was a little lower compared with Kellogg's procedure[11] using cesium thioacetate.¶

The (2*S*,5*R*)-(−)-*cis*- and (2*R*,5*S*)-(+)-*cis*-isomers of **4** were synthesized by cyclo-condensation employing the acids (*R*)-**6a** and (*S*)-**6**, respectively, with *N*-(3-pyridylmethylidine)methylamine **7a** under the conditions of Table 1, entry 7. Thus, the two *cis*-isomers (2*S*,5*R*)-(−)-*cis*-**4** (mp 67.5–69.5 °C, $[\alpha]_D^{23}$ −22.8) and (2*R*,5*S*)-(+)-*cis*-**4** (mp 67.5–69.0 °C, $[\alpha]_D^{23}$ +22.5) were obtained in high chemical (>99%) and optical purity (98% ee) by recrystallization. Their optical purities were determined by HPLC analysis (column; Sumipax OA-2500 bearing a chiral stationary phase) and/or $^1$H NMR measurement using Eu(hfc)$_3$ {tris[(heptafluoropropylhydroxymethylene)camphorato]-europium(III)}. The X-ray structure diagram of the (2*S*,5*R*)-(−)-*cis*-isomer of **4** is illustrated in Fig. 1 to assert the unequivocal stereochemical assignment.

The synthesis of the (2*R*,5*R*)-(+)-*trans*- and (2*S*,5*S*)-(−)-*trans*-isomers of **4** on a practical scale was performed by the Ti(OPr$^i$)$_4$ catalysed cyclo-condensation. Thus, the (2*R*,5*R*)-(+)-*trans*-**4** (32% yield, $[\alpha]_D^{24}$ +131.5) and (2*S*,5*S*)-(−)-*trans*-isomers of **4** (31% yield, $[\alpha]_D^{23}$ +133.8) were obtained using methyl 2-sulfanylpropionate (*R*)-**6c** ($[\alpha]_D^{22}$ +53.5) and (*S*)-**6c** ($[\alpha]_D^{22}$ −52.9), respectively. These isolated yields are moderate since both *trans* optical isomers were oily compounds and have similar $R_f$ values [*trans*-**4** (0.32) and *cis*-**4** (0.30), respectively on thin layer chromatography (Merck, Art. 5715; $C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH, 4:1:1)].

There still remained the problem of how to obtain highly optically pure products of these *trans*-isomers of **4**, since their optical purities essentially depend on the optical purities of the methyl 2-sulfanylpropionate (*R*)-**6c** and (*S*)-**6c**. To solve this problem, we planned the conversion of the (2*S*,5*R*)-(−)-*cis*-isomer of **4** into (2*S*,5*S*)-(−)-*trans*-**4**, and that of the (2*R*,5*S*)-(+)-*cis*-isomer of **4** into the (2*R*,5*R*)-(+)-*trans*-isomer of **4** by means of a highly regioselective epimerization of the 5-position of each highly optically pure *cis*-isomer of **4** (details are described in section IV).

¶ After completion of this work, the reaction of optically active 2-chloropropionic acid with sodium acetylthiolate was found to take place cleanly to give the inverted 2-sulfanylpropionic acid, which will be appropriate for industrial scale production for SM-10661.




**Scheme 5** *Reagents and conditions:* i, MsCl, $Et_3N$–$Et_2O$, 0 °C–room temp.; ii, AcSH, NaH–DMF, 0 °C; iii, for **6a**: 10% aq. HCl, 80 °C; iv, for **6c**: $H^+$–MeOH

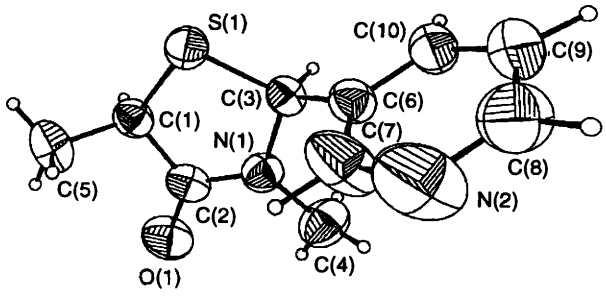



**Fig. 1** X-Ray structure of (2*S*,5*R*)-(−)-*cis*-**4**. There are two crystallographically independent molecules (A or B) in the asymmetric unit. An ORTEP drawing of molecule A is shown.

(*b*) *The four stereoisomers of* 5-(4-*chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* **5**. The synthesis of the four stereoisomers of **5** is basically the same as for those of **4** as illustrated in Scheme 6. Racemic (4-chlorophenyl)sulfanylacetic acid **6j** was prepared from 4-chlorophenylacetic acid in four steps with an overall 72% yield. The racemic acid **6j** could be resolved with cinchonidine and cinchonine to afford (*S*)-(+)-**6j** and (*R*)-(−)-**6j**, respectively. Optically active ephedrine was also effective but inferior in resolving efficiency: the initial salt of (−)-ephedrine and racemic acid **6j** showed the (*R*)-(−)-rich acid (25% yield; 38–42% ee) after decomposition of the salt. When cinchonine or (−)-ephedrine was used, the (*R*)-(−)-rich acid of **6j** could be recovered from the second mother liquor after the salt decomposed. In contrast, the (*S*)-(+)-rich acid of **6j** could hardly be recovered using cinchonidine, because the sulfanylacetic acid was contaminated with considerable amount of its disulfide. A similar result has been reported in the literature.[12]

The assignment of the absolute configuration of the acid (*S*)-(+)-**6j** relied on the X-ray structure determination of the target compounds, *i.e.* the (2*R*,5*S*)-(+)-*cis*- (Fig. 2) and (2*S*,5*S*)-(−)-*trans*-isomers of **5** (Fig. 3). The (2*S*,5*S*)-(−)-*trans*- and (2*R*,5*S*)-(+)-*cis*-isomers of **5** were synthesized from (*S*)-(+)-**6j** (mp 123–125 °C; $[\alpha]_D^{19}$ +84.8) in 15 and 61%, respectively, under the conditions of Table 1, entry 7. In a similar manner, the enantiomers (2*R*,5*R*)-(+)-*trans*-**5** and (2*S*,5*R*)-(−)-*cis*-**5** were prepared in 16 and 58% yield, respectively from (*R*)-(−)-**6j** (mp 123–125 °C; $[\alpha]_D^{26}$ +83.0). These four products of **5** could be purified chemically (>99%) and optically (>99% ee) by recrystallization to give (2*S*,5*S*)-(−)-*trans*-isomer of **5** (mp 137–138 °C; $[\alpha]_D^{28}$ −54.5), (2*R*,5*S*)-(+)-*cis*-isomer of **5** (mp 127–129 °C; $[\alpha]_D^{24}$ +29.0), (2*R*,5*R*)-(+)-*trans*-isomer of **5** (mp 138–139 °C; $[\alpha]_D^{26}$ −54.4) and (2*S*,5*R*)-(−)-*cis*-isomer of **5** (mp 137–139 °C; $[\alpha]_D^{28}$ −28.2). The chemical and optical purities were analysed by HPLC.

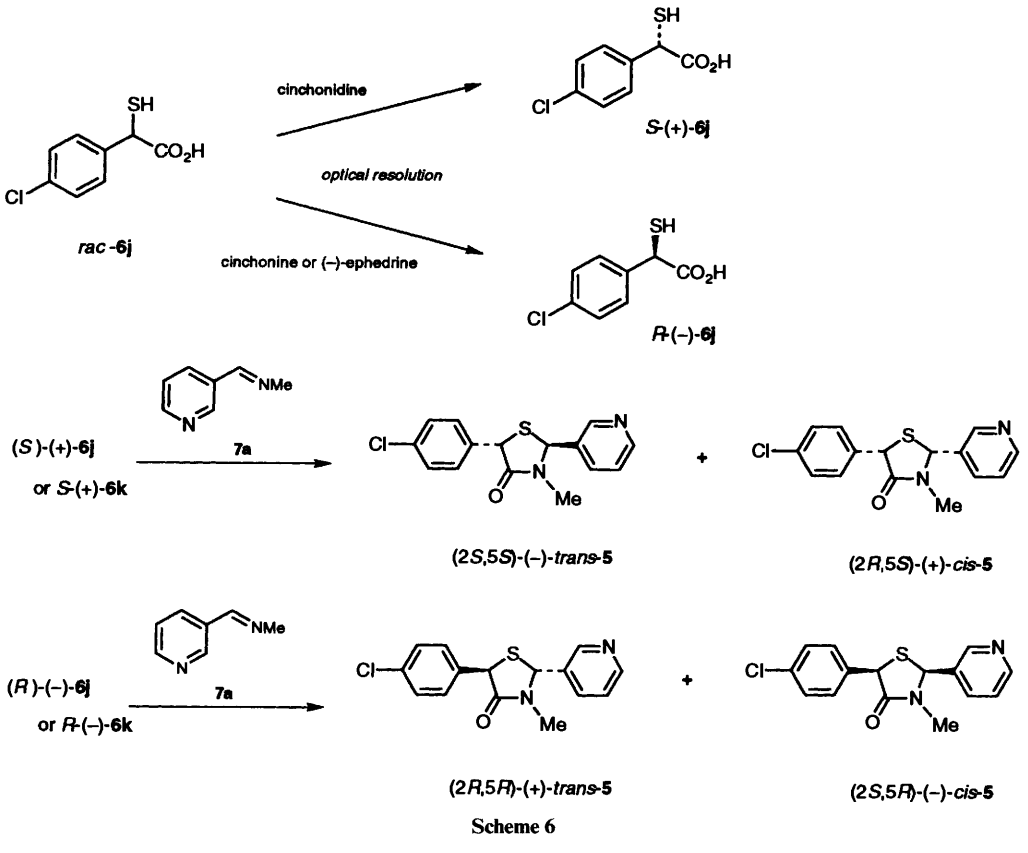
The *trans*-predominant $Ti(OPr^i)_4$ mediated cyclo-condensation was also applicable to this case. The methyl ester [(*R*)-(−)-**6k** ($[\alpha]_D^{26}$ −83.0)] derived from acid (*R*)-(−)-**6j** (mp 123–125 °C; $[\alpha]_D^{26}$ +84.1 about 93% ee) was employed under suitable conditions (Table 2, entry 13) to afford the desired thiazolidine (2*R*,5*R*)-(+)-*trans*-**5** (51% yield; 92% ee). This result indicates that the reaction proceeded with little loss of optical purity (<2% ee).

In conclusion, two *cis*-enantiomers of **4**, and four *cis* and *trans* enantiomers of **5** could be obtained in high chemical and optical purities.

*IV Regioselective Epimerization of the* 5-*Position of Thiazolidin*-4-*ones* **4**, **5** *Promoted by Bases*.—We examined the base-catalysed, site-selective epimerization of the 5-position of thiazolidin-4-ones **4** and **5** (Scheme 7, Table 4) to study the chemical properties of thiazolidin-4-ones and for the synthesis of both highly optically pure *trans* enantiomers of **4**.

First, several bases were screened using racemic *cis*- and *trans*-thiazolidin-4-ones **5** as the substrates. Triethylamine and a catalytic amount (10 mol% *vs.* *cis*-isomer of **5**) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were sufficiently effective to epimerize the *cis*- and *trans*-isomers of **5**. The *cis*:*trans* ratios of *ca.* 4:6 display the thermodynamic equilibrium value of **5** (Table 4, entries 1–3), since the value was constant if the reaction time was prolonged.

When the racemic *cis*-isomer of **4** was used, the epimerization required a stronger base such as sodium methoxide (NaOMe), potassium *tert*-butoxide (Bu$^t$OK) or lithium diisopropylamide




Scheme 6

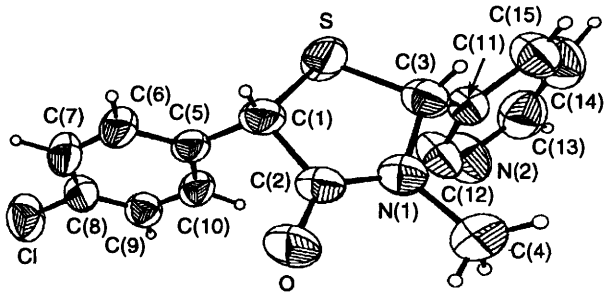



Fig. 2 X-Ray structure of (2*R*,5*S*)-(+)-*cis*-**5** (ORTEP drawing)

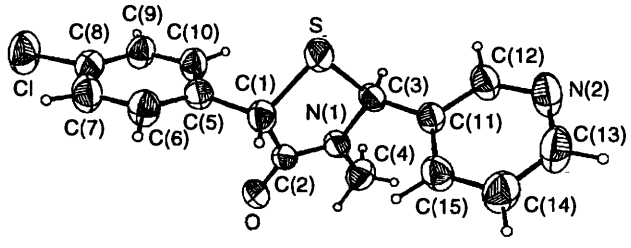


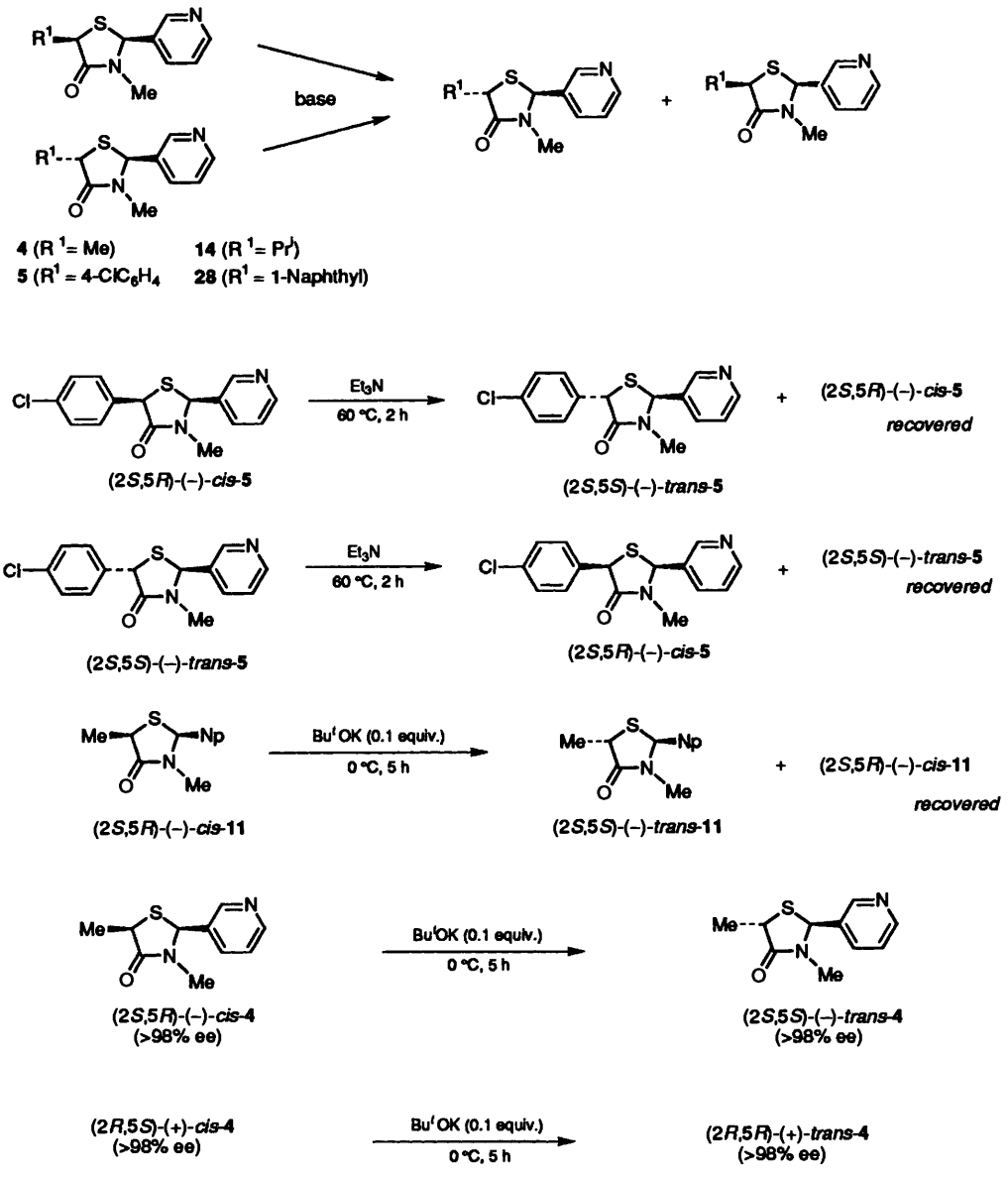

Fig. 3 X-Ray structure of (2*S*,5*S*)-(–)-*trans*-**5** (ORTEP drawing)

(LDA), compared with that used for **5** due to the lower acidity of the 5-position of **4** (entries 1–9 and 12–17). Among them, a catalytic amount (10 mol% *vs.* substrate **4**) of Bu$^t$OK cleanly epimerized the *cis*- and *trans*-isomers of **4** at 0–60 °C. When NaOMe was used harsher conditions were required (80 °C, 5 h) to finish the epimerization. Aqueous NaOH caused the decomposition of the *cis*-isomer of **4**. It is notable that 0.1 equiv. of Bu$^t$OK could epimerize the *cis*-isomer of **4**, but LDA (0.1 equiv.), despite being stronger base, failed to complete the epimerization of the *cis*-isomer of **4** and required an equivalent amount for the purpose (entries 5–9). A plausible explanation for these results is that the lithium counter cation chelates more strongly to the anion of **4** than the potassium cation, so that the use of LDA prevents the complete epimerization of **4** *via* intermolecular disproportionation.

The equilibrium ratios which indicate the thermodynamic stabilities of *cis*- and *trans*-isomers of **4** and **14** are *ca.* 1:1 and 40:60, respectively (entries 13, 14, 19 and 20). Accordingly, the *trans*-ratios values somewhat relied on the steric bulkiness of these 5-substituents. It should be noted that the Ti(OPr$^i$)$_4$ catalysed cyclo-condensation did not epimerize *cis*-**4** and **5** under the present conditions, which indicates the mildness of Ti(OPr$^i$)$_4$ (entries 21 and 22).

Next, we evaluated the regioselectivity of the present epimerization using high optically pure (2*S*,5*R*)-(–)-*cis*- and (2*S*,5*S*)-(–)-*trans*-isomers of **5**, and the (2*S*,5*R*)-(–)-*cis*-isomer of 3,5-dimethyl-2-(1-naphthyl)thiazolidin-4-one **11** as substrates. All of the thiazolidines were crystals so that highly optically pure compounds could be easily obtained by recrystallization. The 1-naphthyl analogue **11** showed sharp discrimination between four optical isomers on HPLC (Sumipax OA-2500 bearing a chiral stationary phase) and so **11** was used for setting optimized conditions.‖

‖ For further synthetic studies of optically active thiazolidin-4-ones **1**, we confirm the method for determining the optical purity of α-sulfanylcarboxylic acids **6** ($R^8$ = H) by the present cyclo-condensation. The derivatization of the acids **6** to the appropriate thiazolidin-4-ones fulfils this purpose, because: (1) thiazolidin-4-ones are generally stable and easy to handle. (2) The derivatization method is easy and the conditions are mild. (3) 5-Alkyl or aryl ($R^1$) substituted thiazolidin-4-ones **1**, ($R^2$ = naphthyl or phenyl, and $R^3$ = Me) are generally suitable for direct analysis of enantiomeric purity using HPLC (column; Sumipax OA-2500 bearing a chiral stationary phase), where the four optical isomers showed distinct retention times. (4) During the derivatization, no substantial racemization (< 2%) occurred, even when easily racemizable (4-chlorophenyl)sulfanylacetic acid was used. (5) $^1$H NMR peaks of the 3-methyl protons of 2-aryl-3-methylthiazolidin-4-ones generally split cleanly using the chiral shift reagent Eu(hfc)$_3$.




Scheme 7

When the (2*S*,5*R*)-(−)-*cis*-isomer of **5** (>99% ee by HPLC analysis) was subjected to the reaction (Table 4, entry 1), the (2*S*,5*S*)-(−)-*trans*-isomer of **5** (>99% ee) was produced and the (2*S*,5*R*)-(−)-*cis*-isomer of **5** (>99% ee) was recovered. Under the same reaction conditions, the (2*S*,5*S*)-(−)-*trans*-isomer of **5** (>99% ee) gave the (2*S*,5*R*)-(−)-*cis*-isomer of **5** (>99% ee) with the recovery of the (2*S*,5*S*)-(−)-*trans*-isomer of **5** (>99% ee). The epimerization of the (2*S*,5*R*)-(−)-*cis*-isomer of **11** (>99% ee) producing the corresponding (2*S*,5*S*)-(−)-*trans* isomer of **11** (>99% ee) diastereoisomers by treatment with 0.1 equiv. of Bu$^t$OK (Table 4, entry 13). These results showed that the present epimerization proceeded with high regioselectivity at the 5-position of these thiazolidin-4-ones.

Based on these results, we finally achieved the production of the highly optically active (2*S*,5*S*)-(−)-*trans*-isomer of **4** (>98% ee; $[\alpha]_D^{24}$ −145.2) and the (2*R*,5*R*)-(+)-*trans*-isomer of **4** (>98% ee; $[\alpha]_D^{23}$ −144.8), which had not previously been synthesized, from the (2*S*,5*R*)-(−)-*cis*- and (2*R*,5*S*)-(+)-*cis*-isomers of **4**, respectively (Scheme 7).

The preparation of optically active 3-methyl-2-(3-pyridyl)-thiazolidin-4-one **22** is regarded as an alternative candidate for the synthesis and screening of various optically active 5-substituted 3-methyl-2-(3-pyridyl)thiazolidin-4-ones *via* *trans*-predominate alkylation and optical resolution and asymmetric synthesis of **22** are now under investigation.

In conclusion, synthetic and related studies of several 2-(3-pyridyl)thiazolidin-4-ones, some of which display highly potent and selective anti-PAF activity such as **4** (PR-1115) and **5** [its hydrochloride of (±)-*cis*: SM-10661] are described. Further investigations on the synthesis of sulfur and nitrogen containing heterocycles directed toward biologically active or functionally useful molecules are now in progress.

## Experimental

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. $^1$H NMR spectra were recorded on a JEOL FX-90Q spectrometer (90 MHz) using TMS (tetramethylsilane) as an internal standard in $CDCl_3$; *J* values are given in Hz. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra were obtained with a Hitachi GC/MS M-80 instrument. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Microanalytical data were provided by Sumika Analysis Center

**Table 4** Epimerization of the 5-position of 5-substituted 2-(3-pyridyl)thiazolidin-4-ones with bases

| Entry | Substrate[a] | Base | Equiv. | Solvent | $T$/°C | $t$/h | *cis*:*trans*[b] | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | (±)-*cis*-**5** | $Et_3N$ | 1.0 | THF | 60 | 2 | 41:59 | 100 |
| 2 | (±)-*cis*-**5** | DBU[c] | 0.1 | THF | R.t.[d] | 5 | 42:58 | 99 |
| 3 | (±)-*trans*-**5** | DBU | 0.1 | THF | R.t. | 5 | 41:59 | 99 |
| 4 | (±)-*cis*-**4** | DBU | 1.0 | THF | 60 | 1 | 1:1 | 100 |
| 5 | (±)-*cis*-**4** | LDA[e] | 1.0 | THF | −78 | 5 | 2:1 | 97 |
| 6 | (±)-*cis*-**4** | LDA | 1.0 | THF | −20 | 2 | 2:1 | 90 |
| 7 | (±)-*cis*-**4** | LDA | 1.0 | THF | 0 | 1 | 1.5:1 | 89 |
| 8 | (±)-*cis*-**4** | LDA | 0.1 | THF | 0 | 5 | 10:1 | 90 |
| 9 | (±)-*cis*-**4** | LDA | 0.1 | THF | 60 | 10 | 3:1 | 90 |
| 10 | (±)-*cis*-**4** | NaH | 1.0 | THF | 0 | 1 | — | 0[f] |
| 11 | (±)-*cis*-**4** | NaH | 1.0 | DMSO | R.t. | 20 | 1:1 | 25[g] |
| 12 | (±)-*cis*-**4** | Bu$^t$OK | 1.0 | THF | 0 | 5 | 1:1 | 52 |
| 13 | (±)-*cis*-**4** | Bu$^t$OK | 0.1 | THF | 0 | 5 | 1:1 | 91 |
| 14 | (±)-*cis*-**4** | Bu$^t$OK | 0.1 | THF | 60 | 5 | 1:1 | 92 |
| 15 | (±)-*cis*-**4** | NaOMe | 0.1 | THF | 80 | 5 | 10:1 | 100 |
| 16 | (±)-*cis*-**4** | NaOMe | 0.1 | MeOH | 80 | 5 | 1:1 | 93 |
| 17 | (±)-*cis*-**4** | NaOMe | 0.1 | MeOH | R.t. | 48 | 8:1 | 95 |
| 18 | (±)-*cis*-**4** | NaOH | 5.0 | $H_2O$ | 100 | 5 | — | 0[f] |
| 19 | (±)-*trans*-**4** | Bu$^t$OK | 0.1 | THF | 0 | 5 | 1:1 | 91 |
| 20 | (±)-*cis*-**14** | Bu$^t$OK | 0.1 | THF | 0 | 2 | 40:60 | 91 |
| 21 | (±)-*cis*-**5** | Ti(OPr$^i$)$_4$ | 1.0 | $CH_2Cl_2$ | R.t. | 10 | 99:1 | 100 |
| 22 | (±)-*cis*-**4** | Ti(OPr$^i$)$_4$ | 1.0 | $CH_2Cl_2$ | R.t. | 10 | 1:0 | 100 |

[a] (±)-*cis*-**4** (*cis*:*trans* = 98:2), (±)-*cis*-**5** (*cis*:*trans* = 99:1), (±)-*trans*-**4** (*cis*:*trans* = 2:98), (±)-*trans*-**5** (*cis*:*trans* = 1:99), and (±)-*cis*-**14** (*cis*:*trans* = 100:0) were used. [b] Ratios of *cis*:*trans* were determined by HPLC analysis (entries 1–3, 20 and 21), or by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectra of **4** (entries 4–9, 11–17, 19 and 22). [c] 1,8-Diazabicyclo[5.4.0]undec-7-ene. [d] R.t. = room temperature. [e] Lithium diisopropylamide. [f] Compound **4** was completely decomposed during the reaction. [g] Compound **4** was almost completely decomposed during the reaction.

(Osaka). HPLC analyses were performed using Hitachi LC-655 (pump) and columns (LiChrosorb Si-60; 10 μ, 4 mm i.d. × 30 cm. Sumipax OA-2500; 5 μ, 4 mm i.d. × 25 cm) with UV (254 nm) detector. Other reagents and the solvents were of commercial grade and were used without further purification. Ether refers to diethyl ether. Silica gel column chromatography was performed on a Merck Art 7734 or 9385.

α-Sulfanylcarboxylic acids **6d**,[13] **6f**[14] and **6j** were prepared by substitution of the corresponding methyl α-chloro (or α-bromo) carboxylate with sodium thioacetate, followed by saponification in 60–90% yield. Esters of α-sulfanylcarboxylic acids **6b**, **6c**,[15] **6e**,[16] **6g**,[17] **6h**, **6i**[12] and **6k** were prepared by esterification under the usual conditions with the corresponding alcohol in the presence of toluene-*p*-sulfonic acid as a catalyst in 1,2-dichloroethane in about 80% yield.

*4-Chlorophenyl(sulfanyl)acetic Acid* **6j**.—Thioacetic acid (14.3 g, 0.171 mol) was added to a stirred suspension of sodium hydride (60% dispersion; 7.48 g, 0.188 mol) in DMF (200 cm$^3$) at 0–5 °C under a nitrogen atmosphere. After evolution of hydrogen gas had ceased, methyl bromo(4-chlorophenyl)-acetate (45.0 g, 0.171 mol) in DMF (100 cm$^3$) was added to the mixture at 0–5 °C. The mixture was stirred for 2 h at room temperature and was then poured onto ice–water and extracted with ether. The organic phase was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine and then dried ($MgSO_4$). After removal of the solvent under reduced pressure the crude oil obtained was distilled to give methyl acetyl-sulfanyl(4-chlorophenyl)acetate (40.6 g, 92%) as a pale orange oil, bp 125–127 °C/0.4 mmHg; $\nu_{max}$(neat)/cm$^{-1}$ 1720 (C=O); δ 2.35 (3 H, s), 3.75 (3 H, s), 5.28 (1 H, s) and 7.25–7.40 (4 H, m). To a stirred solution of KOH (9.54 g, 0.17 mol) in methanol (170 cm$^3$) at room temperature was added methyl acetyl-sulfanyl(4-chlorophenyl)acetate (36.6 g, 0.142 mol) and the whole kept at 80 °C for 2 h under a nitrogen atmosphere. After removal of the methanol under reduced pressure, conc. aqueous HCl (20 cm$^3$) was added to the mixture, and then the mixture was extracted with ether. The organic phase was washed with water and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude crystals, which were washed with hexane–ether (5/1; 50 cm$^3$) to give the *product* (28.8 g, 90%) as colourless crystals, mp 97–98 °C (Pr$^i$OH) (Found: C, 47.5; H, 3.4. $C_8H_7ClO_2S$ requires C, 47.41; H, 3.48%); $\nu_{max}$(Nujol)/cm$^{-1}$ 2600 (–SH) and 1750 (C=O); δ 0.50–0.85 (1 H, br), 2.60 (1 H, d, *J* 8), 4.65 (1 H, d, *J* 8) and 7.30–7.45 (4 H, m).

*Benzyl 2-sulfanylpropionate* **6b**. Colourless liquid, bp 99–102 °C/0.7 mmHg (Found: C, 61.0; H, 6.3. $C_{10}H_{12}O_2S$ requires C, 61.20; H, 6.16%); $\nu_{max}$(neat)/cm$^{-1}$ 2600 (–SH) and 1720 (C=O); δ 1.55 (3 H, d, *J* 7), 2.18 (1 H, d, *J* 8), 3.30–3.85 (1 H, m), 5.20 (2 H, s) and 7.40 (5 H, br s).

*Methyl 2-sulfanyldecanoate* **6h**. Colourless liquid, bp 200 °C (bulb-to-bulb distillation, oven temp.)/1.0 mmHg (Found: C, 60.2; H, 9.9. $C_{11}H_{22}O_2S$ requires C, 60.51; H, 10.15%); $\nu_{max}$(neat)/cm$^{-1}$ 2600 (–SH) and 1720 (C=O); δ 0.60–1.50 (17 H, m), 2.10–2.30 (1 H, m), 3.25–3.60 (1 H, m) and 3.80 (3 H, s).

*Methyl 4-chlorophenyl(sulfanyl)acetate* **6k**. Colourless liquid, bp 220 °C (bulb-to-bulb distillation, oven temp.)/1.0 mmHg (Found: C, 49.8; H, 4.0. $C_9H_9ClO_2S$ requires C, 49.89; H, 4.19%); $\nu_{max}$(neat)/cm$^{-1}$ 2600 (–SH) and 1740 (C=O); δ 2.60 (1 H, d, *J* 8), 3.83 (3 H, s), 4.65 (1 H, d, *J* 8) and 7.20–7.45 (4 H, m).

*N-(3-Pyridylmethylidene)methylamine* **7a**.—To a stirred aqueous solution of methylamine (40%; 100 cm$^3$) was added nicotinaldehyde (pyridine-3-carbaldehyde) (10.7 g, 0.10 mol) at room temperature, and the mixture was stirred for 1 h. The water and methylamine were then evaporated under reduced pressure from the mixture and the residue was distilled to give the *product* (10.5 g, 88%) as a pale yellow liquid, bp 102–103 °C/20 mmHg (Found: C, 69.8; H, 6.6; N, 23.05. $C_7H_8N_2$ requires C, 69.97; H, 6.71; N, 23.32%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1680 (C=N); δ 3.55 (3 H, d, *J* 2) and 7.20–8.90 (5 H, m).

The other imines **7b**,[18] **7c**,[19] **7d**,[20] **7e**, **7f**[18] and **7g** were prepared by the reported method.[18]

*N-(1-Naphthylmethylidene)methylamine* **7e**. Pale yellow liquid, bp 85–86 °C/0.2 mmHg (Found: C, 83.9; H, 7.0; N, 8.8.

$C_{11}H_{11}N$ requires C, 84.04; H, 7.05; N, 8.91%); $\nu_{max}$(neat)/cm$^{-1}$ 1660 (C=N); $\delta$ 3.60 (3 H, d, *J* 2) and 7.30–9.00 (8 H, m).

N-(3-*pyridylmethylidene*)-2-(N,N-*dimethylamino*)*ethylamine* **7g**. Colourless liquid, bp 152–154 °C/20 mmHg (Found: C, 67.6; H, 8.4; N, 23.5. $C_{10}H_{15}N_3$ requires C, 67.76; H, 8.53; N, 23.71%); $\nu_{max}$(neat)/cm$^{-1}$ 1660 (C=N); $\delta$ 2.30 (6 H, s), 2.65 (2 H, t, *J* 7), 3.75 (2 H, t, *J* 7) and 7.20–8.90 (5 H, m).

(±)-cis-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-cis-**4**.—(Table 1, entry 3) To a stirred solution of 2-sulfanylpropionic acid **6a** (1.06 g, 10 mmol) in $CH_2Cl_2$ (20 cm$^3$) was added *N*-(3-pyridylmethylidene)methylamine **7a** (1.20 g, 10 mmol) in $CH_2Cl_2$ (5 cm$^3$) at room temperature followed by stirring for 5 h. After removal of the solvent, the crude residue was subjected to flash column chromatography on $SiO_2$ (Merck, Art 9385) using $C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH (4:1:1) as the slower eluent to give the *product* (1.62 g, 78%) as pale orange crude crystals (*cis*:*trans* = 4:1 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum). The pure (±)-*cis*-**4** isomer was obtained by recrystallization as colourless crystals, mp 98–99 °C (Pr$^i$OH) (Found: C, 57.55; H, 5.8; N, 13.4. $C_{10}H_{12}N_2OS$ requires C, 57.66; H, 5.81; N, 13.44%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1670 (C=O); $\delta$ 1.65 (3 H, d, *J* 7), 2.70 (3 H, s), 3.95 (1 H, q, *J* 7), 5.50 (1 H, s), 7.20–7.80 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-trans-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**4**.—(Table 1, entry 20) To a stirred solution of benzyl 2-sulfanylpropionate **6b** (392 mg, 2 mmol) and titanium(IV) isopropoxide (568 mg, 2 mmol) in $CH_2Cl_2$ (4 cm$^3$) was added *N*-(3-pyridylmethylidene)methylamine **7a** (240 mg, 2 mmol) in $CH_2Cl_2$ (2 cm$^3$) at room temperature followed by stirring for 2 h. After the addition of water (20 cm$^3$), the organic phase was separated by Celite filtration using $CH_2Cl_2$ (20 cm$^3$), and was dried ($Na_2SO_4$). After removal of the solvent, the crude residue was subjected to flash column chromatography on $SiO_2$ (Merck, Art 9385) using $C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH (4:1:1) as the faster eluent to give the *product* (320 mg, 77%) as pale orange crude crystals (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum). The pure (±)-*trans*-**4** isomer was obtained by recrystallization as colourless crystals, mp 80–82 °C (Pr$^i$OH) (Found: C, 57.5; H, 5.8; N, 13.3. $C_{10}H_{12}N_2OS$ requires C, 57.66; H, 5.81; N, 13.44%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1670 (C=O); $\delta$ 1.60 (3 H, d, *J* 7), 2.75 (3 H, d, *J* 2), 3.80–4.10 (1 H, m), 5.50 (1 H, d, *J* 2), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-trans-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**5**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (68%) as pale orange crude crystals [*cis*:*trans* = 1:20 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 5:1 as eluent)]. The pure (±)-*trans*-**5** isomer was obtained by flash column chromatography on $SiO_2$ using $C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH (4:1:1) as the faster eluent followed by recrystallization as colourless crystals, mp 121–122 °C (Pr$^i$OH) [*cis*:*trans* = 0:100 by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 10:1 as eluent)] (Found: C, 59.1; H, 4.3; N, 9.1. $C_{15}H_{13}ClN_2OS$ requires C, 59.11; H, 4.30; N, 9.19%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ ($CDCl_3$) 2.80 (3 H, d, *J* 1), 5.15 (1 H, d, *J* 2), 5.69 (1 H, d, *J* 2), 7.20–7.80 (6 H, m) and 8.50–8.70 (2 H, m).

(±)-cis-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-cis-**5**.—(Table 2, method B) A similar method as for the synthesis of (±)-*cis*-**4** gave the *product* (77%) as pale orange crude crystals [*cis*:*trans* = 3.0:1 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 5:1 as eluent)]. The pure (±)-*cis*-**5** isomer was obtained in a similar manner as for the synthesis of (±)-*trans*-**5** isomer as colourless crystals, mp 140–141 °C (Pr$^i$OH) (*cis*:*trans* = 100:0 by HPLC analysis) (Found: C, 59.0; H, 4.3; N, 9.1. $C_{15}H_{13}ClN_2OS$ requires C, 59.11; H, 4.30; N, 9.19%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ 2.79 (3 H, s), 5.10 (1 H, s), 5.60 (1 H, s), 7.20–7.80 (6 H, m) and 8.50–8.70 (2 H, m).

(±)-trans-2-(4-*Chlorophenyl*)-3,5-*dimethylthiazolidin*-4-*one* (±)-trans-**8**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (81%) (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum) as a colourless liquid (Found: C, 54.4; H, 5.05; N, 5.5. $C_{11}H_{12}ClNOS$ requires C, 54.65; H, 5.00; N, 5.79%); $\nu_{max}$(neat)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.60 (3 H, d, *J* 7), 2.75 (3 H, d, *J* 2), 3.80–4.10 (1 H, m), 5.40 (1 H, d, *J* 2) and 7.20–7.40 (4 H, m).

(±)-trans-3,5-*Dimethyl*-2-(p-*tolyl*)*thiazolidin*-4-*one* (±)-trans-**9**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (78%) (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum) as a colourless liquid (Found: C, 64.9; H, 6.7; N, 6.1. $C_{12}H_{15}NOS$ requires C, 65.12; H, 6.83; N, 6.33%); $\nu_{max}$(neat)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.60 (3 H, d, *J* 7), 2.30 (3 H, s), 2.75 (3 H, d, *J* 2), 3.80–4.10 (1 H, m), 5.40 (1 H, d, *J* 2) and 7.00–7.40 (4 H, m).

(±)-trans-3,5-*Dimethyl*-2-(4-*nitrophenyl*)*thiazolidin*-4-*one* (±)-trans-**10**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (55%) (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum) as colourless crystals, mp 133–135 °C (EtOH) (Found: C, 52.2; H, 4.7; N, 11.0. $C_{11}H_{12}N_2O_3S$ requires C, 52.36; H, 4.80; N, 11.10%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O) and 1380 (–$NO_2$); $\delta$ 1.60 (3 H, d, *J* 7), 2.75 (3 H, br s), 3.80–4.10 (1 H, m), 5.50 (1 H, d, *J* 2) and 7.10–7.80 (4 H, m).

(±)-trans-3,5-*Dimethyl*-2-(1-*naphthyl*)*thiazolidin*-4-*one* (±)-trans-**11**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (72%) (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum) as a colourless liquid (Found: C, 69.9; H, 5.7; N, 5.2. $C_{15}H_{15}NOS$ requires C, 70.01; H, 5.87; N, 5.44%); $\nu_{max}$(neat)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.55 (3 H, d, *J* 7), 2.80 (3 H, s), 3.80–4.10 (1 H, m), 6.20 (1 H, d, *J* 2) and 7.00–8.40 (7 H, m).

(±)-trans-3,5-*Dimethyl*-2-(4-*methoxyphenyl*)*thiazolidin*-4-*one* (±)-trans-**12**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (62%) (*cis*:*trans* = 1:4 determined by integration of the resonance of the 3-methyl protons in the $^1$H NMR spectrum) as colourless crystals, mp 90–92 °C (Pr$^i$OH) (Found: C, 60.7, H, 6.35; N, 5.8. $C_{12}H_{15}NO_2S$ requires C, 60.73; H, 6.37; N, 5.90%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.60 (3 H, d, *J* 7), 2.75 (3 H, d, *J* 2), 3.80 (3 H, s), 3.80–4.10 (1 H, m), 5.40 (1 H, d, *J* 2) and 6.75–7.40 (4 H, m).

(±)-trans-5-*Ethyl*-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**13**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (74%) [*cis*:*trans* = 1:7.3 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 10:1 as eluent)] as a colourless liquid (Found: C, 59.15; H, 6.4; N, 12.4. $C_{11}H_{14}N_2OS$ requires C, 59.43; H, 6.35; N, 12.60%); $\nu_{max}$(neat)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.10 (3 H, t, *J* 7), 1.75–2.00 (2 H, m), 2.70 (3 H, s), 3.75–4.00 (1 H, m), 5.50 (1 H, s), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-trans-5-*Isopropyl*-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**14**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (72%) [*cis*:*trans* = 1:13 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 20:1 as eluent)] as colourless crystals, mp 85–86 °C (Found: C, 60.9; H, 6.8; N, 11.6. $C_{12}H_{16}N_2OS$ requires C, 60.98; H, 6.83; N, 11.85%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.05 (3 H, d, *J* 7), 1.25 (3 H, d, *J* 7), 2.40–2.70 (1 H, m), 2.70 (3 H, s), 4.00–4.20 (1 H, m), 4.42 (1 H, d, *J* 2), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-cis-5-*Isopropyl*-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-cis-**14**.—(Table 2, method B) A similar method as for the synthesis of (±)-*cis*-**4** gave the *product* (73%) (*cis*:*trans* = 3.0:1 determined by HPLC) as colourless crystals, mp 88–90 °C (Found: C, 61.0; H, 6.8; N, 11.6. $C_{12}H_{16}N_2OS$ requires C, 60.98; H, 6.83; N, 11.85%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ 1.10 (3 H, d, *J* 7), 1.25 (3 H, d, *J* 7), 2.40–2.80 (1 H, m), 2.70 (3 H, s), 4.10 (1 H, d, *J* 3), 5.45 (1 H, s), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-trans-3-*Methyl*-5-*octyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**15**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (66%) [*cis*:*trans* = 1:12 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 20:1 as eluent)] as a colourless liquid, mp 85–86 °C (Found: C, 66.5; H, 8.4; N, 9.0. $C_{17}H_{26}N_2OS$ requires C, 66.62; H, 8.56; N, 9.14%); $\nu_{max}$(neat)/cm$^{-1}$ 1690 (C=O); $\delta$ 0.70–2.10 (17 H, m), 2.75 (3 H, s), 3.80–4.10 (1 H, m), 5.50 (1 H, br s), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(±)-trans-*Methyl*-5-*phenyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**16**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (75%) [*cis*:*trans* = 1:20 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 5:1 as eluent)] as colourless crystals, mp 142–144 °C (Found: C, 66.8; H, 5.2; N, 10.1. $C_{15}H_{14}N_2OS$ requires C, 66.64; H, 5.22; N, 10.36%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1690 (C=O); $\delta$ 2.80 (3 H, d, *J* 1), 5.15 (1 H, d, *J* 2), 5.69 (1 H, d, *J* 2), 7.20–7.80 (7 H, m) and 7.50–7.70 (2 H, m).

(±)-3-(N,N-*Dimethylaminoethyl*)-5-*octyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* **17**.—(Table 2, method A) A similar method as for the synthesis of (±)-*trans*-**4** gave the *product* (68%) (*cis*:*trans* = 1:3 determined from the $^1$H NMR spectrum) as a yellow liquid (Found: C, 65.9; H, 8.95; N, 11.3. $C_{20}H_{33}N_3OS$ requires C, 66.07; H, 9.15; N, 11.56%); $\nu_{max}$(neat)/cm$^{-1}$ 1670 (C=O); $\delta$ 0.60–2.10 (17 H, m), 2.13 (*cis*, 1.5 H, s), 2.15 (*trans*, 4.5 H, s), 2.20–2.90 (4 H, m), 3.80–4.10 (1 H, m), 5.90 (1 H, br s), 7.20–7.40 (1 H, m), 7.55–7.75 (1 H, m) and 8.50–8.70 (2 H, m).

(±)-3-*Methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-**22**.—To a stirred solution of α-sulfanylacetic acid (9.20 g, 0.10 mol) in $CH_2Cl_2$ (100 cm$^3$) was added *N*-(pyridylmethylidene)methylamine **7a** (12.0 g, 0.10 mmol) at room temperature followed by stirring for 2 h. After removal of the solvent, the crude solid obtained was recrystallized from Pr$^i$OH to give the *product* (13.9 g, 72%) as colourless crystals, mp 95–97 °C (Pr$^i$OH) (Found: C, 55.7; H, 5.15; N, 14.2. $C_9H_{10}N_2OS$ requires C, 55.64, H, 5.19; N, 14.42%); $\nu_{max}$(Nujol)/cm$^{-1}$ 1670 (C=O); $\delta$ 2.80 (3 H, s), 3.70 (2 H, s), 5.85 (1 H, br s), 7.20–7.40 (1 H, m), 7.55–7.75 (1 H, m) and 8.50–8.70 (2 H, m).

(±)-trans-5-*Allyl*-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-trans-**23**.—To a stirred solution of diisopropylamine (111 mg, 1.48 mmol) in THF (2.0 cm$^3$) was added butyllithium (1.48 mol dm$^{-3}$; 0.74 cm$^3$) at 0 °C. After 15 min, the mixture was cooled to −78 °C and then compound **22** (194 mg, 1.0 mmol) in THF (1.0 cm$^3$) was added dropwise. After 30 min, allyl bromide (133 mg, 1.1 mmol) in THF (1.0 cm$^3$) was added dropwise followed by stirring for 1 h, and then the mixture was allowed to warm to 0 °C and stirred for 1 h. The mixture was then quenched with phosphate buffer solution (pH 7.0; 5.0 cm$^3$) and extracted with ethyl acetate. The organic phase was washed with water and brine and then dried ($Na_2SO_4$). After removal of the solvent, the crude oil [*cis*:*trans* = 1:8.35 determined by HPLC (LiChrosorb Si-60; $C_6H_{14}$–EtOH, 20:3 as eluent)] was subjected to flash column chromatography on $SiO_2$ (Merck, Art 9385) using $C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH (4:1:1) as eluent to give the *product* (136 mg, 57%) as a pale yellow oil (Found: C, 61.3; H, 5.85; N, 11.7. $C_{12}H_{14}N_2OS$ requires C, 61.51, H, 6.02; N, 11.96%); $\nu_{max}$(neat)/cm$^{-1}$ 1670 (C=O) and 900 (–CH=CH$_2$); $\delta$ 2.00–2.50 (2 H, m), 2.75 (3 H, s), 4.15 (1 H, m), 4.90–5.40 (2 H, m), 5.50–6.20 (2 H, m), 7.20–7.75 (2 H, m) and 8.40–8.70 (2 H, m).

(*S*)-Methyl 2-(mesyloxy)propionate **24**. Colourless liquid, $[\alpha]_D^{27}$ −55.5 (*c* 1.91, EtOH), and (*R*)-Methyl 2-(mesyloxy)propionate **26**, colourless liquid, $[\alpha]_D^{27}$ +53.5 (*c* 1.34, EtOH) were prepared by the known procedure.[21]

(R)-*Methyl* 2-(*Acetylsulfanyl*)*propionate* **25**.—To a stirred suspension of sodium hydride (60% dispersion; 3.80 g, 0.095 mol) in DMF (200 cm$^3$) was added thioacetic acid (8.36 g, 0.11 mol) at 0–5 °C under a nitrogen atmosphere. After the evolution of hydrogen gas had ceased, compound **24** (18.2 g, 0.10 mol) was added at 0–5 °C followed by stirring at that temperature for 2 h. Then the reaction mixture was poured onto HCl (1 mol dm$^{-3}$)–ice and extracted with ether (200 cm$^3$ × 2). The combined extracts were washed with water and brine, and then dried ($MgSO_4$). After removal of the solvent, the crude residue was distilled to give the *product* (11.2 g, 69%) as a yellow liquid, bp 108–109 °C/30 mmHg; $[\alpha]_D^{25}$ +145.3 (*c* 0.728, EtOH); $\delta$ 1.55 (3 H, d, *J* 7), 2.35 (3 H, s), 3.75 (3 H, s) and 4.25 (1 H, q, *J* 7).

(R)-2-*Sulfanylpropionic acid* (R)-**6a**.[10,11] A mixture of compound **25** (6.00 g, 0.02 mol) and 10% aqueous HCl (100 cm$^3$) was heated at 80 °C for 2 h under a nitrogen atmosphere. After cooling down, the mixture was extracted with ethyl acetate (100 cm$^3$). The organic phase was washed with brine and dried ($Na_2SO_4$). After removal of the solvent, the crude residue was distilled to give the *product* (2.82 g, 72%) as a yellow liquid, bp 106–109 °C/19 mmHg; $[\alpha]_D^{25}$ +45.0 (*c* 0.728, EtOH); $[\alpha]_D^{23}$ +51.5 (*c* 1.42, EtOAc) about 90% ee based on the reported value;[14] $\delta$ 1.50 (3 H, d, *J* 7), 2.20 (1 H, d, *J* 8), 3.30–3.60 (1 H, m) and 11.5 (1 H, br s).

(S)-*Methyl*-2-(*acetylsulfanyl*)*propionate* **27**. In a similar manner as for the preparation of compound **25**, the reaction of (*R*)-methyl 2-(mesyloxy)propionate **26** gave the *product* as a yellow liquid (64%), bp 106–107 °C/18 mmHg; $[\alpha]_D^{26}$ −139.8 (*c* 1.42, EtOH).

(S)-2-*Sulfanylpropionic acid* (S)-**6a**. In a similar manner as for the preparation of (*R*)-**6a**, the reaction of compound **27** gave the *product* (71%) as a yellow liquid, bp 106–107 °C/20 mmHg; $[\alpha]_D^{25}$ −46.7 (*c* 0.99, EtOH) about 93% ee based on the reported value.[12,13]

(R)-*Methyl* 2-*sulfanylpropionate* (R)-**6c**. By the known procedure,[10] the *product* was obtained as a yellow liquid, bp 78–80 °C/20 mmHg; $[\alpha]_D^{25}$ +55.1 (*c* 1.81, $CHCl_3$); $\delta$ 1.50 (3 H, d, *J* 7), 2.10 (1 H, d, *J* 8), 3.30–3.60 (1 H, m) and 3.80 (3 H, s).

(S)-*Methyl* 2-*sulfanylpropionate* (S)-**6c**. Yellow liquid, bp 78–80 °C/20 mmHg; $[\alpha]_D^{25}$ −56.1 (*c* 1.75, $CHCl_3$).

(2S,5R)-(−)-cis-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2S,5R)-(−)-*cis*-**4**.—To a stirred solution of (*R*)-**6a** (3.19 g, 30 mmol) in THF (60 cm$^3$) was added *N*-(3-pyridylmethylidine)methylamine **7a** (3.61 g, 30 mmol) at 0–5 °C under a

nitrogen atmosphere, the mixture was then allowed to stand for 12 h at 0–5 °C. After adding toluene (50 $cm^3$) to the mixture, the solvent was removed under reduced pressure to give a crude solid (4.16 g), which was washed with ether–$C_6H_{14}$, 1:1 (4 $cm^3$ × 3) and recrystallized two times ($C_6H_{14}$–$Pr^iOH$, 1:1) to give the pure *product* (2.17 g, 35%) as colourless crystals, mp 67.5–69.0 °C; $[\alpha]_D^{23}$ −22.7 (*c* 0.41, $CHCl_3$); *cis*:*trans* = 99:1 and 98% ee determined by HPLC (Sumipax OA-2500; $C_6H_{14}$–EtOH, 10:1 as eluent).

*X-Ray Analysis of* (2S,5R)-(−)-cis-**4**.—Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu-Kα radiation ($\lambda$ = 1.5418 Å). Crystal data are as follows: $C_{10}H_{12}N_2OS$, *M* 208.283, monoclinic, space group $P2_1$, *a* = 23.345(3), *b* = 6.306(2), *c* = 7.552(1) Å, $\beta$ = 108.90(1)°, *V* = 1051.9 $Å^3$, *Z* = 4, *F*(000) = 440, $D_x$ = 1.315 g $cm^{-3}$, $\mu$(Cu-Kα) = 24.343 $cm^{-1}$. A total of 2190 reflections with $\theta$ < 70° were collected by $\omega$–2$\theta$ scan technique. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final *R* and $R_w$ factors were 0.029 and 0.042, respectively, for 1849 observed reflections [$I > 3\sigma(I)$]. There are two crystallographically independent molecules in the asymmetric unit. The two independent molecules in the asymmetric unit were conformationally almost identical. All calculations were carried out on a micro VAX II using SDP package.

(2R,5S)-(+)-cis-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2R,5S)-(+)-cis-**4**.—In a similar manner as for the synthesis of (2*S*,5*R*)-(−)-*cis*-**4**, the reaction of compound (*S*)-**6a** (3.86 g, 36.4 mmol) and compound **7a** (4.37 g, 36.4 mmol) gave the *product* (2.80 g, 37%) as colourless crystals, mp 66.5–68.5 °C; $[\alpha]_D^{26}$ +22.5 (*c* 0.423, $CHCl_3$); *cis*:*trans* = 99:1 and 98% ee analysed by HPLC.

(2R,5R)-(+)-trans-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2R,5R)-(+)-trans-**4**.—To a stirred solution of compound (*R*)-**6c** (3.19 g, 30 mmol) in $CH_2Cl_2$ (60 $cm^3$) was added $Ti(OPr^i)_4$ (6.33 g, 30 mmol) and compound **7a** (3.61 g, 30 mmol) in $CH_2Cl_2$ (10 $cm^3$) successively, followed by stirring for 2 h. After the addition of water (20 $cm^3$), the organic phase was separated by Celite filtration using $CH_2Cl_2$ (20 $cm^3$), and was dried ($Na_2SO_4$). After removal of the solvent, the crude residue was subjected to flash column chromatography on $SiO_2$ (Merck, Art 9385) using $C_6H_{14}$–$CH_2Cl_2$–$Pr^iOH$ (4:1:1) as eluent to give the *product* (2.00 g, 32%) as a yellow oil, $[\alpha]_D^{24}$ +131.5 (*c* 0.340, $CHCl_3$); *cis*:*trans* = 2:98 and 88% ee determined by HPLC (Sumipax OA-2500; $C_6H_{14}$–EtOH, 10:1 as eluent).

(2S,5S)-(−)-trans-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2S,5S)-(−)-trans-**4**. In a similar manner as for the synthesis of (2*R*,5*R*)-(+)-*trans*-**4**, the reaction of compound (*S*)-**6c** (3.19 g, 30 mmol) and compound **7a** (3.61 g, 30 mmol) gave the *product* (1.93 g, 31%) as a yellow oil, $[\alpha]_D^{23}$ −133.8 (*c* 0.281, $CHCl_3$); *cis*:*trans* = 4:96 and 90% ee analysed by HPLC.

(S)-(4-*Chlorophenyl*)*sulfanyl acetic Acid* (S)-**6j**.—To a stirred suspension of cinchonidine (43.9 g, 0.150 mol) in degassed EtOH (900 $cm^3$) was added compound (±)-**6j** (37.6 g, 0.186 mol) at 30 °C. After the suspension had dissolved, it was seeded with material from a small-scale resolution, and allowed to stand at room temperature for 2 h. The first salt (42.6 g, 58%) obtained was recrystallized from degassed EtOH (2.00 $dm^3$) to give the second salt (22.9 g, 31%). The second salt was successively recrystallized from degassed EtOH (1.00 $dm^3$) to give the third salt (15.8 g, 21%) which was decomposed with 10% $H_2SO_4$ (50 $cm^3$) and extracted with ether (200 $cm^3$ × 2). The organic phase was dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure to give the *product* (5.93 g, 20%) as colourless crystals, mp 123–125 °C; $[\alpha]_D^{17}$ +84.8 (*c* 0.748, EtOH).

(R)-(4-*Chlorophenyl*)*sulfanylacetic Acid* (R)-**6j**.—To a stirred suspension of cinchonine (54.7 g, 0.186 mol) in degassed EtOH (270 $cm^3$) was added compound (±)-**6j** (37.6 g, 0.186 mol) at room temperature. And then, the solution was seeded with material from a small-scale resolution, and allowed to stand at room temperature for 10 h. The first salt (33.0 g, 36%) obtained was recrystallized from degassed EtOH (550 $cm^3$) to give the second salt (10.8 g, 12%), which was decomposed with 10% $H_2SO_4$ (50 $cm^3$) and extracted with ether (200 $cm^3$ × 2). The organic phase was dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure to give the *product* (4.45 g, 12%) as colourless crystals, mp 123–125 °C; $[\alpha]_D^{26}$ −84.1 (*c* 0.503, EtOH). Recrystallization of a sample of (*R*)-**6j** from $C_6H_{14}$–benzene, 1:1 two times gave two crops, $[\alpha]_D^{23}$ −89.7 (*c* 0.368, EtOH) and $[\alpha]_D^{23}$ −90.4 (*c* 0.450, EtOH), respectively, which showed nearly constant values, so that these were thought to be practically optically pure.

(2R,5S)-(+)-cis- *and* (2S,5S)-(−)-trans-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2R,5S)-(+)-cis-**5** *and* (2S,5S)-(−)-trans-**5**.—To a stirred solution of compound (*S*)-**6j** (10.72 g, 53 mmol) in THF (100 $cm^3$) was added compound **7a** (6.37 g, 53 mmol) at 0 °C under a nitrogen atmosphere, followed by stirring at 0 °C for 12 h. After the addition of toluene (50 $cm^3$), the solvent was removed under reduced pressure to give the crude solid (17.15 g), which was washed with ether (20 $cm^3$ × 3) to give the *product* (9.36 g, 58%), *cis*:*trans* = 92:8 and 92% ee determined by HPLC (Sumipax OA-2500; $C_6H_{14}$–EtOH, 5:1 as eluent), which was recrystallized from $C_6H_{14}$–$Pr^iOH$, 2:1 to give the pure *product* as colourless crystals, mp 127–129.5 °C; $[\alpha]_D^{24}$ +29.0 (*c* 0.815, $CHCl_3$); *cis*:*trans* = 100:0 and 100% ee analysed by HPLC. The mother liquor and the ether used for washing were combined, condensed and the residue subjected to flash column chromatography ($C_6H_{14}$–$CH_2Cl_2$–$Pr^iOH$, 5:1:1) to give the *product* (2.42 g, 15%), *cis*:*trans* = 5:95 and 90% ee analysed by HPLC, which was recrystallized from $Pr^iOH$ to give the *pure product* as colourless crystals, mp 137–138 °C; $[\alpha]_D^{28}$ −54.5 (*c* 1.17, $CHCl_3$); *cis*:*trans* = 0:100 and 100% ee analysed by HPLC.

*X-Ray Analysis of* (2R,5S)-(+)-cis-**5**.—Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu-Kα radiation ($\lambda$ = 1.5418 Å). Crystal data are as follows: $C_{15}H_{13}ClN_2OS$, *M* 304.799, orthorhombic, space group $P2_12_12_1$, *a* = 12.784(2), *b* = 18.925(2), *c* = 6.165(1) Å, *V* = 1491.5 $Å^3$, *Z* = 4, *F*(000) = 632, $D_x$ = 1.357 g $cm^{-3}$, $\mu$(Cu-Kα) = 35.5 $cm^{-1}$. A total of 1685 reflections with $\theta$ < 70° were collected by $\omega$–2$\theta$ scan technique. The structure was solved by direct methods using MITHRIL and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final *R* and $R_w$ factors were 0.037 and 0.057, respectively, for 1494 observed reflections [$I > 3\sigma(I)$].

*X-Ray Analysis of* (2S,5S)-(−)-trans-**5**.—Intensity data were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu-Kα radiation ($\lambda$ = 1.5418 Å). Crystal data are as follows: $C_{15}H_{13}ClN_2OS$, *M* 304.799, orthorhombic, space group $P2_1$, *a* = 7.921(1), *b* = 12.376(1), *c* = 7.424(1) Å, $\beta$ = 101.49(1)°, *V* = 713.2 $Å^3$, *Z* = 2, *F*(000) = 316, $D_x$ = 1.419 g $cm^{-3}$, $\mu$(Cu-Kα) = 37.2 $cm^{-1}$. A

total of 1413 reflections with $\theta < 70°$ were collected by $\omega$–$2\theta$ scan technique. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares. Non-hydrogen atoms were refined with anisotropic thermal parameters. The final $R$ and $R_w$ factors were 0.032 and 0.047, respectively, for 1374 observed reflections [$I > 3\sigma(I)$]. The intensities of twenty two Friedel pairs (*hkl* and $\overline{hkl}$), for which differences in intensities were largest, were collected on the diffractometer. All the relations between |Fc(*hkl*)| and |Fc($\overline{hkl}$)| are consistent with those between $|F_o(hkl)|$ and $|F_o(\overline{hkl})|$, indicating that *trans*-**5** has the (2*S*,5*S*) configuration. The enantiomeric structure gave $R$ and $R_w$ values of 0.038 and 0.057, and so was rejected on the basis of significant test (W. C. Hamilton, *Acta Crystallogr.*, 1965, **18**, 502). Tables of atomic coordinates, bond lengths and angles, and thermal parameters for compounds (2*S*,5*R*)-(−)-*cis*-**4**, (2*R*,5*S*)-(+)-*cis*-**5** and (2*S*,5*S*)-(−)-*trans*-**5** have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

(2S,5R)-(−)-cis- *and* (2R,5R)-(+)-trans-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2S,5R)-(−)-cis-**5** *and* (2R,5R)-(+)-trans-**5**.—In a similar manner as for compounds (2*R*,5*S*)-(+)-*cis*-**5** and (2*S*,5*S*)-(−)-*trans*-**5**, the reaction of compound (*R*)-**6j** (1.23 g, 6.12 mmol) and compound **7a** (0.74 g, 6.12 mmol) to give as one *product* [(2*S*,5*R*)-(−)-*cis*-**5**; 1.08 g, 58%] (*cis*:*trans* = 95:5 and 91% ee analysed by HPLC) and as the other *product* [(2*R*,5*R*)-(+)-*trans*-**5**; 299 mg, 16%] (*cis*:*trans* = 5:95 and 90% ee analysed by HPLC), respectively. Each of them was recrystallized from Pr$^i$OH to give pure (2*S*,5*R*)-(−)-*cis*-**5** as colourless crystals, mp 127–129.5 °C; $[\alpha]_D^{26}$ −28.9 (*c* 0.651, $CHCl_3$); *cis*:*trans* = 100:0 and 100% ee analysed by HPLC, and pure (2*R*,5*R*)-(+)-*trans*-**5** as colourless crystals, mp 137–138.5 °C; $[\alpha]_D^{26}$ +54.7 (*c* 0.945, $CHCl_3$); *cis*:*trans* = 0:100 and 100% ee analysed by HPLC.

*Methyl* (R)-(4-*Chlorophenyl*)*sulfanylacetic Acid* (R)-**6k**.—In a similar manner as for the known method,[11] compound (*R*)-**6j** ($[\alpha]_D^{26}$ −84.1) was converted into the *product* as a colourless liquid, $[\alpha]_D^{26}$ −83.0 (*c* 0.821, EtOH).

trans-*Selective Cyclization of* (R)-**6k**. In a similar manner as for the synthesis of (±)-*trans*-**5**, the reaction of compound (*R*)-**6k** (216 mg, 1.0 mmol) and compound **7a** (120 mg, 1.0 mmol) gave (2*R*,5*R*)-(+)-*trans*-**5** (173 mg, 57%); *cis*:*trans* = 4:96 and 92% ee determined by HPLC (Sumipax OA-2500; $C_6H_{14}$–EtOH, 5:1 as eluent).

*Epimerization of* (±)-cis-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-cis-**5**.—(Table 4, entry 1) To a stirred solution of compound (±)-*cis*-**5** (305 mg, 1.0 mmol) in THF (2.0 cm$^3$) was added triethylamine (101 mg, 1.0 mmol) in THF (1.0 cm$^3$) at room temperature under an argon atmosphere. The reaction mixture was heated at 60 °C for 2 h and was then neutralized by the addition of acetic acid (65 mg, 1.0 mmol). Removal of the solvent under reduced pressure followed by flash column chromatographic purification ($C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH, 4:1:1) gave a mixture of (±)-*cis*-**5** and (±)-*trans*-**5** (total, 303 mg, *cis*:*trans* = 41:59 by HPLC analysis).

*Epimerization of* (±)-cis-3,5-*Dimethyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (±)-cis-**4**.—(Table 4, entry 7) To a stirred solution of Bu$^t$OK (18 mg, 0.16 mmol) in THF (2.0 cm$^3$) was added compound (±)-*cis*-**4** (336 mg, 1.60 mmol) in THF (1.0 cm$^3$) at 0 °C under an argon atmosphere, followed by stirring for 5 h. Phosphate buffer solution (pH 7.0; 5.0 cm$^3$) was added and then the mixture was extracted with chloroform (20 cm$^3$ × 2). The combined extracts were dried ($Na_2SO_4$) and the solvent was removed under reduced pressure to give a mixture of (±)-*cis*-**4** and (±)-*trans*-**4** (total, 306 mg, *cis*:*trans* = 1:1 by $^1$H NMR analysis).

*Regioselective Epimerization of* (2S,5R)-(−)-cis-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2S,5R)-(−)-cis-**5**.—The reaction was carried out using pure (2*S*,5*R*)-(−)-*cis*-**5** (128.1 mg, $[\alpha]_D^{26}$ −28.9; >99% ee by HPLC analysis) under the same conditions as for (±)-*cis*-**5**. HPLC analysis of the crude products showed only two peaks of (2*S*,5*S*)-(−)-*trans*-**5** (33%) and (2*S*,5*R*)-(−)-*cis*-**5** (67%; unchanged). The crude material was purified by thin layer chromatography ($C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH, 4:1:1) to give (2*S*,5*S*)-(−)-*trans*-**5** {40 mg, $[\alpha]_D^{27}$ −54.5 (*c* 0.404, $CHCl_3$)} and (2*S*,5*R*)-(−)-*cis*-**5** {82 mg, $[\alpha]_D^{27}$ −29.1 (*c* 0.851, $CHCl_3$)} recovered, both of which were shown to be >99% chemically and optically pure by HPLC analyses.

*Regioselective Epimerization of* (2S,5S)-(−)-trans-5-(4-*Chlorophenyl*)-3-*methyl*-2-(3-*pyridyl*)*thiazolidin*-4-*one* (2S,5S)-(−)-trans-**5**.—In a similar manner to the foregoing epimerization, the use of (2*S*,5*S*)-(−)-*trans*-**5** ($[\alpha]_D^{28}$ −54.5; >99% ee by HPLC analysis) gave (2*S*,5*R*)-(−)-*cis*-**5** (39%) and (2*S*,5*S*)-(−)-*trans*-**5** (61%; recovered), both of which were shown to be >99% chemically and optically pure by HPLC analyses.

(2S,5R)-(−)-cis-3,5-*Dimethyl*-2-(1-*napthyl*)*thiazolidin*-4-*one* (2S,5R)-(−)-cis-**11**.—The reaction of compound (*R*)-**6a** (318 mg, 3.0 mmol) with compound **7e** (5.07 mg, 3.0 mmol) by Table 2, method B gave the *product* (689 mg, 81% after short column chromatographic purification ($C_6H_{14}$–EtOAc, 3:1 as eluent) on $SiO_2$. Recrystallization from Pr$^i$OH gave the *pure product* (331 mg) as colourless crystals, mp 79–81 °C; $[\alpha]_D^{24}$ −368.9 (*c* 0.315, $CHCl_3$); 100% ee determined by HPLC (Sumipax OA-2500; $C_6H_{14}$–EtOH, 10:1 as eluent).

*Regioselective Epimerization of* (2S,5R)-(−)-cis-3,5-*Dimethyl*-2-(1-*naphthyl*)*thiazolidin*-4-*one* (2S,5R)-(−)-*cis*-**11**.—The reaction was carried out using pure (2*S*,5*R*)-(−)-*cis*-**11** (225 mg, >99% ee by HPLC) under the same conditions as for (±)-*cis*-**5**. HPLC analysis of the crude products showed only two peaks of (2*S*,5*S*)-(−)-*trans*-**11** (49%) and (2*S*,5*R*)-(−)-*cis*-**11** (51%; unchanged). Chromatographic purification ($C_6H_{14}$–EtOAc, 3:1 as eluent) of the mixture on $SiO_2$ gave the (2*S*,5*S*)-(−)-*trans*-**11** (76 mg) as a colourless liquid, $[\alpha]_D^{24}$ −477.8 (*c* 0.761, $CHCl_3$), which was shown to be >99% chemically and optically pure by HPLC analyses.

*Synthesis of* (2R,5R)-(+)-trans-3,5-*Dimethyl*-2-(3-*pyridyl*)-*thiazolidin*-4-*ones* [(2R,5R)-(+)-trans-**4**] *by the Regioselective Epimerization of* (2R,5S)-(+)-cis-**4**.—In a similar manner as for the epimerization of (±)-*cis*-**4**, the reaction of (2*R*,5*S*)-(+)-*cis*-**4** (300 mg, $[\alpha]_D^{26}$ +22.5) and careful chromatographic purification ($C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH, 5:1:1 as eluent) on $SiO_2$ gave (2*R*,5*R*)-(+)-*trans*-**4** (46 mg) as a pale yellow liquid, $[\alpha]_D^{23}$ +144.8 (*c* 0.461, $CHCl_3$); >98% chemically and optically pure by HPLC analysis.

*Synthesis of* (2S,5S)-(−)-trans-3,5-*Dimethyl*-2-(3-*pyridyl*)-*thiazolidin*-4-*ones* [(2S,5S)-(−)-trans-**4**] *by the Regioselective Epimerization of* (2S,5R)-(−)-cis-**4**.—In a similar manner as for the epimerization of (±)-*cis*-**4**, the reaction of (2*S*,5*R*)-(−)-*cis*-**4** (400 mg; $[\alpha]_D^{23}$ −22.7) and careful chromatographic purification ($C_6H_{14}$–$CH_2Cl_2$–Pr$^i$OH, 5:1:1 as eluent) on $SiO_2$ gave (2*S*,5*S*)-(−)-*trans*-**4** (55 mg) as a pale yellow oil. $[\alpha]_D^{23}$ −145.4 (*c* 0.461, $CHCl_3$); >98% chemically and optically pure by HPLC analysis.

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