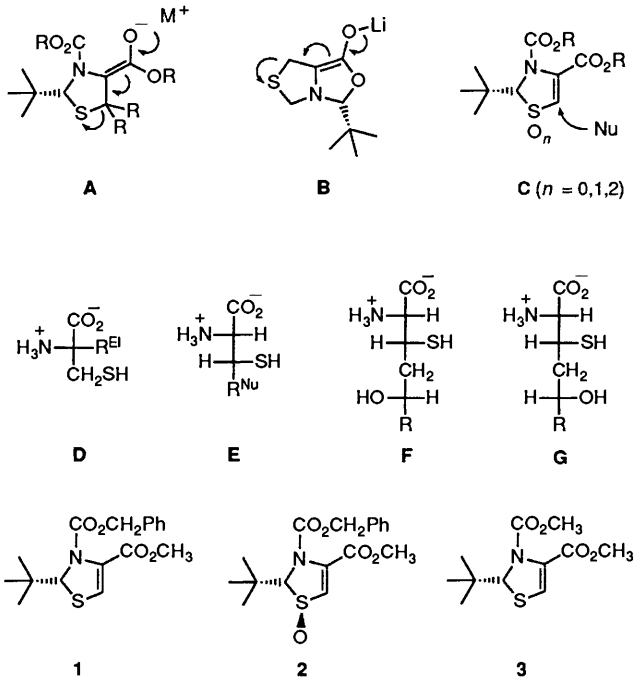
Stereoselective Chain Elongation at C-3 of Cysteine through 2,3-Dihydrothiazoles, without Racemization. Preparation of 2-Amino-5-hydroxy-3-mercaptoalkanoic Acid Derivatives[1,†]

André Jeanguenat and Dieter Seebach *
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland

The enantio pure thiazolines **1**–**3** have been prepared from cysteine; detailed procedures for the dimethyl ester **3** are described (intermediates **4**–**6**). Addition of a cuprate (to give **7**), of Danishefski's diene (to give **8**) and of enamines (to give **10a**–**13a**,**14**) to the thiazoline double bond are highly diastereoselective (single isomers of **10a**–**13a** are obtained). The keto-alkylated products **10a**–**13a** are reduced to 5-(β-hydroxyalkyl)thiazolidinedicarboxylates **10b**–**13b** (or the epimers **10c** and **13c**). The configurations at the up to three new stereogenic centres have been assigned by NMR spectroscopy (*cf.* the bicyclic lactones **10d** and **10e**). In one case, a free α-amino-β-mercapto-δ-hydroxy carboxylic acid was prepared (**15**). The overall process constitutes a stereoselective replacement of H^{Re} at C-3 in L- or (*R*)-cysteine by a chain of carbon atoms, the key step being a Michael addition to an enantiopure 2,3-dehydrocysteine derivative **3**.

Modified amino acids are valuable building blocks for the preparation of peptides or peptide analogues. In our efforts to bring about *C*-alkylations of proteinogenic amino acids,[2] cysteine has always taken a special role: owing to the fact that the sulphide group cannot be prevented from undergoing β-elimination even in geometrically unfavourable situations,‡,[3] enolates of type **A** and **B** cannot be trapped with electrophiles[4] except under very special *in situ* conditions.[5] For this reason, it has not been possible to prepare α-branched cysteines **D**, other than those in which R^E is derived from an aromatic aldehyde,[6] with self-regeneration of the stereogenic centre. The same problem was to be expected in Michael additions to thiazolines and, even more so, to their sulphoxides or sulphones (*e.g.* **C**), because the primary adducts are enolates possessing the structural features which lead to β-elimination (*cf.* **A**).

In this paper successful nucleophilic additions§ to thiazolines are described which eventually produce the cysteine derivatives of **E**, **F** and **G** in which the diastereotopic hydrogen atom H^{Re} in the 3-position of L-cysteine itself has been substituted, with carbon-chain extension.



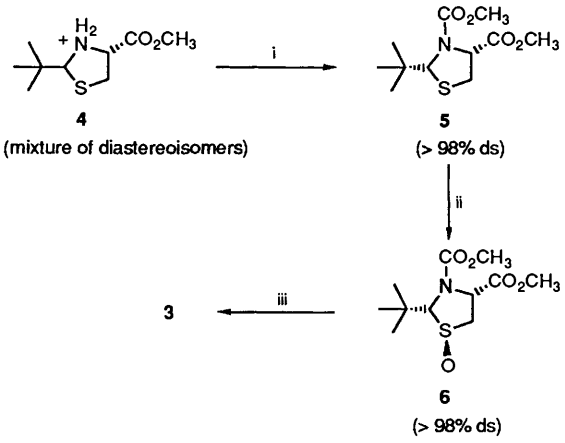
Discussion

Improved Preparation of the Starting Materials.—Extensive procedures for the preparation of the Z-protected thiazoline **1** have been described previously.[8] The diastereoselectivity of its sulphoxidation (**1** ⟶ **2**) was found to be much greater with periodate (97% ds) than with *m*-chloroperbenzoic acid (60% ds). The sulphoxide was made in order to increase the electrophilicity of the thiazoline double bond. The configuration on sulphur is assigned as *R* by analogy with the thiazoline lacking the 4-methoxycarbonyl group which has been oxidized exclusively from the face *trans* to the *tert*-butyl group, as proved by X-ray crystal structure analysis.[8] The presence of the benzyl group in **1** and **2** caused several problems with these thiazolines: (*i*) they did not crystallize very well, an observation also noted for the intermediates in the conversion of cysteine into **1** and **2**; (*ii*) debenzylations with H_2/Pd–C are hampered by the presence of sulphur in the molecule; and (*iii*) the benzylic hydrogens are sufficiently acidic to interfere with reactions involving strong base. We therefore prepared the 3-methoxycarbonyl derivative **3**, following the procedure[8] elaborated for **1**, see Scheme 1. The yields were quite similar, and the configuration of the intermediate **5** was deduced from nuclear Overhauser effects measured in the ^{1}H NMR spectrum. Again, the mixture of diastereoisomers **4** was cleanly converted into a single product

† Submitted to mark the 150th anniversary of the Chemical Society/Royal Society of Chemistry.

‡ *In* **A** and **B** the C–S bond cleaved is approximately perpendicular to the π orbital of the enolate. Formally, RS^- elimination is the reversal of a 5-*endo*-*trig* cyclization (Baldwin's terminology) which is 'forbidden' in cases involving only elements of the first period. Sulphur and all the other elements of higher periods do not follow these rules.

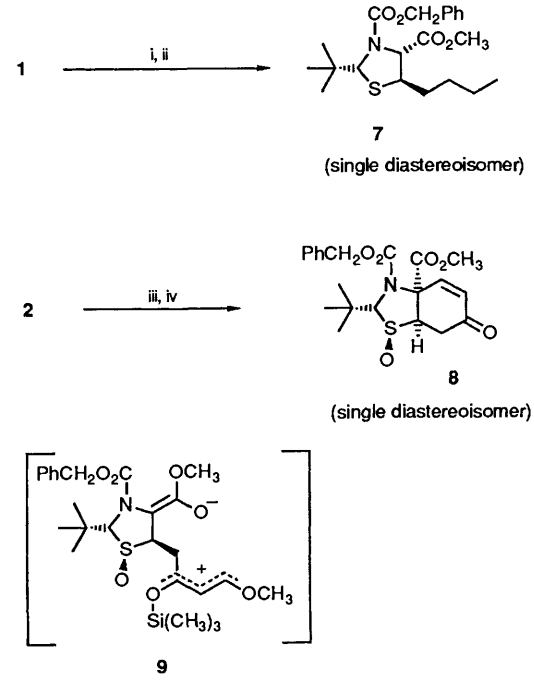
§ In the cases of dioxolanecarboxylates, derived from tartaric acid, and of dioxanones, β-elimination of the corresponding enolates could be avoided by switching from $LiNR_2$ bases to the metal-free phosphazene bases (for instance 'P4').[7] These new bases have not been tested with the sulphur-containing systems.



Scheme 1 Preparation of the dimethyl ester **3** from cysteine (overall yield 44%). *Reagents:* i, $ClCO_2CH_3$–NEt_3–CH_2Cl_2; ii, H_2O_2–HOAc; iii, TBDMSOTf–NH_3–CH_2Cl_2.

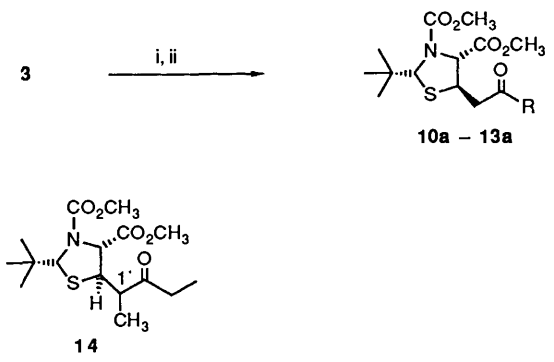
upon *N*-acylation, and the sulphoxidation was highly diastereoselective.[9a] The Pummerer rearrangement in the conversion of **6** into the thiazoline dimethyl ester **3** was carried out on a 30 g scale using the expensive TBDMS-triflate;[9b] other reagents, for instance acetic or trifluoroacetic anhydride, did not work satisfactorily. The products **3**, **5** and **6** were nicely crystalline.

Michael and Diels–Alder Additions to the Thiazolines **1** *and* **2**.—With the analogous oxazolidine esters we have been able to carry out cuprate additions in high yields,[10] but with the thiazolines studied here, we encountered severe problems, as expected (see the introduction). After extensive experimentation, a maximum yield of 21% was realized with the Michael acceptor



Scheme 2 Cuprate addition to **1** and [4 + 2]-cycloaddition of a Danishefski diene to **2**. *Reagents:* i, $Bu_2Cu(CN)Li_2$–BF_3·OEt_2 (4 equiv.)–Et_2O, −30 °C; ii, NH_4Cl–NH_3–H_2O; iii, CH_2=C(OSiMe$_3$)–CH=CHOMe–toluene, reflux: iv, HCl (1 mol dm^{-3})–H_2O.

1; the sulphoxide **2** did not furnish isolable amounts of adducts at all. As specified in Scheme 2, treatment with dibutyl cyanocuprate,[11] with BF_3 activation,[12] led to the *trans*-product



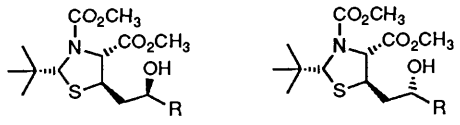
Compound	R	Yield (%)
10a	$CH(CH_3)_2$	61
11a	*c*-C_3H_5	70
12a	*c*-C_6H_{11}	74
13a	C_6H_5	34

Scheme 3 Products **10a–13a** and **14** from **3** and enamines derived from methyl ketones and from pentan-3-one. *Reagents:* i, 1-(1-alkylvinyl)pyrrolidine (5 equiv.)–EtOH, reflux; ii, 5% tartaric acid–H_2O.

7 in this poor yield, but with excellent diastereoselectivity. The reaction was slow at −30 °C, and the bulk of the material in the crude product mixture was highly polar, not eluting from the column in the chromatographic purification; this is compatible with the expected products of β-elimination (see **A** and **C** above). The configuration of **7** was deduced from nuclear Overhauser effects (NOE) measured in the ^1H NMR spectrum.

We had better luck with 1-methoxy-3-(trimethylsilyloxy)-butadiene[13] as the nucleophile (Scheme 2): the bicyclic derivative **8** was isolated as a single isomer in almost 80% yield after treatment of the primary adduct with aqueous HCl. Again, the configuration, resulting from attack at the face *trans* to the *tert*-butyl group but *cis* to the sulphoxide oxygen,[14] was deduced from NOE measurements. In this case, concerted cycloaddition avoids formation of an enolate, and a dipolar intermediate **9**, with an enolate as the anionic centre, would probably collapse too fast for β-elimination to take place.[15]

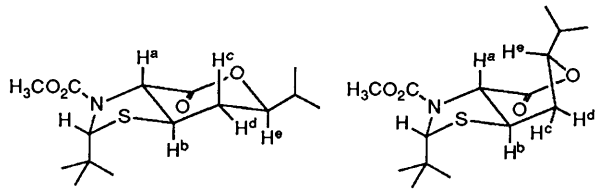
Michael Additions of Enamines to the Thiazoline **3** *in Refluxing Ethanol and Conversions of the Ketones Obtained.*—Enamines prepared from methyl ketones (3-methylbutan-2-one, cyclopropyl and cyclohexyl methyl ketone and acetophenone) by condensation[16] with pyrrolidine, were allowed to react with the dimethylthiazolinedicarboxylate **3**. For optimum yields to be realized, it was necessary for a solution of the components, with the enamine in fivefold excess, to be heated under reflux in ethanol. The reaction mixture turned black, and a bright rainbow-coloured streak developed upon chromatography of the crude product. It was, however, quite simple to spot the fraction containing the desired products **10a–13a** (see Experimental section), and to isolate them as single diastereoisomers in the yields given in Scheme 3 (**10a–12a** are oily substances, only the phenyl-substituted derivative **13a** crystallized). With the enamine from diethyl ketone a non-separable mixture (5:4) of 1′-epimers **14** resulted (64%). The *cis,trans* configuration of the substituents on the thiazolidine ring of **10–14** was derived from NMR measurements, namely, the *ca.* 9 Hz coupling between 4-H and 5-H and the positive nuclear Overhauser effect observed between the protons of the *tert*-butyl group and 5-H, but not 4-H. The success of the Michael additions with **3** and enamines in ethanol probably rests upon the fact that the enolate moiety of the intermediate zwitterion is



10b – 13b **10c – 13c**

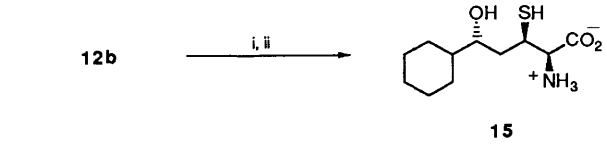
(specification of R as for **10a – 13a**)

Ketone	Reducing agent	Products	Total yield (%) (**b** + **c**)	Ratio (**b**:**c**)
10a	Bu^s_3BHLi	**10b** + **10c**	99	91:9
	$NaBH_4$		91	35:65
11a	Bu^s_3BHLi	**11b** + **11c**	83	83:17
12a	Bu^s_3BHLi	**12b** + **12c**	90	79:21
13a	Bu^s_3BHLi	**13b** + **13c**	99	36:64



10d (from 10b) **10e (from 10c)**

Proton	δ	J/Hz		δ	J/Hz
a	4.05	ab 12.4	a	4.27	ab 12.8
b	3.84	bc 12.2	b	3.6–3.8	bc 10.6
c, d	2.4–2.5	bd 3.4, ce 10.4	c, d	1.8–2.4	bd 8.4, ce 8.6
e	4.32	de 6.2	e	4.27	de 7.2



12b i, ii **15**

Scheme 4 Monocyclic **10–13b**, **c**, bicyclic **10d**, **e** and open-chain derivatives **15** of 2-amino-5-hydroxy-3-mercaptopentanoic acid. *Reagents:* i, HCl (6 mol dm^{-3})–H_2O, reflux, 8 h; ii, propylene oxide–EtOH (O_2-free).

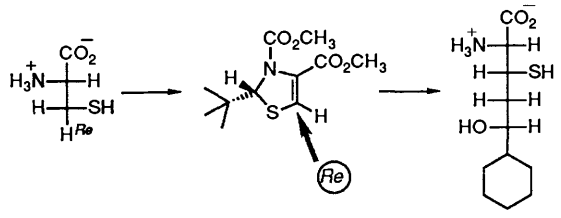
quenched in the protic medium much more rapidly than it undergoes β-elimination.

Attempts to hydrolyse the keto diesters to free 2-amino-5-oxo-3-mercapto carboxylic acids under acidic conditions failed completely, probably due to condensations taking place between the keto and the amino functions. We therefore decided to reduce the ketone group to a secondary hydroxy group and then try again, the resulting amino-hydroxy-mercapto carboxylic acids being, in any case, the more interesting compounds. The results of reductions with two different borohydrides are listed below the product formula **10–13b**, **c** in Scheme 4. The yields ranged from 83 to 99% and the diastereoselectivities from 64 to 91%. The two epimers **b** and **c** could be readily separated by flash chromatography;[17] all major diastereoisomers were isolated as oily samples in analytically pure form, and fully characterized. The epimers differ very characteristically; those assigned the *R*-configuration on the newly formed hydroxylated stereogenic centre (**b**) are less polar (moving much faster during chromatography, R_f 0.34–0.37 *vs.* 0.19–0.26 for **c**), the 4-H and 5-H signals appearing at higher and lower field, respectively, in the ^1H NMR spectrum than those in the **c** series (δ = 4.30 and 4.00 *vs.* 4.4 and 3.7). The configurational assignment to the two series (2′*R* for **b** and 2′*S* for **c**) was deduced from the NMR analysis of the bicyclic products **10d** and **10e** which were obtained by lactonization of **10b** and **10c**, respectively, which were heated under reflux in toluene, in the presence of dibutylethylenedioxytin, with a tiny wire basket full of 4 Å molecular sieves suspended in the vapours from the tip of the cooling coil inside the reflux condenser.*[,18] As can be seen from the data in Scheme 4, the main difference between the NMR spectra of **10d** and **10e** is the coupling constants J_{bc} and J_{bd} which are quite different in the former (12.2 and 3.4 Hz) and rather close in the latter (10.6 and 8.4 Hz). This is interpreted by assuming a quasi-chair for the conformation of the six-membered ring in **10d** and a quasi-boat in **10e**.

Hydrolysis to the free amino acid was attempted with the cyclohexyl derivative **12b**, as a representative example. In addition to the usual problems associated with the isolation of pure free amino acids, the SH group in the desired amino-hydroxy-mercapto carboxylic acid **15** causes further complications, necessitating the least number of manipulations possible with rigorous exclusion of oxygen. Thus, hydrolysis of **12b** in refluxing HCl was followed by treatment with propylene oxide in ethanol for removal of HCl,[19] both in an inert atmosphere, to give a pure, crystalline sample of the tetrafunctionalized compound **15** as a single stereoisomer to which we assign the structure shown in Scheme 4. When oxygen was not excluded, or when ion-exchange chromatography (DOWEX 50WX8) was used to liberate **15**, impure and inhomogeneous samples were obtained.

Conclusions

The results described herein constitute another example of the self-regeneration of a stereogenic centre,†[,2] see Scheme 5. In order to confer electrophilic and stereoselective reactivity to C-3 of cysteine, a double bond is introduced, with elimination of the original stereogenic centre of the amino acid, but with preservation of chirality by incorporation of a temporary stereogenic centre at C-2 of the thiazoline ring **3**. The acetal centre serves to provide a chirality centre and to differentiate



L-Cysteine (2*R*) **3** (2*R*) **15** (2*R*, 3*R*, 5*R*)

Scheme 5 Self-regeneration of the stereogenic centre of cysteine by conversion into a chiral, non-racemic heterocyclic acetal with Michael acceptor reactivity at C-3 (of cysteine)

* The intramolecular transesterifications **10b** ⟶ **10d** and **10c** ⟶ **10e** could not be accomplished with 2 mol dm^{-3} HCl or with trifluoroacetic acid–THF.

† Originally, we used the term 'self-reproduction of chirality centres',[4] but it was later pointed out to us that 'self-reproduction' should be reserved as a technical term for systems which can reproduce themselves, such as living organisms. We realize that there is a number of examples in the literature in which a chiral non-racemic molecule containing a single stereogenic centre is converted into another non-racemic chiral molecule with one, and only one, stereogenic centre at a different carbon atom, as in the present case, the conversion of cysteine into **3**. To the best of our knowledge, the systematic use of the principle of self-regeneration of stereogenic centres, as part of a synthetic methodology was first realized by us: D. Seebach and R. Naef, *Helv. Chim. Acta*, 1981, **64**, 2704.

the reactivity of the two double-bond faces. After stereoselective addition of R^{Nu} and H, both to the face of the double bond remote from the substituent at the acetal centre (see **3** ⟶ **10–13**, above), establishing two stereogenic centres on the original three-carbon skeleton of cysteine (and regenerating one at the carbon which had been a stereogenic centre to begin with), the acetal may be hydrolysed, destroying the auxiliary centre (see **3** ⟶ **15** in Scheme 5). As the diastereoselectivities in the generation of the acetal centre (see **5** in Scheme 1) and in the addition to the heterocyclic double bond (**1** ⟶ **8**; **10–13**) are high, the final product (see **15**) is enantiomerically pure. Thus, the process leading from L-cysteine to **15** is an overall stereoselective replacement of one of the diastereotopic hydrogens in the amino acid.

Experimental

General.—THF was distilled under Ar and over $LiAlH_4$ prior to use and transferred with syringes. Flasks, stirring bars and hypodermic needles used for the generation of organolithium reagents were dried for *ca.* 12 h at *ca.* 150 °C and allowed to cool in a dessicator over anhydrous silica gel. The side arm of the reaction flasks was stoppered with a septum cap, and the flasks were connected to an Ar line by three-way taps. A positive pressure of Ar was established by performing the operation 'flask evacuation/Ar introduction' several times.

TLC was carried out on Merck precoated silica gel 60 F-264 plates. Reaction components were visualized under UV_{254} illumination and by development with a solution of anisaldehyde (9.2 cm^3), acetic acid (3.75 cm^3), conc. H_2SO_4 (12.5 cm^3) and ethanol (388 cm^3), or with aqueous $KMnO_4$.

Flash column chromatography was performed on silica gel 60 (230–400 mesh; 0.04–0.063 mm; Fluka) according to the procedure of Still *et al.*[17]

M.p.s were obtained with open glass capillaries and a Büchi 510 apparatus, and are uncorrected.

$[\alpha]_D$ Values were measured at room temperature with a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

IR Spectra were measured at $CHCl_3$ solutions, as films (Perkin-Elmer 1600 Series FTIR or Perkin-Elmer 782) or KBr discs (Perkin-Elmer 283).

^1H NMR spectra were measured with a Varian EM 390 (90 MHz), a Varian Gemini (200 MHz) or a Bruker WM 300 (300 MHz) spectrometer. ^{13}C NMR spectra were measured with a Varian CFT-20 (20 MHz), a Varian Gemini (50 MHz), a Varian XL-300 (75 MHz) or a Bruker WM-300 (100 MHz) spectrometer. Chemical shifts (δ) are reported in ppm downfield of tetramethylsilane ($\delta = 0$) and coupling constants J are given in Hz.

Mass spectra were run on a Hitachi-Perkin-Elmer RMU-6M spectrometer; fragment ions indicated in m/z units with relative intensities (%) in parentheses.

(2R)-*Methyl*-3-*Benzyloxycarbonyl*-2-tert-*butyl*-1-*oxido*-2,3-*dihydro*-1,3-*thiazole*-4-*carboxylate* (**2**).—(*a*) *MCPBA-oxidation.* A quantity of MCPBA (0.95 g, 2.98 mmol, Fluka, 55%, with 35% water and 10% MCBA) was added to a solution of **1** (1.0 g, 2.98 mmol) in acetone (20 cm^3). The reaction was stirred for 12 h after which the solvent was evaporated and the residue was taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$. After drying ($MgSO_4$) and evaporation of the solvent white crystals [0.88 g, 83.5%, ds* = 60% from ^1H NMR spectroscopy (300 MHz) and ^{13}C NMR (100 MHz) spectroscopy] were isolated.

(b) $NaIO_4$-*oxidation.* Sodium periodate (2.07 g, 9.7 mmol) was added to a suspension of **1** (2.14 g, 6.38 mmol) in ethanol–water (1:1; 40 cm^3). The solution was acidified to pH = 4 (H_3PO_4) and stirred for 5 days at room temp. The solvent was evaporated and the residue was taken up in ethyl acetate and washed three times with saturated aqueous $NaHCO_3$. After drying ($MgSO_4$) and evaporation of the solvent, yellow crystals were isolated [2.21 g, 98.5%, ds = 97% from ^1H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectroscopy]. A diastereoisomerically pure product was obtained after one crystallisation from methanol; m.p. 110.5–111.5 °C; $[\alpha]_D$ +69.7 (*c* 0.6 in $CHCl_3$); ν(KBr)/cm^{-1} 3100, 3065m, 2980m, 1740br s, 1725s, 1615w, 1600m, 1480m, 1465m, 1455m, 1430s, 1390s, 1370br s, 1290br s, 1250s, 1215s, 1170m, 1130w, 1095w, 1050s, 1030s, 960w, 915w, 900w, 850w, 800w, 775m, 760s and 700s; δ_H(300 MHz; $CDCl_3$; other diastereoisomer in brackets) 1.04 (1.18) [s, 9 H, $(CH_3)_3C$], 3.62 (3.63) (s, 3 H, OCH_3), 4.89 (4.77) (s, 1 H, 2-H), 5.15 (5.13) (d, *J* 12, 1 H, CH_2Ph), 5.22 (5.23) (d, *J* 12, 1 H, CH_2Ph), 6.680 (6.682) (s, 1 H, 5-H) and 7.37 (7.36) (m, 5 H, Ph); δ_C(100 MHz; $CDCl_3$; other diastereoisomer in brackets): δ 26.44 (26.31), 36.69 (37.68), 52.99 (53.25), 69.83 (70.12), 92.36 (84.98), 117.73 (120.74), 128.72 (128.75), 134.14 (133.99), 145.02 (143.15), 152.98 (152.33) and 160.75 (160.20); m/z 351 [M^+], 307, 259, 244, 216 (10%), 168 (5), 132 (3), 91 (100) and 65 (9) [Found: C, 57.85; H, 6.15; N, 4.0. Calc. for $C_{17}H_{21}NO_5S$ (*M*, 351.42): C, 58.10; H, 6.02; N, 3.99%].

(2R)-*Dimethyl* 2-tert-*Butyl*-2,3-*dihydro*-1,3-*thiazole*-3,4-*dicarboxylate* **3**.—A solution of **6** (30.2 g, 109 mmol) in CH_2Cl_2 (300 cm^3) was treated with *tert*-butyldimethylsilyl trifluoromethanesulphonate (30.0 cm^3, 130 mmol) at room temp. and under an Ar-atmosphere. After 10 min triethylamine (18.0 cm^3, 130 mmol) was added. The resulting solution was stirred for 3 days and during which time it became progressively dark. After removal of the solvent the oily residue was filtered on a 4 cm silica-gel layer using ether as the solvent. The product was chromatographed on a short column (25 cm; ether–pentane 1:3). From the column white crystals (12.9 g, 51.4% relative to the reacted starting material) and an educt (3.4 g) were isolated. The product was crystallised from ether–pentane, m.p. 75.4–77.0 °C; $[\alpha]_D$ +125.6 (*c* 1 in $CHCl_3$); ν($CHCl_3$)/cm^{-1} 3010, 2980, 1724, 1710, 1584, 1440, 1362, 1316, 1255, 1995, 1119, 1049, 976, 891 and 811; δ_H(200 MHz; $CDCl_3$) 0.89 [s, 9 H, $(CH_3)_3C$], 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 5.44 (s, 1 H, 2-H) and 6.82 (s, 1 H, 5-H); m/z 259 (3%) [M^+], 228 (6), 202 (9), 157 (100), 126 (2) and 112 (4) [Found: C, 51.2; H, 6.75; N, 5.62. Calc. for $C_{11}H_{17}NO_4S$ (*M*, 259.33): C, 50.95; H, 6.61; N, 5.40%].

(4R)-2-tert-*Butyl*-4-*methoxycarbonyl*-1,3-*thiazolidinium Chloride* **4**.—A mixture of (*R*)-cysteine methyl ester hydrochloride (158 g, 700 mmol), pivalaldehyde (153 ml, 1400 mmol) and triethylamine (107 cm^3, 770 mmol) in pentane (800 cm^3) was refluxed for 24 h with continuous removal of water using a Dean–Stark trap. The resulting suspension was filtered, the residue was washed with ether and the filtrate was evaporated to give **4** as a colourless oil (138.6 g, 99%), which crystallised with time at −30 °C; δ_H(90 MHz; $CDCl_3$) 0.98 and 1.08 (2 × s, 9 H, $(CH_3)_3C$], 2.50–2.83 (m, 1 H, 4-H), 3.15–3.52 (m, 2 H, 5-H), 3.91 (s, 3 H, OCH_3) and 4.61 and 4.71 (2 × s, 1 H, 2-H, 7:5 mixture of diastereoisomers).

(2R,4R)-*Dimethyl* 2-tert-*Butyl*-1,3-*thiazolidine*-3,4-*dicarboxylate* **5**.—Triethylamine (219.0 cm^3, 1569 mmol) was carefully added to a solution of **4** (125.0 g, 523 mmol) and methyl chloroformate (46.7 cm^3, 677 mmol), taking care that the temperature remained below 5 °C. After 10 h of stirring, the solution was washed consecutively with a saturated aqueous

* Diastereoselectivity (fraction of the major diastereoisomer formed).

$NaHCO_3$ and saturated aqueous NaCl and dried with $MgSO_4$. After evaporation of the solvent compound **5** (124.8 g, 91.4%) was isolated as white crystals, which were crystallised from pentane for analytical purposes; m.p. 73.4–74.4 °C; $[\alpha]_D$ −106.3 (*c* 1.2 in $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2960, 2910, 2870, 1765, 1700, 1480, 1440, 1390, 1365, 1330, 1300, 1270, 1190, 1175, 1140, 1110, 1035 and 1010; δ_H(90 MHz; $CDCl_3$) 1.08 [s, 9 H, $(CH_3)_3C$], 3.17–3.58 (m, 2 H, 5-H), 3.98 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.82 (t, *J* 9, 1 H, 4-H) and 5.01 (s, 1 H, 2-H); NOE-measurements (300 MHz): irradiation of the signal at 1.08 ppm (Bu^t): enhancement of the signal at 5.01 (2-H), no enhancement at 4.82 (4-H); irradiation at δ 4.82 (4-H): no enhancement at 1.08 ppm (Bu^t); δ_C(20 MHz; $CDCl_3$) 26.8, 33.8, 39.2, 51.9, 53.0, 64.5, 74.0, 155.5 and 170.7; *m/z* 246 (2%), 206 (17), 205 (27), 204 (100) [$M^+ - 57$], 160 (23), 100 (11), 86 (12), 59 (21), 57 (10) and 42 (10) [Found: C, 50.55; H, 7.35; N, 5.35; S, 12.35. Calc. for $C_{11}H_{19}O_4NS$ (*M*, 261.34): C, 50.55; H, 7.33; N, 5.36; S, 12.27%].

(1R,2R,4R)-*Dimethyl* 2-tert-*Butyl*-1-*oxido*-1-*thiazolidine*-3,4-*dicarboxylate* **6**.—Hydrogen peroxide (15.4 cm^3, 150.0 mmol) was carefully added to a solution of **5** (39.0 g, 149.2 mmol) in acetic acid (300 cm^3). After being stirred for 12 h the solution was evaporated under reduced pressure at room temp. The residue was triturated in ether and filtered. The product (39.6 g, 95.6%) was obtained in the form of white crystals. Part of this was crystallised from ethyl acetate–hexane for analytical purposes: m.p. 107.7–108.0 °C; $[\alpha]_D$ −76.1 (*c* 1 in $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3002, 1979, 1755, 1714, 1442, 1368, 1330, 1175, 1047 (SO) and 975; δ_H(200 MHz; $CDCl_3$) 0.89 [s, 9 H, $(CH_3)_3C$], 2.88–3.04 and 3.28–3.42 (2 × m, 2 H, 5-H), 3.57 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 4.79 (br s, 1 H, 2-H) and 5.12 (m, 1 H, 4-H); *m/z* 277 (8%) [M^+], 217 (11), 204 (19), 195 (4), 170 (20), 160 (10), 155 (30), 153 (11), 148 (17), 142 (14), 127 (23), 101 (20) and 28 (100) [Found: C, 47.8; H, 7.0; N, 4.9. Calc. for $C_{11}H_{19}NO_5S$ (*M*, 277.34): C, 47.64; H, 6.91; N, 5.05%].

(2R,4R,5R)-3-*Benzyl* 4-*Methyl* 5-*Butyl*-2-tert-*butyl*-1,3-*thiazolidine*-3,4-*dicarboxylate* **7**.—A solution of n-BuLi (1.5 mol dm^{-3} in hexane; 15.82 cm^3, 23.82 mmol) was added over an interval of 10 min to a suspension of CuCN (1.07 g, 11.91 mmol) in absolute THF (25 cm^3) at −78 °C under an Ar-atmosphere. The heterogeneous solution was heated at −30 °C for 10 min until all of the CuCN had dissolved. After being recooled to −78 °C, a solution of the thiazoline **1** (2.0 g, 5.96 mmol) in absolute THF (25 cm^3) was carefully added. As no reaction took place, $BF_3{\cdot}OEt_2$ (3.02 cm^3, 24 mmol) was added and the resulting solution allowed to warm to −30 °C. After being stirred for 12 h, the mixture was hydrolysed with 1:1 aqueous saturated NH_4Cl–conc. NH_4OH for 1 h. After extraction with ether, the organic layer was washed repeatedly with a 1:1 saturated aqueous NH_4Cl–conc. NH_4OH and dried ($MgSO_4$) and the solvent was evaporated off. The resulting orange oil (2.40 g) was chromatographed three times (ether–pentane 1:10) to give diastereoisomerically pure **7** (0.50 g, 21.3%); $[\alpha]_D$ −12.0 (*c* 0.9 in $CHCl_3$); $\nu(CHCl_3)$ 2950, 2880, 1755, 1720, 1495, 1480, 1465, 1455, 1435, 1380, 1360, 1315, 1210, 1195, 1170, 1120, 1110, 1025, 1010 and 970; δ_H[300 MHz; $(CD_3)_2SO$; 80 °C] 0.72–1.05 and 1.15–1.40 (2 × m, 7 H, *n*-butyl), 0.96 [s, 9 H, $(CH_3)_3C$], 1.45–1.50 (m, 1 H, *n*-butyl), 1.90–2.04 (m, 1 H, *n*-butyl), 3.60–3.75 (m, 1 H, 5-H), 3.63 (s, 3 H, OCH_3), 4.36 (d, *J* 8.6, 1 H, 4-H), 5.00–5.21 (m, 3 H, 2-H, CH_2Ph) and 7.23–7.43 (m, 5 H, Ph); NOE measurement: irradiation of the signal at 1.0 ppm (Bu^t): enhancement of the signals at 3.69 ppm (5-H) and 5.1 ppm (2-H); no enhancement of the signal at 4.36 ppm (4-H); *m/z* 362, 336 (10%) [$M^+ - 57$], 292 (19) [$M^+ - 57 - 44$], 142 (3), 91 (100) and 86 (3) [Found: C, 64.3; H, 7.9; N, 3.3. Calc. for $C_{21}H_{31}NO_4S$ (*M*, 393.55): C, 64.09; H, 7.94; N, 3.56%].

(1R,6R,7R,8R)-9-*Benzyl* 1-*Methyl* 8-tert-*Butyl*-7-*oxido*-4-*oxo*-7-*thia*-9-*azabicyclo*[4.3.0]*non*-2-*ene*-1,9-*dicarboxylate* **8**.—A solution of **2** (0.35 g, 1.0 mmol) in toluene (10 cm^3) and 1.0 ml (5.3 mmol) (*E*)-1-methoxy-3-trimethylsiloxybuta-1,3-diene (Danishefsky's diene) was refluxed under Ar for 90 h. After being cooled the brown solution was hydrolysed with HCl (0.5 mol dm^{-3}; 10 cm^3) for 2 h. The organic phase was separated and filtered on a thin layer of silica gel (0.2 cm). A brown wax (0.28 g, 78%) was isolated and after purification by flash chromatography (ether–pentane 75:15), pure **8** (0.17 g (47%) was obtained. The product was crystallised from ether–pentane, m.p. 139.5–140.2 °C; $[\alpha]_D$ +177.9 (*c* 1 in $CHCl_3$); ν(KBr)/cm^{-1} 3020, 2980, 1759, 1748, 1711, 1692, 1401, 1392, 1308, 1246, 1175, 1060, 960, 811, 758 and 706; δ_H(200 MHz; $CDCl_3$) 1.08 [s, 9 H, $(CH_3)_3C$], 2.84–3.18 (m, 2 H, 5-H), 3.65–3.85 (m, 4 H, CO_2CH_3, 6-H), 4.94 (s, 1 H, 8-H), 5.19 (m, 2 H, CH_2Ph), 6.23 (d, *J* 10, 1 H, 2-H), 7.0–7.2 (br, 1 H, 3-H) and 7.70 (s, 5 H, phenyl); NOE-measurements: irradiation of the signal at 1.08 ppm (Bu^t): enhancement of the signals at 3.65–3.85 ppm (6-H). Irradiation of the signal at 4.94 ppm (8-H): no enhancement of the signals at 3.65–3.85 ppm (6-H); *m/z* 419 [M^+], 362, 284, 242 (2%), 108 (2), 91 (100), 65 (9) and 57 (5) [Found: C, 60.35; H, 6.25; N, 3.25. Calc. for $C_{21}H_{25}NO_6S$ (*M*, 419.50): C, 60.13; H, 6.01; N, 3.34%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(3-*methyl*-2-*oxobutyl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **10a**.—A solution of the thiazoline **3** (1.0 g, 3.90 mmol) and pyrrolidino enamine of isopropyl methyl ketone [prepared according to ref. 16(*b*), b.p. 65–6 °C/15 Torr; 2.7 g, 19.40 mmol] in ethanol (5 cm^3) was refluxed for 24 h. After being cooled the brown–black solution was hydrolysed with tartaric acid (5.0 g, 33.02 mmol) water (30 cm^3). The mixture was extracted with ether, washed with saturated $NaHCO_3$ and dried ($MgSO_4$) and the solvent was evaporated off. The resulting brown oil was purified by flash chromatography (ether–pentane 2:7). The development of a TLC-plate with anisaldehyde (see general) permitted the localisation of the desired product: all enamine-adducts showed a characteristic red spot when the plate was warmed. The colourless oil (0.81 g, 61%) was isolated as a single diastereoisomer, b.p. *ca.* 235 °C/0.15 Torr (bulb-to-bulb distillation); $[\alpha]_D$ −9.0 (*c* 1.2 in $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2960, 2876, 1760, 1713, 1483, 1466, 1440, 1363, 1330, 1259, 1995, 1174, 1023, 912, 777 and 731; δ_H(200 MHz; $CDCl_3$) 1.01 [s, 9 H, $(CH_3)_3C$], 1.08 [d, *J* 6.5, 6 H, $(CH_3)_2CH$], 2.57 [septet, *J* 6.5, 1 H, $(CH_3)_2CH$], 2.68–2.84 (m, 1 H, CH_2), 3.05–3.26 (br m, 1 H, CH_2), 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.09 (td, J_1 9, J_2 5, 1 H, 5-H), 4.31 (br, 1 H, 4-H) and 5.11 (br, 1 H, 2-H); NOE-measurement: irradiation of the signal at 1 ppm (Bu^t and Pr^i): enhancement of the signal at 4.09 ppm (5-H) and at 5.11 (2-H), no enhancement at 4.31 ppm (4-H); *m/z* 346 (12.1%) [$M^+ + 1$], 330 (7.4), 302 (5.4), 288 (100) [$M^+ - 57$], 244 (13.2), 228 (6.1), 200 (7.2), 169 (39.3), 158 (58.2), 144 (26.3), 127 (21.9), 114 (13.1), 100 (20.9) and 71 (54.0) [Found: C, 55.75; H, 8.1; N, 3.8. Calc. for $C_{16}H_{27}NO_5S$ (*M*, 345.46): C, 55.63; H, 7.88; N, 4.05%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(2-*cyclopropyl*-2-*oxoethyl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **11a**.—Following the procedure for the preparation of **10a**, the thiazoline **3** (1.5 g, 5.85 mmol) and the pyrrolidino enamine of cyclopropyl methyl ketone [prepared according to ref. 16(*b*), b.p. 93 °C/0.3 Torr; 4.0 g, 29.55 mmol] in ethanol (7.5 cm^3) were refluxed for 20 h. After flash chromatographic purification (ether–pentane 45:55) a colourless oil (1.4 g, 70%) was isolated, b.p. *ca.* 170 °C/5 × 10^{-5} Torr (bulb-to-bulb distillation); $[\alpha]_D$ −0.77 (*c* 1.9 in $CHCl_3$); ν(film)/cm^{-1} 2956, 1757, 1702, 1441, 1363, 1331, 1259, 1195, 1174, 1104, 1017, 973, 914 and 778; δ_H(200 MHz; $CDCl_3$)

0.80–1.08 (m, 4 H, CH_2-cyclopropyl), 1.00 [s, 9 H, $(CH_3)_3C$], 1.77–1.96 (m, 1 H, CH-cyclopropyl), 2.78–2.94 (m, 1 H, CH_2CO), 3.21–3.41 (br m, 1 H, CH_2CO), 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.06 (td, J_1 9, J_2 5, 1 H, 5-H), 4.33 (br, 1 H, 4-H) and 5.01 (br, 1 H, 2-H); *m/z* 344 (15.5%) [$M^+ + 1$], 328 (5.7), 286 (100) [$M^+ - 57$], 242 (6.7), 167 (59.5), 158 (60.8), 144 (17.2), 100 (13) and 69 (69.9) [Found: C, 56.1; H, 7.4; N, 3.85. Calc. for $C_{16}H_{25}NO_5S$ (*M*, 343.44): C, 55.96; H, 7.34; N, 4.08%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(2-*cyclohexyl*-2-*oxoethyl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **12a**.—Following the procedure for the preparation of **10a**, the thiazoline **3** (1.0 g, 3.90 mmol) and the pyrrolidino enamine of cyclohexyl methyl ketone [prepared according to ref. 16(*b*), b.p. 118 °C/15 Torr; 3.5 g, 19.60 mmol] ethanol (5 cm^3) were refluxed for 18 h. After flash chromatographic purification (ether–pentane 1:4) a colourless oil (1.1 g, 74.2%) was isolated, b.p. 220 °C/3.10^{-5} Torr (bulb-to-bulb distillation); $[\alpha]_D$ −1.82 (*c* 1.2 in $CHCl_3$); *v*(film)/cm^{-1} 2931, 2854, 1758, 1708, 1483, 1441, 1363, 1331, 1258, 1195, 1174, 1118, 1010 and 777; δ_H(200 MHz; $CDCl_3$) 0.99 [s, 9 H, $(CH_3)_3C$], 1.09–1.40 (m, 5 H, cyclohexyl), 1.54–1.87 (m, 5 H, cyclohexyl), 2.19–2.37 (m, 1 H, CH-cyclohexyl), 2.62–2.81 (m, 1 H, CH_2CO), 3.02–3.21 (br m, 1 H, CH_2CO), 3.68 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 4.06 (td, J_1 9, J_2 5, 1 H, 5-H), 4.30 (br m, 1 H, 4-H) and 4.99 (br s, 1 H, 2-H); NOE-measurement: irradiation of the signal at 0.99 ppm (Bu^t): enhancement of the signal at 4.06 (5-H) and at 4.99 (2-H); *m/z* 386 (12.3%) [$M^+ + 1$], 328 (100) [$M^+ - 57$], 284 (5), 209 (41.2), 158 (51.2), 144 (18.7), 127 (17.5), 111 (16.6), 100 (9.1) and 83 (67.3) [Found: C, 59.1; H, 8.2; N, 3.6. Calc. for $C_{19}H_{31}NO_5S$ (*M*, 385.52): C, 59.19; H, 8.10; N, 3.63%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-*benzoylmethyl*-1,3-*thiazolidine*-3,4-*dicarboxylate* **13a**.—Following the procedure for the preparation of **10a**, the thiazoline **3** (1.0 g, 3.90 mmol) and the pyrrolidino enamine of acetophenone [prepared according to ref. 16(*b*), b.p. 64 °C/0.01 Torr; 4.3 g, 24.90 mmol] in ethanol (5 cm^3) were refluxed for 15 h. After flash chromatographic purification (ether–pentane 15:35, then 2:3), a slightly yellow oil (0.5 g, 34.2%) was isolated, which crystallised after several weeks at room temp., b.p. 120 °C/5.10^{-4} Torr (bulb-to-bulb distillation), m.p. 73.6–75.2 °C (ether–pentane); $[\alpha]_D$ +43.2 (*c* 1 in $CHCl_3$); *v*(film)/cm^{-1} 3060, 2954, 1700br, 1597, 1580, 1483, 1434, 1370–1160br, 1118, 1054, 1012, 906 and 805; δ_H(200 MHz; $CDCl_3$) 1.06 [s, 9 H, $(CH_3)_3C$], 3.23–3.40 (m, 1 H, CH_2), 3.65–3.85 (br m, 1 H, CH_2), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.28 (td, J_1 9, J_2 4.2, 1 H, 5-H), 4.51 (br m, 1 H, 4-H), 5.08 (br s, 1 H, 2-H), 7.42–7.59 (m, 3 H, phenyl) and 7.90–7.96 (m, 2 H, phenyl); *m/z* 380 (0.06%) [$M^+ + 1$], 365 (1.3), 322 (100) [$M^+ - 57$], 203 (13.2), 158 (28), 144 (13.0), 105 (71.6) and 77 (41.5) [Found: C, 60.3; H, 6.9; N, 3.5. Calc. for $C_{19}H_{25}NO_5S$ (*M*, 379.48): C, 60.14; H, 6.64; N, 3.69%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(3-*oxopentan*-2-*yl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **14**.—Following the procedure for the preparation of **10a**, the thiazoline **3** (2.0 g, 7.70 mmol) and the pyrrolidino enamine of diethyl ketone [prepared according to ref. 16(*a*), b.p. 62–7 °C/8 Torr; 5.4 g, 38.0 mmol] in ethanol (30 cm^3) were refluxed for 36 h. After flash chromatographic purification (ether–pentane 15:35), a colourless oil (1.7 g, 63.8%) was isolated, b.p. 170 °C/0.01 Torr (bulb-to-bulb distillation); *v*(film)/cm^{-1} 2957, 1750, 1714, 1482, 1440, 1395, 1364, 1332, 1280, 1260, 1196, 1176, 1114, 1029, 975 and 778; δ_H(200 MHz; $CDCl_3$) 0.85–1.10 [m, 12 H $(CH_3)_3C$ and CH_2CH_3], 1.18 (d, 3 H, $CHCH_3$), 2.31–2.61 (m, 2 H, CH_2CH_3), 2.61–2.75 and 2.75–2.92 (2 × m, 1 H, $CHCH_3$, 5:4 mixture of diastereoisomers), 3.67 and 3.68 (2 s, 3 H, OCH_3), 3.73 and 3.75 (2 s, 3 H, OCH_3), 4.10–4.23 (m, 1 H, 5-H), 4.41 and 4.89 (br, 1 H, 4-H), 5.01 and 5.13 (2 s, br, 1 H, 2-H); NOE-measurements: irradiation of the signal at 0.95 ppm (Bu^t): enhancement of the signal at 4.1 ppm (5-H) and at 5.15 ppm (2-H); no enhancement at 4.4 and 4.9 ppm (4-H). Irradiation of the signal at 5.1 ppm (2-H and 4-H): no enhancement of the signal at 4.1 ppm (5-H); *m/z* 344 [$M^+ - 1$], 330 (4%) [$M^+ - 15$], 314 [$M^+ - 31$], 302 (3.4), 288 (100) [$M^+ - 57$], 230 (7.0), 204 (6.9), 169 (14.2), 158 (23.9), 144 (12), 113 (12.3) and 91 (15.5) [Found: C, 55.55; H, 7.95; N, 3.75. Calc. for $C_{16}H_{27}NO_5S$ (*M*, 345.46): C, 55.63; H, 7.88; N, 4.05%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(2-*hydroxy*-3-*methylbutyl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **10b** *and* **10c**.—(*a*) L-*Selectride*. A solution of lithium tri-*sec*-butylborohydride (5.1 cm^3, 5.1 mmol, 1 mol dm^{-3} in THF) was carefully added to a solution of the ketone **10a** (0.88 g, 2.55 mmol) in THF (30 cm^3) at −78 °C under Ar atmosphere. After 3 h the mixture was hydrolysed with saturated aqueous NH_4Cl at −78 °C. After ether extraction the organic layer was washed with saturated NH_4Cl and dried with $MgSO_4$ and the solvent was evaporated off. The oily residue (0.9 g, 99%) was submitted directly to flash chromatography (ether–pentane 1:3). The pure diastereoisomer **10b** (0.20 g, R_f = 0.34 in ether–pentane 1:1) and a mixture of **10b** and **10c** (0.23 g) were isolated, ds = 90.6% from ^1H NMR spectroscopy, 200 MHz.

(*b*) *Sodium borohydride*. A solution of sodium borohydride (0.07 g, 2.00 mmol) was added to a solution of the ketone **10a** (0.35 g, 1.00 mmol) in methanol (1 cm^3) at room temperature. After 1 h of stirring, the solvent was evaporated off and the residue was taken up in water and extracted with ether. After drying ($MgSO_4$) and evaporation of the solvent, a mixture of diastereoisomers (**10b**:**10c** = 35:65) was isolated as a colourless oil (0.32 g, 91%). After one flash chromatographic purification, a mixture of **10b** and **10c** (0.4 g) and a pure sample of **10c** (0.10 g, R_f 0.26 in ether–pentane 1:2) were obtained.

Diastereoisomer **b** (2′*R*): $[\alpha]_D$ −20.0 (*c* 1.1 in $CHCl_3$); *v*($CHCl_3$)/cm^{-1} 3498, 2957, 2873, 1755, 1714, 1484, 1443, 1356, 1332, 1259, 1196, 1119, 1011 and 779; δ_H(200 MHz; $CDCl_3$) 0.86 (d, *J* 4, 3 H, CH_3CH), 0.90 (d, *J* 4, 3 H, CH_3CH), 1.00 [s, 9 H, $(CH_3)_3C$], 1.50–1.72 (br m, 2 H, CH_2), 1.88 (br, 1 H, OH), 2.05–2.23 [m, 1 H, $CH(CH_3)_2$], 3.25–3.40 (br m, 1 H, CHOH), 3.70 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.98 (dt, J_1 3.5, J_2 10, 1 H, 5-H), 4.31 (br, 1 H, 4-H) and 5.01 (br, 1 H, 2-H); *m/z* 332 [$M^+ - 15$], 314 [$M^+ - 33$], 290 (100%) [$M^+ - 57$], 246 (7), 230 (9.9), 218 (2.8), 158 (10.8), 144 (45), 114 (7.3), 100 (11.1) and 71 (46.2).

Diastereoisomer **c** (2′*S*): $[\alpha]_D$ −46.94 (*c* 1 in $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 0.91 [t, *J* 6, 6 H, $(CH_3)_2CH$], 0.99 [s, 9 H, $(CH_3)_3C$], 1.56–1.81 (br m, 2 H, CH_2), 1.99 (br, 1 H, OH), 2.15 [td, J_1 4.5, J_2 14, 1 H, $CH(CH_3)_2$], 3.38–3.53 (m, 1 H, CHOH), 3.71 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.66–3.85 (m, 1 H, 5-H), 4.47 (br, 1 H, 4-H) and 5.04 (br, 1 H, 2-H) [Found: C, 55.0; H, 8.55; N, 4.0. Calc. for $C_{16}H_{29}NO_5S$ (*M*, 347.48): C, 55.31; H, 8.41; N, 4.03%].

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-[(2R)-2-*cyclopropyl*-2-*hydroxyethyl*]-1,3-*thiazolidine*-3,4-*dicarboxylate* **11b** *and* **11c**.—Following the procedure for the preparation of **10b** [part (*a*)] a solution of L-Selectride (1 mol dm^{-3} in THF; 1.58 cm^3, 1.58 mmol) was added to the ketone **11a** (0.30 g, 0.75 mmol) in THF (15 cm^3). After 1.5 h, the reaction mixture was hydrolysed and the resulting mixture of diastereoisomers was submitted directly to flash chromatography (ether–pentane, 1:1). The pure diastereoisomer **b** (0.25 g, 83%, R_f 0.36 in ether–pentane, 3:2) and the pure diastereoisomer **c** (0.05 g, 16%, R_f 0.22 in ether–pentane, 3:2) were isolated, ds = 83% (^1H NMR spectroscopy, 200 MHz).

Diastereoisomer **b** (2′*R*): $[\alpha]_D$ −18.2 (*c* 1 in $CHCl_3$); *ν*(film)/cm^{-1} 3487, 3079s, 2956, 1680–1760br, 1484, 1435, 1330, 1200, 1119, 1005, 972, 917 and 777; δ_H(200 MHz; $CDCl_3$) 0.11–0.37, 0.41–0.61 and 0.80–1.10 (3 × m, 4 H, CH_2-cyclopropyl), 1.00 [s, 9 H, $(CH_3)_3C$], 1.62–1.95 (m, 2 H, 1′-H), 2.23–2.44 (m, 1 H, CH-cyclopropyl), 2.85 (dt, J_1 3.5, J_2 9.5, 1 H, C*H*OH), 3.70 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.98 (dt, J_1 4, J_2 9.5, 1 H, 5-H), 4.32 (br, 1 H, 4-H) and 5.01 (br, 1 H, 2-H); δ_C(50 MHz; $CDCl_3$) 1.9, 2.5, 17.5, 26.24, 39.0, 40.9, 52.0, 52.8, 69.9, 73.4, 73.8, 75.2, 156.2 and 171.1; *m*/*z* 330 (0.5%) [M^+ − 15], 312 (0.5) [M^+ − 33], 288 (100) [M^+ − 57], 228 (5.4), 222 (4.2), 158 (11.8), 144 (8.5), 125 (5.3), 114 (5.2), 100 (6.5), 81 (5.5) and 69 (33.3) [Found: C, 55.9; H, 8.05; N, 4.0. Calc. for $C_{16}H_{27}NO_5S$ (*M*, 345.46): C, 55.63; H, 7.88; N, 4.05%].

Diastereoisomer **c** (2′*S*): δ_H(200 MHz; $CDCl_3$) 0.19–0.64 and 0.81–1.10 (m, 4 H, CH_2-cyclopropyl), 0.99 [s, 9 H, $(CH_3)_3$], 1.81–2.00 (m, 2 H, 1′-H), 1.82–1.97 (m, 1 H, CH-cyclopropyl), 2.81–2.96 (m, 1 H, C*H*OH), 3.71 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.84 (dt, J_1 4.5, J_2 9.5, 1 H, 5-H), 4.38 (br, 1 H, 4-H) and 5.01 (br, 1 H, 2-H).

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-[(2R)-2-*cyclohexyl*-2-*hydroxyethyl*]-1,3-*thiazolidine*-3,4-*dicarboxylate* **12b** *and* **12c**.—Following the procedure for the preparation of **10b** [part (*a*)], a solution of L-Selectride (1 mol dm^{-3} in THF; 2.20 cm^3, 2.20 mmol) was added to the ketone **12a** (0.42 g, 1.09 mmol) in THF (15 cm^3). After 6 h the reaction mixture was hydrolysed and the resulting mixture of diastereoisomers was submitted directly to flash chromatography (ether–pentane 1:2). Compound **12** was isolated as a mixture of diastereoisomers (0.38 g, 90%; ds = 79%). After another flash chromatographic separation (ether–pentane 15:35), pure **12b** (0.14 g, 33%) and a mixture of **12b** and **12c** (0.06 g) were isolated.

Diastereoisomer **b** (2′*R*): $[\alpha]_D$ −9.63 (*c* 0.5 in $CHCl_3$); *ν*(film)/cm^{-1} 3487, 2928, 2853, 1680–1760, 1484, 1442, 1333, 1175, 1120, 1032, 931 and 780; δ_H(200 MHz; $CDCl_3$) 1.01 [s, 9 H, $(CH_3)_3C$], 0.84–1.40 and 1.54–1.89 (2 × m, 12 H, CH_2-cyclohexyl and 1′-H), 2.06–2.24 (m, 1 H, CH-cyclohexyl), 3.27–3.41 (br m, 1 H, C*H*OH), 3.71 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.99 (dt, J_1 5, J_2 9.5, 1 H, 5-H), 4.31 (br, 1 H, 4-H) and 5.02 (br, 1 H, 2-H); δ_C(50 MHz; $CDCl_3$) 25.6, 25.7, 26.0, 26.4, 27.7, 28.6, 38.5, 39.0, 43.5, 52.1, 52.6, 61.1, 69.9, 74.6, 156.4 and 171.2; *m*/*z* 386 (0.5%) [M^+ − 1], 372 (1.7) [M^+ − 15], 354 (1.4) [M^+ − 33], 330 (100) [M^+ − 57], 270 (8.9), 246 (6.6), 181 (5.5), 158 (13.8), 144 (27), 133 (7.2), 111 (43.4) and 83 (48.6) [Found: C, 58.75; H, 8.6; N, 3.45. Calc. for $C_{19}H_{33}NO_5S$ (*M*, 387.54): C, 58.89; H, 8.58; N, 3.61%].

Diastereoisomer **c** (2′*S*): $[\alpha]_D$ −40.36 (*c* 1.1 in $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.00 [s, 9 H, $(CH_3)_3C$], 0.80–1.45 and 1.52–1.86 (2 × m, 12 H, CH_2-cyclohexyl and 1′-H), 2.08–2.26 (m, 1 H, CH-cyclohexyl), 3.37–3.53 (br m, 1 H, C*H*OH), 3.72 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.65–3.86 (m, 1 H, 5-H), 4.49 (br, 1 H, 4-H) and 5.06 (br, 1 H, 2-H).

(2R,4R,5R)-*Dimethyl* 2-tert-*Butyl*-5-(2-*hydroxy*-2-*phenylethyl*)-1,3-*thiazolidine*-3,4-*dicarboxylate* **13b** *and* **13c**.—Following the procedure for the preparation of **10b** [part (*a*)], a solution of L-Selectride (1 mol dm^{-3} in THF; 20 cm^3, 2.00 mmol) was added to the ketone **13a** (0.47 g, 1.24 mmol) in THF (15 cm^3). After 8 h the reaction mixture was hydrolysed and the resulting mixture of diastereoisomers was directly submitted to flash chromatography (ether–pentane, 2:3). The pure diastereoisomer **b** (0.17 g, 36%) and the pure diastereoisomer **c** (0.30 g, 64%) were separated (ds = 64%, **c** in excess).

Diastereoisomer **b** (2′*R*): R_f 0.34 (ether–pentane, 2:3).

Diastereoisomer **c** (2′*S*): R_f 0.19 (ether–pentane, 2:3); $[\alpha]_D$ −55.03 (*c* 0.9 in $CHCl_3$); *ν*($CHCl_3$)/cm^{-1} 3560s, 3491br, 3008, 2957, 2872, 1752, 1700, 1444, 1365, 1335, 1260, 1177, 1120 and 1013; δ_H(200 MHz; $CDCl_3$) 0.97 [s, 9 H, $(CH_3)_3C$], 2.02–2.21 and 2.40–2.52 (2 × m, 2 H, CH_2), 2.25–2.40 (br, 1 H, OH), 3.31–3.52 (m, 1 H, C*H*OH), 3.70 (s, 6 H, 2 OCH_3), 4.29–4.57 (br, 1 H, 4-H), 4.70 (dt, J_1 3.5, J_2 7.0, 1 H, 5-H), 4.95–5.16 (br, 1 H, 2-H) and 7.28–7.45 (m, 5 H, Ph); *m*/*z* 324 (13.5%) [M^+ + 57], 264 (2.4), 251 (3.5), 230 (2.2), 202 (5.5), 158 (22.1), 144 (13.1), 105 (28.6), 91 (11.8) and 79 (51.3) [Found: C, 59.75; H, 7.2; N, 3.5. Calc. for $C_{19}H_{27}NO_5S$ (*M*, 381.49): C, 59.82; H, 7.13; N, 3.67%].

(1R,4R,6R,8R)-*Methyl* 8-tert-*Butyl*-4-*isopropyl*-2-*oxo*-3-*oxa*-7-*thia*-9-*azabicyclo*[4.3.0]*nonane*-9-*carboxylate* **10d**.—The ester **10b** (40 mg, 0.12 mmol) was dissolved in toluene (2 cm^3). After adding dibutylethylenedioxytin (4 mg, 0.014 mmol), the reaction mixture was refluxed for 1 h. A tiny wire basket containing 4 Å molecular sieves was suspended in the vapours from the tip of the cooling coil inside the reflux condenser.[18] After evaporation of the solvent, the residue was purified by flash chromatography (ether–pentane, 1:3). A colourless oil was isolated (quantitative yield); *ν*(film)/cm^{-1} 2958, 1766, 1714, 1441, 1392, 1312, 1262, 1216, 1156, 1092, 1000, 911, 858, 783 and 733; δ_H(200 MHz; $CDCl_3$; see also Scheme 4) 1.00 [s, 9 H, $(CH_3)_3C$], 0.96–1.03 [m, 6 H, $(CH_3)_2CH$], 1.84–2.07 [m, 2 H, $(CH_3)_2CH$, 5-H], 2.42–2.50 (m, 1 H, 5-H), 3.75 (s, 3 H, OCH_3), 3.84 (dt, 1 H, 6-H), 4.05 (d, 1 H, 1-H), 4.32 (dt, 1 H, 4-H) and 5.07 (s, 1 H, 8-H); *m*/*z* 315 (0.2%) [M^+], 313 (0.7), 300 (1.4), 272 (1.8), 258 (100) [M^+ − 57], 214 (11.8) [M^+ − 57 − 43], 182 (1.8), 158 (6.1), 154 (9.8), 144 (9), 127 (4.4), 100 (52), 86 (12.9) and 69 (13.6) [Found: C, 56.9; H, 8.0; N, 4.25. Calc. for $C_{15}H_{25}NO_4S$ (*M*, 315.43): C, 57.12; H, 7.99; N, 4.44%].

(1R,4S,6R,8R)-*Methyl* 8-tert-*Butyl*-4-*isopropyl*-2-*oxo*-3-*oxa*-7-*thia*-9-*azabicyclo*[4.3.0]*nonane*-9-*carboxylate* **10e**.—The ester **10c** (130 mg, 0.37 mmol) and dibutyltin diethoxide (10 mg, 0.034 mmol) were heated in toluene under the same conditions as for the synthesis of **10d**. Flash chromatography yielded a colourless oil (60 mg, 51%); δ_H(200 MHz; $CDCl_3$; see also Scheme 4) 0.99 [s, 9 H, $(CH_3)_3C$], 0.94–1.03 [m, 6 H, $(CH_3)_2CH$], 1.84–2.41 [m, 3 H $(CH_3)_2CH$, 5-H), 3.60–3.77 (ddd, 1 H, 6-H), 3.74 (s, 3 H, OCH_3), 4.27 (dt, 1 H, 4-H), 4.40 (d, 1 H, 1-H) and 5.12 (s, 1 H, 8-H).

(2R,3R,5R)-2-*Amino*-5-*cyclohexyl*-5-*hydroxy*-3-*mercaptopentanoic Acid* **15**.—The thiazoline **12b** (215 mg, 0.55 mmol) was dissolved in a mixture if conc. HCl (8 cm^3) and oxygen-free water (7 cm^3). After being refluxed for 8 h, the mixture was extracted with oxygen-free ether. Evaporation of the water phase yielded a white material (amino acid hydrochloride, 86 mg) which was treated directly with propylene oxide (2 cm^3) in oxygen-free ethanol (6 cm^3) (reflux for 15 min). After evaporation of the solvent, the residue was dissolved in water. The aqueous phase was washed with oxygen-free ethyl acetate and then evaporated to give a white powder (50 mg, 37%), m.p. 188.4–190 °C; $[\alpha]_D$ −29.7 (*c* 0.6 in MeOH); *ν*(KBr)/cm^{-1} 3440, 3150, 3050, 2925, 2858, 1630, 1500, 1450, 1400 and 1349; δ_H(200 MHz; CD_3OD) 1.05–2.35 (m, 13 H, cyclohexyl, 4-H), 3.61 (m, 1 H, 5-H), 3.91 (m, 1 H, 3-H) and 4.07 (m, 1 H, 2-H); *m*/*z* 229 (1.2%) [M^+ − 18], 213, 184 (8), 155 (100), 121 (95), 95 (57), 79 (29) and 67 (31).

References

1 Part of the Ph.D. Thesis of A. J., No. 9522, ETH Zürich, 1991.

2 For a review article covering most of the earlier work see: D. Seebach, R. Imwinkelried and T. Weber in *Modern Synthetic Methods*, ed. R. Scheffold, Springer Verlag, Berlin, Heidelberg, New York, Tokyo, 1986, vol. 4, pp. 125–259.

3 J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silbermann and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736.

4 D. Seebach, M. Boes, R. Naef and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
5 (*a*) D. Seebach and T. Weber, *Tetrahedron Lett.*, 1983, **24**, 3315; (*b*) D. Seebach and T. Weber, *Helv. Chim. Acta*, 1984, **67**, 1650.
6 A Detailed discussion is given in the full paper of ref. 5(*b*), and for a comprehensive publication on analogous systems containing nitrogen and oxygen instead of sulphur (imidazoline- and oxazoline-carboxylates) see: D. Seebach, J. D. Aebi, M. Gander-Coquoz and R. Naef, *Helv. Chim. Acta*, 1987, **70**, 1194.
7 R. Schwesinger, *Nachr. Chem. Tech. Lab.*, 1990, **38**, 1214; D. Seebach and T. Pietzonka, *Chem. Ber.*, in the press.
8 D. Seebach, A. Jeanguenat, J. Schmidt and T. Maetzke, *Chimia*, 1989, **43**, 314.
9 (*a*) W. Ando and L. Huang, *Tetrahedron Lett.*, 1986, **27**, 3391; (*b*) N. Tokitoh, Y. Igarachi and W. Ando, *Tetrahedron Lett.*, 1987, **28**, 5903.
10 G. Stucky and D. Seebach, *Chem. Ber.*, 1989, **122**, 2365.
11 B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, *Tetrahedron*, 1984, **40**, 5005.
12 Y. Yamamoto, *Angew. Chem.*, 1986, **98**, 945; *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 947.
13 S. Danishefsky, *Acc. Chem. Res.*, 1981, **14**, 400; S. Danishefsky, *Chemtracts: Organic Chemistry*, 1989, 273.
14 The face selectivity of reactions of vinyl sulphoxides has been studied both experimentally and theoretically: S. D. Kahn, K. D. Dobbs and W. J. Hehre, *J. Am. Chem. Soc.*, 1988, **110**, 4602; G. A. Posner, *Acc. Chem. Res.*, 1987, **20**, 72.
15 See the mechanistic discussions in the review article cited in ref. 13.
16 (*a*) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, 1963, **85**, 207; (*b*) W. A. White and H. Weingarten, *J. Org. Chem.*, 1967, **32**, 213.
17 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
18 When put into the reaction mixture, molecular sieves do not efficiently remove the methanol formed. We have observed and used the effect of placing the molecular sieves into the gas phase many times before, see for instance: A. K. Beck, M. Gautschi and D. Seebach, *Chimia*, 1990, **44**, 291.
19 U. Schöllkopf, W. Hartwig, K. H. Pospischil and H. Kehne, *Synthesis*, 1981, 966.

Paper 1/02688G
Received 5*th June* 1991
Accepted 12*th June* 1991