Tetrahedron Vol. 46, No. 24, pp. 8267-8290, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

SYNTHETIC STUDIES TOWARDS CYCLIC PEPTIDES. CONCISE SYNTHESIS OF THIAZOLINE AND THIAZOLE CONTAINING AMINO ACIDS

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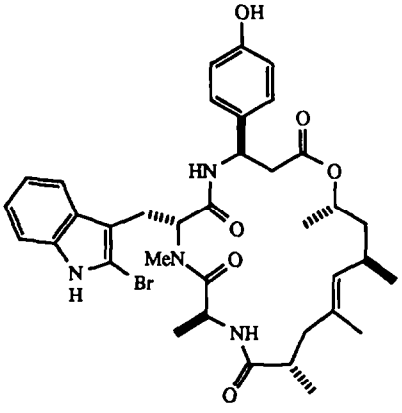
(*Received in UK 5 September* 1990)

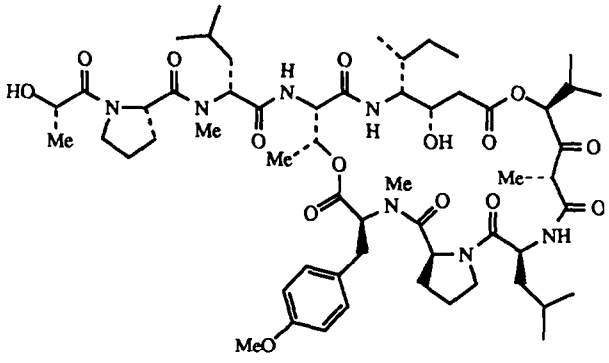
Abstract: Concise and efficient syntheses of optically pure thiazoline and thiazole containing amino acids of the constitution (26) and (27), based on simple condensation reactions between cysteine esters and *N*-protected imino ethers (22) and (25) derived from chiral amino acids, are described. The synthetic procedures are compatible with a range of amino acid side chains and protecting groups, and allow the preparation of a variety of small optically pure peptides *i.e.* (32) and (34) suitable for elaboration to naturally occurring cyclic peptides *e.g.* the lissoclinamides (3) and (4).

During the past ten years a very wide range of structurally novel and biologically interesting cyclic peptides *e.g.* (1) → (4) have been isolated and characterized from marine organisms[1]. Whereas many of these small peptides display useful antimicrobial or neurophysiological properties, others exhibit potent antileukemic activity. Indeed, some members show great promise as potential antineoplastic agents, and didemnin B (2) from the tunicate *Tridedemnum solidum* , for example, is now in phase II clinical trials[2]. A particularly intriguing family of cyclic peptides produced by tunicates is the lissoclinamides[3]. These secondary metabolites contain at least one thiazoline or thiazole and usually an oxazoline amino acid residue *e.g.* (3) and (4). Although it is known that both the oxazoline and the thiazoline rings play an important role in the biological activity of these cyclic peptides, their modes of action have not been determined. Clearly the overall conformations of the molecules are important, and several factors, including the presence of metal ions, could influence these molecular arrangements. Indeed, molecular modelling studies on lissoclinamide and other related peptides, based on molecular dynamics, n.m.r spectroscopy, and X-ray structure data[3,4] suggest that these peptides could be involved in a significant way in metal chelation and metal transport phenomena *in vivo*[5].

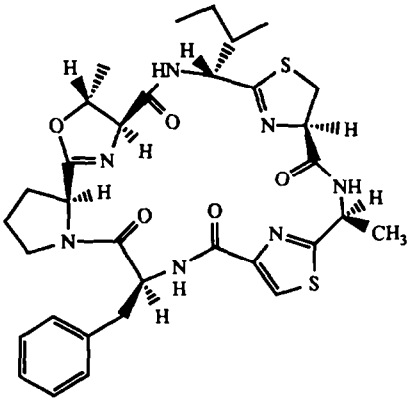
With a view to constructing a model for the biological activity of the lissoclinamides, in addition to investigating their ionophore properties, we have embarked on a program towards the synthesis of certain of their number[6]. In this paper we describe concise syntheses of homochiral thiazoline and thiazole containing amino acids *e.g.* (26) and (27), which are suitably substituted for further elaboration to advanced precursors on the way to the lissoclinamides (3) and (4).



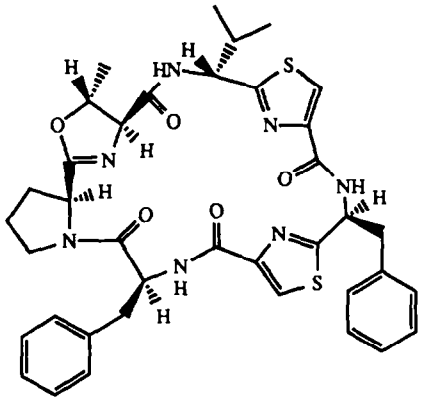
(1); Jasplakinolide



(2); Didemnin B



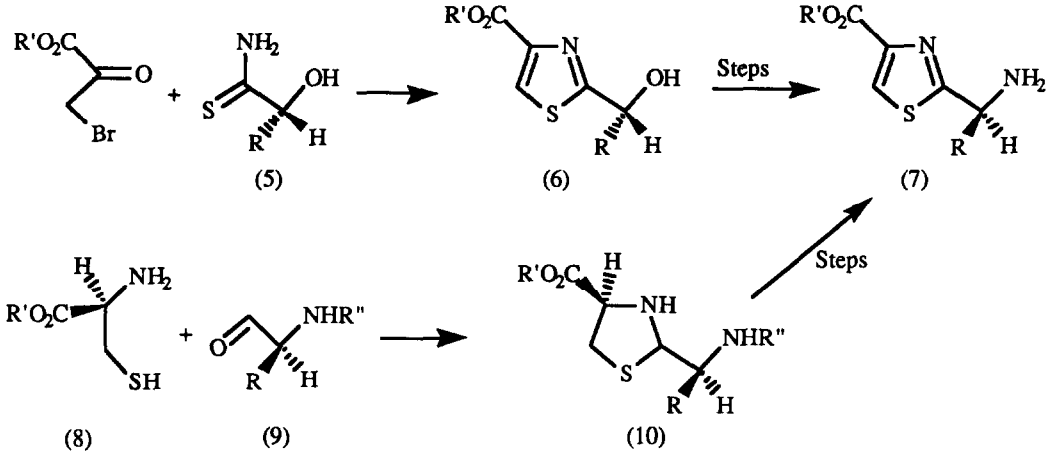
(3); Lissoclinamide-3



(4); Lissoclinamide-5

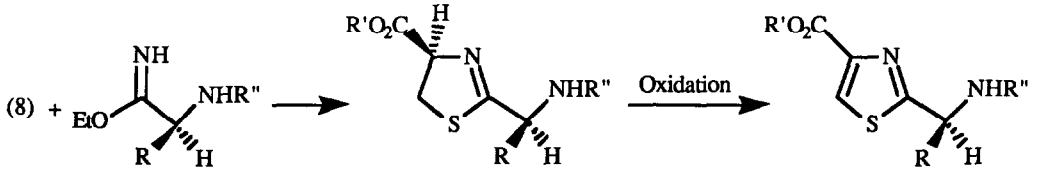
Previous studies, by other workers, have shown that thiazole containing amino acids *e.g.* (7) can be synthesized from chiral α-hydroxy acids, following conversion into the corresponding α-hydroxy thioamides (5), condensation with an α-bromopyruvate, and manipulation of the hydroxyl group in the resulting hydroxyalkyl substituted thiazole (6)[7]. Furthermore, thiazolidine containing amino acids, *viz* (10), can be obtained when cysteine esters (8) are condensed with an α-amino aldehyde (9); oxidation of the thiazolidines then leads to the corresponding thiazole containing amino acids (7) (Scheme 1)[8]. In addition to involving many synthetic manipulations, neither of the routes summarized in Scheme 1 allows the synthesis of thiazoline units found within cyclic peptides like the lissoclinamides. Herein we show that both thiazoline and thiazole containing amino acids of the constitution (26) and (27) can be obtained efficiently and in optically pure form

from simple condensation reactions between cysteine esters and *N*-protected imino ethers (11) derived from chiral amino acids (Scheme 2).



Scheme 1

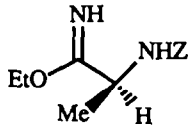
Thus, based on an observation by Shiba *et al*[9], we first examined the condensation between the imino ether of *N*-benzyloxycarbonyl protected alanine (12) and (**R**)-cysteine methyl ester hydrochloride (8, R'=Me). This reaction proceeded smoothly, leading to the thiazoline (13*a*) which was then oxidised to the corresponding thiazole (14*a*; 81%) using activated manganese dioxide. That this reaction proceeded without overoxidation of the 2-position in (13*a*) was gratifying in view of a report that 2-aminoalkyl thiazoles undergo oxidation to the corresponding ketones in the presence of activated manganese dioxide[10] In a similar manner, (**R**)-cysteine benzhydryl ester (8, R'=$CHPh_2$)[11] was reacted with (12) producing (13*b*) and then (14*b*).



Scheme 2

Saponification of the thiazole ester (14*a*), or acidolysis of the benzhydryl ester (14*b*) followed by a coupling reaction between the resulting carboxylic acid (15) and *t*-butyl *N*-(**S**)-phenylalanyl-(**S**)-prolinate (16*a*)[12] next led to the tripeptide (17*a*) as a white solid, m.p. 60-1°C which had an optical rotation of -88.7°. The ^1H n.m.r. spectrum of (17*a*) at 25°C was interesting, and showed two sets of signals due to the presence

of two conformers in slow exchange; however at 130°C in DMSO the rate of exchange was rapid enough for a single set of peaks to be observed. Similar results were obtained with the tripeptide (17*b*), obtained by the coupling of thiazole (15) and the dipeptide (16*b*). The synthesis of the tripeptides (17*a*) and (17*b*) as homogeneous diastereoisomers established that no racemisation of the chiral centre in the imino ether (12*a*) had occurred during its conversion into the thiazoline (13*a*), or during the conversion of (13*a*) into the thiazole (14*a*), or during the manipulation of the thiazole (14*a*) by standard methods used in peptide chemistry.



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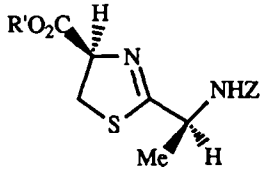
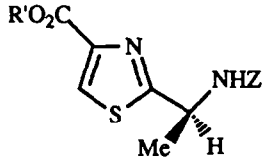
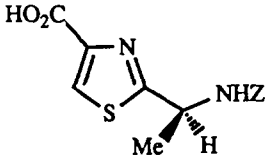


(13)



(14)

a, R'= Me; *b*, R'= $CHPh_2$; Z= $PhCH_2OCO$



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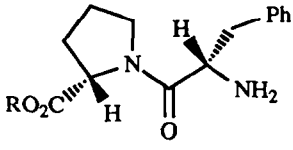

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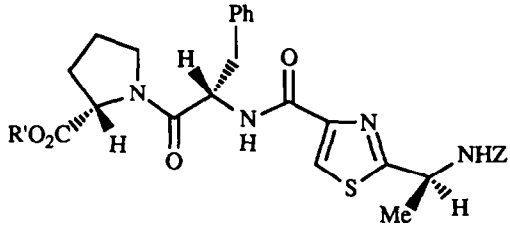
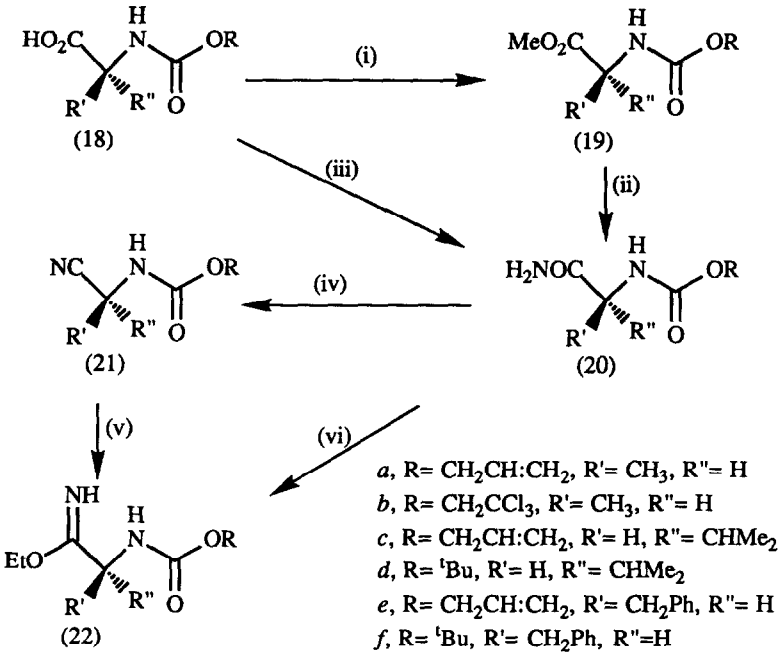


(17)

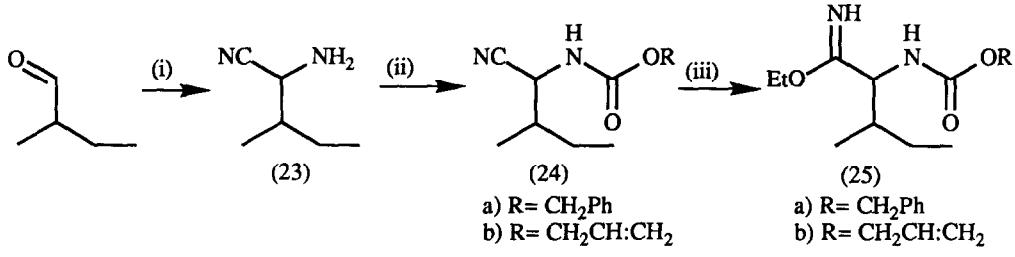
a, R= ^tBu; *b*, R= CH_2Ph

Having established the principles for a simple synthesis of optically pure thiazoline and thiazole containing amino acids, based on Scheme 2, we proceeded to develop its scope with a range of substituted chiral imino ethers (22). Thus, a range of imino ethers (22) derived from *N*-protected chiral amino acids was first prepared according to the procedures summarized in Scheme 3. We commend the procedure based on direct alkylation of the carboxamide (20) using triethyloxonium hexafluorophosphate as a convenient high yielding procedure[13]. In no instance was alkylation of the urethane protecting group observed; however, attempts to perform the alkylation with triethyloxonium tetrafluoroborate resulted in extensive cleavage of the amine protecting groups. In addition, the imino ether corresponding to isoleucine (25) was smoothly produced as outlined in Scheme 4.



Reagents: (i) AcCl/ MeOH; (ii) NH_3/ MeOH; (iii) a) EtOCOCl/ Et_3N, -78°C, b) NH_4OH; (iv) TsCl/ pyridine or $(CF_3CO)_2O$/ CH_2Cl_2; (v) HCl/ EtOH; (vi) $Et_3O^+PF_6^-$

Scheme 3

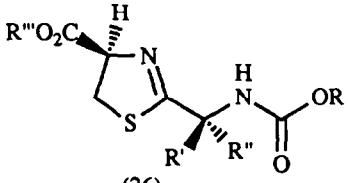


Reagents: (i) KCN/ NH_4OAc; (ii) ROCOCl/ K_2CO_3; (iii) HCl/ EtOH

Scheme 4

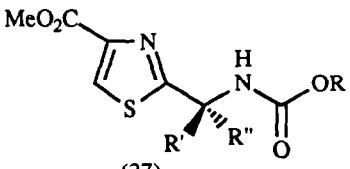
The imino ethers (22) and (25) underwent condensation reactions with cysteine esters to produce a range of thiazoline containing *N*-protected amino acids *i.e.* (26) in good to modest yields. In those instances where we intended to incorporate the thiazoline unit into a precursor for cyclic peptide synthesis we elected to use the benzhydryl ester nitrate of cysteine[11] in place of the methyl ester hydrochloride in view of the base sensitivity of

the thiazoline ring system. Also, in order to avoid racemisation at the thiazoline chiral centre, the reactions were worked up as soon as all the imino ether was consumed, as we observed extensive racemisation at this centre if the reactions were left standing for any period of time. The thiazoline methyl esters (26) underwent smooth oxidation to the corresponding thiazoles (27) in the presence of activated manganese dioxide, showing that the overall synthetic procedure was compatible with a range of amino acid side chains and protecting groups.



(26)

a, R= $CH_2CH{:}CH_2$, R'= CH_3, R"= H, R'"= Me
b, R= CH_2CCl_3, R'= CH_3, R"= H, R'"= Me
c, R= $CH_2CH{:}CH_2$, R'= H, R"= $CHMe_2$, R'"= Me
d, R= ^tBu, R'= H, R"= $CHMe_2$, R'"= Me
e, R= $CH_2CH{:}CH_2$, R'= CH_2Ph, R"= H, R'"= Me
f, R= ^tBu, R'= CH_2Ph, R"=H, R'"=Me
g, R= CH_2Ph, R' and R"= H and EtCHMe, R'"= Me
h, R= $CH_2CH{:}CH_2$, R' and R"=H and EtCHMe, R'"= Me
i, R= $CH_2CH{:}CH_2$, R' and R"=H and EtCHMe, R'"= $CHPh_2$

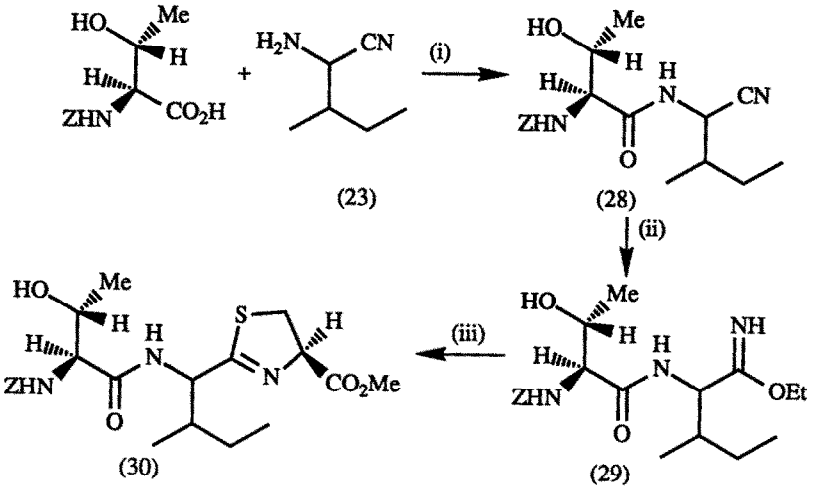


(27)

a, R= $CH_2CH{:}CH_2$, R'= CH_3, R"= H, R'"= Me
b, R= CH_2CCl_3, R'= CH_3, R"= H, R'"= Me
c, R= $CH_2CH{:}CH_2$, R'= H, R"= $CHMe_2$
d, R= ^tBu, R'= H, R"= $CHMe_2$
e, R= $CH_2CH{:}CH_2$, R'= CH_2Ph, R"= H
f, R= ^tBu, R'= CH_2Ph, R"=H

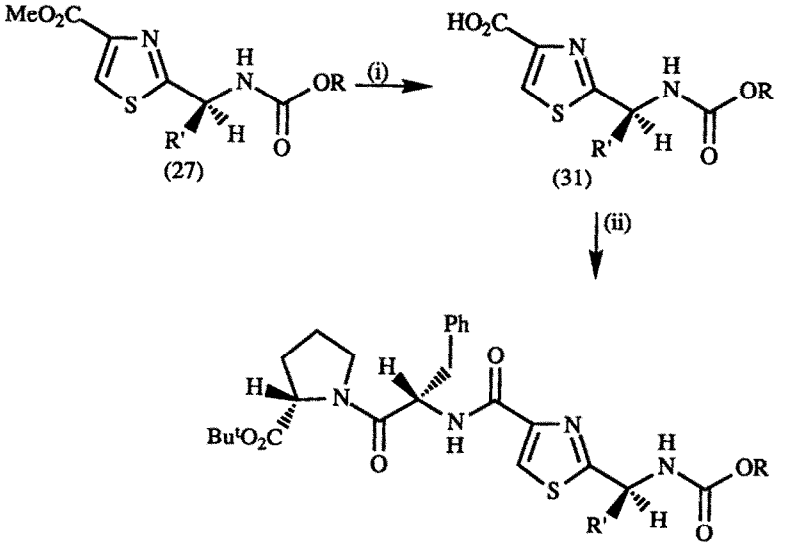
In addition, we were able to show that when the imino ether (29) derived from the dipeptide (28) was reacted with cysteine methyl ester hydrochloride, a concise and convergent synthesis of the dipeptide cysteine thiazoline derivative (30) could be achieved in good yield as shown in Scheme 5.

Finally, the thiazole containing amino acids (27) were shown to be useful precursors of a range of small optically active peptides, *e.g.* (32) and (34) (Scheme 6 and 7), under conditions which were both compatible with the *N*-protecting groups and which did not lead to any racemisation at their chiral centers. In conclusion we have demonstrated that the condensation reactions between cysteine derivatives and imino ethers derived from amino acids provide a concise and convenient approach towards the synthesis of thiazoline and thiazole containing amino acids. These procedures are presently being applied in studies of the total synthesis of biologically important cyclic peptides and their analogues.



Reagents: (i) DCC/ *N*-hydroxybenzotriazole; (ii) HCl/ EtOH; (iii) (R)-Cysteine methyl ester hydrochloride

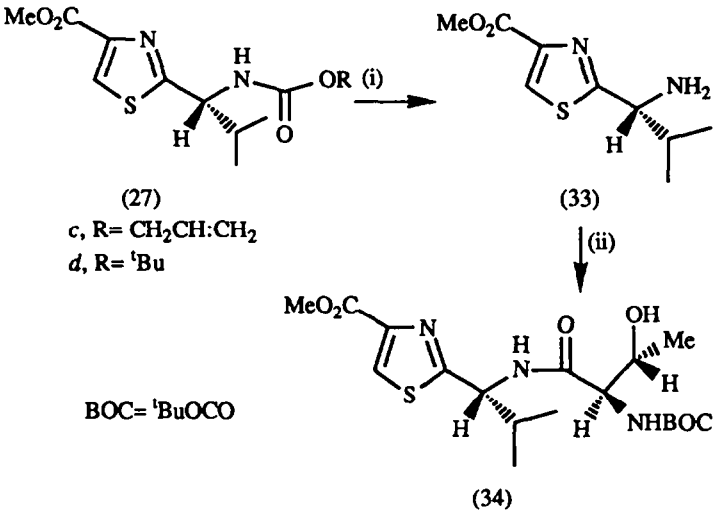
Scheme 5



a, R= $CH_2CH{:}CH_2$, R'= CH_3
b, R= $CH_2CH{:}CH_2$, R'= CH_2Ph

Reagents: (i) NaOH; (ii) a) $(COCl)_2$/ DMF, b) (S)-Phe-(S)-Pro-^{t}Bu/ Et_3N

Scheme 6



Reagents: (i) HCl or $RhH(PPh_3)_3$/ EtOH/ H_2O; (ii) BOC-(S)-Thr/ $(EtO)_2POCN$

Scheme 7

Experimental

Details of equipment and general laboratory procedures are as reported in a previous paper[14]. Activated manganese dioxide suitable for organic oxidations was purchased from the Aldrich chemical company, and used without further treatment.

2-[(S)-1-Benzyloxycarbonylaminoethyl]-4-methoxycarbonylthiazole (14*a*). - Activated manganese dioxide (25g, ca 10eq) was added to a solution of 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (13*a*)[15] (5.0g, 15.0mMol) dissolved in CH_2Cl_2 (50ml). The mixture was stirred at RT for 18 hours, then filtered through celite, and evaporated *in vacuo* to give a yellow oil. This oil was dissolved in ether, and hexane was added causing 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*) (4.5g, 91%) to precipitate as a white solid. mp 77-8°C; (Found C,56.2; H,5.15; N,8.5. $C_{15}H_{16}N_2O_4S$ requires: C,56.25; H,5.0; N,8.75%); $[\alpha]_D$ -8.6° (c 1.9 in $CHCl_3$, 25°C); υ_{max} ($CHCl_3$) 3426 m, 2940 m, 1710 s, and 904 m cm^{-1}; λ_{max} (EtOH) 266 (2200) nm; δ_H 1.64 (d, *J* 6.9Hz, CH_3), 3.93 (s, OCH_3), 5.11 (s, OCH_2Ph), 5.1-5.3 (m, NCH), 5.48 (br, NH), 7.3-7.4 (m, ArH), 8.10 (s, SCH:); δ_C 21.49 (q, CH_3), 49.44 (d, NCH), 52.31 (q, OCH_3), 66.99 (t, OCH_2Ph), 127.58, 128.01, 128.12, and 128.45 (4xd, ArCH + :CHS), 136.16 (s, ArC), 146.64 (s, NC:), 155.65 (s, NCO_2), 161.71 (s, SC:N), 174.56 (s, CO_2); m/z (FAB) 321 (11, MH^+), 91 (100).

2-[(S)-1-Benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*). - Benzhydryl (R)-cysteinate nitrate (8, R'= $CHPh_2$)[11] (3.4g, 9.7mMol) was added to a solution of 2-benzyloxycarbonylamino-(S)-propioimino ethyl ether (12)[9] (2.2g, 8.8mMol) in anhydrous ethanol (30ml). The mixture was stirred at RT for 18 hours, then the solvents were evaporated *in vacuo*, leaving a white solid. This

was taken up in ethyl acetate, washed with water, dried, and then evaporated *in vacuo*. The residue was purified by flash chromatography (1:1 ether/hexane), to give 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*) (1.0g, 24%) as a colourless oil. δ_H 1.45, and 1.55 (2xd, *J* 6.8, and 7.2Hz, CH_3), 3.5-3.7 (m, CH_2S), 4.5-4.8 (m, NCH), 5.12, and 5.14 (2xs, OCH_2), 5.2-5.3 (m, :NCH), 5.5-5.7 (m, NH), 6.93, and 6.94 (2xs, Ph_2CH), 7.2-7.4 (m, ArH); m/z (FAB) 475 (16, MH^+), 243 (13), 167 (100), 152 (16), 91 (86).

2-[(S)-1-Benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-thiazole (14*b*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*) (1.0g, 2.1mMol). The reaction required just 4 hours at RT, and the residue was purified by flash chromatography (40% hexane in ether), to give 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxy-carbonyl-thiazole (14*b*) (0.8g, 81%) as a white solid. mp 108-10°C; $[\alpha]_D$ -11.9° (c 0.9 in $CHCl_3$, 25°C); υ_{max} ($CHCl_3$) 3426 w, and 1720 s cm^{-1}; λ_{max} (EtOH) 206 (3890) nm; δ_H 1.63 (d, *J* 6.8Hz, CH_3), 5.0-5.2 (3H, m, OCH_2Ph + NCH), 5.58 (d, *J* 7.0Hz, NH), 7.14 (s, $OCHPh_2$), 7.2-7.5 (15H, m, ArH), 8.16 (s, SCH:); δ_C 21.03 (q, CH_3), 48.98 (d, NCH), 66.54 (t, OCH_2Ph), 77.10 (d, Ph_2CHO), 126.78, 127.16, 127.48, and 127.97 (4xd, ArCH + :CHS), 135.72, and 139.40 (2xs, ArC), 146.34 (s, NC:), 155.06 (s, NCO_2), 159.55 (s, SC:N), 173.58 (s, CO_2); m/z (FAB) 473 (100, MH^+).

2-[(S)-1-Benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15). Method A from methyl ester (14*a*). - A saturated aqueous solution of sodium hydroxide (5ml) was added to a solution of 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*) (250mg, 0.8mMol) in MeOH (5ml). The solution was stirred at RT for 45 minutes, then acidified with 50% hydrochloric acid, and extracted with ether (2x50ml). The combined extracts were dried, and evaporated *in vacuo*, to leave 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (220mg, 92%) as a white powder. The mp, and ^1H nmr spectrum were in agreement with those reported in the literature[16].

Method B from benzhydryl ester (14*b*). - 2-[(S)-1-Benzyloxycarbonylaminoethyl]-4-diphenylmethoxy-carbonyl-thiazole (14*b*) (0.8g, 1.7mMol) was added to trifluoroacetic acid (3.5ml), and the solution was then stirred at RT for 30 minutes. Ether (35ml) was then added, and the resulting precipitate of 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole trifluoroacetate (15) (250mg, 35%) was dried under high vacuum. The mp, and ^1H nmr spectrum were in agreement with those reported in the literature[16].

Tripeptide (17*a*) derived from 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) and *t*-butyl (*N*-(S)-phenylalanyl)-(S)-prolinate (16*a*). - *p*-Nitrophenol (0.55g, 4.0mMol) was added to a suspension of 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (1.1g, 3.6mMol) in dichloromethane (40ml). Dicyclohexylcarbodiimide (0.82g, 4.0mMol) was then added, and the resulting mixture stirred at RT for 5 hours. The reaction mixture was then filtered, and evaporated *in vacuo*. The residue was subjected to flash chromatography (10%Et_2O in CH_2Cl_2), to give 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-*p*-nitrophenyloxycarbonyl-thiazole contaminated with *p*-nitrophenol. This active ester was then added to a solution of *t*-butyl (*N*-(S)-phenylalanyl)-(S)-prolinate (16*a*)[12] (1.1g, 3.5mMol) in dichloromethane (40ml). The resulting solution was stirred at RT for 2 days, then washed with saturated aqueous sodium carbonate solution (5x100ml), and dilute aqueous sodium hydroxide solution (2x100ml). The organic phase was dried, and evaporated *in vacuo* to leave a white foam that was recrystallised from ether by the addition of hexane, to

give the desired tripeptide (17*a*) (1.6g, 75%) as a white solid. mp 60-1°C; (Found C,62.6; H,6.45; N,9.25. $C_{32}H_{38}N_4O_6S$ requires: C,62.35; H,6.3; N,9.2%); $[\alpha]_D$ -88.7° (c 0.4 in $CHCl_3$, 23°C); υ_{max} ($CHCl_3$) 3420 m, 2940 m, 1725 s, 1640 s, and 1160 s cm^{-1}; λ_{max} (EtOH) 214 (2960), and 235 (1730) nm; δ_H (DMSO-d_6, 130°C) 1.41 (s, $OC(CH_3)_3$), 1.53 (d, *J* 7.0Hz, CH_3), 1.7-2.3 (4H, m, CH_2CH_2), 3.0-3.3 (m, CH_2Ph), 3.4-3.9, and 4.2-4.4 (2xm, 2xNCH), 4.97 (pentet, *J* 7.1Hz, NCHTh), 5.07 (s, OCH_2Ph), 7.1-7.5 (m, ArCH), 7.64 (d, *J* 7.5Hz, NH), 7.82 (d, *J* 8.0Hz, NH), 8.03 (s, SCH:); δ_C (RT, major conformer) 20.93 (q, CH_3), 24.34, and 28.57 (2xt, CH_2CH_2), 27.54 (q, $(CH_3)_3$), 38.10 (t, CH_2Ph), 46.50 (t, CH_2N), 48.99, 51.59, and 59.34 (3xd, NCH), 66.49 (t, $PhCH_2O$), 80.68 (s, $OCMe_3$), 122.89 (d, SCH:), 126.30, 126.62, 127.65, 127.92, 128.83, and 129.28 (6xd, ArCH), 136.05 (s, ArC), 148.94 (s, NC:), 155.28 (s, NCO_2), 160.05 (s, SC:N), 169.37, 170.56, and 173.54 (3xs, CO_2); m/z (FAB) 607 (4, MH^+), 436 (11), 408 (13), 199 (17), 116 (52), 91 (100).

Tripeptide (17*b*) derived from 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) and benzyl (*N*-(S)-phenylalanyl)-(S)-prolinate trifluoroacetate (16*b*). - Benzyl (*N*-(S)-phenylalanyl)-(S)-prolinate trifluoroacetate (16*b*)[17] (400mg, 0.85mMol) and hydroxybenzotriazole (115mg, 0.85mMol) were added to a suspension of 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (230mg, 0.75mMol) in dichloromethane (5ml). Triethylamine (0.2ml, excess) was then added, followed by dicyclohexylcarbodiimide (175mg, 0.85mMol). The resulting mixture was stirred at RT for 18 hours, then the dichloromethane was evaporated *in vacuo*, and the residue suspended in ethyl acetate (10ml). The mixture was filtered, diluted with ethyl acetate, and washed with dilute hydrochloric acid and saturated aqueous sodium carbonate solution. The solution was then dried, and evaporated *in vacuo*. The residue was subjected to flash chromatography (ether), to give the desired tripeptide (17*b*) (200mg, 42%) as a white foam. mp 58-9°C; (Found C,65.6; H,6.0; N,8.8. $C_{36}H_{36}N_4O_6S$ requires: C,65.5; H,5.7; N,8.7%); $[\alpha]_D$ -74.0° (c 0.5 in $CHCl_3$, 23°C); υ_{max} ($CHCl_3$) 3416 m, 2942 m, 1720 s, and 1645 s cm^{-1}; λ_{max} (EtOH) 213 (2750), and 240 (1830) nm; δ_H (110°C, DMSO-d_6) 1.1-1.5 (m, CH_2), 1.65 (d, *J* 6.9Hz, CH_3), 1.7-2.4 (m, CH_2), 3.1-3.3 (m, CH_2Ph), 3.5-3.6 (m, CH_2N), 3.8-3.9, 4.5-4.7, and 5.0-5.2 (3x1H, m, NCH), 5.20, and 5.27 (2x2H, s, OCH_2Ph), 7.3-7.5 (m, ArH), 7.8-8.1 (2H, m, 2xNH), 8.18 (s, SCH:); δ_C (RT, major conformer) 19.76 (q, CH_3), 24.86, and 28.90 (2xt, CH_2CH_2), 37.75 (t, CH_2Ph), 46.86 (t, CH_2N), 48.30, 52.79, and 59.06 (3xd, NCH), 66.97 (t, $PhCH_2O$), 123.41 (d, SCH:), 126.62, 128.09, 128.18, 128.30, 128.45, and 129.46 (6xd, ArCH), 135.53, 136.37, and 136.93 (3xs, ArC), 148.72 (s, NC:), 155.71 (s, NCO_2), 160.99 (s, SC:N), 170.62, 171.49, and 172.05 (3xs, CO_2); m/z (FAB) 641 (5, MH^+), 408 (7), 206 (47), 91 (100).

Methyl *N*-allyloxycarbonyl-(S)-alanate (19*a*). - Acetyl chloride (10ml) was added dropwise to methanol (150ml) cooled to 0°C. The resulting solution was added to *N*-allyloxycarbonyl-(S)-alanate (18*a*)[18] (12.3g, 71.1mMol), and the solution was then stirred at RT for 18 hours. Evaporation of the solvents left methyl *N*-allyloxycarbonyl-(S)-alanate (19*a*) (12.8g, 96%) as a colourless oil. (Found C,51.3; H,7.3; N,7.2. $C_8H_{13}NO_4$ requires: C,51.3; H,7.0; N,7.5%); $[\alpha]_D$ -0.1° (c 1.0 in $CHCl_3$, 23°C); υ_{max} (film) 3330 m, 2942 w, 1715 s, and 1525 s cm^{-1}; δ_H 1.41 (d, *J* 7.2Hz, CH_3), 3.75 (s, OCH_3), 4.0-4.8 (3H, m, NCH + OCH_2), 5.1-5.5 (3H, m, NH + CH_2:), 5.7-6.2 (m, :CH); δ_C 17.63 (q, CH_3), 49.21 (d, NCH), 51.70 (q, OCH_3), 65.14 (t, OCH_2), 116.93 (t, $:CH_2$), 132.37 (d, :CH), 155.28 (s, NCO_2), 173.05 (s, CO_2); m/z (EI) 187 (1, M^+), 128 (100), 102 (15), 84 (60), 70 (34), 57 (21), 41 (100).

N-Allyloxycarbonyl-(S)-alanamide (20*a*). - A solution of methyl *N*-allyloxycarbonyl-(S)-alanate (19*a*) (12.8g, 68.5mMol) in methanol (200ml) was saturated with anhydrous ammonia, and the resulting solution was then allowed to stir at RT for 18 hours. The solvents were evaporated *in vacuo*, leaving a white solid which

was recrystallised from methanol by the addition of ether and hexane to give *N*-allyloxycarbonyl-(S)-alanamide (20*a*) (11.3g, 96%) as a white crystalline solid. mp 128-9°C; (Found C,49.1; H,7.35; N,16.1. $C_7H_{12}N_2O_3$ requires: C,48.8; H,7.0; N,16.3%); $[\alpha]_D$ +1.4° (c 0.8 in EtOH, 23°C); υ_{max} (nujol) 3470 m, 3240 w, 3190 m, 3060 m, 1705 s, and 1668 s cm^{-1}; δ_H (acetone d_6) 1.29 (d, *J* 7.4Hz, CH_3), 4.13 (pentet, *J* 7.3Hz, NCH), 4.45 (d, *J* 5.2Hz, OCH_2), 5.09 (dq, *J* 10.0, and 1.5Hz, CH_2:), 5.23 (dq, *J* 17.2, and 1.7Hz, CH_2:), 5.7-6.0 (m, CH:), 6.38 (brd, *J* 19.3Hz, NH), 6.94 (br, NH_2); δ_C (acetone d_6) 18.58 (q, CH_3), 51.69 (d, NCH), 66.60 (t, OCH_2), 117.65 (t, :CH_2), 134.30 (d, :CH), 158.60 (s, NCO_2); m/z (FAB) 173 (100, MH^+), 156 (53), 128 (186), 93 (100), 75 (75), 57 (78).

N-Allyloxycarbonyl-(S)-alanylnitrile (21*a*). - Trifluoroacetic anhydride (8.0ml, 57.0mMol) was added to a suspension of *N*-allyloxycarbonyl-(S)-alanamide (20*a*) (8.0g, 46.5mMol) in dichloromethane (50ml) cooled to 0°C, and the resulting solution was then stirred at RT for 3 hours. The solvents were evaporated *in vacuo*, and the residue was purified by dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2), to give *N*-allyloxycarbonyl-(S)-alanylnitrile (21*a*) (6.8g, 95%) as a colourless oil. $[\alpha]_D$ -72.3° (c 3.9 in $CHCl_3$, 25°C); υ_{max} (film) 3320 s, 3000 m, 2950 m, 2250 w, 1715 s, and 1530 s cm^{-1}; δ_H 1.59 (d, *J* 7.1Hz, CH_3), 4.5-4.9 (3H, m, OCH_2 + NCH), 5.0-5.6 (3H, m, :CH_2 + NH), 5.8-6.3 (m, :CH); δ_C 19.09 (q, CH_3), 38.05 (d, NCH), 66.22 (t, OCH_2), 118.06 (t, :CH_2), 119.20 (s, CN), 131.99 (d, :CH), 154.90 (s, NCO_2); m/z (EI) 155 (1, MH^+), 154 (1), 128 (10), 127 (10), 87 (13), 69 (24), 68 (22), 57 (100).

2-Allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*). Method A from *N*-allyloxycarbonyl-(S)-alanylnitrile (21*a*). - Dry hydrogen chloride gas was passed through a solution of *N*-allyloxycarbonyl-(S)-alanylnitrile (21*a*) (9.8g, 63.6mMol) in dry ether (100ml), and dry ethanol (10ml), cooled to 0°C. After one hour, the flow of hydrogen chloride was discontinued, and the solution was stirred at RT for a further hour. The reaction mixture was then poured slowly into a saturated aqueous solution of sodium carbonate (100ml), and extracted with ether (2x100ml). The combined organic layers were dried, and evaporated *in vacuo*, to leave 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (7.0g, 55%) as a colourless oil which was used without purification. υ_{max} (film) 3318 m, 3000 w, 1724 s, 1660 s, and 1530 cm^{-1}.

Method B from *N*-allyloxycarbonyl-(S)-alanamide (20*a*). - Triethyloxonium hexafluorophosphate (5.0g, 20.0mMol) was added to a suspension of *N*-allyloxycarbonyl-(S)-alanamide (20*a*) (3.0g, 17.4mMol) in dry CH_2Cl_2 (40ml). The resulting solution was stirred at RT for 18 hours, then washed with dilute aqueous sodium carbonate, dried, and evaporated *in vacuo*, to leave 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (3.3g, 95%) as a colourless oil that was used without further purification.

Methyl *N*-β-trichloroethyloxycarbonyl-(S)-alanate (19*b*). - The method was as described for methyl *N*-allyloxycarbonyl-(S)-alanate (19*a*), using *N*-β-trichloroethyloxycarbonyl-(S)-alanate (18*b*)[19] (23.0g, 87.2mMol), and giving methyl *N*-β-trichloroethyloxycarbonyl-(S)-alanate (19*b*) (23.6g, 97%) as a colourless oil. (Found C,30.6; H,3.6; N,5.0. $C_7H_{10}Cl_3NO_4$ requires: C,30.2; H,3.6; N,5.0%); $[\alpha]_D$ -13.4° (c 0.65 in $CHCl_3$, 23°C); υ_{max} (film) 3456 m, 3000 w, 2960 m, and 1735 s cm^{-1}; δ_H 1.44 (d, *J* 7.1Hz, CH_3), 3.75 (s, OCH_3), 4.38 (pentet, *J* 7.4Hz, NCH), 4.71 (s, OCH_2), 5.68 (br, NH); δ_C 17.84 (q, CH_3), 49.59 (d, NCH), 52.13 (q, OCH_3), 74.35 (t, OCH_2), 95.20 (s, CCl_3), 153.66 (s, NCO_2), 172.73 (s, CO_2); m/z (EI) 282 (13), 280 (36), 278 (33, M^+), 246 (17), 222 (30), 220 (88), 218 (100), 182 (19), 133 (36), 102 (53).

N-β-Trichloroethyloxycarbonyl-(S)-alanamide (20*b*). - The method was as described for *N*-

allyloxycarbonyl-(S)-alanamide (20*a*), using methyl *N*-β-trichloroethyloxycarbonyl-(S)-alanate (19*b*) (23.6g, 84.9mMol). The product was purified by recrystallisation from methanol by the addition of ether, giving *N*-β-trichloroethyloxycarbonyl-(S)-alanamide (20*b*) (12.1g, 54%) as white crystals. mp 88-90°C; $[\alpha]_D$ -6.1° (c 2.3 in EtOH, 23°C); υ_{max} (nujol) 3430 s, 3200 s, 1730 s, and 1675 s cm^{-1}; δ_H (acetone d_6) 1.30, and 1.35 (2xd, *J* 6.9, and 7.1Hz, CH_3), 4.0-4.5 (m, NCH), 4.74 (s, OCH_2), 6.1-7.4 (br, $CONH_2$); δ_C (acetone d_6) 17.61, and 18.75 (2xq, CH_3), 51.31, and 54.77 (2xd, NCH), 74.93 (t, OCH_2), 96.71 (s, CCl_3), 154.89, and 158.25 (2xs, NCO_2), 175.75, and 177.05 (2xs, CON); m/z (FAB) 267 (13), 265 (37), 263 (40, M^+), 250 (12), 248 (25), 246 (27), 222 (31), 220 (96), 218 (100), 135 (15), 133 (37), 131 (40).

N-β-Trichloroethyloxycarbonyl-(S)-alanylnitrile (21*b*). - Tosyl chloride (8.5g, 45.0mMol) was added to a solution of *N*-β-trichloroethyloxycarbonyl-(S)-alanamide (20*b*) (12.0g, 45.6mMol) in pyridine (120ml). The solution was heated at reflux for one hour, then allowed to cool and concentrated *in vacuo*. The residue was partitioned between ether, and 50% hydrochloric acid, the organic phase was washed with water, dried, and then evaporated *in vacuo* to give a red oil. The residue was subjected to dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2), to give *N*-β-trichloroethyloxycarbonyl-(S)-alanylnitrile (21*b*) (4.0g, 36%) as colourless crystals. mp 62-3°C; (Found C,29.4; H,2.8; N,11.4. $C_6H_7Cl_3N_2O_2$ requires: C,29.4; H,2.9; N,11.4%); $[\alpha]_D$ -52.4° (c 2.5 in $CHCl_3$, 23°C); υ_{max} (nujol) 3338 s, 2258 w, 1705 s, 1540 s, 1260 s, and 748 s cm^{-1}; δ_H 1.62 (d, *J* 7.2Hz, CH_3), 4.6-4.9 (3H, m, NCH + OCH_2), 5.76 (brd, *J* 7.6Hz, NH); δ_C 19.03 (q, CH_3), 38.27 (d, NCH), 74.78 (t, OCH_2), 94.77 (s, CCl_3), 118.61 (s, CN), 153.33 (s, NCO_2); m/z (FAB) 249 (13), 247 (37), 245 (38, M^+), 222 (33), 220 (95), 218 (100), 209 (23), 182 (23), 133 (40), 131 (40), 95 (35), 88 (62).

2-(β-Trichloroethyloxycarbonylamino)-(S)-propioimino ethyl ether (22*b*). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (Method A), using *N*-β-trichloroethyl-oxycarbonyl-(S)-alanylnitrile (21*b*) (4.0g, 16.3mMol). 2-(β-Trichloroethyloxycarbonylamino)-(S)-propioimino ethyl ether (22*b*) (4.2g, 88%) was obtained as an oil and used without purification. υ_{max} (film) 3315 m, 3004 m, 1740 s, 1665 s, 1540 s, and 1255 cm^{-1}.

N-Allyloxycarbonyl-(R)-valine (18*c*). - Allyl chloroformate (11.0ml, 100.0mMol) was added to a well stirred solution of (R)-valine (10.0g, 85.5mMol), and potassium carbonate (17.7g, 128.0mMol), in water (200ml), and THF (200ml). The solution was then stirred at RT for 18 hours, the THF was evaporated *in vacuo*, and the remaining solution was extracted with ether (2x200ml). The aqueous layer was acidified to pH 2 with conc. hydrochloric acid, and then extracted with chloroform (3x200ml). The combined organic layers were dried, then evaporated *in vacuo*, to leave *N*-allyloxycarbonyl-(R)-valine (18*c*) (15.5g, 90%) as a colourless oil. υ_{max} (film) 3700-2300 br, 2965 s, 1700 s, and 1520 s cm^{-1}; δ_H 0.91, and 1.00 (2xd, *J* 4.9, and 4.9Hz, $(CH_3)_2$), 2.18 (septet, *J* 6.6Hz, Me_2CH), 4.28 (dd, *J* 8.8 and 4.6Hz, NCH), 4.57 (d, *J* 5.4Hz, OCH_2), 5.1-5.3 (3H, m, $:CH_2$ + NH), 5.7-6.2 (m, :CH), 6.82 (br, CO_2H); δ_C 17.25, and 18.76 (2xq, $(CH_3)_2$), 30.84 (d, Me_2CH), 58.96 (d, NCH), 65.95 (t, OCH_2), 117.69 (t, $:CH_2$), 132.37 (d, :CH), 156.58 (s, NCO_2), 175.11 (s, CO_2); m/z (FAB) 202 (74, MH^+), 156 (64), 116 (47), 93 (54), 72 (100).

N-Allyloxycarbonyl-(R)-valinamide (20*c*). - Triethylamine (13.0ml, 100.0mMol) was added to a solution of *N*-allyloxycarbonyl-(R)-valine (18*c*) (15.0g, 78.0mMol) in dry THF (150ml). The solution was cooled to -78°C under a nitrogen atmosphere, then ethyl chloroformate (9.0ml, 90mMol) was added dropwise. The reaction mixture was allowed to warm to -30°C over 3 hours, then 0.88 ammonia solution (30ml, excess) was added, and the reaction allowed to warm to RT. After the reaction had stirred at RT for a further 1 hour, the

solvents were evaporated *in vacuo*, and the residue was redissolved in ethyl acetate (150ml), and washed with dilute aqueous sodium carbonate solution. The organic phase was dried, and evaporated *in vacuo*, to give a white solid. Recrystallisation from chloroform by the addition of hexane, gave *N*-allyloxycarbonyl-(**R**)-valinamide (20*c*) (11.2g, 72%) as white crystals. mp 139-40°C; (Found C,54.0; H,8.2; N,13.85. $C_9H_{16}N_2O_3$ requires: C,54.0; H,8.0; N,14.0%); $[\alpha]_D$ +4.2° (c 2.6 in EtOH, 23°C); υ_{max} (nujol) 3380 s, 3316 s, 3200 s, and 1656 s cm^{-1}; δ_H (CD_3OD) 0.94, and 0.97 (2xd, *J* 6.7, and 6.7Hz, $(CH_3)_2$), 2.02 (septet, *J* 6.7Hz, Me_2CH), 3.95 (d, *J* 6.6Hz, NCH), 4.54 (d, *J* 5.4Hz, OCH_2), 5.1-5.5 (m, $:CH_2$), 5.7-6.3 (m, :CH); δ_C (CD_3OD) 18.18, and 19.69 (2xq, $(CH_3)_2$), 31.77 (d, Me_2CH), 61.62 (d, NCH), 66.52 (t, OCH_2), 117.64 (t, $:CH_2$), 134.16 (d, :CH), 158.27 (s, NCO_2), 176.69 (s, CON); m/z (FAB) 201 (43, MH^+), 156 (91), 149 (100), 131 (35), 116 (30), 72 (76).

N-Allyloxycarbonyl-(**R**)-valinylnitrile (21*c*). - The method was as described for *N*-allyloxycarbonyl-(**S**)-alanylnitrile (21*a*), using *N*-allyloxycarbonyl-(**R**)-valinamide (20*c*) (11.0g, 55.0mMol). The crude product was purified by flash chromatography (CH_2Cl_2), to give *N*-allyloxycarbonyl-(**R**)-valinylnitrile (21*c*) (8.9g, 89%).

2-Allyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether (22*c*) from *N*-allyloxycarbonyl-(**R**)-valinylnitrile (21*c*). - The method was as described for 2-allyloxycarbonylamino-(**S**)-propioimino ethyl ether (22*a*) (Method A), using *N*-allyloxycarbonyl-(**R**)-valinylnitrile (21*c*) (2.5g, 13.6mMol). 2-Allyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether (22*c*) (2.6g, 83%) was obtained as a colourless oil and used without purification. δ_H 0.93 (t, *J* 7.4Hz, $(CH_3)_2$)), 1.22 (t, *J* 8.2Hz, CH_3), 1.9-2.4 (m, Me_2CH), 4.0-4.4 (3H, m, NCH + OCH_2Me), 4.5-4.7 (m, OCH_2), 4.9-5.4 (4H, m, 2xNH + $:CH_2$), 5.8-6.3 (m, :CH).

2-Allyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether (22*c*) from *N*-allyloxycarbonyl-(**R**)-valinamide (20*c*). - The method was as described for 2-allyloxycarbonylamino-(**S**)-propioimino ethyl ether (22*a*) (Method B), using *N*-allyloxycarbonyl-(**R**)-valinamide (20*c*) (3.9g, 19.5mMol). 2-Allyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether (22*c*) (4.3g, 97%) was obtained as a colourless oil and used without purification.

N-*t*-Butyloxycarbonyl-(**R**)-valinamide (20*d*). - The method was as described for *N*-allyloxycarbonyl-(**R**)-valinamide (20*c*), using *N*-*t*-butyloxycarbonyl-(**R**)-valine (18*d*) (17.3g, 75.0mMol). The product was purified by recrystallisation from chloroform by the addition of hexane, giving *N*-*t*-butyloxycarbonyl-(**R**)-valinamide (20*d*) (15.5g, 96%) as white crystals. mp 150-1°C; (Found C,55.65; H,9.55; N,12.6. $C_{10}H_{20}N_2O_3$ requires: C,55.5; H,9.3; N,12.95%); $[\alpha]_D$ +1.0° (c 1.0 in EtOH, 26°C); υ_{max} (nujol) 3375 s, 3318 s, 3190 s, 1675 s, 1630 s, 1510 s, 1320 s, 1250 s, 1170 s, 1044 m, and 1020 m cm^{-1}; δ_H (CD_3OD) 0.92, and 0.95 (2xd, *J* 6.6, and 6.6Hz, $(CH_3)_2$), 1.44 (s, $(CH_3)_3$), 1.8-2.3 (m, Me_2CH), 3.88 (d, *J* 6.2Hz, NCH); δ_C (CD_3OD) 18.28, and 19.75 (2xq, $(CH_3)_2$), 28.74 (s, $(CH_3)_3$), 31.88 (d, Me_2CH), 61.24 (d, NCH), 80.58 (s, $OCMe_3$), 157.73 (s, NCO_2), 177.01 (s, CON); m/z (FAB) 217 (36, MH^+), 161 (100), 117 (55), 116 (34), 72 (55), 57 (69).

2-*t*-Butyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether (22*d*). - The method was as described for 2-allyloxycarbonylamino-(**S**)-propioimino ethyl ether (22*a*) (Method B), using *N*-*t*-butyloxycarbonyl-(**R**)-valinamide (20*d*) (15.5g, 71.7mMol). 2-*t*-Butyloxycarbonylamino-3-methyl-(**R**)-butanoimino ethyl ether

(22*d*) (11.8g, 67%) was obtained as a colourless oil and used without purification.

Methyl *N*-allyloxycarbonyl-(S)-phenylalanate (19*e*). - The method was as described for methyl *N*-allyloxycarbonyl-(S)-alanate (19*a*), using *N*-allyloxycarbonyl-(S)-phenylalanate (18*e*)[18] (14.0g, 56.2mMol). Methyl *N*-allyloxycarbonyl-(S)-phenylalanate (19*e*) (13.0g, 88%) was obtained as a colourless oil. $[\alpha]_D$ +43.3° (c 0.8 in $CHCl_3$, 23°C); υ_{max} (film) 3338 m, 2958 m, 1720 s, and 1510 s cm^{-1}; δ_H 3.11 (d, *J* 5.8Hz, CH_2Ph), 3.72 (s, OCH_3), 4.5-4.8 (3H, m, NCH + OCH_2), 5.0-5.5 (3H, m, NH + CH_2:), 5.7-6.2 (m, :CH), 7.0-7.5 (m, ArH); δ_C 38.21 (t, CH_2Ph), 52.03 (q, OCH_3), 54.84 (d, NCH), 65.62 (t, OCH_2), 117.52 (t, :CH_2), 126.89, 128.41, and 129.06 (3xd, ArCH), 132.47 (d, :CH), 135.73 (s, ArC), 155.39 (s, NCO_2), 171.86 (s, CO_2); m/z (FAB) 264 (100, MH^+), 204 (59), 160 (44), 91 (42).

N-Allyloxycarbonyl-(S)-phenylalanamide (20*e*). - The method was as described for *N*-allyloxycarbonyl-(S)-alanamide (20*a*), using methyl *N*-allyloxycarbonyl-(S)-phenylalanate (19*e*) (13.0g, 49.4mMol). *N*-Allyloxycarbonyl-(S)-phenylalanamide (20*e*) (12.1g, 99%) was obtained as a white solid. mp 115-6°C; (Found C,62.6; H,6.7; N,11.3. $C_{13}H_{16}N_2O_3$ requires: C,62.9; H,6.45; N,11.3%); $[\alpha]_D$ +4.9° (c 2.1 in EtOH, 23°C); υ_{max} (nujol) 3370 s, 3320 s, 3180 s, 1685 s, 1650 s, and 1525 s cm^{-1}; δ_H (CD_3OD) 2.83 (1H, dd, *J* 13.7, and 9.5Hz, CH_2Ph), 3.12 (1H, dd, *J* 13.7, and 5.2Hz, CH_2Ph), 4.33 (dd, *J* 9.4, and 5.2Hz, NCH), 4.44 (d, *J* 4.9Hz, OCH_2), 5.1-5.3 (m, CH_2:), 5.7-5.9 (m, :CH), 7.1-7.4 (m, ArH); δ_C (CD_3OD) 37.20 (t, CH_2Ph), 55.53 (d, NCH), 64.50 (t, OCH_2), 115.58 (t, :CH_2), 125.68, 127.31, and 128.29 (3xd, ArCH), 132.12 (d, :CH), 136.54 (s, ArC), 155.98 (s, NCO_2), 171.96 (s, CO_2); m/z (FAB) 249 (32, MH^+), 204 (21), 154 (100), 137 (100), 136 (100).

2-Allyloxycarbonylamino-3-phenyl-(S)-propioimino ethyl ether (22*e*). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (18*a*) (Method B), using *N*-allyloxycarbonyl-(S)-phenylalanamide (12*e*) (12.0g, 48.4mMol). 2-Allyloxycarbonylamino-3-phenyl-(S)-propioimino ethyl ether (22*e*) (13.0g, 97%) was obtained as a colourless oil and used without purification. υ_{max} (film) 3310 m, 2990 w, 1700 s, and 1660 s cm^{-1}; δ_H 1.29 (t, *J* 7.6Hz, CH_3), 2.9-3.3 (m, CH_2Ph), 3.9-4.3 (3H, m, NCH + OCH_2Me), 4.4-4.7 (m, OCH_2), 5.0-5.4 (m, :CH_2), 5.7-6.6 (2H, m, :CH + NH), 7.0-7.4 (m, ArH).

N-*t*-Butyloxycarbonyl-(S)-phenylalanamide (20*f*). - The method was as described for *N*-allyloxycarbonyl-(R)-valinamide (20*c*), using *N*-*t*-butyloxycarbonyl-(S)-phenylalanine (18*f*) (28.0g, 105.6mMol). The product was purified by recrystallisation from chloroform by the addition of hexane, giving *N*-*t*-butyloxycarbonyl-(S)-phenylalanamide (20*f*) (27.2g, 98%) as a white solid. mp 133-4°C; $[\alpha]_D$ +10.9° (c 0.4 in EtOH, 24°C); υ_{max} (nujol) 3490 s, 3470 s, 3198 m, 1652 s, 1460 m, and 1446 m cm^{-1}; δ_H (CD_3OD) 1.34 (s, $(CH_3)_3$), 2.79 (1H, dd, *J* 13.8, and 9.0Hz, CH_2Ph), 3.13 (1H, dd, *J* 13.8, and 5.5Hz, CH_2Ph), 4.29 (dd, *J* 9.2, and 5.5Hz, NCH), 7.24 (s, ArH); δ_C (CD_3OD) 28.63 (q, $(CH_3)_3$), 39.47 (t, CH_2Ph), 57.13 (d, NCH), 80.75 (s, $OCMe_3$), 127.61, 129.29, and 130.32 (3xd, ArCH), 138.60 (s, ArC), 157.35 (s, NCO_2), 181.35 (s, CON).

2-*t*-Butyloxycarbonylamino-3-phenyl-(S)-propioimino ethyl ether (22*f*). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (Method B), using *N*-*t*-butyloxycarbonyl-(S)-phenylalanamide (20*f*) (27.4g, 93.8mMol). 2-*t*-Butyloxycarbonylamino-3-phenyl-(S)-propioimino ethyl ether (22*f*) (30.0g, 99%) was obtained as a colourless oil and used without purification. δ_H 1.41 (t, *J* 7.6Hz, CH_3), 1.46 (s, $(CH_3)_3$), 3.0-3.3 (m, CH_2Ph), 4.0-4.6 (3H, m, OCH_2 + NCH), 4.8-5.1 (m, NH). 5.84 (br, NH), 7.1-7.5 (m, ArH).

(RS)-Isoleucinylnitrile (23). - Ammonium acetate (118g, 1.6M), and potassium cyanide (35.8g, 0.55M) were added to a solution of 2-methyl butanal (46.5g, 0.54M) in ethanol (1100ml). The solution was stirred at RT for 18 hours, then the solvents were evaporated *in vacuo*. The residue was suspended in ether (500ml), and the product was extracted into 50% hydrochloric acid (500ml). The aqueous layer was washed with ether (2x500ml), and then the pH was adjusted to 12 with a saturated aqueous solution of sodium hydroxide. The product was extracted with ether (2x500ml), and the combined organic layers were dried, then evaporated *in vacuo*, to leave (RS)-isoleucinylnitrile (23) (31.0g, 55%) as a yellow oil. υ_{max} (film) 3380 m, 2978 s, 2240 w, 1460 m, and 738 m cm^{-1}; δ_H 0.8-1.25 (6H, m, $CH_3CHCH_2CH_3$), 1.25-2.0 (3H, m, CH_2CH), 3.72 (t, *J* 7.2Hz, NCH); δ_C 10.69, 13.94, and 14.49 (3xq, $CH_3CH_2CHCH_3$), 24.29, and 25.43 (2xt, $MeCH_2$), 38.70, and 38.86 (2xd, MeCH), 47.75 (d, NCH), 120.77, and 121.26 (2xs, CN); m/z (FAB) 113 (18, MH^+), 112 (20, M^+), 86 (59), 85 (66).

N-Benzyloxycarbonyl-(RS)-isoleucinylnitrile (24*a*). - Benzylchloroformate (5.0ml, 54.0mMol) was added dropwise to a mixture of (RS)-isoleucinynitrile (23) (5.0g, 45.0mMol), and potassium carbonate (4.2g, 30mMol) in ether (150ml). The reaction was then stirred for 72 hours, filtered, washed with 50% hydrochloric acid, dried, and evaporated *in vacuo*. The residue was subjected to dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2), to give *N*-benzyloxycarbonyl-(RS)-isoleucinylnitrile (24*a*) (10.7g, 97%) as a pale yellow oil. υ_{max} (film) 3315 m, 2990 m, 2458 w, 1705 s, 1534 m, and 1260 m cm^{-1}; δ_H 0.7-1.0 (6H, m, $CH_3CHCH_2CH_3$), 1.0-1.9 (3H, m, $MeCHCH_2Me$), 4.3-4.5 (m, NCH), 5.02 (s, OCH_2), 7.2-7.3 (m, ArH); δ_C 10.80, 11.45, 13.94, and 14.76 (4xq, $CH_3CHCH_2CH_3$), 24.94, and 25.43 (2xt, $MeCH_2$), 37.56, and 37.83 (2xd, MeCHEt), 47.58, and 47.80 (2xd, NCH), 66.82, and 67.41 (2xt, OCH_2), 117.52, and 117.96 (2xs, CN), 127.98, 128.19, and 128.41 (3xd, ArCH), 135.67, and 136.14 (2xs, ArC), 155.23 (s, NCO_2).

N-Allyloxycarbonyl-(RS)-isoleucinylnitrile (24*b*). - The method was as described for *N*-benzyloxycarbonyl-(RS)-isoleucinylnitrile (24*a*), using allyl chloroformate (5.0ml, 45.8mMol). *N*-Allyloxycarbonyl-(RS)-isoleucinylnitrile (24*b*) (7.8g, 89%) was obtained as a colourless oil. υ_{max} (film) 3320 m, 2980 m, 2260 w, 1710 s, 1525 s, and 1260 s cm^{-1}; δ_H 0.8-2.1 (9H, m, $CH_3CH_2CHCH_3$), 4.4-4.8 (3H, m, NCH + OCH_2), 5.1-5.5 (3H, m, CH_2: + NH), 5.7-6.2 (m, CH:); δ_C 10.37, 10.48, and 14.43 (3xq, $CH_3CH_2CHCH_3$), 24.61, and 25.05 (2xt, $MeCH_2$), 37.40, and 37.51 (2xd, MeCHEt), 47.31, and 47.48 (2xd, NCH), 65.73 (t, OCH_2Ph), 117.41 (t, :CH_2), 117.74 (s, CN), 131.93 (d, :CH), 155.12 (2xs, CON); m/z (FAB) 197 (92, MH^+), 170 (100), 130 (48), 126 (32), 86 (100), 68 (48).

2-Benzyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*a*). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (Method A), using *N*-benzyloxycarbonyl-(RS)-isoleucinylnitrile (24*a*) (6.0g, 17.3mMol). The oily 2-benzyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*a*) (6.4g, 94%) obtained was used without purification. υ_{max} (film) 1660 s cm^{-1}.

2-Allyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*b*). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (Method A), using *N*-allyloxycarbonyl-(RS)-isoleucinylnitrile (24*b*) (7.8g, 39.8mMol). Work up gave 2-allyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*b*) (6.1g, 63%) as a yellow oil which was used without further purification. υ_{max} (film) 3310 m, 2985 m, 1708 s, 1650 s, 1528 m, and 1248 m cm^{-1}; δ_H 0.8-2.2 (12H, m, $CH_3CH_2CHCH_3$ + CH_3), 4.0-4.5 (3H, m, OCH_2Me + NCH), 4.5-4.7 (2H, m, OCH_2), 5.0-5.5 (3H, m, :CH_2 + NH), 5.8-6.2 (m, :CH).

2-[(S)-1-Allyloxycarbonylaminoethyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*a*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 1-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (4.15g, 15.3mMol). The 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*a*) (5.0g, 89%) was used without purification.

2-[(S)-1-β-Trichloroethyloxycarbonylaminoethyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*b*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 2-(β-trichloroethyloxycarbonylamino)-(S)-propioimino ethyl ether (22*b*) (4.2g, 14.4mMol). The reaction was complete after 4 hours, and the residue was subjected to dry flash chromatography (hexane to ether), to give 2-[(S)-1-β-trichloroethyloxycarbonylaminoethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*b*) (3.3g, 63%) as a yellow oil. δ_H 1.48, and 1.68 (2xd, *J* 7.3, and 6.5Hz, CH_3), 3.3-3.8 (m, CH_2S), 3.86, and 3.91 (2xs, OCH_3), 4.1-4.7 (m, NCH), 4.76 (s, OCH_2), 4.8-5.2 (s, :NCH), 5.8-6.0 (br, NH); δ_C 20.22 (q, CH_3), 35.44, and 35.60 (2xt, CH_2S), 50.01, and 50.83 (2xd, NCH), 52.61, and 52.72 (2xq, OCH_3), 74.66 (t, OCH_2), 77.59 (d, :NCH), 95.36 (s, $OCCl_3$), 153.54, and 154.14 (2xs, NCO_2), 170.17, 170.66, and 171.90 (3xs, SC:N + CO_2).

2-[(R)-1-Allyloxycarbonylamino-2-methyl-propyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*c*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 2-allyloxycarbonylamino-3-methyl-(R)-butanoimino ethyl ether (22*c*) (2.6g, 11.4mMol). The product was purified by flash chromatography (20% ether in CH_2Cl_2) to give 2-[(R)-1-allyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*c*) (1.5g, 44%) as a colourless oil. υ_{max} (film) 3320 w, 2970 m, 1720 s, and 1615 s cm^{-1}; δ_H 0.88, and 0.95 (2xd, *J* 6.4, and 6.6Hz, $(CH_3)_2$), 2.16 (hextet, *J* 6.5Hz, Me_2CH), 3.44 (1H, d, *J* 2.1Hz, CH_2S), 3.55 (1H, d, *J* 1.0Hz, CH_2S), 3.74 (s, OCH_3), 4.0-4.3 (m, NCH), 4.3-4.6 (3H, m, OCH_2 + :NCH), 4.9-5.6 (3H, m, :CH_2 + NH), 5.6-6.2 (m, :CH); δ_C 16.98, and 19.09 (2xq, $(CH_3)_2$), 32.15 (d, Me_2CH), 35.12 (t, CH_2S), 52.40 (q, OCH_3), 58.91 (d, NCH), 65.62 (t, OCH_2), 77.43 (d, :NCH), 117.41 (t, :CH_2), 132.64 (d, :CH), 155.77 (s, NCO_2), 170.72 (s, SC:N), 175.65 (s, CO_2).

2-[(R)-1-*t*-Butyloxycarbonylamino-2-methyl-propyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*d*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 2-*t*-butyloxycarbonylamino-3-methyl-(R)-butanoimino ethyl ether (22*d*) (11.8g, 48.4mMol). Dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2) gave 2-[(R)-1-*t*-butyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*d*) (6.0g, 39%) as a colourless oil. (Found C,53.0; H,7.8; N,8.85. $C_{14}H_{24}N_2O_4S$ requires: C,53.1; H,7.65; N,8.85%); $[\alpha]_D$ +53.5° (c 0.9 in $CHCl_3$, 26°C); υ_{max} (film) 3350 m, 2978 s, 1705 s, 1618 m, 1495 s, 1364 s, 1170 s, and 738 s cm^{-1}; λ_{max} (EtOH) 223 (553), and 259 (602) nm; δ_H 0.92, and 0.99 (2xd, *J* 6.8, and 6.8Hz, $(CH_3)_2$), 1.45 (s, $(CH_3)_3$), 2.1-2.3 (m, Me_2CH), 3.4-3.7 (m, CH_2S), 3.80 (s, OCH_3), 4.47 (dd, *J* 8.7, and 4.8Hz, NCH), 5.0-5.2 (2H, m, :NCH + NH); δ_C 16.38, and 18.49 (2xq, $(CH_3)_2$), 27.54 (q, $(CH_3)_3$), 31.39 (d, Me_2CH), 34.31 (t, CH_2S), 51.65 (q, OCH_3), 57.77 (d, NCH), 77.22 (d, :NCH), 78.84 (s, $OCMe_3$), 154.63 (s, NCO_2), 170.18 (s, SC:N), 175.54 (s, CO_2); m/z (FAB) 317 (65, MH^+), 261 (94), 217 (28), 146 (41), 72 (95), 57 (100).

2-[(S)-1-Allyloxycarbonylamino-2-phenyl-ethyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*e*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 1-allyloxycarbonylamino-2-phenyl-(S)-propioimino ethyl ether (22*e*) (13.0g, 47.1mMol). The reaction required just two hours, and dry flash chromatography (CH_2Cl_2) gave 2-[(S)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*e*) (3.6g, 20%) as a yellow oil. $[\alpha]_D$ +38.5° (c 2.9 in $CHCl_3$, 25°C); υ_{max} (film) 3320 m, 2960 m, 1720 s, 1620 m, 1245 s, and 704 m cm^{-1}; λ_{max} 222 (550), and 253 (526) nm; δ_H 3.2-3.5 (m, CH_2Ph), 3.6-3.9 (m, CH_2S), 3.99 (s, OCH_3), 4.75 (d, *J* 5.2Hz, OCH_2), 4.9-5.8 (5H, m, 2xNCH + CH_2: + NH), 5.9-6.4 (m, :CH), 7.3-7.5 (m, ArH); δ_C 35.12 (t, CH_2S), 39.51 (t, CH_2Ph), 52.35 (q, OCH_3), 54.46 (d, NCH), 65.46 (t, OCH_2), 76.95 (d, :NCH), 117.31 (t, :CH_2), 126.62, 128.14, and 129.28 (3xd, ArCH), 132.47 (d, :CH), 135.73 (s, ArC), 155.12 (s, NCO_2), 170.34 (s, CO_2); m/z (FAB) 349 (100, MH^+), 291 (12), 204 (21), 160 (25), 91 (62).

2-[(S)-1-*t*-Butyloxycarbonylamino-2-phenyl-ethyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*f*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 1-*t*-butyloxycarbonylamino-2-phenyl-(S)-propioimino ethyl ether (22*f*) (30.0g, 93.8mMol). The reaction required just 4 hours, and the products were purified by dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2) to give 2-[(S)-1-*t*-butyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*f*) (9.4g, 27%) as a yellow oil. $[\alpha]_D$ +37.9° (c 0.8 in $CHCl_3$, 26°C); υ_{max} (film) 3310 m, 2960 m, 1700 s, 1606 m, 1488 m, and 1164 s cm^{-1}; λ_{max} (EtOH) 218 (1540), and 254 (1500) nm; δ_H 1.43 (s, $(CH_3)_3$), 3.0-3.3 (m, CH_2Ph), 3.4-3.7 (m, CH_2S), 3.81 (s, OCH_3), 4.7-5.4 (3H, m, 2xNCH + NH), 7.27 (s, ArH); δ_C 27.81 (q, $(CH_3)_3$), 34.75 (t, CH_2S), 39.24 (t, CH_2Ph), 51.97 (q, OCH_3), 54.03 (d, NCH), 77.54 (d, :NCH), 79.28 (s, $OCMe_3$), 126.30, 127.82, and 129.06 (3xd, ArCH), 135.94 (s, ArC), 154.36 (s, NCO_2), 170.34 (s, SC:N), 175.87 (s, CO_2).

2-[(RS)-(1-Benzyloxycarbonylamino)-2-methyl-butyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*g*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 2-benzyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*a*) (3.0g, 7.6mMol). The product was purified by flash chromatography (ether), to give 2-[(1-benzyloxycarbonylamino)-3-methyl-butyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*g*) (600mg, 16%) as a colourless oil. $[\alpha]_D$ +24.2° (c 1.0 in $CHCl_3$, 23°C); υ_{max} (film) 3320 m, 2960 m, 1720 s, and 1615 m cm^{-1}; λ_{max} (EtOH) 215 (3247), 237 (1680), and 252 (1573) nm; δ_H 0.8-1.0 (6H, m, $C\underline{H}_3CH_2CH\underline{CH}_3$), 1.0-2.1 (3H, m, $MeCHCH_2Me$), 3.4-3.7 (2H, m, SCH_2), 3.80 (s, OCH_3), 4.59, and 4.72 (2x1H, dd, *J* 8.5 and 4.9Hz, and 9.4 and 4.9Hz, NCH), 5.1-5.3 (3H, m, OCH_2Ph + :NCH), 5.3-5.6 (m, NH), 7.3-7.4 (m, ArH); δ_C 11.18, 11.29, 13.29, 13.57, and 15.24 (5xq, $\underline{C}H_3CH_2CH\underline{C}H_3$), 23.96, 24.18, 26.02, and 26.13 (4xt, $MeCH_2$), 34.91, 35.23, and 35.40 (3xt, CH_2S), 38.59, and 38.70 (2xd, MeCHEt), 52.11 (q, OCH_3), 56.85, 57.01, 57.99, and 58.26 (4xd, NCH), 66.60 (t, OCH_2Ph), 77.20, 77.49, and 77.60 (3xd, :NCH), 127.33, 127.65, and 128.09 (3xd, ArCH), 136.16 (s, ArC), 155.66, and 155.82 (2xs, NCO_2), 170.56 (s, SC:N), 175.61, and 176.09 (2xs, CO_2); m/z (FAB) 365 (100, M^+), 257 (32), 236 (22), 209 (22), 176 (49), 146 (22), 109 (34), 92 (71).

2-[(RS)-(1-Allyloxycarbonylamino)-2-methyl-butyl]-4-methoxycarbonyl-(R)-Δ2-thiazoline (26*h*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using 2-allyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*b*) (1.0g, 4.1mMol). The product was purified by flash chromatography (1:1 ether/hexane, then ether) to give 2-[(RS)-(1-allyloxycarbonylamino)-2-methyl-butyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*h*) (0.3g, 23%), as a yellow oil. υ_{max} (film) 3340 w, 2965 m, 1725 s, 1618 m, and 1510 m cm^{-1}; δ_H 0.8-2.2 (9H, m, $CH_3CH_2CHCH_3$),

3.3-3.6 (m, CH_2S), 3.79 (s, OCH_3), 4.4-4.8 (3H, m, NCH + OCH_2), 5.0-5.6 (4H, m, CH_2: + NH + :NCH), 5.7-6.2 (m, CH:); δ_C 11.50, 11.66, 11.78, 13.60, 13.88, and 15.55 (6xq, $\underline{C}H_3CH_2CH\underline{C}H_3$), 24.17, 24.46, 26.29, and 26.45 (4xt, $MeCH_2$), 35.17, 35.55, and 35.69 (3xt, CH_2S), 38.60, 38.80, and 38.91 (3xd, MeCHEt), 52.52 (q, OCH_3), 56.93, 57.21, 58.19, and 58.43 (4xd, NCH), 65.26, and 65.64 (t, OCH_2Ph), 77.57, and 77.60 (2xd, :NCH), 117.34, and 117.40 (2xt, $:CH_2$), 132.76, 133.04, and 133.21 (3xd, :CH), 155.97, and 156.14 (2xs, CON), 170.99 (s, N:CS), 175.39, 175.91, 176.08, and 176.62 (4xs, CO_2); m/z (FAB) 315 (100, MH^+), 257 (29), 255 (13), 170 (75), 146 (25), 126 (12).

2-[(RS)-(1-Allyloxycarbonylamino)-2-methyl-butyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (26*i*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxy-carbonyl-(R)-Δ2-thiazoline (13*b*), using 2-allyloxycarbonylamino-3-methyl-(RS)-pentanimino ethyl ether (25*b*) (1.0g, 4.1mMol). The product was purified by flash chromatography (1:1 ether/hexane, then 20%hexane in ether) to give 2-[(RS)-(1-allyloxycarbonylamino)-2-methyl-butyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (26*i*) (0.4g, 21%), as a colourless oil. (Found C,66.6; H,6.8; N,5.8. $C_{26}H_{30}N_2O_4S$ requires: C,66.9; H,6.5; N,6.0%); $[\alpha]_D$ +13.4° (c 1.6 in $CHCl_3$, 23°C); υ_{max} (film) 3340 w, 3070 w, 3040 w, 2970 m, 2940 m, 1720 s, 1610 m, and 700 m cm^{-1}; δ_H 0.8-1.0 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.2-1.6 (m, $MeCH_2$), 1.8-2.0 (m, MeCHEt), 3.5-3.6 (m, CH_2S), 4.5-4.8 (3H, m, NCH + OCH_2), 5.1-5.6 (4H, m, NH + CH_2: + :NCH), 5.8-6.0 (m, :CH) 6.94, and 6.95 (2xs, Ph_2CHO), 7.2-7.4 (m, ArH); δ_C 11.54, 11.64, 11.69, 11.77, 13.50, 13.77, 15.49, and 15.51 (8xq, $C\underline{H}_3CH_2CHC\underline{H}_3$), 24.03, 24.34, 26.29, and 26.38 (4xt, $MeCH_2$), 35.08, 35.52, and 35.66 (3xt, CH_2S), 38.70, and 38.89 (2xd, MeCHEt), 56.76, 57.07, 58.01, and 58.27 (4xd, NCH), 65.70 (t, OCH_2), 76.99, 77.31, 77.64, 77.92, 78.01, 78.07, and 78.13 (7xd, :NCH + Ph_2CH), 117.38, and 117.59 (2xt, $:CH_2$), 126.82, 126.95, 127.14, 127.16, 127.89, 127.97, 128.06, 128.19, 128.45, and 128.50 (10xd, ArCH), 132.75 (d, :CH), 139.52, and 139.57 (2xs, ArC), 155.84, and 156.02 (2xs, NCO_2), 169.30 (s, SC:N), 175.10, 175.60, 175.84, and 176.54 (4xs, CO_2); m/z (FAB) 489 (20, $M+Na^+$), 467 (13, MH^+), 301 (4), 255 (10), 167 (100).

2-[(S)-1-Allyloxycarbonylaminoethyl]-4-methoxycarbonylthiazole (27*a*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(S)-1-allyloxy-carbonylaminoethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*a*) (6.0g, 22.0mMol). The product was purified by dry flash chromatography (1:1 hexane/CH_2Cl_2 to CH_2Cl_2), to give 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (27*a*) (3.0g, 50%) as a white solid. mp 42-3°C; (Found C,49.1; H,5.5; N,10.1. $C_{11}H_{14}N_2O_4$ requires: C,48.9; H,5.2; N,10.4%); $[\alpha]_D$ +0.8° (c 2.85 in $CHCl_3$, 21°C); υ_{max} (film) 3340 m, 2960 w, and 1720 s cm^{-1}; λ_{max} 210 (2420), and 233 (2143) nm; δ_H 1.63 (d, *J* 6.9Hz, CH_3), 3.92 (s, OCH_3), 4.56 (d, *J* 5.4Hz, OCH_2), 5.1-5.4 (3H, m, NCH + $:CH_2$), 5.61 (br, NH), 5.8-6.0 (m, :CH), 8.09 (s, SCH:); δ_C 20.55 (q, CH_3), 48.88 (d, NCH), 51.43 (q, OCH_3), 65.03 (t, OCH_2), 116.87 (t, $:CH_2$), 126.95 (d, SCH:), 131.99 (d, :CH), 145.86 (s, NC:), 154.96 (s, NCO_2), 160.97 (s, SC:N), 174.30 (s, CO_2); m/z (FAB) 271 (100, MH^+).

2-[(S)-1-β-Trichloroethyloxycarbonylaminoethyl]-4-methoxycarbonylthiazole (27*b*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(S)-1-β-trichloroethyloxycarbonylaminoethyl]-4-carbomethoxy-(R)-Δ2-thiazoline (26*b*) (3.3g, 9.1mMol). The crude product was subjected to dry flash chromatography (20% ether in hexane to ether), to give 2-[(S)-1-β-trichloroethyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (27*b*) (2.5g, 76%) as a white solid. mp 117-8°C; (Found C,33.3; H,3.1; N,7.55. $C_{10}H_{11}Cl_3N_2O_4$ requires: C,33.3; H,3.1; N,7.8%); $[\alpha]_D$ -39.2° (c 0.1 in $CHCl_3$, 23°C); υ_{max} (film) 3330 s, 3120 m, 3050 m, 2960 m, 1726 s, 1240 s, 828 s, and 740 s cm^{-1};

λ_{max} (EtOH) 210 (2540), and 230 (2110) nm; δ_H 1.68 (d, *J* 6.9Hz, CH_3), 3.92 (s, OCH_3), 4.73 (s, OCH_2), 5.19 (pentet, *J* 7.0Hz, NCH), 5.95 (brd, *J* 7.3Hz, NH), 8.11 (s, SCH:); δ_C 21.31 (q, CH_3), 49.53 (d, NCH), 52.08 (q, OCH_3), 74.53 (t, OCH_2), 95.15 (s, CCl_3), 127.38 (d, SCH:), 146.56 (s, NC:), 153.60 (s, NCO_2) 161.40 (s, SC:N), 173.21 (s, CO_2); m/z (FAB) 365 (19), 363 (36), 361 (32, M^+), 218 (16), 181 (25), 170 (65), 138 (100), 112 (32), 91 (34).

2-[(**R**)-1-Allyloxycarbonylamino-2-methyl-propyl]-4-methoxycarbonylthiazole (27*c*). - The method was as described for 2-[(**S**)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(**R**)-1-allyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-(**R**)-Δ2-thiazoline (26*c*) (1.0g, 3.3mMol). The product was purified by flash chromatography (20% ether in CH_2Cl_2) to give 2-[(**R**)-1-allyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-thiazole (27*c*) (560mg, 56%) as a colourless oil. υ_{max} (film) 3310 m, 3095 w, 2958 m, 1710 s, 1520 s, and 1220 s cm^{-1}; δ_C 16.92, and 18.76 (2xq, $(CH_3)_2$), 32.69 (d, Me_2CH), 51.92 (q, OCH_3), 58.36 (d, NCH), 65.19 (t, OCH_2), 116.98 (t, $:CH_2$), 126.73 (d, SCH:), 132.10 (d, :CH), 146.23 (s, NC:), 155.39 (s, NCO_2), 161.08 (s, SC:N), 172.35 (s, CO_2).

2-[(**R**)-1-*t*-Butyloxycarbonylamino-2-methyl-propyl]-4-methoxycarbonylthiazole (27*d*). - The method was as described for 2-[(**S**)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(**R**)-1-*t*-butyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-(**R**)-Δ2-thiazoline (26*d*) (4.0g, 12.7mMol). The product was purified by recrystallisation from ether by the addition of hexane, giving 2-[(**R**)-1-*t*-butyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-thiazole[20] (27*d*) (3.5g, 88%) as a white solid. mp 107-8°C; (Found C,53.6; H,7.36; N,8.85. $C_{14}H_{22}N_2O_4S$ requires: C,53.5; H,7.05; N,8.9%); $[\alpha]_D$ +26.5° (c 0.9 in $CHCl_3$, 26°C); υ_{max} ($CHCl_3$) 3420 w, 1710 s, 1475 m, and 1200 s cm^{-1}; λ_{max} (EtOH) 223 (7120), and 259 (10360) nm; δ_H 0.90, and 0.98 (2xd, *J* 5.8Hz, and 5.8Hz, $(CH_3)_2$), 1.44 (s, $(CH_3)_3$), 2.2-2.7 (m, Me_2CH), 3.95 (s, OCH_3), 4.8-5.4 (2H, m, NCH + NH), 8.09 (s, SCH:); δ_C 17.51, and 19.89 (2xq, $(CH_3)_2$), 28.57 (q, $(CH_3)_3$), 35.54 (d, Me_2CH), 52.69 (q, OCH_3), 58.36 (d, NCH), 80.42 (s, $OCMe_3$), 127.35 (d, SCH:), 147.29 (s, NC:), 155.68 (s, NCO_2), 162.14 (s, SC:N), 172.27 (s, CO_2); m/z (FAB) 315 (MH^+, 79), 289 (41), 259 (99), 245 (47), 198 (32), 166 (36), 146 (49), 116 (58).

2-[(**S**)-1-Allyloxycarbonylamino-2-phenyl-ethyl]-4-methoxycarbonylthiazole (27*e*). - The method was as described for 2-[(**S**)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(**S**)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-(**R**)-Δ2-thiazoline (26*e*) (3.6g, 10.3mMol). The product was purified by dry flash chromatography (1:1 hexane/CH_2Cl_2 to 10% ether in CH_2Cl_2), to give 2-[(**S**)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-thiazole (27*e*) (3.1g, 86.6%) as a colourless oil. (Found C,58.85; H,5.5; N,7.9. $C_{17}H_{18}N_2O_4S$ requires: C,59.0; H,5.2; N,8.1%); $[\alpha]_D$ +4.3° (c 1.9 in $CHCl_3$, 27°C); υ_{max} (film) 3320 m, 2950 w, 1710 s, 1520 m, and 1240 s cm^{-1}; λ_{max} (EtOH) 230 (960), and 258 (1028) nm; δ_H 3.38 (d, *J* 6.5Hz, CH_2Ph), 4.01 (s, OCH_3), 4.58 (dt, *J* 5.4, and 1.2Hz, OCH_2), 5.1-6.2 (5H, m, CH_2:CH + NCH + NH), 7.0-7.5 (m, ArH), 8.12 (s, SCH:); δ_C 40.71 (t, CH_2Ph), 51.95 (q, OCH_3), 54.02 (d, NCH), 65.36 (t, OCH_2), 117.22 (t, $:CH_2$), 126.54, 127.29, 128.14, and 128.84 (4xd, ArCH + SCH:), 132.06 (d, :CH), 135.78 (s, ArC), 146.30 (s, NC:), 155.16 (s, NCO_2), 161.28 (s, SC:N), 172.46 (s, CO_2); m/z (FAB) 347 (100, MH^+), 246 (22), 214 (24), 91 (41).

2-[(**S**)-1-*t*-Butyloxycarbonylamino-2-phenyl-ethyl]-4-methoxycarbonylthiazole (27*f*). - The method was as described for 2-[(**S**)-1-benzyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (14*a*), using 2-[(**S**)-1-*t*-butyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-(**R**)-Δ2-thiazoline (26*f*) (3.2g, 8.8mMol). The

product was purified by flash chromatography (10% ether in CH_2Cl_2), to give 2-[(S)-1-*t*-butyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-thiazole (27*f*) (3.0g, 94%) as a white solid. υ_{max} ($CHCl_3$) 3422 s, 2924 m, and 1712 s cm^{-1}; λ_{max} (EtOH) 217 (1980), and 255 (1960) nm; δ_H 1.39 (s, $(CH_3)_3$), 3.2-3.6 (m, CH_2Ph), 3.96 (s, OCH_3), 5.2-5.4 (2H, m, 2xNCH), 7.0-7.4 (m, ArH), 8.08 (s, SCH:); δ_C 27.92 (q, $(CH_3)_3$), 41.14 (t, CH_2Ph), 51.92 (q, OCH_3), 53.07 (d, NCH), 79.82 (s, $OCMe_3$), 126.57, 127.17, 128.19, and 129.06 (4xd, ArCH + SCH:), 136.10 (s, ArC), 146.56 (s, NC:), 154.58 (s, NCO_2), 161.40 (s, SC:N), 173.25 (s, CO_2).

(*N*-Benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinylnitrile (28). - Hydroxy-benzotriazole (1.1g, 8.2mMol) was added to a solution of *N*-benzyloxycarbonyl-(S)-threonine (2.1g, 8.2mMol), and (RS)-isoleucinylnitrile (23) (0.9g, 8.2mMol) in dichloromethane (50ml) at 0°C. Dicyclohexylcarbodiimide (1.9g, 9.0mMol) was added to this solution, and the mixture was then stirred at RT for 18 hours. The reaction mixture was then filtered, and the filtrate was washed with dilute hydrochloric acid, and dilute sodium carbonate solutions. The organic phase was dried, and then evaporated *in vacuo*. The residue was purified by dry flash chromatography (CH_2Cl_2 to 30% ether in CH_2Cl_2), to give (*N*-benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinylnitrile (28) (2.7g, 94%) as a colourless oil. υ_{max} (film) 3400 s, 3040 m, 2980 s, 2940 s, 2250 w, 1710 s, and 1670 s cm^{-1}; δ_H 0.7-2.0 (12H, m, $CH_3CHCH_2CH_3$ + CH_3CHO), 3.4-3.6 (m, OH), 4.1-4.3 (m, MeCHO), 4.3-4.5 (m, NCHCO), 4.7-4.9 (m, CHCN), 5.0-5.2 (m, OCH_2Ph), 5.8-6.0 (m, NH), 7.3-7.5 (6H, m, ArH + NH); δ_C 10.91, and 14.76 (2xq, $CH_3CH_2CHCH_3$), 18.11, and 18.38 (2xq, CH_3CHO), 24.67, 25.05, and 25.43 (3xt, $MeCH_2$), 37.29, and 37.45 (2xd, MeCHEt), 45.15, and 45.36 (2xd, NCH), 58.80, and 59.23 (2xd, NCH), 66.82 (d, MeCHO), 67.19 (t, $PhCH_2O$), 117.25, 117.36, 117.74, and 117.85 (4xs, CN) 127.71, 128.03, and 128.36 (3xd, ArCH), 135.83 (s, ArC), 156.74 (s, NCO_2), 170.29, 170.51, and 170.67 (3xs, CO_2); m/z (CI) 348 (7, MH^+), 321 (3), 303 (1), 240 (74), 231 (36), 213 (31), 91 (73), 57 (100).

(*N*-Benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinimino ethyl ether (29). - The method was as described for 2-allyloxycarbonylamino-(S)-propioimino ethyl ether (22*a*) (Method A), using (*N*-benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinylnitrile (28) (2.9g, 8.35mMol). (*N*-Benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinimino ethyl ether (29) was obtained as an off white solid which was used without further purification. δ_H (acetone-d_6) 0.7-1.5 (15H, m, $CH_3CH_2CHCH_3$ + CH_3CHO + OCH_2CH_3), 3.9-4.8 (5H, m, OCH_2 + 2xNCH + MeCHO), 5.10 (s, OCH_2Ph), 6.42 (br, NH), 7.2-7.5 (m, ArH).

Thiazoline (30) derived from (*N*-benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinimino ethyl ether (29) and (R)-cysteine methyl ester hydrochloride. - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-diphenylmethoxycarbonyl-(R)-Δ2-thiazoline (13*b*), using (*N*-benzyloxycarbonyl-(S)-threonyl)-(RS)-isoleucinimino ethyl ether (29) (2.5g, 6.4mMol), and (R)-cysteine methyl ester hydrochloride (1.1g, 6.4mMol). The product was purified by flash chromatography (10% ethanol in ether), to give thiazoline (30) (0.6g, 21%) as a colourless oil.

2-[(S)-1-Allyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*a*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (Method A), using 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (27*a*) (3.0g, 11.1mMol). 2-[(S)-1-Allyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*a*) (2.5g, 88%) was obtained as a white solid. mp 123-4°C; $[\alpha]_D$ +1.2° (c 1.8 in $CHCl_3$, 21°C); υ_{max} (nujol) 3320 s, 2800 br, and 1780 s cm^{-1}; λ_{max} 212 (5600) nm; δ_H 1.58 (d, *J* 7.0Hz, CH_3), 4.50 (dt, *J* 5.8, and 1.4Hz, OCH_2), 4.9-5.4 (3H, m, NCH + :CH_2), 5.6-6.2 (m, :CH), 7.06 (2H, br, NH + OH), 8.25 (s, SCH:); δ_C 21.13 (q, CH_3), 50.17 (d, NCH), 65.93 (t,

OCH_2), 117.40 (t, :CH_2), 128.72 (d, SCH:), 134.03 (d, :CH), 147.63 (s, NC:), 156.41 (s, NCO_2), 162.20 (s, SC:N), 176.18 (s, CO_2); m/z (FAB) 279 (20, $M+Na^+$), 257 (100, MH^+).

2-[(S)-1-β-Trichloroethyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*b*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (Method A), using 2-[(S)-1-β-trichloroethyloxycarbonylaminoethyl]-4-carbomethoxy-thiazole (27*b*) (100mg, 0.3mMol), and sodium hydroxide (36mg, 0.9mMol). 2-[(S)-1-β-Trichloroethyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*b*) (80mg, 83%) was obtained as a colourless oil. δ_H 1.74 (d, *J* .8.2Hz, CH_3), 4.78 (s, OCH_2), 5.07 (q, *J* 7.9Hz, NCH), 8.27 (s, SCH).

2-[(S)-1-Allyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*c*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (Method A), using 2-[(S)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-thiazole (27*c*) (2.9g, 8.4mMol). 2-[(S)-1-Allyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*c*) (2.6g, 93%) was obtained as a white solid. mp 126-8°C; (Found C,57.9; H,5.0; N,8.2; S,9.2. $C_{16}H_{16}N_2O_4S$ requires: C,57.8; H,4.85; N,8.4; S,9.6%); $[\alpha]_D$ -2.2° (c 1.1 in EtOH, 27°C); υ_{max} (nujol) 3340 m, 2500 br, and 1790 s cm^{-1}; λ_{max} (EtOH) 218 (1630), and 258 (1500) nm; δ_H (acetone-d_6) 3.12 (1H, dd, *J* 14.0, and 9.6Hz, CH_2Ph), 3.48 (1H, dd, *J* 14.0, and 5.5Hz, CH_2Ph), 4.1-4.7 (4H, m, OCH_2 + NH + CO_2H), 4.9-5.5 (3H, m, :CH_2 + NCH), 5.5-6.1 (m, :CH), 7.0-7.4 (m, ArH), 8.26 (s, SCH:); δ_C (acetone-d_6) 41.23 (t, CH_2Ph), 55.75 (d, NCH), 65.83 (t, OCH_2), 117.24 (t, :CH_2), 127.37, 128.83, 129.10, and 130.13 (4xd, ArCH + SCH:), 133.98 (d, :CH), 138.31 (s, ArC), 147.85 (s, NC:), 156.41 (s, NCO_2), 162.26 (s, SC:N), 174.39 (s, CO_2); m/z (FAB) 333 (100, MH^+), 154 (35), 136 (30).

2-[(S)-1-*t*-Butyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*d*). - The method was as described for 2-[(S)-1-benzyloxycarbonylaminoethyl]-4-carboxy-thiazole (15) (Method A), using 2-[(S)-1-*t*-butyloxycarbonylamino-2-phenyl-ethyl]-4-carbomethoxy-thiazole (27*d*) (3.0g, 8.3mMol). 2-[(S)-1-*t*-Butyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*d*) (0.7g, 24%) was obtained as a white solid. υ_{max} (nujol) 2800 br, and 1708 s cm^{-1}; δ_H (CD_3OD) 1.35 (s, $(CH_3)_3$), 3.11 (1H, dd, *J* 13.8, and 9.8Hz, CH_2Ph), 3.47 (1H, dd, *J* 13.8, and 5.1Hz, CH_2Ph), 5.17 (dd, *J* 9.8, and 5.1Hz, NCH), 7.26 (s, ArH), 8.26 (s, SCH:); δ_C (CD_3OD) 28.58 (q, $(CH_3)_3$), 41.74 (t, CH_2Ph), 55.55 (d, NCH), 80.80 (s, $OCMe_3$), 127.55, 128.91, 129.23, and 130.15 (4xd, ArCH + SCH:), 138.23 (s, ArC), 148.03 (s, NC:), 156.97 (s, NCO_2), 163.69 (s, SC:N), 175.66 (s, CO_2).

Tripeptide (32*a*) derived from 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*a*) and *t*-butyl (*N*-(S)-phenylalanyl)-(S)-prolinate (16*a*). - Oxalyl chloride (4.0ml, excess) was added dropwise to a solution of 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carboxy-thiazole (31*a*) (2.5g, 9.8mMol) in dichloromethane (70ml), and dry DMF (2 drops) cooled to 0°C. The resulting solution was stirred at 0°C for 1 hour, then the solvents were evaporated *in vacuo*, leaving 2-[(S)-1-allyloxycarbonylaminoethyl]-4-carbonylchloride-thiazole as a red oil. This oil was redissolved in dichloromethane (75ml), and *t*-butyl (*N*-(S)-phenylalanyl)-(S)-prolinate (16a)[12] (4.8g, 15.0mMol) was added followed by triethylamine (10ml). The resulting solution was stirred at RT for 18 hours, then washed with dilute hydrochloric acid (100ml), and saturated aqueous sodium carbonate solution (100ml), dried, and the solvents evaporated *in vacuo*. The residue was subjected to flash chromatography (ether), to give the desired tripeptide (32*a*) (3.6g, 65%) as a white foam. mp 57-8°C; $[\alpha]_D$ -38.2° (c 2.0 in $CHCl_3$, 22°C); υ_{max} ($CHCl_3$) 3400 w, 2940 w, 1720 s, 1640 s, and 1155 s cm^{-1}; λ_{max}

(EtOH) 210 (10700) nm; δ_H (RT) 1.46, and 1.49 (2xs, $OC(CH_3)_3$), 1.58, and 1.60 (2xd, *J* 6.9Hz, and 7.3Hz, CH_3), 1.8-2.3 (4H, m, CH_2CH_2), 3.0-3.8 (5H, m, $PhCH_2$ + NCH_2 + NCH), 4.4-4.5 (m, NCH), 4.61 (d, *J* 5.5Hz, OCH_2), 5.0-5.4 (4H, m, $:CH_2$ + NCHTh + $NHCO_2$), 5.8-6.0 (1H, m, :CH), 7.1-7.4 (6H, m, ArH + NH), 7.94, and 7.98 (2xs, SCH:); δ_C (RT) 19.36, and 21.40 (2xq, CH_3), 24.66, and 24.84 (2xt, CH_2), 27.65, and 27.77 (2xq, $(CH_3)_3$), 28.91, and 30.40 (2xt, CH_2), 37.24, and 38.33 (2xt, CH_2Ph), 45.94, and 46.81 (2xt, CH_2N), 48.11, and 49.04 (2xd, NCH), 49.04, and 51.87 (2xd, NCH), 59.49, and 59.62 (2xd, NCH), 65.65, and 65.72 (2xt, OCH_2), 81.17, and 82.37 (2xs, $OCMe_3$), 117.76, and 117.86 (2xt, $:CH_2$), 123.00, 123.34, 126.50, 126.67, 128.20, 128.41, 129.30, 129.54, 132.54, and 132.70 (10xd, ArCH + :CH + :CHS), 136.27, and 137.00 (2xs, ArC), 148.62, and 149.15 (2xs, NC:), 155.61, and 155.66 (2xs, NCO_2), 160.39, 161.04 (2xs, SC:N), 169.74, 169.87, 170.23, 170.95, 171.91, and 173.36 (6xs, CO_2 + CON).

Tripeptide (32*b*) derived from 2-[(S)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*c*) and *t*-butyl (*N*-(S)-phenylalanyl)-(S)-prolinate (16*a*). - The method was as described for tripeptide (32*a*), using 2-[(S)-1-allyloxycarbonylamino-2-phenyl-ethyl]-4-carboxy-thiazole (31*c*) (5.0g, 15.1mMol). Flash chromatography (ether) gave the desired tripeptide (32*b*) (5.2g, 55%) as a white foam. $[\alpha]_D$ -10.8° (c 0.2 in $CHCl_3$, 27°C); υ_{max} ($CHCl_3$) 3400 w, 2970 s, 1720 s, 1640 s, and 1190 s cm^{-1}; λ_{max} (EtOH) 217 (1970), and 257 (1980) nm; δ_H (RT) 1.43, and 1.56 (2xs, $(CH_3)_3$), 1.6-1.8, and 1.9-2.3 (4H, m, CH_2CH_2), 3.1-3.9 (7H, m, 2xCH_2Ph + CH_2N + CHN), 4.4-4.5 (m, NCH), 4.62 (d, *J* 5.7Hz, OCH_2), 5.2-5.4 (3H, m, $:CH_2$ + NCHTh), 5.5-5.7 (m, $NHCO_2$), 5.8-6.1 (m, :CH), 7.1-7.4 (m, ArH), 7.96, and 8.02 (2xs, SCH:), 8.05, and 8.36 (br, NH); δ_C (RT major conformer) 25.59 (t, CH_2), 28.79 (q, $(CH_3)_3$), 29.83 (t, CH_2), 39.34 (t, CH_2Ph^*), 42.17 (t, CH_2Ph^*), 47.81 (t, CH_2N^*), 52.67 (d, NCH), 55.03 (d, NCH), 60.54 (d, NCH), 66.73 (t, OCH_2), 82.11 (s, $OCMe_3$), 118.69 (t, $:CH_2$), 124.15 (d, :CH), 127.64, 127.83, 129.16, 129.41, 130.24, and 130.56 (6xd, ArCH), 133.28 (d, SCH:), 136.86, and 137.07 (2xs, ArC), 150.33 (s, NCO_2), 156.28 (s, NC:), 161.17 (s, SC:N), 170.58, 170.73, and 171.82 (3xs, 2xNCO + CO_2); m/z (FAB) 633 (16, MH^+), 570 (9), 434 (49), 333 (37), 214 (50), 116 (100). A * indicates that the peak assignments may be interchanged.

2-[(R)-1-Amino-2-methyl-propyl]-4-methoxycarbonylthiazole (33). Method A from 2-[(R)-1-allyloxycarbonylamino-2-methyl-propyl]-4-methoxycarbonylthiazole (27*c*). - Triethylamine (0.5ml, excess), and tris(triphenylphosphine)rhodium(1) chloride (200mg, 0.2mMol) were added to a solution of 2-[(R)-1-allyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-thiazole (27*c*) (500mg, 1.7mMol) in ethanol (30ml), and water (3ml). The solution was heated at reflux under nitrogen for 2 hours, then the solvents were evaporated *in vacuo*. the residue was redissolved in ethyl acetate (50ml), washed with saturated aqueous sodium carbonate, dried, then evaporated *in vacuo* to leave 2-[(R)-1-amino-2-methyl-propyl]-4-carbomethoxy-thiazole[20] (33) (310mg, 86%) as an oil that was used without further purification. υ_{max} (nujol) 3600-1900 br, and 1710 s cm^{-1}; δ_H (CD_3OD) 0.98, and 1.11 (2xd, *J* 6.5Hz, and 6.5Hz, $(CH_3)_2$), 2.4-2.5 (m, Me_2CH), 3.92 (s, OCH_3), 4.67 (d, *J* 5.1Hz, NCH), 8.51 (s, SCH:); δ_C (CD_3OD) 18.45, and 18.72 (2xq, $(CH_3)_2$), 33.67 (d, Me_2CH), 52.90 (q, OCH_3), 58.70 (d, NCH), 130.86 (d, SCH:), 148.61 (s, NC:), 163.55 (s, SC:N), 167.19 (s, CO_2); m/z (FAB) 215 (MH^+, 100), 198 (22), 154 (34), 136 (27), 72 (31).

2-[(R)-1-Amino-2-methyl-propyl]-4-methoxycarbonylthiazole hydrochloride (33). Method B from 2-[(R)-1-*t*-butyloxycarbonyl-amino-2-methyl-propyl]-4-methoxycarbonylthiazole (27*d*). - Acetyl chloride (1.5ml) was added dropwise to methanol (15ml), cooled to 0°C. 2-[(R)-1-*t*-Butyloxycarbonylamino-2-methyl-propyl]-4-carbomethoxy-thiazole (27*d*) (1.5g, 4.8mMol) was added to the solution, and the reaction was allowed to stir at RT for 4 hours. The solvents were evaporated *in vacuo*, to leave 2-[(R)-1-amino-2-methyl-propyl]-4-

carbomethoxy-thiazole hydrochloride[20] (33) (1.2g, 99%) as a white solid.
2-[(R)-1-(*N*-*t*-Butyloxycarbonyl-(S)-threonyl)-amino-2-methyl-propyl]-4-methoxycarbonylthiazole (34). - *N*-*t*-Butyloxycarbonyl-(S)-threonine (1.3g, 6.0mMol) was added to a solution of 2-[(R)-1-amino-2-methyl-propyl]-4-carbomethoxy-thiazole hydrochloride (33) (1.4g, 5.6mMol) in dry DMF (50ml) cooled to 0°C. To the resulting solution was added diethyl cyanophosphonate (1.0ml, 6.0mMol), followed by triethylamine (3.0ml, excess). The solution was stirred at RT for 18 hours, then the DMF was evaporated *in vacuo* as an azeotrope with xylene. The residue was dissolved in dichloromethane (50ml), and washed with dilute hydrochloric acid (50ml), and aqueous sodium carbonate (50ml), the organic layer was then dried, and evaporated *in vacuo*. The residue was subjected to flash chromatography (ether) to give 2-[(S)-1-(*N*-*t*-Butyloxycarbonyl-(R)-threonyl)-amino-2-methyl-propyl]-4-carbomethoxy-thiazole (34) (1.3g, 55%) as a white foam. mp 58-60°C; $[\alpha]_D$ -27.2° (c 0.5 in $CHCl_3$, 27°C); υ_{max} ($CHCl_3$) 3410 m, 1710 s, and 1670 s cm^{-1}; λ_{max} (EtOH) 218 (1370), and 254 (1330) nm; δ_H (RT) 0.8-1.0 (m, $(CH_3)_2$), 1.1-1.4 (m, $C\underline{H}_3CHO$), 1.42, and 1.43 (2xs, $(CH_3)_3$), 2.43 (septet, *J* 6.5Hz, $CHMe_2$), 3.86, and 3.87 (2xs, OCH_3), 4.1-4.5 (3H, m, CHO + NCH + OH), 5.1-5.2 (m, NCHTh), 5.3-5.5 (br, NH) 7.9-8.1 (br, NH), 8.29, and 8.32 (2xs, SCH:); δ_C 17.06, 18.77, and 19.40 (3xq, $(CH_3)_2$ + CH_3), 28.31 (q, $(CH_3)_3$), 32.92 (d, Me_2CH), 52.44 (q, OCH_3), 58.75, and 59.12 (2xd, NCH), 66.74 (d, CHO), 80.44 (s, $OCMe_3$), 127.36 (d, SCH:), 146.83 (s, NC:), 156.78 (s, NCO_2), 161.94 (s, SC:N), 172.08, and 172.95 (2xs, CO_2 + CON); m/z (FAB) 416 (23, MH^+), 316 (79), 215 (64), 146 (100).

Acknowledgements: We thank ICI for financial support through their Strategic Research Fund. We also thank Mr. D. Toplis for assistance with experimental work, and Dr. S.D. Mills (ICI Pharmaceuticals) for helpful discussions.

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