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Synthesis of Optically Active 2-(1-Hydroxyalkyl)-thiazole-4-carboxylic Acids and 2-(1-Aminoalkyl)-thiazole-4-carboxylic Acids

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Two routes are outlined for the synthesis of (*R*)- or (*S*)-2-(1-aminoalkyl)-thiazole-4-carboxylic acids starting from commercial available (*S*)-amino acids.

Several peptides of biological activity and pharmaceutical interest which are biosynthesized by an ribosome-independent pathway and contain thiazole components have been isolated in the last few years from moulds and lower sea animals[2–14]. Except for the achiral dithiazole residue of the antitumor drug bleomycin[15], most of these thiazole components are 2-(1-aminoalkyl)-thiazole-4-carboxylic acids. They appear to have been biosynthesized from cysteine-containing dipeptides. Apart from the 2-(1-aminomethyl)-thiazole-4-carboxylic acid, the homologs are chiral and the natural compounds have *R* or *S* configuration. The free amino acids racemise easily in acidic solution, but the amino esters as well as the corresponding acylamino acids are configurationally stable. Therefore, the protecting group of the 2-(1-benzyloxycarbonylaminoalkyl)-thiazole-4-carboxylic esters can be removed by hydrogen bromide/acetic acid without any loss of optical activity.

Several authors[16,17,18] described the almost complete racemisation in the Hantzsch synthesis of these compounds from optically active acylaminothiocarboxamides and bromopyruvate. Recently, the formation of six 2-(1-Boc-aminoalkyl)-thiazole-4-carboxylic esters by Hantzsch synthesis "without loss of optical purity" has been reported but the optical rotation of the compounds was not given[19]. We reproduced accurately the synthesis of ethyl 2-(1-Boc-aminoethyl)-thiazole-4-carboxylate and found a completely racemised product. This was established by measurement of the optical rotation and by HPLC with a Pirkle column, which separates the enantiomers cleanly [The melting points of the *R*-enantiomer and the racemate of ethyl 2-(1-Boc-aminoethyl)-thiazole-4-carboxylate are nearly the same].

As precursors for the syntheses of the *dolastatin 3* isomers, optically active derivatives of 2-(1-aminoalkyl)-thiazole-4-carboxylic acids were synthesized by Shioiri and Hamada[14b] and by us[14a], using different methods. The japanese group[14b] formed the thiazolidine from cysteine methyl ester and an optically active α-acylaminoaldehyde, prepared from the corresponding amino acid; oxidation with active manganese dioxide gave the optically active thiazole compound. This type of synthesis had been first performed by Yoshimura et al.[20] who condensed an aldopentose derivative with cysteine and subsequently oxidized the thiazolidine to give the diastereomerically pure thiazolecarboxylic acid.

We elaborated two syntheses of the Hantzsch type which start from the cheap (*S*)-amino acids and lead to (*R*)- *or* (*S*)-2-(1-aminoalkyl)-thiazole-4-carboxylic acids. Compounds of both configurations were found in peptides of non-ribosomal origin.

The enantiomeric purity was analysed by HPLC with the Pirkle column[21]. The compounds described in this work are obtained by route A or B with an ee of 90–100%[22]. This small racemisation arises from the thiazole synthesis or from impure starting materials, particularly from the α-hydroxy-

carboxylic acids, because their preparation from α-amino acids is accompanied by racemisation in the range of 3–6%. The optically pure thiazole compounds are easily obtained by recrystallization of a crystalline derivative.

Synthesis of Optically Active α-Acyloxythiocarboxamides and α-Acylaminothiocarboxamides

These components of the Hantzsch synthesis can be obtained by treating the amides with the Lawesson reagent[23] (Method A). The reaction proceeds smoothly but the separation of phosphorus-containing impurities is often difficult. We prefer the synthesis of these compounds by addition of hydrogen sulfide to nitriles (Method B), which are accessible by dehydration of the amides. The addition of hydrogen sulfide in ethanol as solvent is catalysed by ammonia and potassium sulfide[24] or triethanolamine. In the reaction of (*S*)-benzyloxycarbonylalaninenitrile with hydrogen sulfide and triethanolamine as catalyst, partial racemisation of the thioamide (not of the nitrile) was observed.

Synthesis of (*R*)-2-(1-Aminoalkyl)-thiazole-4-carboxylic Acids from (*S*)-Amino Acids (Route A)

The starting materials are the (*S*)-α-acyloxycarboxylic acids which can be obtained from (*S*)-amino acids with retention of configuration and an e.e. of 88–94%. The corresponding thioamides **3** (Table 3) are directly accessible by treatment of the α-acyloxycarboxamides **1** (Table 1) with the Lawesson reagent or by dehydration of amides **1** and subsequent

Table 1. α-Acetoxycarboxamides **1** Obtained from the α-Acetoxycarboxylic Acids via Carboxylic Acid Chlorides

Product	Yield [%]	b.p. [°C]/torr[a] or m.p. [°C] (solvent)	Molecular Formula[b] or Lit. m.p. [°C]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[c] δ [ppm]
(*S*)-**1a**	96	m.p. 60 (petroleum ether/ethyl acetate)	m.p. 59–60[30]	−10.4° (1.94, chloroform)	1.50 (d, 3H, *J* = 7 Hz); 2.17 (s, 3H); 5.17 (d, 1H, *J* = 7 Hz); 6.72 (br. s, 2H)
(*S*)-**1b**[d]	98	m.p. 85 (petroleum ether/ethyl acetate)	$C_8H_{15}NO_3$ (173.2)	−31.0° (0.88, chloroform)	0.91 (d, 3H, *J* = 6 Hz); 1.58 (m, 3H); 2.08 (s, 3H); 4.88 (m, 1H); 7.15 (br. s, 1H); 7.48 (br. s, 1H)
(*S,S*)-**1c**[e]	93	b.p. 93/0.001	$C_8H_{15}NO_3$ (173.2)	−14.9° (2.35, chloroform)	0.90 (t, 3H, *J* = 7 Hz); 0.97 (d, 3H, *J* = 7 Hz); 1.4 (m, 2H); 1.87 (m, 1H); 2.17 (s, 3H); 5.05 (d, 1H, *J* = 4 Hz); 6.47 (br. s, 1H); 6.77 (br. s, 1H)
(*S*)-**1d**[f]	89	b.p. 85/0.001	$C_7H_{13}NO_3$ (159.2)	−18.0° (1.36, chloroform)	1.00 (d, 6H, *J* = 7 Hz); 2.18 (s, 3H); 2.22 (m, 1H); 5.00 (d, 1H, *J* = 5 Hz); 6.47 (br. s, 1H); 6.77 (br. s, 1H)
(*S*)-**1e**[g]	83	b.p. 120/0.001	$C_{11}H_{13}NO_3$ (207.2)	+3.8° (5.82, chloroform)	2.03 (s, 3H); 3.13 (d, 1H, *J* = 7 Hz); 3.16 (d, 1H, *J* = 5 Hz); 5.31 (dd, 1H, *J* = 5 Hz, *J'* = 7 Hz); 6.24 (br. s, 1H); 6.49 (br. s, 1H); 7.20 (s, 5H)

[a] Bulb-to-bulb distillation.
[b] Satisfactory microanalyses obtained: C ±0.22, H ±0.14, N ±0.21.
[c] 60 MHz.
[d] e.e. could not be estimated, e.e. of the corresponding α-acetoxycarboxylic acid 90%.
[e] d.e. 90%.
[f] e.e. could not be estimated, e.e. of the corresponding α-acetoxycarboxylic acid 88%[31].
[g] e.e. could not be estimated, e.e. of the corresponding α-acetoxycarboxylic acid 91%[32].

Table 2. α-Acetoxy nitriles **2**

Product	Yield [%]	b.p. [°C]/torr[a]	Molecular Formula[b]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[c] δ [ppm]
(*S*)-**2b**[d]	90	86/10	$C_8H_{13}NO_2$ (155.2)	−86.6° (1.13, chloroform)	0.95 (d, 6H, *J* = 5 Hz); 1.80 (m, 3H); 2.10 (s, 3H); 5.35 (t, 1H, *J* = 7 Hz)
(*S,S*)-**2c**[e]	91	85–90/10	$C_8H_{13}NO_2$ (155.2)	−78.6° (4.17, chloroform)	0.96 (t, 3H, *J* = 7 Hz); 1.1 (d, 3H, *J* = 8 Hz); 1.48 (m, 2H); 1.95 (m, 1H); 2.14 (s, 3H); 5.33 (d, 1H, *J* = 6 Hz)
(*S*)-**2d**[d]	89	70/10	$C_7H_{11}NO_2$ (141.2)	−99.1° (4.77, chloroform)	1.08 (d, 3H, *J* = 7 Hz); 1.12 (d, 3H, *J* = 7 Hz); 2.15 (s, 3H); 2.17 (m, 1H); 5.17 (d, 1H, *J* = 6 Hz)
(*S*)-**2e**[d]	93	80–85/0.05	$C_{11}H_{11}NO_2$ (189.2)	−52.5° (1.16, chloroform)	2.05 (s, 3H); 3.14 (d, 2H, *J* = 7 Hz); 5.46 (t, 1H, *J* = 7 Hz); 7.29 (s, 5H)

[a] Bulb-to-bulb distillation.
[b] Satisfactory microanalyses obtained: C ±0.18, H ±0.26, N ±0.26.
[c] 60 MHz for **2b**, **2d**, and **2e**; 80 MHz for **2c**.
[d] The optical purity could not be analysed. Compare remarks in Table 1.
[e] d.e. 90%.

Table 3. Thiocarboxamides **3**[a] and **8** from Amides (Method A) or Nitriles (Method B)

Product	Yield [%] (Method)	m.p. [°C] (solvent)	Molecular Formula[b] Lit. m.p. [°C]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[c] δ [ppm]
(*S*)-**3a**	70 (A)	oil	$C_5H_9NO_2S$ (147.2)	−44.2° (4.87, chloroform)	1.6 (d, 3H, J = 7 Hz); 2.17 (s, 3H); 5.47 (q, 1H, J = 7 Hz); 7.87 (br. s, 1H); 8.37 (br. s, 1H)
(*S*)-**3b**	79 (B)	71 (petroleum ether/ diethyl ether)	$C_8H_{15}NO_2S$ (189.3)	−57.2° (0.97, chloroform)	0.96 (d, 6H, J = 6 Hz); 1.85 (m, 3H); 2.18 (s, 3H); 5.53 (m, 1H); 7.68 (br. s, 1H); 8.15 (br. s, 1H)
(*S,S*)-**3c**	96 (B)	58–59 (petroleum ether/ diethyl ether)	$C_8H_{15}NO_2S$ (189.3)	−29.4° (1.38, chloroform)	0.90 (t, 3H, J = 7 Hz); 0.96 (d, 3H, J = 7 Hz); 1.38 (m, 2H); 2.2 (s, 3H); 2.25 (m, 1H); 5.45 (d, 1H, J = 4 Hz); 7.85 (br. s, 1H); 8.45 (br. s, 1H)
(*S*)-**3d**	91 (B)	oil	$C_7H_{13}NO_2S$ (175.25)	−20.9° (3.24, ethanol)	0.95 (d, 3H, J = 7 Hz); 1.00 (d, 3H, J = 7 Hz); 2.22 (s, 3H); 2.50 (m, 1H); 5.43 (d, 1H, J = 4 Hz); 7.70 (br. s, 1H); 8.30 (br. s, 1H)
(*S*)-**3e**	61 (B)	108–110 (petroleum ether/ diethyl ether)	$C_{11}H_{13}NO_2S$ (223.3)	−78.0° (2.50, chloroform)	2.07 (s, 3H); 3.17 (dd, 1H, J = 7 Hz, J' = 14 Hz); 3.43 (dd, 1H, J = 5 Hz, J' = 14 Hz); 5.71 (dd, 1H, J = 5 Hz, J' = 7 Hz); 7.30 (s, 5H); 7.45 (br. s, 1H); 8.05 (br. s, 1H)
(*S*)-**8a**	86 (A)	111 (ethyl acetate)	$C_{11}H_{14}N_2O_2S$ (238.3)	+6.0° (1.25, chloroform)	[d]1.33 (d, 3H, J = 7 Hz); 4.40 (dq, 1H, J = 7 Hz, J' = 7 Hz); 5.05 (s, 2H); 7.33 (d, 1H, J = 7 Hz); 7.36 (s, 5H); 9.14 (br. s, 1H); 9.59 (br. s, 1H)
(*S*)-**8b**	73 (A)	157	157.5[19]	−65.8° (0.77, chloroform)	0.98 (d, 6H, J = 5.5 Hz); 1.45 (s, 9H); 1.50–1.90 (m, 3H); 4.60 (m, 1H); 5.45 (d, 1H, J = 8 Hz); 8.08 (br. s, 1H); 8.55 (br. s, 1H)
(*S,S*)-**8c**	86 (B)	75–76	$C_{14}H_{20}N_2O_2S$ (280.4)	−5.0° (2.42, chloroform	0.89 (t, 3H, J = 7 Hz); 0.91 (d, 3H, J = 7 Hz); 1.21 (m, 1H); 1.74 (m, 2H); 4.38 (dd, 1H, J = 9 Hz, J' = 8 Hz); 5.06 (s, 2H); 5.88 (d, 1H, J = 9 Hz); 7.30 (s, 5H); 8.15 (br. s, 1H); 8.40 (br. s, 1H)

[a] The optical purity could not be analysed. Compare the remarks in Table 1 concerning the purity of the starting materials.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.22, N ±0.24, S ±0.30.
[c] 60 MHz for **3a**, **3b**, **3d**, and **3e**; 80 MHz for **3c**, **8a**, **8b**, and **8c**.
[d] Solvent: DMSO-d_6.

Table 4. Thiazoles **4**

Product	Yield [%]	b.p. [°C]/torr[a] or m.p. [°C] (solvent)	Molecular Formula[b]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[c] δ [ppm]
(*S*)-**4a**[d]	73	b.p. 90/0.001	$C_{10}H_{13}NO_4S$ (243.3)	−46.5° (1.0, chloroform)	1.40 (t, 3H, J = 7 Hz); 1.71 (d, 3H, J = 7 Hz); 2.15 (s, 3H); 4.43 (q, 2H, J = 7 Hz); 6.17 (q, 1H, J = 7 Hz); 8.15 (s, 1H)
(*S*)-**4b**[e]	91	b.p. 90–100/0.001	$C_{13}H_{19}NO_4S$ (285.4)	−57.6° (1.25, chloroform)	0.98 (d, 6H, J = 6 Hz); 1.40 (t, 3H, J = 7 Hz); 1.95 (m, 3H); 2.15 (s, 3H); 4.45 (q, 2H, J = 7 Hz); 6.30 (t, 1H, J = 7 Hz); 8.20 (s, 1H)
(*S,S*)-**4c**[f]	79	b.p. 105–110/0.001	$C_{13}H_{19}NO_4S$ (285.4)	−41.8° (3.64, chloroform)	0.89 (t, 3H, J = 7 Hz); 0.94 (d, 3H, J = 7 Hz); 1.4 (t, 3H, J = 7 Hz); 1.43 (m, 2H); 2.05 (s, 3H); 2.21 (m, 1H); 4.45 (q, 2H, J = 7 Hz); 6.1 (d, 1H, J = 6 Hz); 8.24 (s, 1H)
(*S*)-**4d**[g]	91	m.p. 52–53	$C_{12}H_{17}NO_4S$ (271.3)	−38.6° (1.09, chloroform)	0.98 (d, 6H, J = 7 Hz); 1.40 (t, 3H, J = 7 Hz); 2.20 (s, 3H); 2.42 (m, 1H); 4.45 (q, 2H, J = 7 Hz); 6.03 (d, 1H, J = 6 Hz); 8.20 (s, 1H)
(*S*)-**4e**[h]	84	b.p. 175/0.001	$C_{16}H_{17}NO_4S$ (319.4)	−54.1° (1.35, chloroform)	1.40 (t, 3H, J = 7 Hz); 2.05 (s, 3H); 3.25 (dd, 1H, J = 8 Hz, J' = 14 Hz); 3.51 (dd, 1H, J = 5 Hz, J' = 14 Hz); 4.25 (q, 2H, J = 7 Hz); 6.33 (dd, 1H, J = 5 Hz, J' = 8 Hz); 7.18 (s, 5H); 8.07 (s, 1H)

[a] Bulb-to-bulb distillation.
[b] Satisfactory microanalyses obtained: C ±0.26, H ±0.27, N ±0.34, S ±0.33.
[c] 60 MHz for **4a**, **4b**, and **4d**; 80 MHz for **4c** and **4e**.
[d] e.e. = 94%.
[e] e.e. = 98%.
[f] d.e. = 90%.
[g] e.e. = 90%.
[h] e.e. > 95%.

Table 5. Thiazoles **5**

Product	Yield [%]	b.p. [°C]/torr[a] or m.p. [°C] (solvent)	Molecular Formula[b]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[c] δ [ppm]
(*S*)-**5a**[d]	92	b.p. *105/0.005*	$C_8H_{11}NO_3S$ (201.25)	−19.9° (1.20, chloroform)	1.40 (t, 3H, J = 7 Hz); 1.65 (d, 3H, J = 7 Hz); 4.40 (q, 2H, J = 7 Hz); 4.90 (br. s, 1H); 5.27 (q, 1H, J = 7 Hz); 8.13 (s, 1H)
(*S*)-**5b**[e]	89	b.p. 120–130/0.001	$C_{10}H_5NO_3S$ (229.3)	−45.3° (1.60, dichloromethane)	0.98 (d, 6H, J = 6 Hz); 2.82 (m, 3H); 3.65 (br. s, 1H); 3.92 (s, 3H); 5.14 (t, 1H, J = 6.5 Hz); 8.08 (s, 1H)
(*S,S*)-**5c**[f]	92	b.p. 110–115/0.001	$C_{11}H_{17}NO_3S$ (243.3)	−27.0° (1.51, chloroform)	0.90 (t, 3H, J = 7 Hz); 0.95 (d, 3H, J = 7 Hz); 1.40 (t, 3H, J = 7 Hz); 1.45 (m, 2H); 2.01 (m, 1H); 4.03 (d, 1H, J = 5 Hz); 4.41 (q, 2H, J = 7 Hz); 5.01 (dd, 1H, J = 5 Hz, J' = 5 Hz); 8.18 (s, 1H)
(*S*)-**5e**[g]	91	m.p. 82–84 (petroleum ether/ ethyl acetate)	$C_{13}H_{13}NO_3S$ (263.3)	−63.0° (0.37, chloroform)	2.97 (dd, 1H, J = 8.5 Hz, J' = 14 Hz); 3.37 (dd, 1H, J = 3.5 Hz, J' = 14 Hz); 3.81 (br. s, 1H); 3.86 (s, 3H); 5.20 (m, 1H); 7.17 (s, 5H); 8.00 (s, 1H)

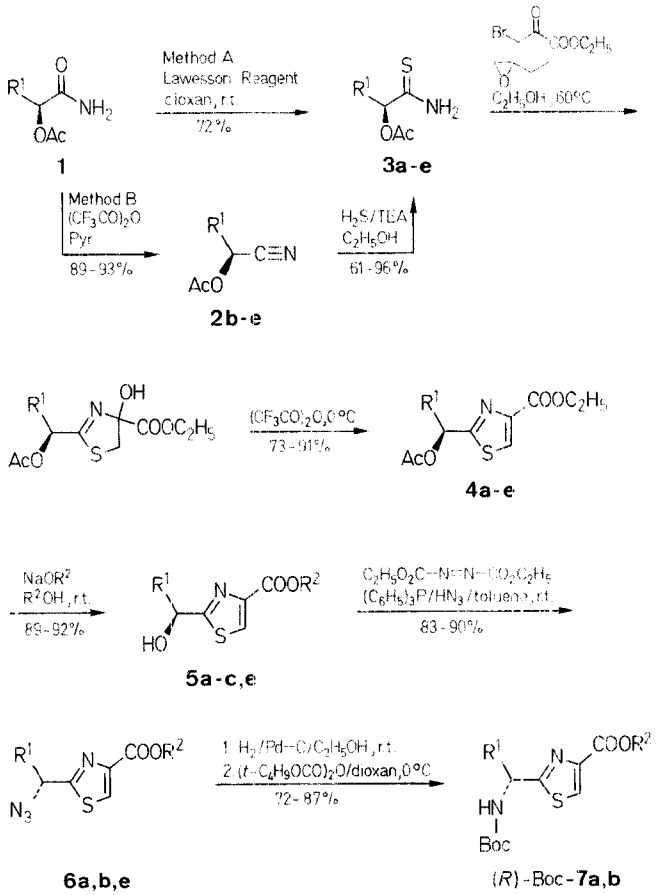
[a] Bulb-to-bulb distillation.
[b] Satisfactory microanalyses obtained: C ±0.22, H ±0.15, N ±0.12, S ±0.32.
[c] 60 MHz for **5a**; 80 MHz for **5b**, **5c**, and **5e**.
[d] Ethyl ester: e.e. = 94%.
[e] Methyl ester: e.e. = 98%.
[f] Ethyl ester: d.e. = 90%.
[g] Methyl ester: e.e. = 100%.

Table 6. Thiazoles **6** and **7**

Product	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	$[\alpha]_D^{20}$ (c, solvent)	^{1}H-NMR ($CDCl_3$)[b] δ [ppm]
(*R*)-**6a**[c]	85	oil	$C_8H_{10}N_4O_2S$ (226.3)	+7.9° (4.38, chloroform)	1.43 (t, 3H, J = 7 Hz); 1.73 (d, 3H, J = 7 Hz); 4.43 (q, 2H, J = 7 Hz); 5.07 (q, 1H, J = 7 Hz); 8.25 (s, 1H)
(*R*)-**6b**[d]	83	oil	$C_{10}H_{14}N_4O_2S$ (254.3)	+51.3° (0.51, chloroform)	1.00 (d, 6H, J = 6.5 Hz); 1.83 (m, 3H); 3.95 (s, 3H); 4.93 (t, 1H, J = 7 Hz); 8.17 (s, 1H)
(*R*)-**6e**[d]	90	73 (petroleum ether)	$C_{13}H_{12}N_4O_2S$ (288.3)	+8.0° (2.03, chloroform)	3.08 (dd, 1H, J = 9 Hz, J' = 14 Hz); 3.50 (dd, 1H, J = 4.5 Hz, J' = 14 Hz); 3.95 (s, 3H); 5.13 (dd, 1H, J = 4.5 Hz, J' = 9 Hz); 7.25 (s, 5H); 8.13 (s, 1H)
(*R*)-Boc-**7a**[e,g]	72	89.5 (petroleum ether/ ethyl acetate)	$C_{13}H_{20}N_2O_4S$ (300.4)	+38.6° (0.67, dichloromethane)	1.40 (t, 3H, J = 7 Hz); 1.44 (s, 9H); 1.64 (d, 3H, J = 7 Hz); 4.43 (q, 2H, J = 7 Hz); 5.11 (dd, 1H, J = 8 Hz, J' = 7 Hz); 5.38 (d, 1H, J = 8 Hz); 8.11 (s, 1H)
(*R*)-Boc-**7b**[e,h]	87	oil	$C_{15}H_{24}N_2O_4S$ (328.4)	+50.4° (1.46, chloroform)	1.00 (d, 6H, J = 6 Hz); 1.45 (s, 9H); 1.50–2.18 (m, 3H); 3.96 (s, 3H); 4.88–5.44 (m, 2H); 8.15 (s, 1H)
(*S*)-Z-**7a**[f,i]	64	76 (diethyl ether/ petroleum ether)	$C_{16}H_{18}N_2O_4S$ (334.4)	−17.2° (2.8, dichloromethane)	1.38 (t, 3H, J = 7 Hz); 1.64 (d, 3H, J = 7 Hz); 4.40 (q, 2H, J = 7 Hz); 5.13 (s, 2H); 5.18 (dq, 1H, J = 8 Hz, J' = 7 Hz); 5.80 (d, 1H, J = 8 Hz); 7.30 (s, 5H); 8.06 (s, 1H)
(*S*)-Boc-**7b**[f,j]	83	oil	$C_{16}H_{26}N_2O_4S$ (342.5)	−51.2° (1.10, chloroform)	1.02 (m, 6H); 1.43 (t, 3H, J = 7 Hz); 1.47 (s, 9H); 1.70–2.05 (m, 3H); 4.46 (q, 2H, J = 7 Hz); 5.11 (m, 2H); 8.10 (s, 1H)
(*S,S*)-Z-**7c**[f,k]	97	70–71	$C_{19}H_{24}N_2O_4S$ (376.5)	−18.9° (2.41, chloroform)	0.90 (m, 3H); 0.92 (d, 3H, J = 7 Hz); 1.35 (m, 2H); 1.38 (t, 3H, J = 7 Hz); 2.18 (m, 1H); 4.41 (q, 2H, J = 7 Hz); 5.01 (dd, 1H, J = 9 Hz, J' = 6 Hz); 5.12 (s, 2H); 5.78 (d, 1H, J = 9 Hz); 7.31 (s, 5H); 8.07 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.16, N ±0.29, S ±0.26.
[b] 80 MHz.
[c] Ethyl ester.
[d] Methyl ester.
[e] Catalytic hydrogenation of the azide followed by acylation of the amine.
[f] Two-step Hantzsch synthesis of the acylaminothiocarboxamide.
[g] Ethyl ester: e.e. = 100%.
[h] Methyl ester: e.e. > 99%.
[i] Ethyl ester: e.e. = 76%.
[j] Ethyl ester: e.e. > 96%.
[k] Ethyl ester: d.e. > 94%.

addition of hydrogen sulfide to the nitriles **2** (Table 2). The amides and thioamides could often be obtained optically pure by recrystallization. Reaction of the thioamides **3** with ethyl bromopyruvate in ethanol forms the thiazole compounds **4** with 40–60% e.e. The choice of the solvent is important since in dioxan or toluene complete racemisation was observed. An optically pure product can be obtained by a two-step modification of the Hantzsch synthesis by addition of ethyloxirane (1,2-epoxybutane) which traps the hydrobromic acid and stops the reaction at the stage of the dihydrothiazole. Separation of the intermediate and its cautious dehydration by trifluoroacetic anhydride forms the optically pure thiazole **4** (Table 4). Transesterification of the thiazole-4-carboxylic ester **4** forms the hydroxy compounds **5** (Table 5). Substitution of the hydroxy group by the azide group and simultaneous Walden inversion is achieved by the Mitsunobu reaction[25,26]. The subsequent catalytic hydrogenation of the azides **6** (Table 6) proceeds smoothly to give the ethyl (*R*)-2-(1-aminoalkyl)-thiazole-4-carboxylates **7**, which are acylated to *N*-Boc derivatives (Table 6; Scheme **A**).



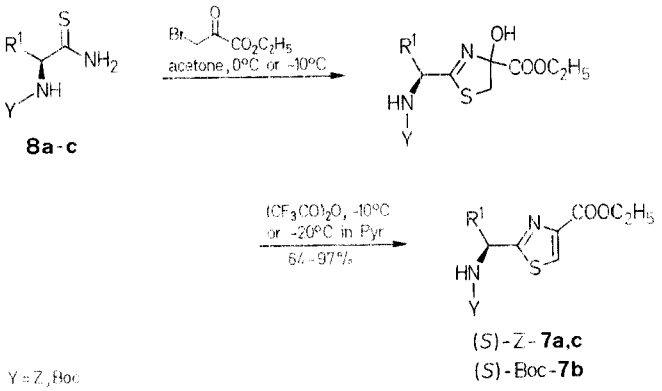
TEA = triethanolamine
Boc = *t*-butoxycarbonyl

	R^1	R^2
a	CH_3	C_2H_5
b	*i*-C_4H_9	CH_3
c	*sec*-C_4H_9	C_2H_5
d	*i*-C_3H_7	–
e	$C_6H_5-CH_2$	CH_3

Scheme **A** (Route A)

Synthesis of (*S*)-2-(1-Aminoalkyl)-thiazole-4-carboxylic Acid Derivatives from (*S*)-Amino Acids (Route B)

The nearly complete racemisation in the condensation of ethyl bromopyruvate with optically active α-acylaminothiocarboxamides[16,17,18] can also be avoided[27] by the two-step Hantzsch reaction. The condensation in acetone[28,29] is the method of choice. The free bases are dehydrated by trifluoroacetic anhydride. The choice of the *N*-protecting group is important: Phthaloylamino thiocarboxamides and *p*-nitrobenzyloxycarbonylamino compounds mostly give racemic thiazoles. With benzyloxycarbonyl- and *t*-butoxycarbonylamino thiocarboxamides, the optically active thiazole products are formed in good yields (Table 6). The *N*-protecting group can be cleaved with hydrogen bromide/acetic acid or trifluoroacetic acid without cleavage of the ester group and without loss of optical purity (Scheme **B**).



Scheme **B** (Route B)

Silica gel (Riedel-de-Haen; 0.063–0.2 mm) was used for column chromatography. HPLC was carried out with a LKB instrument. For separation of enantiomers a chiral column (Bakerbond: DNBPG) was used. Melting points (Kofler) are uncorrected. Optical rotations were measured in 1 dm cells of 1 ml capacity using a Perkin-Elmer 241 polarimeter. ^{1}H-NMR spectra were recorded with Varian T 60 (60 MHz) or Bruker WP 80 (80 MHz) instruments.

(*S*)-2-Acetoxy-3-methylbutanenitril (2b)[33]:

To a well stirred solution of (*S*)-2-acetoxy-3-methylbutanamide (**1b**; 19.1 g, 0.12 mol) in dry pyridine (19 ml) placed in an ice bath there is added dropwise trifluoroacetic anhydride (17 ml, 0.12 mol) at 0°C. The ice bath is removed and stirring is continued for 15 min. Then, ether (25 ml) is added and the mixture is stirred for 15 min. Finally, water (33 ml) is added, the top layer separated, and the aqueous layer extracted with ether (2 × 20 ml). The combined organic layers are washed with water (10 ml), dried with magnesium sulfate, and evaporated. The residue is distilled to afford pure **2b**: yield: 15.1 g (89%).

(*S*)-2-Acetoxypropanethioamide (3a):

Method A, using the Lawesson Reagent: To a stirred solution of (*S*)-2-acetoxypropanamide (**1a**; 10.4 g, 79.2 mmol) in dry dioxan (100 ml) is added Lawesson reagent (16.0 g, 39.6 mmol) and stirring is continued for 16 h. The unsoluble material is then filtered off and the filtrate is evaporated. The oily residue is treated with ice water (100 ml) and extracted with ether (3 × 50 ml), and the combined organic layers are washed with saturated sodium hydrogen carbonate solution till pH = 7. After drying with magnesium sulfate, filtration, and evaporation, the crude product is placed on a silica-gel column and eluted with petroleum ether/ethyl acetate (4:6) to give **3a**: yield: 8.37 g (72%).

(*S*)-2-Acetoxy-3-methylbutanethioamide (3b):

Method B, from the Nitrile: Hydrogen Sulfide is bubbled for 24 h through a solution of (*S*)-2-acetoxy-3-methylbutanenitril (**2b**; 14 g,

99 mmol) in dry ethanol (100 ml) containing triethanolamine (3 g, 20 mmol), at slightly elevated pressure. The solution is evaporated and the residue is taken up in ethyl acetate (100 ml). The organic layer is washed with water (3 × 15 ml), dried with magnesium sulfate, and evaporated to give practically pure **3b**, which can be recrystallised from petroleum ether/ethyl acetate; yield: 7.93 g (84%).

Ethyl (*S*)-2-(1-Acetoxyethyl)-thiazole-4-carboxylate (4a):

Ethyl (4RS)-2-[(1S)-1-Acetoxyethyl]-4-hydroxy-3,4-dihydrothiazole-4-carboxylate:

To a stirred solution of (*S*)-2-acetoxypropanethioamide (**3a**; 8.32 g, 56.4 mmol) and ethyloxirane (4.54 g, 63 mmol) in dry ethanol (50 ml) is added dropwise a solution of ethyl bromopyruvate (11.19 g, 57.4 mmol) in dry ethanol (30 ml). The mixture is heated at 60°C for 30 min. After cooling, the solution is evaporated, the residue is placed on a silica gel column, and the product eluted with petroleum ether/ethyl acetate (6:4); yield: 11.5 g.

Ethyl (S)-2-(1-Acetoxyethyl)-thiazole-4-carboxylate (**4a**): To the above crude ester (11.5 g, 44 mmol), trifluoroacetic anhydride (13.8 ml, 99.3 mmol) is added dropwise at 0°C. The mixture is stirred for 30 min, excess trifluoroacetic anhydride is removed in vacuo, and the residue is taken up in toluene (100 ml). The organic layer is washed with saturated sodium hydrogen carbonate till pH = 7. The organic extract is dried with magnesium sulfate and evaporated, and the oily residue is purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) to afford **4a**; yield: 9.63 g (73%).

Ethyl (*S*)-2-(1-Hydroxyethyl)-thiazole-4-carboxylate (5a):

To a stirred solution of ethyl (*S*)-2-(1-acetoxyethyl)-thiazole-4-carboxylate (**4a**; 9.5 g, 39 mmol) in anhydrous ethanol (70 ml) is added sodium ethoxide (0.034 g, 0.5 mmol) dissolved in ethanol (1 ml). The reaction is monitored by TLC. Then, acetic acid is added till pH = 6. The solvent is evaporated and the residue is taken up in toluene (100 ml). This solution is washed with saturated sodium hydrogen carbonate solution (10 ml) and with saturated sodium chloride solution (10 ml), dried with magnesium sulfate, and evaporated. Bulb-to-bulb destillation of the residue affords pure **5a**; yield: 7.25 g (92%).

For preparation of methyl carboxylates, methanol and sodium methoxide is used instead of ethanol and sodium ethoxide.

Ethyl (*R*)-2-(1-Azidoethyl)-thiazole-4-carboxylate (6a):

A mixture of diethyl diazenedicarboxylate (6.87 g, 39.4 mmol) and anhydrous toluene (40 ml) is added dropwise to a solution of ethyl (*S*)-2-(1-hydroxyethyl)-thiazole-4-carboxylate (**5a**; 7.2 g, 35.8 mmol), triphenylphosphine (10.3 g, 39.3 mmol), and hydrazoic acid (1.69 g, 39.3 mmol) in toluene (100 ml) at room temperature. The mixture is stirred overnight, the precipitate is filtered off, and the filtrate is evaporated. Purification of the residue by column chromatography (silica gel, petroleum ether/ethyl acetate, 7:3) gives **6a**; yield: 6.9 g (85%).

Ethyl (*R*)-2-(1-Aminoethyl)-thiazole-4-carboxylate (7a) and Ethyl (*R*)-2-(1-*t*-Butoxycarbonylaminoethyl)-thiazole-4-carboxylate (Boc-7a):

A solution of ethyl (R)-2-(1-azidoethyl)-thiazole-4-carboxylate (**6a**; 2.98 g, 13.17 mmol) in absolute ethanol (80 ml) is hydrogenated over 5% palladium-on-carbon (1.5 g) for 6 h at room temperature. After filtration and evaporation, the residue is placed on a silica gel column, which is eluted first with petroleum ether/ethyl acetate (4:6) to remove minor polar by-products. The second elution (dichloromethane/methanol, 9:1) furnishes **7a**; yield: 2.37 g (90%).

For analytical characterisation and HPLC analysis, compound **7a** (0.37 g, 1.84 mmol) is dissolved in dioxan (6 ml). Then, 1 normal potassium hydrogen carbonate solution (2 ml) and di-*t*-butyl dicarbonate (0.436 g, 2 mmol) are added at 0°C. The solution is stirred for 1 h. The dioxan is removed in vacuo and the aqueous phase is extracted with dichloromethane (3 × 5 ml). The combined organic layers are dried with magnesium sulfate and evaporated. Recrystallisation of the residue from petroleum ether/diethyl ether gives pure Boc-**7a**; yield: 0.446 g (81%).

Ethyl (*S*)-2-(1-Benzyloxycarbonylaminoethyl)-thiazole-4-carboxylate (*Z*-7a):

To a stirred mixture of ethyl bromopyruvate (0.198 g, 1.01 mmol) and dry acetone (1 ml) is added in one portion finely powdered *N*-benzyloxycarbonyl-(*S*)-alaninethioamide (**8a**; 0.241 g, 1.01 mol) at 0°C. After 5 min, the mixture becomes solid. The yellow solid is triturated with ice water and chloroform. Then, sodium hydrogen carbonate is added till pH = 7. The organic layer is separated and the aqueous layer is extracted with chloroform (2 × 5 ml). The combined organic layers are dried with magnesium sulfate for a short time, and evaporated. The oily residue (0.356 g) is immediately treated with trifluoroacetic anhydride (0.5 ml, 3.59 mmol) at −10°C and the mixture is stirred for 10 min at 0°C. Then, excess trifluoroacetic anhydride is removed in vacuo and the residue is taken up in dichloromethane (10 ml). The organic layer is washed with saturated sodium hydrogen carbonate till pH = 7, dried with magnesium sulfate, and evaporated. The crude product is submitted to column chromatography (silica gel, petroleum ether/ethyl acetate, 6:4) to give Z-**7a**; yield: 0.215 g (64%).

Ethyl (*S*)-2-(1-*t*-Butoxycarbonylamino-3-methylbutyl)-thiazole-4-carboxylate (Boc-7b):

To a stirred solution of *N*-*t*-butoxycarbonyl-(*S*)-leucinethioamide (**8b**; 1 g, 4.06 mmol) in dry acetone (6 ml) is added ethyl bromopyruvate (0.87 g, 4.50 mmol) at −10°C. Stirring is continued for 1 h below 0°C. The mixture is then poured into a well-stirred mixture of chloroform (20 ml) and water (20 ml), which is saturated with potassium hydrogen carbonate. The organic phase is separated and the aqueous layer is extracted with chloroform (3 × 10 ml). The combined organic layers are dried with magnesium sulfate, and evaporated. The residue is immediately dissolved in dry dichloromethane (5 ml). The solution is cooled to −20°C and pyridine (0.71 g, 9 mmol) and trifluoroacetic anhydride (0.57 ml, 4.1 mmol) are added with stirring. The temperature is allowed to rise to 0°C during 1 h. The mixture is worked up as described above; however, the combined organic layers are in addition washed with cold aqueous 1 normal potassium hydrogen sulfate (5 ml). Drying with magnesium sulfate and evaporation furnishes a crude product, which is purified by column chromatography (silica gel/petroleum ether/ethyl acetate, 8:2), to give Boc-**7b**; yield: 1.15 g (83%).

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