Monatshefte für Chemie 133, 41–58 (2002)

Monatshefte für Chemie
Chemical Monthly

A Preparatively Simple Access to Homochiral Heterocyclic α-Hydroxy Acids and their Derivatives

Klaus Burger[1,*], **Elisabeth Windeisen**[1], **Elisabeth Heistracher**[1], **Torsten Lange**[1], and **Abdel-Aleem H. Abdel-Aleem**[2]

[1] Department of Organic Chemistry, University of Leipzig, D-04103 Leipzig, Germany
[2] Department of Organic Chemistry, Faculty of Science, Menoufia University, Shebin El-Kom, Egypt

Summary. The synthesis of homochiral heterocyclic α-hydroxy acids starting from (*S*)- and (*R*)-malic acid using hexafluoroacetone as protecting and activating agent is described. The new compounds are useful building blocks for peptide and depsipeptide modification.

Keywords. Hexafluoroacetone; Malic acid; Thiazoles; α-Hydroxy acids; Dipeptide and tripeptide surrogates.

Introduction

α-Hydroxy acids, besides α-amino acids and carbohydrates, belong to the most important representatives of low molecular compounds of the naturally occurring chiral pool [1]. Although the chemistry of α-hydroxy acids never has gained the popularity of that of α-amino acids, they are of eminent importance because of their diversity of biological functions [2, 3].

They play a major part in the metabolism of human beings, animals (citric acid cycle [4]), plants, and microorganisms (glyoxylate cycle [5]), in the gluconeogenesis [6], as metabolites in the CO_2-fixing process of C_4 plants (*Hatch-Slack* cycle [7]), and as intermediates in the biogenesis of certain amino acids [3]. Pantoinic acid is a constituent of the vitamin pantothenic acid and of coenzym A, respectively [8]. Furthermore, α-hydroxy acids have been identified as substructures of molecular transport systems for metals [9]. Blespharismon acts as conjugation hormon of ciliates (*Blespharisma japonica*); the α-hydroxy group is essential for the hormon activity [10]. α-Hydroxy acids can be found not only as constituents of natural products, like depsipeptides [11], but are also present as substructures in man-made biologically active compounds like spasmolytica [12], pesticides [13], and insecticides [14].

Heterocyclic compounds, especially thiazol derivatives, exhibit a broad range of biological activities. The thiazol substructure is present in numerous natural

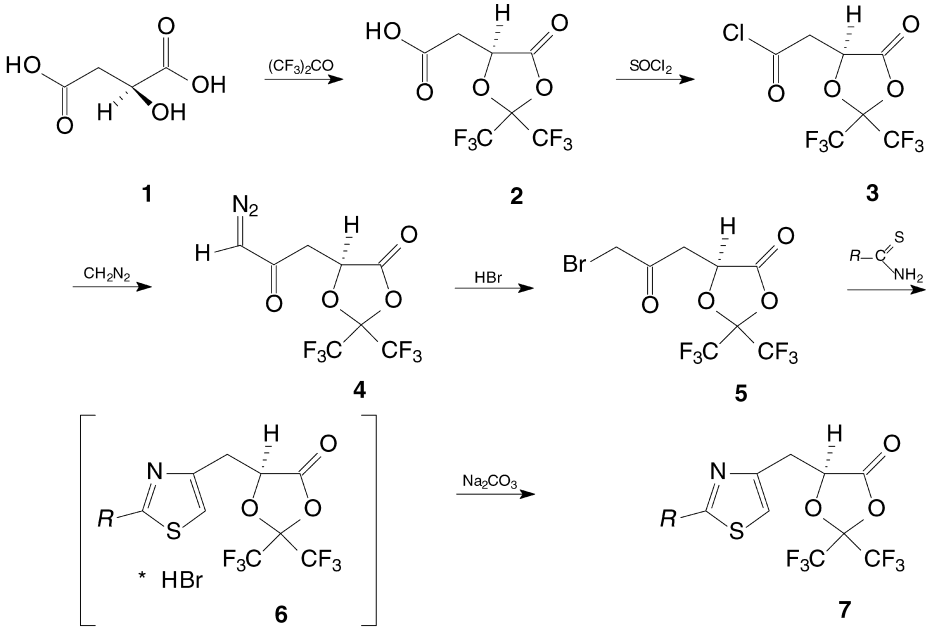
* Corresponding author. E-mail: burger@organic.chemie.uni-leipzig.de

products, drugs, and pesticides [15]. Some of the natural occurring thiazol derivatives exhibiting antibiotic activity are amino acids. As the first representative of this class of compounds, 3-amino-3-(thiazol-2-yl)propanoic acid was isolated from the antibiotic bottromycin (*Streptomyces bottropensis*).

Naturally occurring thiazol-substituted hydroxy acids, like 4-amino-4-(4-carboxythiazol-2-yl)-2-hydroxybutanoic acid, isolated from the macrocycle noshiheptid, are rare [17]. 3-(Thiazol-4-yl)-lactic acid derivatives are unknown to the best of our knowledge. Subsequently, we report on a new, preparatively simple, stereoconservative access to this class of compounds starting from (*S*)- and (*R*)-malic acid.

Results and Discussion

We found that a recently described protection/activation concept for the regioselective functionalization of multifunctional α-amino acids [18] can also be applied to α-hydroxy acids. Upon reaction with hexafluoroacetone, α-hydroxy acids give 2,2-*bis*-(trifluoromethyl)-1,3-dioxolan-4-ones in good to excellent yields [19]. In only one step, protection of both the α-hydroxy and the adjacent carboxy group can be achieved. Concomitantly, the α-carboxy group is activated towards nucleophiles. The new methodology tolerates a variety of functional groups in the side chain, *e.g.* the ω-carboxy groups of malic and citramalic acid remain



1 2 3 4 5 6 7

7a: *R* = H
7b: *R* = *p*-tolyl
7c: *R* = *p*-fluorophenyl
7d: *R* = *p*-chlorophenyl
7e: *R* = 2-furyl
7f: *R* = 2-thienyl
7g: *R* = (2-(*p*-tolyl)-4-trifluoromethyl-5-thiazolyl
7h: *R* = N-methyl-N-phenylamino

Scheme 1

unchanged and can be selectively derivatized [20]. On exclusion of moisture the dioxolan-4-ones are stable at room temperature for weeks; in a refrigerator, they can be stored for months.

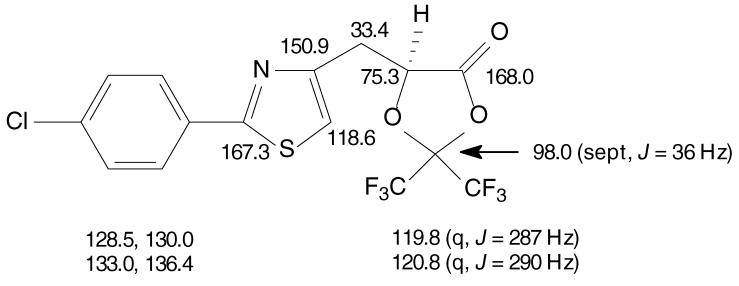
Compounds of type **2** can be applied for a regioselective functionalization of the α-carboxy function. Since protection and activation or funtionalization and deblocking of the hydroxy group can be achieved in each case in one step, the new strategy offers a save of steps compared to conventional strategies. Therefore, compounds of type **2** represent new versatile synthetic intermediates.

Upon heating with thionyl chloride, compound **2** is transformed into the acid chloride **3** [20]. By this operation the position of highest electrophilicity is transferred from the α- to the ω-carboxy group. Compound **3** represents a doubly activated malic acid derivative with two centers of different reactivity towards nucleophiles. Consequently, a new preparatively simple method for efficient regioselective derivatization of α,ω-dicarboxylic acids is now available [21].

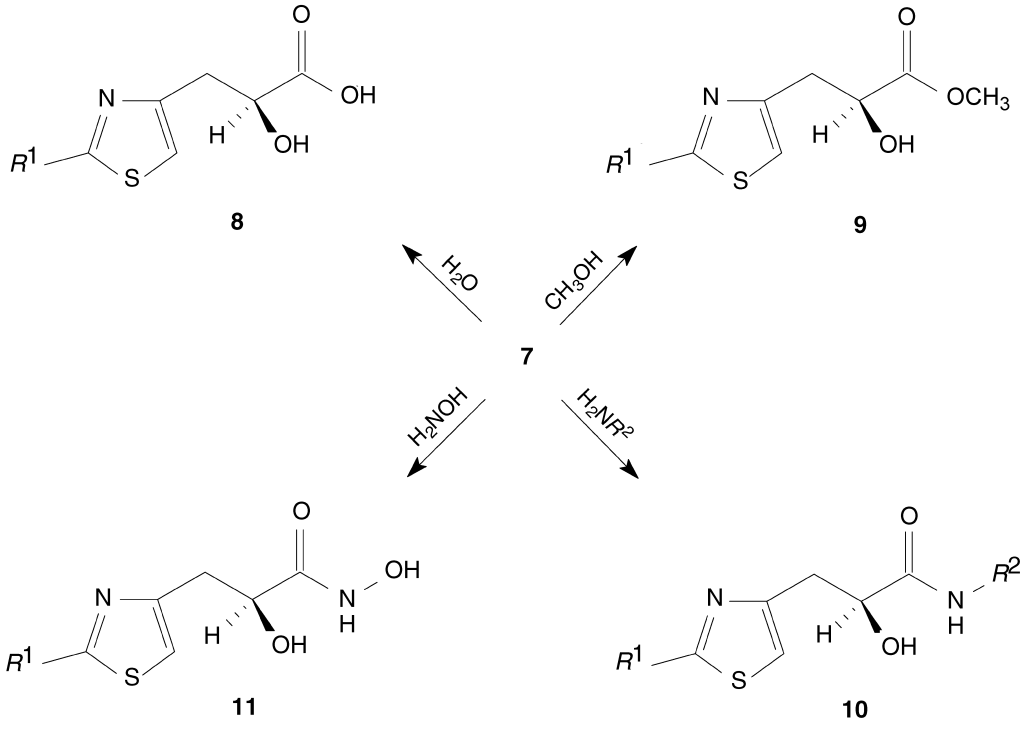
Compounds of type **3** exhibit the typical reactivity pattern of an acid chloride. Reaction with diazomethane affords the corresponding diazoketone (**3** $\rightarrow$ **4**). Treatment of **4** with conc. HBr leads to bromoketone **5** which offers a general access to heterocyclic α-hydroxy acids and their derivatives *via* a *Hantzsch* reaction [22].

Acetone proved to be the best solvent for the reaction of **5** with thioamides and thioureas. When the compounds are heated in acetone, the hydrobromides **6** crystallize after a short induction period. Upon stirring in a two-phase system (aqueous $NaHCO_3$/ether) the thiazolium salts were transformed into the thiazoles (**6** $\rightarrow$ **7**). By this work-up procedure the 2,2-*bis*-(trifluoromethyl)-1,3-dioxolan-4-ones **7** are obtained in high purity. The structure of the new compounds was proved by IR and NMR spectroscopy. An IR absorption in the region of 1865–1840 cm^{-1} unequivocally reveals the presence of a lactone moiety, whereas the ^{13}C NMR spectra show resonance signals for an unchanged dioxolan-4-one and the newly formed thiazole ring system. Exemplary, the ^{13}C NMR chemical shifts of **7d** (Scheme 2) are presented because of its structural similarity with the antiinflammatory drug Myalex® ((2-(4-chlorophenyl)-thiazol-4-yl)-acetic acid, [23]).

Because of the presence of a centre of chirality at C-5, the geminal trifluoromethyl groups are diastereotopic. They resonate as two quartets with a coupling constant of $^4J = 9$ Hz in the region of -2 to -4 ppm. Compounds **7** are synthetically valuable multifunctional building blocks, because they are hydroxy group protected, carboxy activated, homochiral heterocyclic α-hydroxy acid derivatives.



Scheme 2. ^{13}C chemical shifts (δ/ppm) of **7d**



8a: R^1 = *p*-fluorophenyl
8b: R^1 = *p*-chlorophenyl
8c: R^1 = 2-furyl
8d: R^1 = 2-thienyl

9a: R^1 = 2-furyl
9b: R^1 = 2-thienyl
11a: R^1 = *p*-fluorophenyl
11b: R^1 = *p*-chlorophenyl
11c: R^1 = 2-thienyl

10a: R^1 = *p*-fluorophenyl, R^2 = benzyl
10b: R^1 = *p*-chlorophenyl, R^2 = benzyl
10c: R^1 = 2-furyl, R^2 = H
10d: R^1 = 2-thienyl, R^2 = H

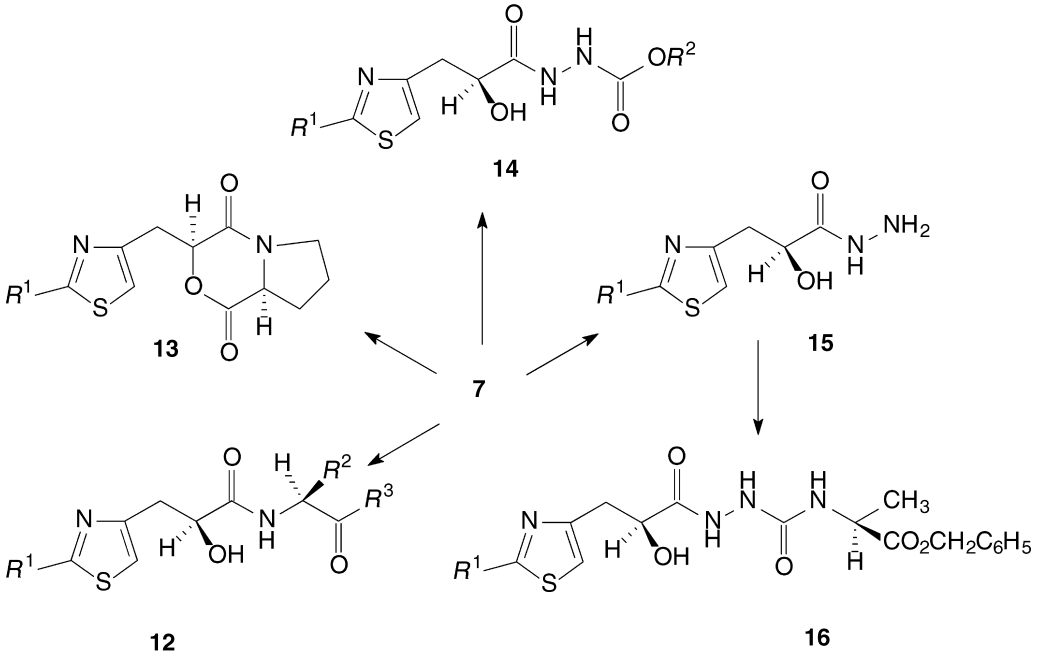
Scheme 3

In Scheme 3, some synthetically useful reactions of **7** are shown. Deprotection to α-hydroxy acids **8** can be achieved by heating in *THF*/water at 40°C. Esters **9** were obtained in nearly quantitative yield on heating with an excess of the corresponding alcohol. Reaction of **7** with ammonia, amines, and hydroxyl amine at room temperature provides ready access to amides **10** and hydroxamic acids **11**. Because of their broad spectrum of biological activities, the development of new synthetic routes to hydroxamic acid derivatives is of current interest [24–27]; peptide hydroxamic acid derivatives have been applied as enzyme inhibitors and metal chelating agents [28].

Aminolytic ring opening reaction of the lactones occurs efficiently when the resulting products are poorly soluble in the solvent used and therefore crystallize spontaneously. The compounds obtained are analytically pure in most cases; the progress of the reaction can be readily monitored by ^{19}F NMR spectroscopy.

All reaction steps starting from compound **1** studied so far were found to occur stereoconservatively. Consequently, the corresponding compounds of the (*R*)-series are obtainable by the same synthetic repertoire starting from (*R*)-malic acid. (*S*)- and (*R*)-configurated heterocyclic α-hydroxy acids and their derivatives, now readily available, are an interesting class of compounds *per se* because some of them are biologically active. On the other hand they are promising building blocks for the construction of peptidomimetics.

From the reaction of **7** with (*S*)-Phe-OMe, besides the expected compound **12** also the symmetrical diketopiperazine was obtained. To get satisfactory yields of **12**, an excess of (*S*)-Phe-OMe has to be added. Diketopiperazine formation can be avoided when the tertiary butylesters, benzylesters, or amides of the corresponding amino acids are used. When **7** was reacted with (*S*)-benzyl prolinate, after peptide bond formation a subsequent intramolecular transesterifacation could be observed. The structural assignment of the newly formed compounds **13** is based on their IR as well as ^{1}H and ^{13}C NMR data. The IR spectra show two absorptions at 1730 and



12a: R^1 = H, R^2 = Me, R^3 = O^{t}Bu
12b: R^1 = *p*-tolyl, R^2 = ^{i}Pr, R^3 = NH_2
12c: R^1 = *p*-fluorophenyl, R^2 = benzyl, R^3 = OMe
12d: R^1 = *p*-fluorophenyl, R^2 = Me, R^3 = O^{t}Bu
12e: R^1 = *p*-chlorophenyl, R^2 = benzyl, R^3 = O^{t}Bu

13a: R^1 = *p*-tolyl
13b: R^1 = *p*-fluorophenyl
13c: R^1 = *p*-chlorophenyl

14a: R^1 = *p*-chlorophenyl, R^2 = Me
14b: R^1 = *p*-chlorophenyl, R^2 = *p*-methoxybenzyl

15a: R^1 = *p*-tolyl
15b: R^1 = *p*-fluorophenyl
15c: R^1 = 2-furyl

16a: R^1 = *p*-fluorophenyl
16b: R^1 = 2-furyl

Scheme 4

1685 cm^{-1}, which we assign to a lactone and a lactame function. An absorption for an OH moiety could not be detected. The resonance signal for the methine proton ($\delta = 5.5$ ppm) was found in the same region as in the starting material, whereas in the ^{13}C spectrum the resonance absorption of the methine carbon was shifted downfield to $\delta = 77–78$ ppm. Furthermore, from the ^{13}C NMR spectra a pyrrolidine and a thiazol substructure can be extracted. The reason for the readily formed six-membered ring system is the low barrier of the *cis*/*trans* isomerization of the amide bond in the case of proline [29]. The development of new routes to chiral pyrrolidine derivatives is of current interest, because they are present as substructures in natural products as well as in a series of drugs [30, 31].

With methoxy carbonyl hydrazine, compounds **7** react to give azaglycine derivatives **14** [31]. On treatment of a solution of **7** in ether with a slight excess of hydrazine hydrate, the hydrazides **15** crystallize spontaneously. Compounds **15** react readily with isocyanates derived from amino acids, *e.g.* benzyl 2-isocyanatopropionate, to give tripeptidomimetics **16** which contain three different types of monomers: α-hydroxy acids, azaamino acids, and α-amino acids.

The design of compounds in which noncovalent forces stabilize secondary structures is an area of peptidomimetic chemistry of current interest [33, 34]. Two strategies have been developed so far. A series of oligomers has been synthesized, like β-peptides [35, 36], sulfonyl peptides [37], and peptoids [38] consisting of only one type of monomer. On the other hand, a growing number of reports deals with the synthesis of structured peptidomimetic compounds built from two or more types of monomers [39]. *Gellman et al.* have recently prepared β-peptide/depsipeptide hybrides that adopt antiparallel β-sheet structures [40]. *Sewald et al.* studied the influence of the replacement of one α-amino acid by its β-homo analogue on the secondary structure of cyclopeptides and found that they can act as γ-turn-mimetics [41].

The described synthetic sequence is well suited for the construction of libraries of small peptide surrogates [42] consisting of two or three types of monomers, respectively. Studies of secondary structure phenomena of peptidomimetics containing the new motifs and their ability to act as metal chelating agents will be reported elsewhere.

Experimental

General

Solvents were purified and dried prior to use. Reagents were used as purchased. Melting points (uncorrected) were determined on a Boetius heating table. Optical rotation indices ($[\alpha]_D^{21}$) were measured with a Polartronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C,H,N analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used; for all compounds, satisfactory elemental analyses were obtained. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by GC/MS on a HP5890 MSD. IR spectra were obtained using a Specord spectrometer (Carl-Zeiss, Jena). ^1H (200.041 or 300.075 MHz), ^{13}C (50.305 or 75.462 MHz), and ^{19}F NMR (188.205 or 282.33 MHz) spectra were recorded on a Varian Gemini 200 or a Varian Gemini 300 spectrometer. *TMS* was used as reference standard for ^1H and ^{13}C NMR spectra (internal), *TFA* for ^{19}F NMR spectra (external). Flash chromatography was performed using silica gel (32–63 μm).

((5S)-2,2-Bis-(trifluoromethyl)-4-oxo-1,3-dioxolan-5-yl)-acetic acid (**2**; $C_7H_4F_6O_5$)

For data, see Ref. [20].

((5S)-2,2-Bis-(trifluoromethyl)-4-oxo-1,3-dioxolan-5-yl)-acetyl chloride (**3**; $C_7H_3ClF_6O_4$)

For data, see Ref. [20].

(5S)-5-(3-Diazo-2-oxopropyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**4**; $C_8H_4F_6N_2O_4$)

To a stirred solution of diazomethane (15.0 mmol) in diethyl ether (10 cm^3), **3** (1.50 g, 5.0 mmol) in diethyl ether (10 cm^3) was slowly added with cooling (0°C). Then the solvent was evaporated *in vacuo* to give yellow crystals.

Yield: 92% (1.41 g); m.p.: 45°C; $[\alpha]_D^{21} = -50.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.85$ (dd, $J = 7.5$ Hz, $J = 16$ Hz, 1H, CH_2), 2.98 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H, CH_2), 5.17 (dd, $J = 3$ Hz, $J = 7.5$ Hz, 1H, CHO), 5.41 (s, 1H, CH=N_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 41.2$ (CH_2), 56.2 (CH=N_2), 71.6 (CHO), 97.9 (sept, $J = 36$ Hz, $C(CF_3)_2$), 119.0 (q, $J = 287$ Hz, CF_3), 119.8 (q, $J = 289$ Hz, CF_3), 167.8 (C=$O_{lactone}$), 187.0 (C=O_{ketone}) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -2.22$ (q, $J = 6$ Hz, 3F, CF_3), -2.06 (q, $J = 6$ Hz, 3F, CF_3) ppm; IR (KBr): $\nu = 2120$, 1845, 1630 cm^{-1}; MS (EI): $m/z = 306$ $[M]^+$, 278 $[M–N_2]^+$, 265 $[M–CHN_2]^+$, 237 $[M–CF_3]^+$, 69 $[CF_3]^+$, 55 $[C_3H_3O]^+$, 28 $[CO]^+$.

(5S)-5-(3-Bromo-2-oxopropyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**5**; $C_8H_5BrF_6O_4$)

To a stirred solution of diazoketone **4** (3.59 g, 10.0 mmol) in *THF* (25 cm^3) at -30°C, conc. HBr (7 cm^3) was added dropwise. After gas formation ceased, the mixture was warmed up to 0°C and the solvents and the HBr were evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 cm^3), washed with cold $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (eluent: $CHCl_3$: hexane = 8:1) and recrystallized from $CHCl_3$/pentane.

Yield: 81% (2.91 g); m.p.: 56°C; $[\alpha]_D^{21} = -23.6$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.26$ (dd, $J = 7$ Hz, $J = 18$ Hz, 1H, CH_2), 3.43 (dd, $J = 4$ Hz, $J = 18$ Hz, 1H, CH_2), 3.95 (s, 2H, CH_2Br), 5.12 (dd, $J = 4$ Hz, $J = 7$ Hz, 1H, CHO) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.0$ (CH_2Br), 40.8 (CH_2), 70.9 (CHO), 97.9 (sept, $J = 36$ Hz, $C(CF_3)_2$), 119.0 (q, $J = 287$ Hz, CF_3), 119.6 (q, $J = 289$ Hz, CF_3), 167.4 (C=$O_{lactone}$), 195.7 (C=O_{ketone}) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -2.31$ (q, $J = 7$ Hz, 3F, CF_3), -1.98 (q, $J = 7$ Hz, 3F, CF_3) ppm; IR (KBr): $\nu = 1845$, 1740 cm^{-1}; MS (EI): $m/z = 360$ $[M + H]^+$, 265 $[M–CH_2Br]^+$, 122 $[CH_2BrCO]^+$, 99 [M–HFA, $–CH_2Br]^+$.

(5S)-5-(Thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-ones (**7**); *general procedure*

To a stirred solution of **5** (1.79 g, 5.0 mmol) in acetone (5 cm^3) at 50°C a solution of the corresponding thioamide or N,N-disubstituted thiourea (5.0 mmol) in acetone (5 cm^3) was added dropwise. After 3 h the solvent was evaporated *in vacuo*, and the residue was suspended in diethyl ether (50 cm^3) and washed with ice-cold $NaHCO_3$ solution. The aqueous phase was extracted with diethyl ether (3x). The combined organic layers were washed with ice cold H_2O (3x) and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was recrystallized from $CHCl_3$/hexane.

(5S)-5-(Thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7a**; $C_9H_5F_6NO_3S$)

5 (1.80 g, 5.0 mmol) was reacted with thioformamide (0.31 g, 5.0 mmol) in acetone (10 cm^3). Yield: 39% (0.63 g); oil; $[\alpha]_D^{21} = -76.1$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.34$ (dd, $J = 7.5$ Hz, $J = 15.5$ Hz, 1H, CH_2), 3.53 (dd, $J = 4.5$ Hz, $J = 15.5$ Hz, 1H, CH_2), 5.15 (dd, $J = 4.5$ Hz, $J = 7.5$ Hz,

1H, CHO), 7.21 (d, $J = 2$ Hz, 1H, (C-5)$H_{thiazol}$), 8.82 (d, $J = 2$ Hz, 1H, (C-2)$H_{thiazol}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.1$ (CH_2), 74.3 (CH), 97.7 (sept, $J = 36$ Hz, $C(CF_3)_2$), 117.3 (C-$5_{thiazol}$), 118.8 (q, $J = 287$ Hz, CF_3), 119.7 (q, $J = 289$ Hz, CF_3), 149.2 (C-$4_{thiazol}$), 153.9 (C-$2_{thiazol}$), 167.2 (C=$O_{lactone}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -3.32$ (s, $(CF_3)_2$) ppm; IR (film): $\nu = 1845\,cm^{-1}$; MS (EI): $m/z = 321$ $[M]^+$, 98 $[C_4H_4NS]^+$, 69 $[CF_3]^+$.

(5S)-5-(2-(4-Methylphenyl)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7b**; $C_{16}H_{11}F_6NO_3S$)

5 (1.80 g, 5.0 mmol) was reacted with 4-methylthiobenzamide (0.75 g, 5.0 mmol) in acetone (10 cm^3). Yield: 90% (1.85 g); m.p.: 55°C; $[\alpha]_D^{21} = -44.4$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta =$ 2.38 (s, 3H, CH_3), 3.29 (dd, $J = 7$ Hz, $J = 15$ Hz, 1H, CH_2), 3.49 (dd, $J = 5$ Hz, $J = 15$ Hz, 1H, CH_2), 5.19 (dd, $J = 5$ Hz, $J = 7$ Hz, 1H, CHO), 7.04 (s, 1$H_{thiazol}$), 7.23 (m, 2H, arom), 7.84 (m, 2H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.4$ (CH_3), 33.7 (CH_2), 74.4 (CHO), 97.6 (sept, $J = 36$ Hz, $C(CF_3)_2$), 116.2 (C-$5_{thiazol}$), 118.8 (q, $J = 288$ Hz, CF_3), 119.7 (q, $J = 289$ Hz, CF_3), 126.5 (C-2_{tolyl}), 129.7 (C-3_{tolyl}), 138.7 (C-4_{tolyl}), 144.7 (C-1_{tolyl}), 149.2 (C-$4_{thiazol}$), 167.3, 169.0 (C=$O_{lactone}$, C-$2_{thiazol}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -2.23$ (s, $(CF_3)_2$) ppm; IR ($CHCl_3$): $\nu = 1840\,cm^{-1}$; MS (EI): $m/z =$ 411 $[M]^+$, 363 [M–F, –CO]$^+$, 342 $[M–CF_3]^+$, 188 [M–HFA, –COCHO]$^+$, 118 $[CH_3C_6H_4CNH]^+$.

(5S)-5-(2-(4-Fluorophenyl)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7c**; $C_{15}H_8F_7NO_3S$)

5 (1.80 g, 5.0 mmol) was reacted with *p*-fluorothiobenzamide (0.77 g, 5.0 mmol) in acetone (10 cm^3). Yield: 95% (1.97 g); m.p.: 58°C; $[\alpha]_D^{21} = -11.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.47$ (dd, $J = 6$ Hz, $J = 16$ Hz, 1H, CH_2), 3.61 (dd, $J = 5$ Hz, $J = 16$ Hz, 1H, CH_2), 5.56 (dd, $J = 5$ Hz, $J = 6$ Hz, 1H, CHO), 7.24 (dd, $J = 9$ Hz, $J = 9$ Hz, 2H, arom), 7.97 (s, 1$H_{thiazol}$), 8.00 (dd, $J = 5$ Hz, $J = 9$ Hz, 2H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.4$ (CH_2), 75.3 (CHO), 98.0 (sept, $J = 36$ Hz, $C(CF_3)_2$), 116.8 (d, $J = 22$ Hz, C-$3_{fluorophenyl}$), 118.1 (C-$5_{thiazol}$), 119.8 (q, $J = 286$ Hz, CF_3), 120.8 (q, $J = 289$ Hz, CF_3), 129.2 (d, $J = 9$ Hz, C-$2_{fluorophenyl}$), 130.8 (d, $J = 3$ Hz, C-$1_{fluorophenyl}$), 150.7 (C-$4_{thiazol}$), 164.7 (d, $J = 249$ Hz, C-$4_{fluorophenyl}$), 167.5, 168.0 (C=$O_{lactone}$, C-$2_{thiazol}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -33.79$ (tt, $J = 5$ Hz, $J = 10$ Hz, 1$F_{fluorophenyl}$), -3.66 (q, $J = 9$ Hz, 3F, CF_3), -3.47 (q, $J = 9$ Hz, 3F, CF_3) ppm; IR (KBr): $\nu = 1855\,cm^{-1}$; MS (EI): $m/z = 415$ $[M]^+$, 346 $[M–CF_3]^+$, 192 [M–HFA, –COCHO]$^+$, 122 $[FC_6H_4CNH]^+$, 71 $[CH_2COCHO]^+$.

(5S)-5-(2-(4-Chlorophenyl)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7d**; $C_{15}H_8ClF_6NO_3S$)

5 (1.80 g, 5.0 mmol) was reacted with *p*-chlorothiobenzamide (0.85 g, 5.0 mmol) in acetone (10 cm^3). Yield: 90% (1.94 g); m.p.: 61°C; $[\alpha]_D^{21} = -32.9$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (acetone-d_6): $\delta = 3.48$ (ddd, $J = 0.5$ Hz, $J = 6$ Hz, $J = 15.5$ Hz, 1H, CH_2), 3.62 (ddd, $J = 0.5$ Hz, $J = 5.5$ Hz, $J = 15.5$ Hz, 1H, CH_2), 5.59 (dd, $J = 5.5$ Hz, $J = 6$ Hz, 1H, CHO), 7.50 (m, 2H, arom), 7.94 (m, 2H, arom), 7.97 (s, 1$H_{thiazol}$) ppm; ^{13}C NMR (acetone-d_6): $\delta = 33.4$ (CH_2), 75.3 (CHO), 98.0 (sept, $J = 36$ Hz, $C(CF_3)_2$), 118.6 (C-$5_{thiazol}$), 119.8 (q, $J = 286$ Hz, CF_3), 120.8 (q, $J = 290$ Hz, CF_3), 128.5, 130.0, 133.0, 136.4 (C, arom), 150.9 (C-$4_{thiazol}$), 167.3, 168.0 (C-$2_{thiazol}$, C=$O_{lactone}$) ppm; ^{19}F NMR (acetone-d_6): $\delta = -3.49$ (m, 6F, $(CF_3)_2$) ppm; IR (KBr): $\nu = 1860\,cm^{-1}$; MS (EI): $m/z = 432$ $[M]^+$, 363 [M–CF_3]$^+$, 71 $[CH_2COCHO]^+$, 69 $[CF_3]^+$, 28 $[CO]^+$.

(5S)-5-(2-(2-Furyl)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7e**; $C_{13}H_7F_6NO_4S$)

5 (1.80 g, 5.0 mmol) was reacted with furan-2-thiocarboxamide (0.64 g, 5.0 mmol) in acetone (10 cm^3). Yield: 65% (1.26 g); oil; $[\alpha]_D^{21} = -46.9$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.28$ (dd,

$J = 8$ Hz, $J = 15$ Hz, 1H, CH_2), 3.48 (dd, $J = 4.5$ Hz, $J = 15$ Hz, 1H, CH_2), 5.18 (dd, $J = 4.5$ Hz, $J = 8$ Hz, 1H, CHO), 6.53 (m, $1H_{furan}$), 6.99 (m, $1H_{furan}$), 7.06 (s, $1H_{thiazol}$), 7.50 (m, $1H_{furan}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.5$ (CH_2), 74.1 (CHO), 97.5 (sept, $J = 36$ Hz, $C(CF_3)_2$), 109.4, 112.2 (C_{furan}), 116.0 (C-$5_{thiazol}$), 118.7 (q, $J = 287$ Hz, CF_3), 119.5 (q, $J = 289$ Hz, CF_3), 143.8, 148.8 (C_{furan}), 149.2 (C-$4_{thiazol}$), 158.6 (C-$2_{thiazol}$), 167.1 (C=$O_{lactone}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -3.25$ (m, 6F, $(CF_3)_2$) ppm; IR ($CHCl_3$): $\nu = 1845$ cm^{-1}; MS (EI): $m/z = 387$ $[M]^+$, 368 $[M–F]^+$, 318 $[M–CF_3]^+$, 71 $[CH_2COCHO]^+$.

(5S)-5-(2-(2-Thienyl)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7f**; $C_{13}H_7F_6NO_3S_2$)

5 (1.80 g, 5.0 mmol) was reacted with thiophene-2-thiocarboxamide (0.72 g, 5.0 mmol) in acetone (10 cm^3). Yield: 88% (1.77 g); oil; $[\alpha]_D^{21} = -39.9$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.25$ (dd, $J = 7.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.44 (ddd, $J = 0.5$ Hz, $J = 4.5$ Hz, $J = 15$ Hz, 1H, CH_2), 5.16 (dd, $J = 4.5$ Hz , $J = 7.5$ Hz, 1H, CHO), 6.98 (s, br, $1H_{thiazol}$), 7.04 (m, $1H_{thiophene}$), 7.36 (m, $1H_{thiophene}$), 7.48 (m, $1H_{thiophene}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.4$ (CH_2), 74.1 (CHO), 97.5 (sept, $J = 36$ Hz, $C(CF_3)_2$), 115.9 (C-$5_{thiazol}$), 118.7 (q, $J = 287$ Hz, CF_3), 119.6 (q, $J = 289$ Hz, CF_3), 126.8, 127.8, 127.9, 136.9 ($C_{thiophene}$), 148.9 (C-$4_{thiazol}$), 162.2 (C-$2_{thiazol}$), 167.1 (C=$O_{lactone}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -3.25$ (q, $J = 7$ Hz, 3F, CF_3), -3.19 (q, $J = 7$ Hz, 3F, CF_3) ppm; IR ($CHCl_3$): $\nu = 1845$ cm^{-1}; MS (GC/EI): $m/z = 403$ $[M]^+$, 180 [M–HFA, –CO, –CHO]$^+$, 71 $[CH_2COCHO]^+$.

(5S)-5-(2-(4-Methylphenyl)-4-trifluoromethyl-2-5′-bisthiazolyl-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7g**; $C_{20}H_{11}F_9N_2O_3S_2$)

5 (1.80 g, 5.0 mmol) was reacted with 4-methylphenyl-4-trifluoromethyl-thiazol-5-thiocarboxamide (1.51 g, 5.0 mmol) in acetone (10 cm^3). Yield: 96% (2.70 g); m.p.: 71°C; $[\alpha]_D^{21} = -30.0$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 3.33 (dd, $J = 7$ Hz, $J = 15$ Hz, 1H, CH_2), 3.50 (dd, $J = 5$ Hz, $J = 15$ Hz, 1H, CH_2), 5.16 (dd, $J = 5$ Hz, $J = 7$ Hz, 1H, CHO), 7.26 (m, 2H, arom), 7.29 (s, $1H_{thiazol}$), 7.86 (m, 2H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 33.1 (CH_2), 74.1 (CHO), 97.6 (sept, $J = 36$ Hz, $C(CF_3)_2$), 118.7 (q, $J = 287$ Hz, CF_3), 119.6 (q, $J = 289$ Hz, CF_3), 120.0 (C-$5_{thiazol}$), 120.6 ($CF_{3\ thiazol}$), 126.7, 129.4, 129.8 (C_{tolyl}), 132.8 (q, $J = 2$ Hz, C-$5_{thiazol}$), 140.1 (q, $J = 37$, C-$4_{thiazol}$), 142.0 (C_{tolyl}), 149.3 (C-$4_{thiazol}$), 155.4 (C-$2_{thiazol}$), 167.0, 168.9 (C=$O_{lactone}$, C-$2_{thiazol}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -2.17$ (s, br, 6F, $(CF_3)_2$), 18.65 (3F, $CF_{3\ thiazol}$) ppm; IR (KBr): $\nu = 1855$ cm^{-1}; MS (EI): $m/z = 562$ $[M]^+$, 339 [M–HFA, –CO, –CHO]$^+$.

(5S)-5-(2-(N-Methyl-N-phenylamino)-1,3-thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-one (**7h**; $C_{16}H_{12}F_6N_2O_3S$)

5 (1.80 g, 5.0 mmol) was reacted with N-methyl-N-phenyl-thiourea (0.89 g, 5.0 mmol) in acetone (10 cm^3). Yield: 60% (1.28 g); oil; $[\alpha]_D^{21} = -27.0$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.08$ (dd, $J = 7$ Hz, $J = 15$ Hz, 1H, CH_2), 3.23 (dd, $J = 4.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.49 (s, 3H, NCH_3), 5.09 (dd, $J = 4.5$ Hz, $J = 7$ Hz, 1H, CHO), 6.22 (s, $1H_{thiazol}$), 7.25 (m, 1H, arom), 7.33–7.48 (m, 4H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.9$ (CH_2), 74.3 (NCH_3), 97.6 (sept, $J = 36$ Hz, $C(CF_3)_2$), 105.0 (C-$5_{thiazol}$), 118.9 (q, $J = 287$ Hz, CF_3), 119.8 (q, $J = 290$ Hz, CF_3), 125.0, 126.6, 129.8, 144.8 (C, arom), 146.2 (C-$4_{thiazol}$), 167.6 (C=$O_{lactone}$), 170.4 (C-$2_{thiazol}$) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -3.19$ (q, $J = 8$ Hz, 3F, CF_3), -2.97 (q, $J = 8$ Hz, 3F, CF_3) ppm; IR (Film): $\nu = 2940$, 1845 cm^{-1}; MS (EI): $m/z = 426$ $[M]^+$, 349 $[M–C_6H_5]^+$, 334 $[349\text{-}CH_3]^+$, 91 $[C_7H_7]^+$.

Hydrolysis of 5-(Thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-ones (**8**); *general procedure*

7 (2.0 mmol) was heated under reflux for 3 h in a mixture of *THF*/H_2O or diethylether/H_2O (25 cm^3, 1:1). After removal of the solvent the residue was dissolved in CH_2Cl_2, washed with H_2O and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue recrystallized from acetone.

3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactic acid (**8a**; $C_{12}H_{10}FNO_3S$)

7c (0.83 g, 2.0 mmol) was heated in a *THF*/H_2O mixture. Yield: 60% (0.32 g); m.p.: 112°C; $[\alpha]_D^{21} = -7.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (acetone-d_6): $\delta = 3.16$ (dd, $J = 7.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.33 (ddd, $J = 1$ Hz, $J = 4$ Hz, $J = 15$ Hz, 1H, CH_2), 4.63 (dd, $J = 4$ Hz, $J = 7.5$ Hz, 1H, CHO), 7.26 (m, 2H, arom), 7.33 (s, br, $1H_{thiazol}$), 8.02 (m, 2H, arom) ppm; ^{13}C NMR (acetone-d_6): $\delta = 36.7$ (CH_2), 70.4 (CHO), 116.7 (d, $J = 22$ Hz, C, arom), 116.7 (C-$5_{thiazol}$), 129.2 (d, $J = 9$ Hz, C, arom), 131.1 (C, arom), 154.8 (C-$4_{thiazol}$), 164.5 (d, $J = 249$ Hz, C, arom), 166.6 (C-$2_{thiazol}$), 175.1 (C=O_{acid}) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -3.19$ (m) ppm; IR (KBr): $\nu = 3700$–2300, 3530, 3510, 1720, 1600, 1520 cm^{-1}; MS (EI): $m/z = 267$ $[M]^+$, 222 $[M–CO_2H]^+$, 192 [222–CHOH]$^+$, 71 $[CH_2COCHO]^+$, 45 $[CO_2H]^+$.

3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactic acid (**8b**; $C_{12}H_{10}ClNO_3S$)

7d (0.86 g, 0.2 mmol) was heated in a *THF*/H_2O mixture. Yield: 88% (0.50 g); m.p.: 116°C; $[\alpha]_D^{21} = -43.9$ ($c = 1.0$, acetone); ^{1}H NMR (acetone-d_6): $\delta = 3.16$ (ddd, $J = 0.5$ Hz, $J = 7.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.34 (ddd, $J = 0.5$ Hz, $J = 4.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.63 (dd, $J = 4.5$ Hz, $J = 7.5$ Hz, 1H, CHO), 7.37 (s, br, $1H_{thiazol}$), 7.51 (m, 2H, arom), 7.97 (m, 2H, arom) ppm; ^{13}C NMR (acetone-d_6): $\delta = 36.8$ (CH_2), 70.5 (CHO), 117.1 (C-$5_{thiazol}$), 128.6, 130.0, 133.3, 136.1 (C, arom), 155.0 (C-$4_{thiazol}$), 166.4 (C-$2_{thiazol}$), 175.2 (C=O_{acid}) ppm; IR (KBr): $\nu = 3400$–2700, 1730, 1600, 1530, 1500 cm^{-1}; MS (EI): $m/z = 284$ $[M]^+$, 239 $[M–CO_2H]^+$, 209 [239-CHOH]$^+$, 71 $[CH_2COCHO]^+$, 45 $[CO_2H]^+$.

3-(2-(2-Furyl)-1,3-thiazol-4-yl)-(S)-lactic acid (**8c**; $C_{10}H_9NO_4S$)

7e (0.77 g, 2.0 mmol) was heated in a diethyl ether/H_2O mixture. Yield: 79% (0.38 g); m.p.: 167°C; $[\alpha]_D^{21} = -27.7$ ($c = 1.3$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.94$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.12 (dd, $J = 4.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.35 (dd, $J = 4.5$ Hz, $J = 8.5$ Hz, 1H, CHO), 5.41 (s, br, 1H, OH), 6.68 (m, $1H_{furan}$), 7.04 (m, $1H_{furan}$), 7.35 (s, $1H_{thiazol}$), 7.85 (m, $1H_{furan}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 35.8$ (CH_2), 69.3 (CHO), 108.7, 112.4 (C_{furan}), 115.2 (C-$5_{thiazol}$), 144.5 (C_{furan}), 153.9 (C-$4_{thiazol}$), 156.1 (C-$2_{thiazol}$), 160.1 (C_{furan}), 174.9 (C=O_{acid}) ppm; IR (KBr): $\nu = 3600$–3200, 3124, 1720, 1513 cm^{-1}; MS (EI): $m/z = 240$ $[M + H]^+$, 208 $[M–H_2O,–OH]^+$, 194 $[M–CO_2H]^+$, 154 $[M–C_4H_3O, –H_2O]^+$.

3-(2-(2-Thienyl)-1,3-thiazol-4-yl)-(S)-lactic acid (**8d**; $C_{10}H_9NO_3S_2$)

7f (0.81 g, 2.0 mmol) was heated in a diethyl ether/H_2O mixture. Yield: 63% (0.32 g); m.p.: 162°C; $[\alpha]_D^{21} = -34.9$ ($c = 0.4$, acetone); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.94$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.12 (ddd, $J = 1$ Hz, $J = 4.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.36 (dd, $J = 4.5$ Hz, $J = 8.5$ Hz, 1H, CHO), 7.14 (m, $1H_{thiophene}$), 7.30 (s, br, $1H_{thiazol}$), 7.60 (m, $1H_{thiophene}$), 7.67 (m, $1H_{thiophene}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 35.9$ (CH_2), 69.4 (CHO), 115.4 (C-$5_{thiazol}$), 126.8, 128.3, 128.4, 136.8 ($C_{thiophene}$), 153.5 (C-$4_{thiazol}$), 160.0 (C-$2_{thiazol}$), 175.0 (C=O_{acid}) ppm; IR (KBr): $\nu = 3600$–3200,

3130, 1710, 1510 cm^{-1}; MS (EI): $m/z = 255$ $[M]^+$, 210 $[M–CO_2H]^+$, 180 [210-CHOH]$^+$, 71 $[CH_2COCHO]^+$, 45 $[CO_2H]^+$.

Alcoholysis of 5-(Thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-ones (**7**); *general procedure*

A solution of **7** (2.0 mmol) in MeOH (25 cm^3) was stirred under reflux for 3 h. After removal of the solvent, the residue was distilled *in vacuo*.

Methyl 3-(2-(2-furyl)-1,3-thiazol-4-yl)-(S)-lactate (**9a**; $C_{11}H_{11}NO_4S$)

7e (0.77 g, 2.0 mmol) was heated in MeOH. Yield: 99% (0.50 g); m.p.: 64°C; $[\alpha]_D^{21} = -35.8$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.18$ (dd, $J = 7$ Hz, $J = 15$ Hz, 1H, CH_2), 3.31 (dd, $J = 4$ Hz, $J = 15$ Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 4.62 (dd, $J = 4$ Hz , $J = 7$ Hz, 1H, CHO), 6.50 (m, $1H_{furan}$), 6.95 (m, $1H_{furan}$), 7.01 (s, $1H_{thiazol}$), 7.48 (m, $1H_{furan}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 35.6$ (CH_2), 52.4 (OCH_3), 70.1 (CHO), 109.0, 112.2 (C_{furan}), 114.7 (C-$5_{thiazol}$), 143.6, 148.8 (C_{furan}), 152.7 (C-$4_{thiazol}$), 157.9 (C-$2_{thiazol}$), 174.1 ($C{=}O_{ester}$) ppm; IR (KBr): $\nu = 3100$, 1725, 1590, 1530, 1500 cm^{-1}; MS (EI): $m/z = 253$ $[M]^+$, 235 $[M–H_2O]^+$, 194 $[M–CO_2CH_3]^+$, 164 [194-CHOH]$^+$, 71 $[CH_2COCHO]^+$, 45 $[CO_2H]^+$.

Methyl 3-(2-(2-thienyl)-1,3-thiazol-4-yl)-(S)-lactate (**9b**; $C_{11}H_{11}NO_3S_2$)

7f (0.81 g, 2.0 mmol) was heated in MeOH. Yield: 91% (0.49 g); oil; $[\alpha]_D^{21} = -23.0$ ($c = 2.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 3.26$ (dd, $J = 6.6$ Hz, $J = 15$ Hz, 1H, CH_2), 3.31 (dd, $J = 4.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.65 (dd, $J = 4.5$ Hz , $J = 6.6$ Hz, 1H, CHO), 7.01 (s, $1H_{thiazol}$), 7.10 (m, $1H_{thiophene}$), 7.41 (m, $1H_{thiophene}$), 7.54 (m, $1H_{thiophene}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 35.3$ (CH_2), 52.7 (OCH_3), 70.2 (CHO), 114.8 (C-$5_{thiazol}$), 127.0, 128.0, 128.1 ($C_{thiophene}$), 152.1 (C-$4_{thiazol}$), 161.0 (C-$2_{thiazol}$), 174.2 ($C{=}O_{ester}$) ppm; IR (KBr): $\nu = 3500$–3210, 3108, 2954, 1741, 1219 cm^{-1}; MS (EI): $m/z = 269$ $[M]^+$, 251 $[M–H_2O]^+$, 210 $[M–C_2H_2S, –H]^+$, 180 $[M–CHOHCO_2CH_3]^+$, 115 $[CH_2CHOHCO_2CH_3]^+$.

Aminolysis of (5S)-5-(Thiazol-4-ylmethyl)-2,2-bis-(trifluoromethyl)-1,3-dioxolan-4-ones (**7**); *general procedure*

Method A: A solution of **7** (2 mmol) in diethyl ether (10 cm^3) was reacted at room temperature with an excess of the corresponding amine, hydroxylamine, hydrazine hydrate, or benzyl (*S*)-prolinate under stirring. After a few minutes the product began to crystallize. After completion of the reaction (^{19}F NMR analysis) the precipitate was filtered off, washed with diethyl ether, and dried *in vacuo*. *Method B*: A solution of **7** (2.0 mmol) in diethyl ether (10 cm^3) was reacted with an excess of the corresponding amino acid ester (5.0 mmol) at room temperature under stirring. After the reaction was complete (^{19}F NMR analysis) the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with H_2O (3x), and dried over $MgSO_4$. After filtration the solvent was evaporated, and the residue was recrystallized from hexane/$CHCl_3$ or from diethyl ether (**12c**).

N-(3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl)-benzylamine (**10a**; $C_{19}H_{17}FN_2O_2S$)

7c (0.83 g, 2.0 mmol) and benzylamine (0.21 g, 2.0 mmol) were reacted in diethyl ether (40 cm^3). Yield: 81% (0.58 g); m.p.: 135°C; $[\alpha]_D^{21} = -69.3$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.98$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.24 (dd, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 4.32 (d, $J = 6$ Hz, 2H, CH_2NH), 4.40 (dd, $J = 3.5$ Hz, $J = 8.5$ Hz, 1H, CHO), 5.80 (s, br, 1H, OH), 7.26 (m, $1H_{thiazol}$, 7H, arom), 7.96 (m, 2H, arom), 8.41 (t, $J = 6$ Hz, 1H, NH) ppm; ^{13}C NMR

(*DMSO*-d_6): $\delta = 36.1$ (CH_2CHOH), 41.5 (CH_2NH), 70.6 (CHO), 115.8 (C-$5_{thiazol}$), 115.9 (d, $J = 22$ Hz, C, arom), 126.3, 126.9, 127.9 (C, arom), 128.0 (d, $J = 9$ Hz, C, arom), 129.6 (d, $J = 3$ Hz, C, arom), 139.3 (C, arom), 154.2 (C-$4_{thiazol}$), 162.8 (d, $J = 248$ Hz, C, arom), 164.6 (C-$2_{thiazol}$), 172.9 ($C{=}O_{amide}$) ppm; IR (KBr): $\nu = 3330$, 1645, 1510 cm^{-1}, MS (EI): $m/z = 356$ $[M]^+$, 265 $[M–C_7H_7]^+$, 222 $[M–C_7H_7,–CONH]^+$, 193 [222-CHO]$^+$, 91 $[C_7H_7]^+$.

N-(3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl)-benzylamine (**10b**; $C_{19}H_{17}ClN_2O_2S$)

7d (0.86 g, 2.0 mmol) and benzylamine (0.21 g, 2.0 mmol) were reacted in diethyl ether (25 cm^3). Yield: 73% (0.54 g); m.p.: 141°C; $[\alpha]_D^{21} = -63.4$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.98$ (dd, $J = 8$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.24 (dd, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 4.32 (d, $J = 6$ Hz, 2H, CH_2NH), 4.40 (dd, $J = 3.5$ Hz, $J = 8$ Hz, 1H, CHO), 5.77 (s, br, 1H, OH), 7.24 (m, 5H, arom), 7.38 (s, 1H$_{thiazol}$), 7.53 (m, 2H, arom), 7.92 (m, 2H, arom), 8.40 (t, $J = 6$ Hz, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.3$ (CH_2CHOH), 41.7 (CH_2NH), 70.6 (CHO), 116.4 (C(5)$_{thiazol}$), 126.5, 127.0, 127.5, 128.0, 129.1, 131.9, 134.4, 139.4 (C, arom), 154.5 (C-$4_{thiazol}$), 164.5 (C-$2_{thiazol}$), 173.0 ($C{=}O_{amide}$) ppm; IR (KBr): $\nu = 3290$, 1650, 1550 cm^{-1}; MS (EI): $m/z = 373$ $[M]^+$, 239 $[M–C_7H_7, –CONH]^+$, 210 [239-CHO]$^+$, 106 $[C_7H_8N]^+$, 91 $[C_7H_7]^+$.

3-(2-(2-Furyl)-1,3-thiazol-4-yl)-(S)-lactamide (**10c**; $C_{10}H_{10}N_2O_3S$)

7e (0.78 g, 2.0 mmol) was reacted with conc. NH_3 (2 cm^3) in diethyl ether (20 cm^3). Yield: 83% (0.40 g); m.p.: 130°C; $[\alpha]_D^{21} = +200$ ($c = 0.1$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.87$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.16 (dd, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.23 (dd, $J = 3.5$ Hz, $J = 9$ Hz, 1H, CHO), 5.58 (s, br, 1H, OH), 6.66 (m, 1H$_{furan}$), 7.04 (m, 1H$_{furan}$), 7.21 (s, 1H$_{thiazol}$), 7.32 (s, 2H, NH_2), 7.82 (m, 1H$_{furan}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.2$ (CH_2), 70.5 (CHO), 108.7, 112.5 (C_{furan}), 115.0 (C-$5_{thiazol}$), 144.4, 148.4 (C_{furan}), 154.6 (C-$4_{thiazol}$), 156.0 (C-$2_{thiazol}$), 175.7 ($C{=}O_{amide}$) ppm; IR (KBr): $\nu = 3600–3000$, 1635, 1520, 1500 cm^{-1}; MS (EI): $m/z = 238$ $[M]^+$, 194 $[M–CONH_2]^+$.

3-(2-(2-Thienyl)-1,3-thiazol-4-yl)-(S)-lactamide (**10d**; $C_{10}H_{10}N_2O_2S_2$)

7f (0.81 g, 2.0 mmol) was reacted with conc. NH_3 (2 cm^3) in diethyl ether (20 cm^3). Yield: 79% (0.40 g); m.p.: 160°C; $[\alpha]_D^{21} = -40.0$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.85$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.12 (dd, $J = 3.6$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.22 (dd, $J = 3.6$ Hz, $J = 9$ Hz, 1H, CHO), 5.56 (m, 1H, OH), 7.18 (m, 1H$_{thiophene}$), 7.22 (s, 1H$_{thiazol}$), 7.31 (s, 2H, NH_2), 7.67 (m, 2H$_{thiophene}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.8$ (CH_2), 71.2 (CHO), 115.9 (C-$5_{thiazol}$), 127.4, 128.9, 129.0, 137.4 ($C_{thiophene}$), 154.8 (C-$4_{thiazol}$), 160.5 (C-$2_{thiazol}$), 176.3 ($C{=}O_{hydroxyamide}$) ppm; IR (KBr): $\nu = 3600$-3000, 1660 cm^{-1}; MS (FAB): $m/z = 255$ $[M + H]^+$, 210 $[M–CONH_2]^+$.

N-(3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl)-hydroxylamine (**11a**; $C_{12}H_{11}FN_2O_3S$)

7c (0.83 g, 2.0 mmol) and hydroxylamine (0.33 g, 10.0 mmol) were reacted in diethyl ether (20 cm^3). Yield: 89% (0.50 g); m.p.: 151°C; $[\alpha]_D^{21} = -23.3$ ($c = 0.3$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.93$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.15 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.29 (dd, $J = 4$ Hz, $J = 8.5$ Hz, 1H, CHO), 7.30 (m, 2H, arom), 7.34 (s, 1H$_{thiazol}$), 7.95 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.5$ (CH_2), 69.7 (CHO), 116.2 (C-$5_{thiazol}$), 116.2 (d, $J = 22$ Hz, C, arom), 128.4 (d, $J = 9$ Hz, C, arom), 130.0 (d, $J = 3$ Hz, C, arom), 154.4 (C-$4_{thiazol}$), 163.1 (d, $J = 248$ Hz, C, arom), 164.9 (C-$2_{thiazol}$), 169.6 ($C{=}O_{hydroxyamide}$) ppm; IR (KBr): $\nu = 3600–3000$, 1650, 1510 cm^{-1}; MS (EI): $m/z = 282$ $[M]^+$, 250 $[M–NHOH]^+$, 222 [250-CO]$^+$, 193 [222-CHO]$^+$, 71 $[CH_2COCHO]^+$, 43 $[CONH]^+$, 28 $[CO]^+$.

N-(3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl)-hydroxylamine (**11b**; $C_{12}H_{11}ClN_2O_3S$)

7d (0.86 g, 2.0 mmol) was reacted with hydroxylamine (0.33 g, 10.0 mmol) in diethyl ether (20 cm^3). Yield: 84% (0.50 g); m.p.: 149°C (decomp.); $[\alpha]_D^{21} = +64.0$ ($c = 1.0$, *DMSO*); ^{1}H NMR *DMSO*-d_6: $\delta = 2.94$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.16 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.30 (dd, $J = 4$ Hz, $J = 8.5$ Hz, 1H, CHO), 7.37 (s, $1H_{thiazol}$), 7.51 (m, 2H, arom), 7.90 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.5$ (CH_2), 69.7 (CHO), 116.6 (C-$5_{thiazol}$), 127.8, 129.3, 132.1, 134.6 (C, arom), 154.6 (C-$4_{thiazol}$), 164.7 (C-$2_{thiazol}$), 169.5 (C=$O_{hydroxyamide}$) ppm; IR (KBr): $\nu = 3600$–2400, 1655, 1530, 1500 cm^{-1}; MS (EI): $m/z = 299$ $[M]^+$, 238 $[M–H_2O,–CONH]^+$, 210 [238-CO]$^+$, 71 $[CH_2COCHO]^+$, 44 $[CO_2]^+$.

N-(3-(2-(2-Thienyl)-1,3-thiazol-4-yl)-(S)-lactoyl)-hydroxylamine (**11c**; $C_{10}H_{10}N_2O_3S_2$ (270.34))

7f (0.81 g, 2.0 mmol) and hydroxylamine (0.20 g, 6.0 mmol) were reacted in diethyl ether (10 cm^3). Yield: 89% (0.48 g); m.p.: 147°C; $[\alpha]_D^{21} = -43.9$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.98$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.20 (ddd, $J = 0.5$ Hz, $J = 4$ Hz, $J = 15$ Hz, 1H, CH_2), 4.38 (dd, $J = 4$ Hz, $J = 9$ Hz, 1H, CHO), 7.16 (m, $1H_{thiophene}$), 7.30 (s, br, $1H_{thiazol}$), 7.61 (m, $1H_{thiophene}$), 7.66 (m, $1H_{thiophene}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.8$ (CH_2), 70.3 (CHO), 115.6 (C-$5_{thiazol}$), 127.1, 128.6, 128.6, 137.6 ($C_{thiophene}$), 154.5 (C-$4_{thiazol}$), 160.6 (C-$2_{thiazol}$), 170.3 (C=$O_{hydroxyamide}$) ppm; IR (KBr): $\nu = 3500$–3000, 2900, 1635, 1530, 1520 cm^{-1}; MS (EI): $m/z = 270$ $[M]^+$, 238 $[M–NHOH]^+$, 210 [238-CO]$^+$, 181 [210-CHO]$^+$, 71 $[CH_2COCHO]^+$.

3-(1,3-Thiazol-4-yl)-(S)-lactoyl-(S)-alanine tert.-butyl ester (**12a**; $C_{13}H_{20}N_2O_4S$)

7a (0.64 g, 2.0 mmol) was reacted with (*S*)-alanine *tert*.-butyl ester (0.58 g, 4.0 mmol) in diethyl ether (10 cm^3). Yield: 60% (0.36 g); m.p.: 70°C; $[\alpha]_D^{21} = -30.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (d, $J = 7$ Hz, 3H, $CH_{3\ ala}$), 1.38 (s, 9H, $C(CH_3)_3$), 3.09 (dd, br, $J = 7.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.30 (dd, br, $J = 3.5$ Hz, $J = 15$ Hz, 1H, CH_2), 4.29–4.37 (m, 2H, CH_{ala}, CHO), 5.36 (d, $J = 4$ Hz, 1H, OH), 7.07 (dd, $J = 0.5$ Hz, $J = 1.5$ Hz, 1H, (C-5)$H_{thiazol}$), 7.37 (d, $J = 7.5$ Hz, 1H, NH), 8.70 (d, $J = 1.5$ Hz, 1H, (C-2)$H_{thiazol}$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.5$ ($CH_{3\ ala}$), 27.9 ($C(CH_3)_3$), 34.7 (CH_2), 48.2 (CH_{ala}), 71.6 (CHO), 81.8 ($C(CH_3)_3$), 115.2 (C-$5_{thiazol}$), 153.0, 153.5, (C-$4_{thiazol}$, C-$2_{thiazol}$), 171.8, 172.4 (C=$O_{amide,\ ester}$) ppm; IR (KBr): $\nu = 3600$–3040, 3370, 2980, 1745, 1665, 1515 cm^{-1}; MS (GC/EI): $m/z = 227$ $[M–OC(CH_3)]^+$, 199 [227-CO]$^+$, 156 [199-$NHCHCH_3$]$^+$, 128 [156-CO]$^+$, 57 $[C(CH_3)_3]^+$.

3-(2-(4-Methylphenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-(S)-valine amide (**12b**; $C_{18}H_{23}N_3O_3S$)

7b (0.82 g, 2 mmol) and (*S*)-valine amide (0.26 g, 2.2 mmol) were reacted in *THF* (25 cm^3). Yield: 69% (0.50 g); m.p.: 170°C (decomp.); $[\alpha]_D^{21} = -42.12$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 0.75$ (d, $J = 7$ Hz, 3H, $CH_{3\ val}$), 0.79 (d, $J = 7$ Hz, 3H, $CH_{3\ val}$), 1.93 (m, 1H, $CH(CH_3)_2$), 2.33 (s, 3H, $CH_{3\ tolyl}$), 2.93 (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.18 (dd, $J = 3$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.18 (m, 1H, CHO), 4.33 (m, 1H, CHO), 5.92 (d, $J = 5.5$ Hz, 1H, OH), 7.14 (s, br, 1H, NH), 7.28 (m, 2H, arom), 7.33 (s, $1H_{thiazol}$), 7.51 (s, br, 1H, NH), 7.54 (s, br, 1H, NH), 7.79 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 17.4$, 19.0 (CH_{3val}), 20.7 (CH_{3tolyl}), 31.0 ($CH(CH_3)_2$), 36.3 (CH_2), 56.3 ($CHCH(CH_3)_2$), 70.6 (CHO), 115.4 (C-$5_{thiazol}$), 125.8, 129.5, 130.5, 139.5 (C, arom), 154.0 (C-$4_{thiazol}$), 166.0 (C-$2_{thiazol}$), 172.4, 172.5 (C=O_{amide}) ppm; IR (KBr): $\nu = 3600$–3000, 2970, 1660, 1640, 1520 cm^{-1}; MS (EI): $m/z = 361$ $[M]^+$, 317 $[M–CONH_2]^+$, 246 [317-NHCH, $–CH(CH_3)_2$]$^+$, 218 [246-CO]$^+$.

3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-(S)-phenylalanine methyl ester (**12c**; $C_{22}H_{21}FN_2O_4S$)

7c (0.83 g, 2.0 mmol) was reacted with (*S*)-phenylalanine methyl ester (1.07 g, 6.0 mmol) in diethyl ether (20 cm^3). Yield: 79% (0.68 g); m.p.: 107°C; $[\alpha]_D^{21} = -29.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR

(acetone-d_6): $\delta = 2.96$ (dd, $J = 8.5$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.08 (dd, $J = 7$ Hz, $J = 14$ Hz, 1H, $CH_{2\,phe}$), 3.13 (dd, $J = 6$ Hz, $J = 14$ Hz, 1H, $CH_{2\,phe}$), 3.26 (dd, br, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.68 (s, 3H, OCH_3), 4.46 (ddd, $J = 3.5$ Hz, $J = 5$ Hz, $J = 8.5$ Hz, 1H, CHO), 4.79 (ddd, $J = 6$ Hz, $J = 7$ Hz, $J = 8$ Hz, 1H, CH_{phe}), 5.18 (d, $J = 5$ Hz, 1H, OH), 7.16 (m, 2H, arom), 7.19–7.29 (m, 5H, arom, $1H_{thiazol}$), 7.55 (d, $J = 8$ Hz, 1H, NH), 8.02 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.8$ (*C*H_2CHOH), 38.3 (CH_{2phe}), 52.4, 53.6 (CH_{phe}, OCH_3), 72.1 (CHO), 116.6 (C-$5_{thiazol}$), 116.8 (d, $J = 22$ Hz, C, arom), 127.6, 129.2, 129.3 (d, $J = 9$ Hz, C, arom), 130.1, 131.0 (d, $J = 3$ Hz, C, arom), 137.6 (C, arom), 155.2 (C-$4_{thiazol}$), 164.6 (d, $J = 248$ Hz, C, arom), 166.8 (C-$2_{thiazol}$), 172.4, 173.2 (C=$O_{amide,\,ester}$) ppm; ^{19}F NMR (acetone-d_6): $\delta = -33.53$ (m, 1F) ppm; IR (KBr): $\nu = 3290$, 1750, 1640, 1510 cm^{-1}; MS (FAB): *m/z* = 429 $[M + H]^+$, 370 [429-CO_2CH_3]$^+$, 222 [370-C_7H_7–CH–NH–CO]$^+$.

3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-(S)-alanine tert.-butyl ester
(**12d**; $C_{19}H_{23}FN_2O_4S$)

7c (0.83 g, 2.0 mmol) and (*S*)-alanine *tert*.-butyl ester (0.58 g, 4.0 mmol) were reacted in diethyl ether (20 cm^3). Yield: 66% (0.52 g); m.p.: 78°C; $[\alpha]_D^{21} = -80.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.28$ (d, $J = 7$ Hz, 3H, $CH_{3\,ala}$), 1.45 (s, 9H, C(CH_3)$_3$), 3.13 (dd, $J = 7.5$ Hz, $J = 15$ Hz, 1H, CH_2), 3.36 (dd, $J = 3.5$ Hz, $J = 15$ Hz, 1H, CH_2), 4.43 (dq, $J = 7$ Hz, $J = 7.5$ Hz, 1H, CH_{ala}), 4.47 (dd, $J = 3.5$ Hz, $J = 7.5$ Hz, 1H, C*H*OH), 5.47 (s, br, 1H, OH), 7.05 (s, $1H_{thiazol}$), 7.11 (m, 2H, arom), 7.52 (d, $J = 7.5$ Hz, 1H, NH), 7.87 (m, 2H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.5$ ($CH_{3\,ala}$), 27.9 (C(*C*H_3)$_3$), 35.0 (CH_2), 48.3 (CH_{ala}), 71.7 (CHOH), 81.9 (*C*(CH_3)$_3$), 115.3 (C-$5_{thiazol}$), 116.1 (d, $J = 22$ Hz, C, arom), 128.4 (d, $J = 9$ Hz, C, arom), 129.4 (d, $J = 3$ Hz, C, arom), 153.7, (C-$4_{thiazol}$), 163.9 (d, $J = 251$ Hz, C, arom), 167.2 (C-$2_{thiazol}$), 171.8, 172.4 (C=$O_{amide,\,ester}$) ppm; IR (film): $\nu = 3600$–3140, 2985, 1720, 1650, 1505 cm^{-1}; MS (EI): *m/z* = 394 $[M]^+$, 321 [M–OC(CH_3)$_3$]$^+$, 293 [321-CO]$^+$, 250 [293-$NHCHCH_3$]$^+$, 222 [250-CO]$^+$.

3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-(S)-phenylalanine tert.-butyl ester
(**12e**; $C_{25}H_{27}ClN_2O_4S$)

7d (0.86 g, 2.0 mmol) and (*S*)-phenylalanine *tert*.-butyl ester (0.66 g, 3.0 mmol) were reacted in diethyl ether (20 cm^3). Yield: 43% (0.42 g); m.p.: 85°C; $[\alpha]_D^{21} = -44.9$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.38$ (s, 9H, C(*C*H_3)$_3$), 2.99 (dd, $J = 6$ Hz, $J = 14$ Hz, $CH_{2\,phe}$), 3.01 (dd, $J = 6$ Hz, $J = 14$ Hz, 1H, $CH_{2\,phe}$), 3.12 (dd, $J = 7$ Hz, $J = 15$ Hz, 1H, CH_2CHOH), 3.31 (dd, $J = 3.5$ Hz, $J = 15$ Hz, 1H, CH_2CHOH), 4.43 (dd, $J = 3.5$ Hz, $J = 7$ Hz, 1H, CHO), 4.75 (ddd, $J = 6$ Hz, $J = 6$ Hz, $J = 8$ Hz, 1H, CH_{phe}), 5.43 (s, br, 1H, OH), 7.00 (m, 2H, arom), 7.05 (s, $1H_{thiazol}$), 7.11 (m, 3H, arom), 7.40 (m, 2H, arom), 7.45 (d, $J = 8$ Hz, 1H, NH), 7.82 (m, 2H, arom) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 27.8$ (C(*C*H_3)$_3$), 34.4 (*C*H_2CHOH), 38.2 ($CH_{2\ phe}$), 53.0 (CH_{phe}), 71.1 (CHO), 82.2 (*C*(CH_3)$_3$), 115.5 (C-$5_{thiazol}$), 126.7, 127.5, 128.1, 129.2, 129.2, 131.3, 136.0, 136.3 (C, arom), 153.6 (C-$4_{thiazol}$), 167.2 (C-$2_{thiazol}$), 170.0, 172.1 (C=$O_{amide,\ ester}$) ppm; IR (KBr): $\nu = 3500$–3100, 3405, 1730, 1640, 1525 cm^{-1}; MS (EI): *m/z* = 487 $[M]^+$, 431 [M–C(CH_3)$_3$]$^+$, 238 [M–$C_{14}H_{18}NO_3$]$^+$.

(3S,6S)-3-(2-(4-Methylphenyl)-thiazol-4-ylmethyl)-2,5-dioxo-1-aza-4-oxabicyclo[4.3.0]nonane
(**13a**; $C_{18}H_{18}N_2O_3S$)

7b (0.82 g, 2.0 mmol) and (*S*)-proline benzyl ester (0.99 g, 4.8 mmol) were reacted in diethyl ether (10 cm^3). Yield: 58% (0.40 g); m.p.: 191°C; $[\alpha]_D^{21} = -246.8$ ($c = 1.1$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.88$ (m, 2H, CH_2), 2.04 (m, 1H, CH_2), 2.25 (m, 1H, CH_2), 2.36 (m, 3H, $CH_{3\ tolyl}$), 3.15 (dd, $J = 9$ Hz, $J = 16$ Hz, 1H, CH_2CHOH), 3.45 (m, 2H, CH_2), 3.54 (dd, $J = 3.5$ Hz, $J = 16$ Hz, 1H, CH_2CHOH), 4.63 (dd, $J = 7$ Hz, $J = 8$ Hz, 1H, CH), 5.56 (dd, $J = 3.5$ Hz, $J = 9$ Hz, 1H, CHO), 7.31 (m, 2H, arom), 7.45 (s, $1H_{thiazol}$), 7.82 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.9$

($CH_{3\,tolyl}$), 22.7 (CH_2), 27.7 (CH_2), 31.3 (*C*H_2CHOH), 44.8 (CH_2), 57.2 (CH), 77.2 (CHO), 115.9 (C-$5_{thiazol}$), 126.0, 129.7, 130.5, 139.9 (C, arom), 152.6 (C-$4_{thiazol}$), 164.0 (C-$2_{thiazol}$), 166.6, 169.6 (C=$O_{dioxomorpholine}$) ppm; IR (KBr): $\nu = 1735, 1680\,cm^{-1}$; MS (FAB in NBA): $m/z = 365$ $[M + Na]^+$, 343 $[M + H]^+$, 218 $[343\text{-}C_6H_7NO_2]^+$.

(3S,6S)-3-(2-(4-Fluorophenyl)-thiazol-4-ylmethyl)-2,5-dioxo-1-aza-4-oxabicyclo[4.3.0]nonane
(**13b**; $C_{17}H_{15}FN_2O_3S$)

7c (0.83 g, 2.0 mmol) and (*S*)-proline benzyl ester (1.23 g, 6.0 mmol) were reacted in diethyl ether (10 cm^3).Yield: 38% (0.26 g); m.p.: 155°C; $[\alpha]_D^{21} = -214.6$ ($c = 0.2$, *DMSO*); ^{1}H NMR (acetone-d_6): $\delta = 1.96$ (m, 2H, CH_2), 2.18 (m, 1H, CH_2), 2.33 (m, 1H, CH_2), 3.18 (ddd, $J = 0.5$, $J = 9$ Hz, $J = 15.5$ Hz, 1H, C*H*$_2$CHOH), 3.53 (m, 2H, CH_2), 3.64 (dd, $J = 3.5$ Hz, $J = 15.5$ Hz, 1H, C*H*$_2$CHOH), 4.61 (dd, $J = 8$ Hz, $J = 8$ Hz, 1H, CH), 5.51 (dd, $J = 3.5$ Hz, $J = 9$ Hz, 1H, CHO), 7.25 (m, 2H, arom), 7.37 (s, br, $1H_{thiazol}$), 8.01 (m, 2H, arom) ppm; ^{13}C NMR (acetone-d_6): $\delta = 23.7$ (CH_2), 28.9 (CH_2), 32.4 (*C*H_2CHOH), 45.7 (CH_2), 58.3 (CH), 78.4 (CHO), 116.8 (C-$5_{thiazol}$), 116.8 (d, $J = 22$ Hz, C, arom), 129.2 (d, $J = 9$ Hz, C, arom), 131.2 (d, $J = 3$ Hz, C, arom), 154.2 (C-$4_{thiazol}$), 164.6 (d, $J = 248$ Hz, C, arom), 165.0 (C-$2_{thiazol}$), 166.6, 170.0 (C=$O_{dioxomorpholine}$) ppm; ^{19}F NMR (acetone-d_6): $\delta = -33.73$ (m) ppm; IR (KBr): $\nu = 1730, 1685\,cm^{-1}$; MS (FAB): $m/z = 347$ $[M + H]^+$, 222 $[347\text{-}C_6H_7NO_2]^+$.

(3S,6S)-3-(2-(4-Chlorophenyl)-thiazol-4-ylmethyl)-2,5-dioxo-1-aza-4-oxabicyclo[4.3.0]nonane
(**13c**; $C_{17}H_{15}ClN_2O_3S$)

7d (0.86 g, 2.0 mmol) and (*S*)-proline benzyl ester (0.82 g, 4.0 mmol) were reacted in diethyl ether (10 cm^3). Yield: 82% (0.59 g); m.p.: 197°C; $[\alpha]_D^{21} = -204.2$ ($c = 0.5$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.86$ (m, 2H, CH_2), 2.03 (m, 1H, CH_2), 2.22 (m, 1H, CH_2), 3.15 (dd, $J = 9$ Hz, $J = 16$ Hz, 1H, C*H*$_2$CHOH), 3.44 (m, 2H, CH_2), 3.53 (ddd, $J = 0.5$ Hz, $J = 3.5$ Hz, $J = 16$ Hz, 1H, C*H*$_2$CHOH), 4.60 (dd, $J = 8$ Hz, $J = 8$ Hz, 1H, CH), 5.54 (dd, $J = 3.5$ Hz, $J = 9$ Hz, 1H, C*H*OH), 7.51 (s, br, $1H_{thiazol}$), 7.54 (m, 2H, arom), 7.92 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 22.8$ (CH_2), 27.9 (CH_2), 31.4 (*C*H_2CHOH), 45.0 (CH_2), 57.4 (CH), 77.3 (CHO), 117.1 (C-$5_{thiazol}$), 127.9, 129.4, 132.1, 134.9 (C, arom), 153.2 (C-$4_{thiazol}$), 164.1 (C-$2_{thiazol}$), 165.3, 169.6 (C=$O_{dioxomorpholine}$) ppm; IR (KBr): $\nu = 1730, 1685\,cm^{-1}$; MS (EI): $m/z = 364$ $[M + H]^+$, 363 $[M]^+$, 319 $[M–CO_2]^+$, 70 $[C_4H_8N]^+$.

3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-azaglycine methyl ester
(**14a**; $C_{14}H_{14}ClN_3O_4S$)

7d (0.86 g, 2.0 mmol) was reacted with methoxy carbonyl hydrazine (0.18 g, 2.0 mmol) in diethyl ether (10 cm^3). Yield: 51% (0.36 g); m.p.: 178°C; $[\alpha]_D^{21} = -46.8$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.96$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.19 (dd, $J = 3.5$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.61 (s, 3H, OCH_3), 4.38–4.43 (m, 1H, CH), 5.74 (d, $J = 6.5$ Hz, 1H, OH), 7.45 (s, $1H_{thiazol}$), 7.49 (m, 2H, arom), 7.95 (m, 2H, arom), 9.04 (s, br, 1H, NH), 9.77 (s, br, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.3$ (CH_2), 51.8 (OCH_3), 69.9 (CH), 116.6 (C-$5_{thiazol}$), 127.6, 129.1, 132.0, 134.4 (C, arom), 154.2 (C-$4_{thiazol}$), 156.4 (C=O_{ester}), 164.6 (C-$2_{thiazol}$), 172.7 (C=$O_{hydrazide}$) ppm; IR (KBr): $\nu = 3300$, 1725, 1680, 1500 cm^{-1}; MS (EI): $m/z = 356$ $[M]^+$, 267 $[M–NHNHCO_2CH_3]^+$, 239 $[267\text{-}CO]^+$, 210 [239-CHO], 71 $[CH_2COCHO]^+$.

3-(2-(4-Chlorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-azaglycine-4-methoxy benzyl ester
(**14b**; $C_{21}H_{20}ClN_3O_5S$)

7d (0.86 g, 2.0 mmol) and 4-methoxybenzylcarbonyl hydrazine (0.36 g, 2.0 mmol) were reacted in diethyl ether (20 cm^3). Yield: 52% (0.48 g); m.p.: 150°C; $[\alpha]_D^{21} = -34.6$ ($c = 0.3$, *DMSO*); ^{1}H NMR

(*DMSO*-d_6): $\delta = 2.96$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.19 (m, 1H, CH_2CHOH), 3.76 (s, 3H, OCH_3), 4.40 (m, 1H, C*H*OH), 5.02 (s, 2H, OCH_2), 5.73 (s, br, 1H, OH), 6.94 (m, 2H, arom), 7.33 (m, 2H, arom), 7.45 (s, $1H_{thiazol}$), 7.56 (m, 2H, arom), 7.95 (m, 2H, arom), 9.13 (s, 1H, NH), 9.78 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.2$ (CH_2CHOH), 54.9 (OCH_3), 65.5 (OCH_2), 69.8 (CHO), 113.5 (C, arom), 116.4 (C-$5_{thiazol}$), 127.5, 128.3, 129.0, 129.7, 131.8, 134.3 (C, arom), 154.1 (C-$4_{thiazol}$), 155.8 (C=O_{ester}), 158.9 (C, arom), 164.4 (C-$2_{thiazol}$), 172.6 (C=$O_{hydrazide}$) ppm; IR (KBr): $\nu = 3600$–3100, 1725, 1670, 1640 1520 cm^{-1}; MS (EI): $m/z = 297$ [M–$CO_2CH_2C_6H_4OCH_3$]$^+$, 266 [297-$NHNH_2$]$^+$, 238 [266-CO]$^+$, 138 [$HOCH_2C_6H_4OCH_3$]$^+$, 121 [$CH_2C_6H_4OCH_3$]$^+$, 77 [C_6H_5]$^+$, 44 [CO_2]$^+$.

3-(2-(4-Methylphenyl)-1,3-thiazol-4-yl)-(S)-lactoyl hydrazine (**15a**; $C_{13}H_{15}N_3O_2S$)

7b (0.82 g, 2.0 mmol) and hydrazine hydrate (0.13 g, 2.5 mmol) were reacted in diethyl ether (30 cm^3). Yield: 91% (0.50 g); m.p.: 139°C; $[\alpha]_D^{21} = -58.7$ ($c = 1.1$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.33$ (s, 3H, CH_3), 2.90 (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.17 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.33 (dd, $J = 4$ Hz, $J = 9$ Hz, 1H, CHO), 4.74 (s, 2H, NH_2), 7.28 (m, 2H, arom), 7.30 (s, $1H_{thiazol}$), 7.79 (m, 2H, arom), 9.06 (s, br, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 21.0$ (CH_3), 36.6 (CH_2), 70.2 (CHO), 115.5 (C-$5_{thiazol}$), 126.1, 129.8, 130.8, 139.9 (C, arom), 154.4 (C-$4_{thiazol}$), 166.3 (C-$2_{thiazol}$), 172.1 (C=$O_{hydrazide}$) ppm; IR (KBr): $\nu = 3275$, 1665, 1635, 1540 cm^{-1}; MS (FAB): $m/z = 278$ [M + H]$^+$, 218 [M–$CONHNH_2$]$^+$.

3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl hydrazine (**15b**; $C_{12}H_{12}FN_3O_2S$)

7d (0.86 g, 2.0 mmol) was reacted with hydrazine hydrate (0.13 g, 2.5 mmol) in diethyl ether (30 cm^3). Yield: 90% (0.51 g); m.p.: 158°C; $[\alpha]_D^{21} = -54.7$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.89$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.15 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.25 (s, br, 2H, NH_2), 4.30 (m, 1H, C*H*OH), 5.50 (d, $J = 6$ Hz, 1H, OH), 7.31 (m, 2H, arom, $1H_{thiazol}$), 7.96 (m, 2H, arom), 8.98 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.3$ (CH_2), 70.0 (CHO), 115.9 (C-$5_{thiazol}$), 116.0 (d, $J = 22$ Hz, C, arom), 128.2 (d, $J = 9$ Hz, C, arom), 129.8 (d, $J = 3$ Hz, C, arom), 154.3 (C-$4_{thiazol}$), 162.9 (d, $J = 248$ Hz, C, arom), 164.7 (C-$2_{thiazol}$), 171.8 (C=$O_{hydrazide}$) ppm; IR (KBr): $\nu = 3270$, 3160, 1665, 1635, 1540, 1520 cm^{-1}; MS (FAB): $m/z = 282$ [M + H]$^+$, 222 [M–$CONHNH_2$]$^+$.

3-(2-(2-Furyl)-1,3-thiazol-4-yl)-(S)-lactoyl hydrazine (**15c**; $C_{10}H_{11}N_3O_3S$)

7e (0.78 g, 2.0 mmol) was reacted with hydrazine hydrate (0.13 g, 2.5 mmol) in diethyl ether (30 cm^3). Yield: 91% (0.46 g); foam; $[\alpha]_D^{21} = -22.7$ ($c = 1.5$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.86$ (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2), 3.12 (ddd, $J = 0.5$ Hz, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2), 4.28 (m, 1H, CHO), 4.30 (s, br, 2H, NH_2), 5.53 (s, br, 1H, OH), 6.67 (m, $1H_{furan}$), 7.04 (m, $1H_{furan}$), 7.31 (s, br, $1H_{thiazol}$), 7.84 (m, $1H_{furan}$), 9.01 (s, br, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 36.3$ (CH_2), 69.9 (CH), 108.7, 112.4 (C_{furan}), 115.0 (C-$5_{thiazol}$), 144.4, 148.3 (C_{furan}), 154.3 (C-$4_{thiazol}$), 156.2 (C-$2_{thiazol}$), 171.8 (C=$O_{hydrazide}$) ppm; IR (KBr): $\nu = 3600$–3000, 1660, 1510 cm^{-1}; MS (EI): $m/z = 253$ [M]$^+$, 222 [M–$NHNH_2$]$^+$, 194 [222-CO]$^+$.

Reaction of (S)-3-(1,3-thiazol-4-yl)-lactoyl hydrazine **15** *with (2S)-benzyl 2-isocyanatopropionates; general procedure*

(*S*)-3-(1,3-Thiazol-4-yl)-lactoyl hydrazine **15** (1.0 mmol) was reacted with the corresponding (*S*)-isocyanate in $CHCl_3$. After completion of the reaction (IR analysis) the solvent was evaporated *in vacuo*, and the residue was purified by chromatography (eluent: ethyl acetate).

3-(2-(4-Fluorophenyl)-1,3-thiazol-4-yl)-(S)-lactoyl-azaglycyl-(S)-alanine benzyl ester (**16a**; $C_{23}H_{23}FN_4O_5S$)

15b (0.28g, 1.0 mmol) and (*2S*)-benzyl 2-isocyanatopropionate (0.21 g, 1.0 mmol) were reacted in 40 cm^3 of $CHCl_3$ (40 ml). Yield: 62% (0.30 g); m.p.: 153°C; $[\alpha]_D^{21} = -32.2$ ($c = 1.4$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (d, $J = 7.5$ Hz, 3H, $CH_{3\ ala}$), 2.97 (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.19 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 4.28 (dq, $J = 7.5$ Hz, $J = 7.5$ Hz, CH_{ala}), 4.41 (dd, $J = 4$ Hz, $J = 9$ Hz, 1H, CHO), 5.14 (s, 2H, OCH_2), 6.68 (d, $J = 7.5$, 1H, NH), 7.33–7.41 (m, 7H, arom, $1H_{thiazol}$), 7.96–8.00 (m, 2H, arom, 1H, NH), 9.61 (s, br, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.0$ ($CH_{3\ ala}$), 36.4 (*C*H_2CHOH), 48.5 (CH_{ala}), 66.0 (OCH_2), 70.2 (CHO), 116.3 (C-$5_{thiazol}$), 116.3 (d, $J = 22$ Hz, C, arom), 127.9, 128.1 (C, arom), 128.5 (d, $J = 9$ Hz, C, arom), 128.6 (C, arom), 130.1 (d, $J = 3$ Hz, C, arom), 136.2 (C, arom), 154.4 (C-$4_{thiazol}$), 157.4 (C=O_{agly}), 163.2 (d, $J = 248$ Hz, C, arom), 165.0 (C-$2_{thiazol}$), 172.8, 173.3 (C=$O_{ester,\ hydrazide}$) ppm; IR (KBr): $\nu = 3360$, 3310, 1725, 1670, 1645, 1550, 1515 cm^{-1}; MS (FAB): $m/z = 487$ $[M + H]^+$, 308 $[M–C_{10}H_{12}NO_2]^+$, 222 [308-CONHNHCO]$^+$.

3-(2-(2-Furyl)-1,3-thiazol-4-yl)-(S)-lactoyl-azaglycyl-(S)-alanine benzyl ester (**16b**; $C_{21}H_{22}FN_4O_6S$)

15c (0.25 g, 1.0 mmol) was reacted with (*2S*)-benzyl 2-isocyanatopropionate (0.21 g, 1.0 mmol) in $CHCl_3$ (10 cm^3). Yield: 61% (0.28 g); m.p.: 173°C; $[\alpha]_D^{21} = -35.8$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.29$ (d, $J = 7$ Hz, 3H, $CH_{3\ ala}$), 2.93 (dd, $J = 9$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 3.14 (dd, $J = 4$ Hz, $J = 14.5$ Hz, 1H, CH_2CHOH), 4.26 (dq, $J = 7.5$ Hz, $J = 7$ Hz, CH_{ala}), 4.35 (m, 1H, CHO), 5.12 (s, 2H, OCH_2), 5.59 (s, br, 1H, OH), 6.64–6.68 (m, $2H_{furan}$), 7.05 (m, $1H_{furan}$), 7.29–7.37 (m, 5H, arom, 1H, C(5)-$H_{thiazol}$), 7.84 (s, 1H, NH), 7.95 (s, 1H, NH), 9.57 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 17.6$ ($CH_{3\ ala}$), 35.9 (*C*H_2CHOH), 48.1 (CH_{ala}), 65.6 (OCH_2), 69.7 (CHO), 108.5, 112.3 (C_{furan}), 115.0 (C-$5_{thiazol}$), 127.5, 127.7, 128.2, 135.8 (C, arom), 144.2, 148.2 (C_{furan}), 153.9 (C-$4_{thiazol}$), 155.9 (C=O_{agly}), 157.0 (C-$2_{thiazol}$), 172.4, 172.9 (C=$O_{ester,\ hydrazide}$) ppm; IR (KBr): $\nu = 3600–2900$, 3375, 3320, 1735, 1615, 1580, 1550 cm^{-1}; MS (FAB): $m/z = 459$ $[M + H]^+$, 280 $[M–C_{10}H_{12}NO_2]^+$, 222 [280-CONHNHCO]$^+$, 194 [222-CO]$^+$.

Acknowledgements

This work was supported by the *Deutsche Forschungsgemeinschaft* (*A.-A. H. Abdel-Aleem*), the *Fonds der Chemischen Industrie*, and the European Community (TMR-Projekt: Fluorine as a unique tool for engineering molecular properties).

References

[1] Seebach D, Kalinowski HO (1976) Nachr Chem Techn Lab **24**: 415
[2] Lehninger AL (1979) Biochemie, 2nd edn. VCH, Weinheim New York, p 340, 363, 514, 524, 576
[3] Umbarger HE (1978) Ann Rev Biochem **47**: 533
[4] a) Lowenstein JM (1967) In: Greenberg DM (ed) Metabolic Pathways, 3rd edn, vol 1. Academic Press, New York, p 147; b) Mathews CK, van Holde KE (1996) Biochemistry, 2nd edn. Benjamin Cummings, p 482
[5] Ref. [4b], p 506
[6] Ref. [4b], p 554
[7] a) Rawn JD (1983) Biochemistry. Harper & Row, New York, p 730; b) Ref. [5], p 613
[8] Ref. [4b], p 647
[9] Kawai S, Itoh K, Takagi S, Iwashita T, Nomoto K (1988) Tetrahedron Lett **29**: 1053
[10] Miyake A (1978) Curr Top Dev Biol **12**: 37

[11] Lübke K, Schröder E, Kloss G (1975) Antibiotika mit Peptolid-Struktur, In: Chemie und Biochemie der Aminosäuren, Peptide und Proteine II. Thieme, Stuttgart, p 140
[12] Roth HJ, Fenner H (1988) Arzneistoffe. Thieme, Stuttgart, p 401
[13] Kobek K, Focke M, Lichtenthaler HK (1988) Z Naturforsch **C 43**: 47
[14] Matsuda F, Tomiyoshi N, Yanagiya M, Matsumoto T (1988) Tetrahedron **44**: 7063
[15] Maeda R (1983) Chem Pharm Bull **31**: 3424
[16] Seto Y, Torii K, Bori K, Inabata K, Kuwata S, Watanabe H (1974) Bull Chem Soc Jpn **47**: 151
[17] Depaire H, Thomas JP, Brun A, Olesker A, Lukacs G (1977) Tetrahedron Lett **18**: 1397
[18] a) Burger K, Kluge M, Fehn S, Koksch B, Hennig L, Müller G (1999) Angew Chem **111**: 1513; (1999) Angew Chem Int Ed **38**: 1414; b) Rühl T, Hennig L, Hatanaka Y, Burger K, Welzel P (2000) Tetrahedron Lett **41**: 4555
[19] Weygand F, Burger K (1966) Chem Ber **99**: 2880
[20] a) Burger K, Windeisen E, Pires R (1995) J Org Chem **60**: 7641; b) Pires R, Burger K (1996) Synthesis 1277
[21] Burger K, Windeisen E, Lange T (unpublished results)
[22] For heterocyclic amino acids see: Burger K, Gold M, Neuhauser H, Rudolph M, Höß E (1992) Synthesis 1145
[23] a) Chalmers TM, Kellgren JH, Platt DS (1969) Ann Rheum Dis **28**: 595; b) Hepworth W, Newbould BB, Platt DS, Stacey GJ (1969) Nature **221**: 582
[24] Reddy AS, Kumar MS, Reddy GR (2000) Tetrahedron Lett **41**: 6285 and references cited therein
[25] Thouin E, Lubell WD (2000) Tetrahedron Lett **41**: 457 and references cited therein
[26] Barlaam B, Koza P, Berriot J (1999) Tetrahedron **55**: 7221
[27] Golebiowski A, Klopfenstein S (1998) Tetrahedron Lett **39**: 3397 and references cited therein
[28] Chen JJ, Spatola AF (1997) Tetrahedron Lett **38**: 1511
[29] Scherer G, Kramer ML, Schutkowski M, Reimer U, Fischer G (1998) J Am Chem Soc **120**: 5568
[30] a) Koning H, Speckamp WN (1996) In: Helmchen G, Hoffmann RW, Mulzer J, Schaumann E (eds) Stereoselective Synthesis (Houben-Weyl), E 21, vol 3. Thieme Stuttgart, p 1953; b) Speckamp WN, Moolenaar MJ (2000) Tetrahedron **56**: 3817
[31] Pilli RA, Russowsky D (1997) Trends Org Chem **6**: 101
[32] Ganthe J (1989) Synthesis 405
[33] Soth MJ, Nowick JS (1997) Curr Opin Chem Biol **1**: 120
[34] Gellman SH (1998) Acc Chem Res **31**: 173
[35] Seebach D, Overhand M, Kühnle FNM, Martinoni B, Oberer L, Hommel U, Widmer H (1996) Helv Chim Acta **79**: 913
[36] Appella DH, Christianson LA, Karle IL, Powell DR, Gellman SH (1996) J Am Chem Soc **118**: 13071
[37] Gennari C, Salom B, Potenza D, Longari C, Fioravanzo E, Carugo O, Sardone N (1966) Chem Eur J **2**: 644
[38] Armand P, Kirshenbaum K, Goldsmith RA, Farr-Jones S, Barron AE, Truong KTV, Dill KA, Mierke DF, Cohen FE, Zuckermann RN, Bradley EK (1998) Proc Natl Acad Sci USA **95**: 4309
[39] a) Soth MJ, Nowick JS (1999) J Org Chem **64**: 276 and references cited therein; b) Aubé J (ed) (2000) Recent Advances in Peptidomimetics. Tetrahedron Symposium-in-Print No 83, **56**: 9725
[40] Krauthäuser S, Christianson LA, Powell DR, Gellman SH (1997) J Am Chem Soc **119**: 11719
[41] Schumann F, Müller A, Koksch M, Müller G, Sewald N (2000) J Am Chem Soc **122**: 12009
[42] Dutta AS (1993) Small Peptides, Chemistry, Biology and Clinical Studies. Elsevier, Amsterdam London New York Tokyo

Received May 21, 2001. Accepted (revised) July 6, 2001