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Substituted 1,2-Thiazetidine 1,1-Dioxides. Synthesis of (*RS*)- and (*S*)-1,2-Thiazetidine-3-acetic Acid 1,1-Dioxide and its Reactions with Amino Acids and Dipeptides

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Summary. (*RS*)-2-*tert*-Butyldimethylsilyl-1,2-thiazetidine-3-acetic acid 1,1-dioxide prepared from (*RS*)-*S*-benzyl-β-homocysteine was condensed *via DCC/NHS* with various L-amino acid esters or dipeptide esters yielding *N*-silylated β-sultam peptides. A β-sultam active ester was isolated as an intermediate. Desilylation with *TBAF* in *THF* yielded stable *N*-unsubstituted products, and deprotection of the benzyl esters was achieved by catalytic hydrogenation. (*S*)-*S*-Benzyl-β-homocysteine was obtained by fractional crystallization of the brucine salt of the racemate and transformed into benzyl (*S*)-1,2-thiazetidine-3-acetate, which was on the other hand synthesized by an enantiospecific route from ω-benzyl *Boc-L*-aspartate. Some β-sultam peptides were prepared from the (*S*)-enantiomer, and finally some β-sultam peptides containing D-*Ala* units were obtained.

Keywords. 1,2-Thiazetidine 1,1-Dioxide; β-Sultam; β-Sultam Peptide.

Introduction

In a preceding paper we have reported about the synthesis and properties of *N*-alkylated and *N*-acylated derivatives of (*RS*)-1,2-thiazetidine-3-acetic acid 1,1-dioxide [1], and compared their properties with those of analogue β-lactam peptides [2]. Here we report about preparation and properties of another type of the so-called β-sultam peptides, especially those oligopeptides in which the β-sultam ring forms the N-terminus. The *N*-silylated (*RS*)-1,2-thiazetidine-3-acetic acid 1,1-dioxide or the (*S*)-enantiomer were used as appropriate building blocks.

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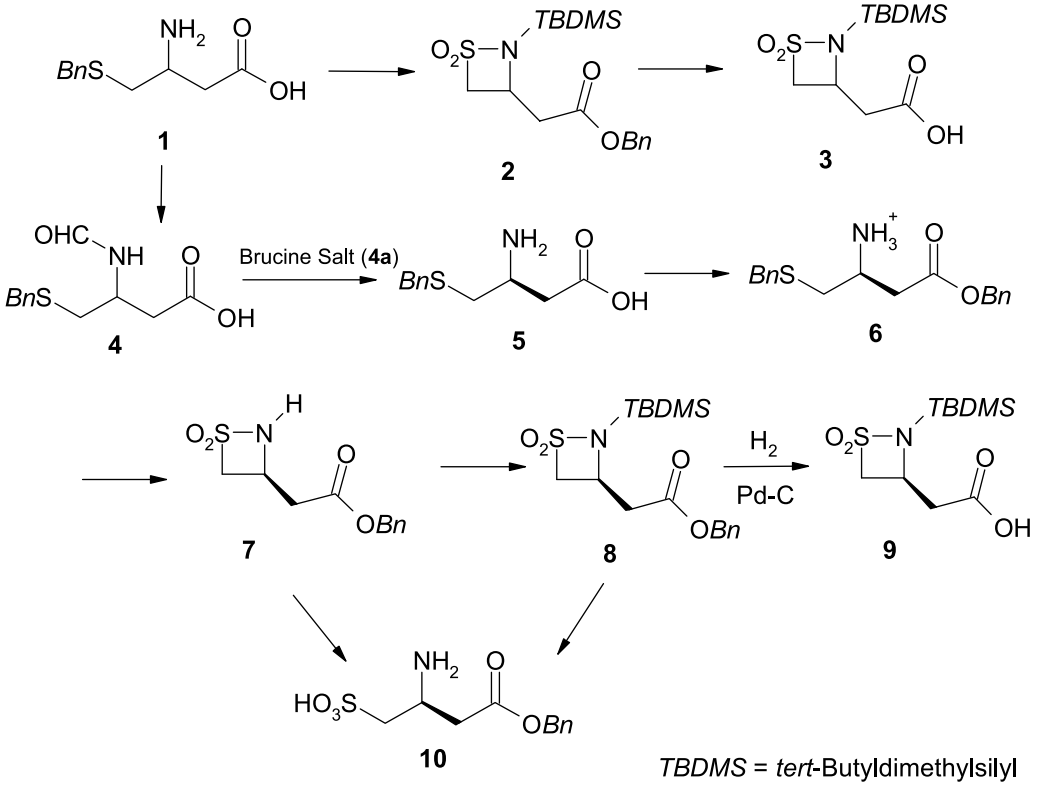
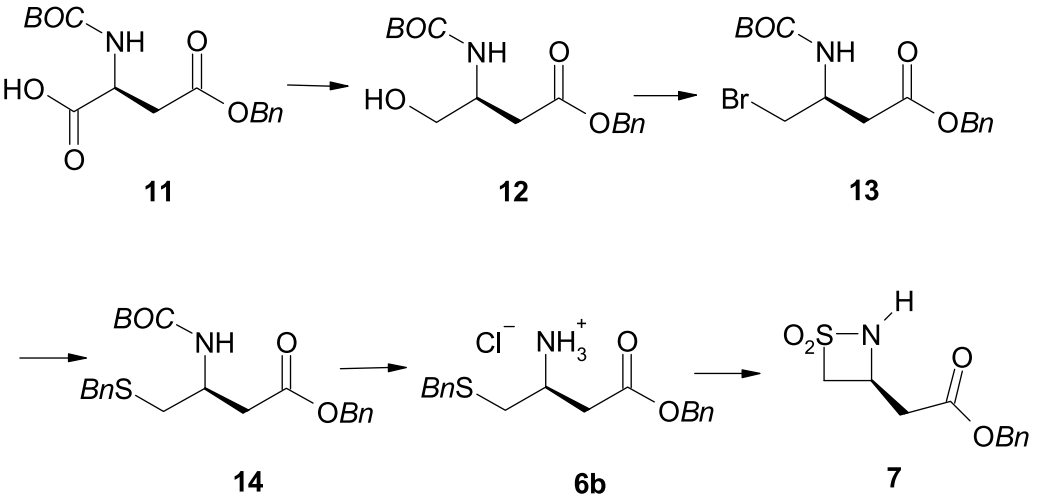
Results and Discussion

Synthesis

Benzyl (*RS*)-2-*tert*-butyldimethylsilyl-1,2-thiazetidine-3-acetate 1,1-dioxide (**2**) [3] was prepared from (*RS*)-*S*-benzyl-β-homocysteine (**1**) [4] by oxidative chlorination followed by ring closure with ammonia and silylation (Scheme 1). The acid **3** was prepared by hydrogenolysis in the presence of Pd–C. The (*S*)-enantiomer **8** was prepared by an analogue synthesis from (*S*)-*S*-benzyl-β-homocysteine (**5**). First, we tried to get **5** by enzymatic resolution of the benzyl ester of **1** [5] using lipase from *Candida cylindracea*, and porcine pancreatic lipase, but without success. It was finally obtained by fractional crystallization of the diastereomers of the brucine salt [6] of the *N*-formyl derivative **4** and deformylation. Compound **5** was then cyclized *via* the tosylate **6a** and the hydrochloride **6b** after oxidative chlorination to benzyl (*S*)-β-sultam-3-acetate (**7**). Silylation yielded **8**, which was debenzylated to the acid **9**. Compounds **7** and **8** were sensitive against hydrolysis, both were hydrolyzed to the taurine derivative **10** under mild conditions. In contrast, the acid **9** was obtained as a crystalline solid, which could be stored over a longer period. We could not isolate the pure (*R*)-enantiomer of **5** from the mother liquor of crystallization. In all experiments we isolated a mixture of diastereomers. The maximum ratio *R*:*S* was 6:4.



Scheme 1



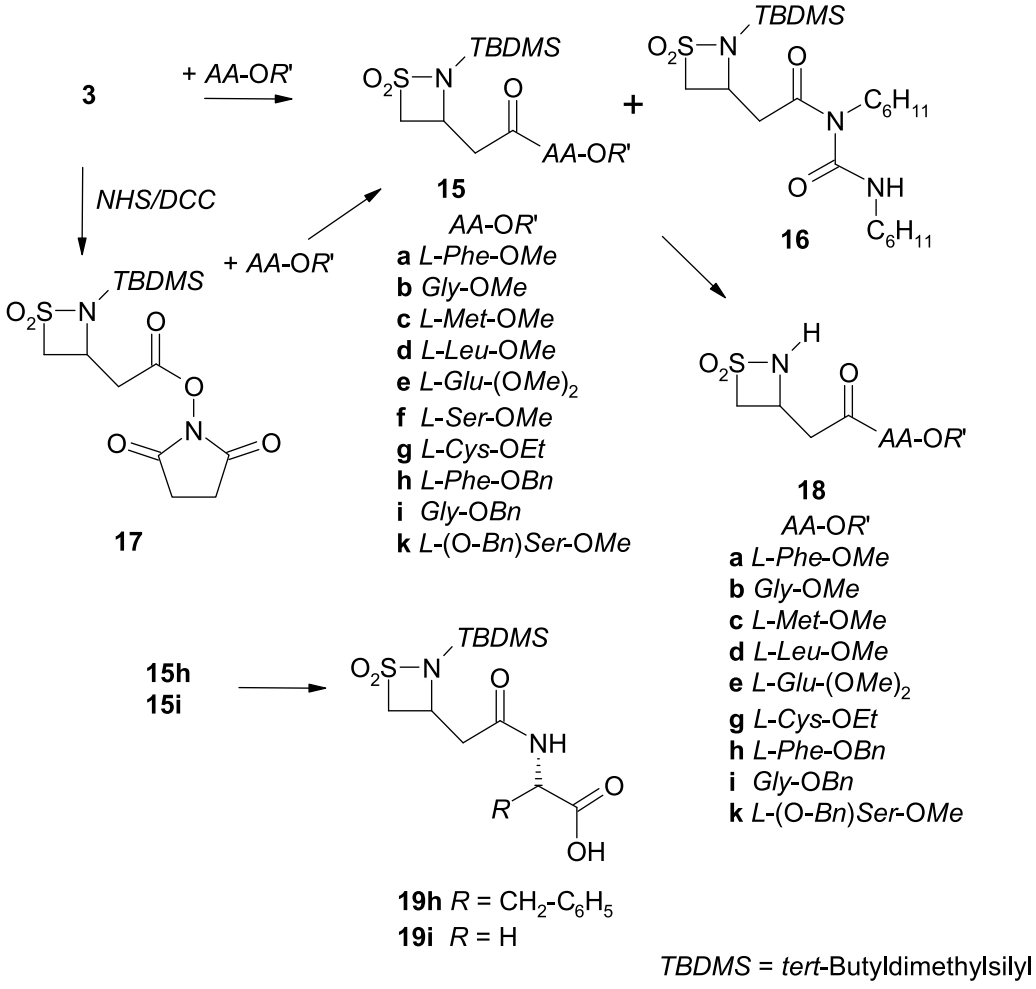
Scheme 2

To prove that the stereochemical assignment of **5** was correct, we prepared **7** by an unambiguous alternative selective route from *Boc-L-Asp*(O*Bn*) (**11**) [7]. Reduction with BH_3-*THF* gave the alcohol **12** [8], which was transformed into the bromo derivative **13** using P(*Ph*)$_3$ and CBr_4 [9]. Reaction with NaH and benzylmercaptane gave the *N-Boc* benzylmercapto derivative **14**, from which after deprotection with trifluoroacetic acid the hydrochloride **6b** was obtained. Finally, oxidative chlorination and ring closure with ammonia yielded the pure (*S*)-enantiomer **7**, with yield of 93% (Scheme 2), and being identical with the compound **7** prepared *via* the first described route from **5** (Scheme 1).

The coupling of **3** with amino acid esters in CH_2Cl_2 *via DCC* [10] at room temperature yielded beside little of the β-sultam peptides the *N*-acylurea **16** as the main product, caused by a basic catalyzed $N \rightarrow O$ acyl migration, for which the amino acid ester or *DCC* could have act as a catalyst. Even at low temperatures (ice/salt cooling) it was not possible to suppress this side reaction entirely. A more effective route for the synthesis of the β-sultam peptides we found being the modified carbodiimide procedure [11], by which 2 equivalents of *N*-hydroxysuccinimide (*NHS*) were added to the reaction mixture, and by which the yield of *N*-silylated β-sultam peptides raised up to 90% (Scheme 3).

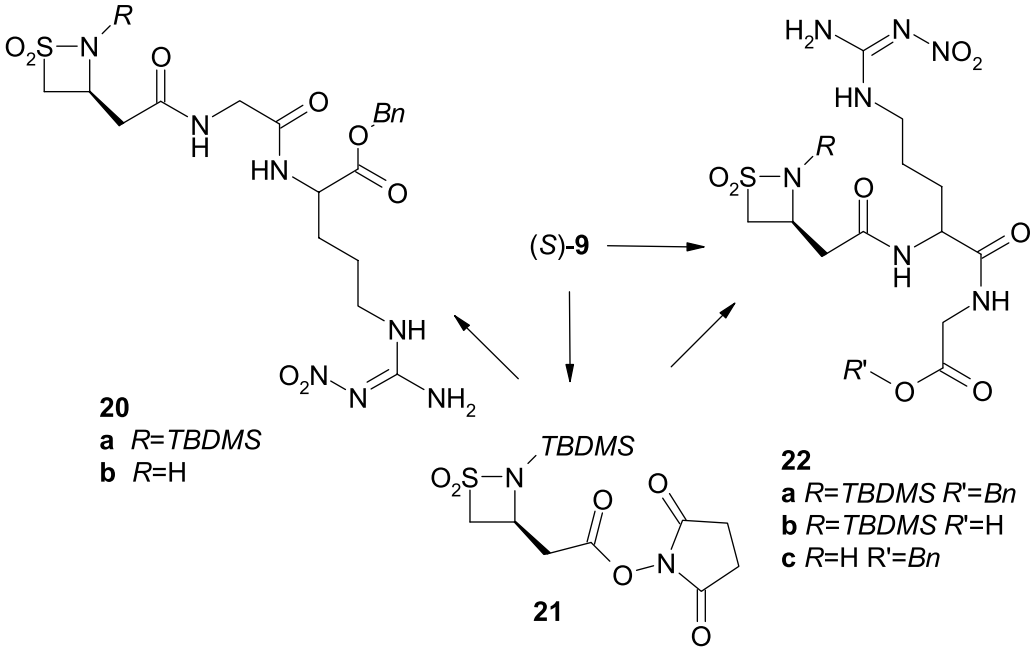
Compound **3** could also be condensed with *NHS*/*DCC* [12] to yield the active ester **17**, a stable and good crystallizable solid, which could be aminolysed by amino acid esters in CH_2Cl_2 yielding the β-sultam peptides **15**. However, there seems to be no advantage of this procedure compared with the modified carbodiimide procedure, as products had to be worked up in the same way by column chromatography (CC) and yields were finally significantly lower. Therefore, the *N*-silylated β-sultam peptides **15a**–**15k** finally were prepared by the modified method. They were isolated as viscous liquids, which could be stored in a refrigerator for several months.

Removal of protecting groups had to be done very carefully. All hydrolytic reactions of the ester groups with aqueous bases (NaOH, KOH) [13] were completely unsuitable, as hydrolysis of the β-sultam ring seemed to be the more



Scheme 3

favored reaction. Only the catalytic hydrogenation of **15h** and **15i** in *Et*OH with Pd–C/H_2 yielded the *N*-silylated β-sultam peptides **19h** and **19i** with nearly quantitative yields. Desilylation [14] of **15** was possible by treatment with *TBAF* and glacial acetic acid in *THF*. The crude products were purified by CC yielding the *N*-unprotected β-sultam peptide esters **18** with 70–80% yield. As **18a** and **18d** are relatively apolar, they were extracted by *Ac*O*Et* from the silica gel, while the more polar compounds **18b** and **18g** had to be extracted with *Me*OH. Compounds **18b** and **18g** and the benzyl ester **18h** were obtained as colorless crystals, whereas the methyl ester **18a** was isolated as a viscous liquid. Desilylation of **15f** was even successful, but the product decomposed during CC. Therefore, we prepared **15k**, and by desilylation **18k**, a stable crystalline product. But not only the hydrogenation of **18k** with Pd–C/H_2 in *Et*OH, but also deprotection with ammonium formiate [15] in *Et*OH did not yield the desired product. The benzyl ether seems to be stable against these procedures, as **18k** was in all experiments either reisolated or completely destroyed, probably by autoprotolytic decomposition [16].

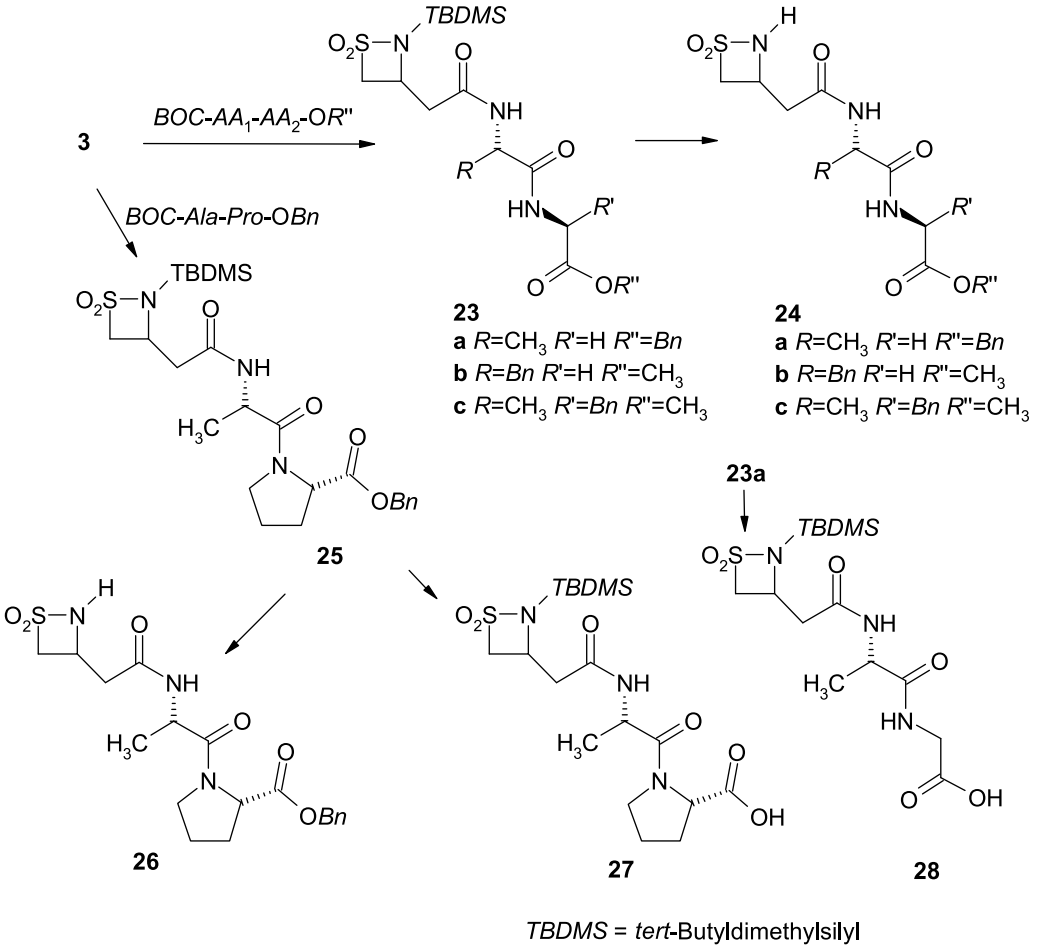


Scheme 4

Starting with the enantiomer (*S*)-**9** we prepared the sultam dipeptide **22a** either by direct coupling with the dipeptide L-(NO_2)*Arg*-*Gly*-O*Bn* or after isolation of **21**, which was then reacted with the dipeptide to **22a**. This was transformed by catalytic hydrogenation into the free acid **22b**, and by a desilylation reaction with *TBAF* into the *N*-deprotected **22c** (Scheme 4). Both are stable compounds. The isomeric compound **20a** was prepared from (*S*)-**9** with the dipeptide *Gly*-L-(NO_2)*Arg*-O*Bn*, and by desilylation with *TBAF* **20b** became accessible.

By reactions of *Boc*-dipeptides with compound **3** (Scheme 5) in the presence of *DCC* and *NHS* we obtained the *N*-silylated sultam dipeptides **23a**–**23c** with yields up to 60%. The free acid **28** was prepared from **23a** by hydrogenation of the benzyl ester group, whereas desilylation with *TBAF* yielded the *N*-deprotected compounds **24a**–**24c** as colorless crystalline compounds with yields of 30–60%. The proline derivatives **25**, **26**, and **27** were obtained by an analogue reaction with the parent dipeptide *Boc*-L-*Ala*-L-*Pro*-O*Bn*.

Finally, we studied the properties of some related compounds (Scheme 6). The sulfonyl urea **32** was obtained from the α,α-dimethylated β-sultam **29** [17] by reaction with phenyl isocyanate in the presence of dibutyltin dilaurate, and by reaction between **29** and benzyl bromoacetate **30** was prepared, which gave after hydrogenation and reaction with *Boc*-D-*Ala*-D-*Ala*-O*Bn* in the presence of pentafluorophenol and *EDC* the D-*Ala*-D-*Ala* β-sultam **31**. The D-*Ala*-D-*Ala* (*S*)-β-sultam **33**, on the other hand, was obtained by reaction between the appropriate dipeptide and **8**, and the D-*Ala* (*R*)-β-sultam **35** was synthesized by oxidative cyclization of the dipeptide **34**.



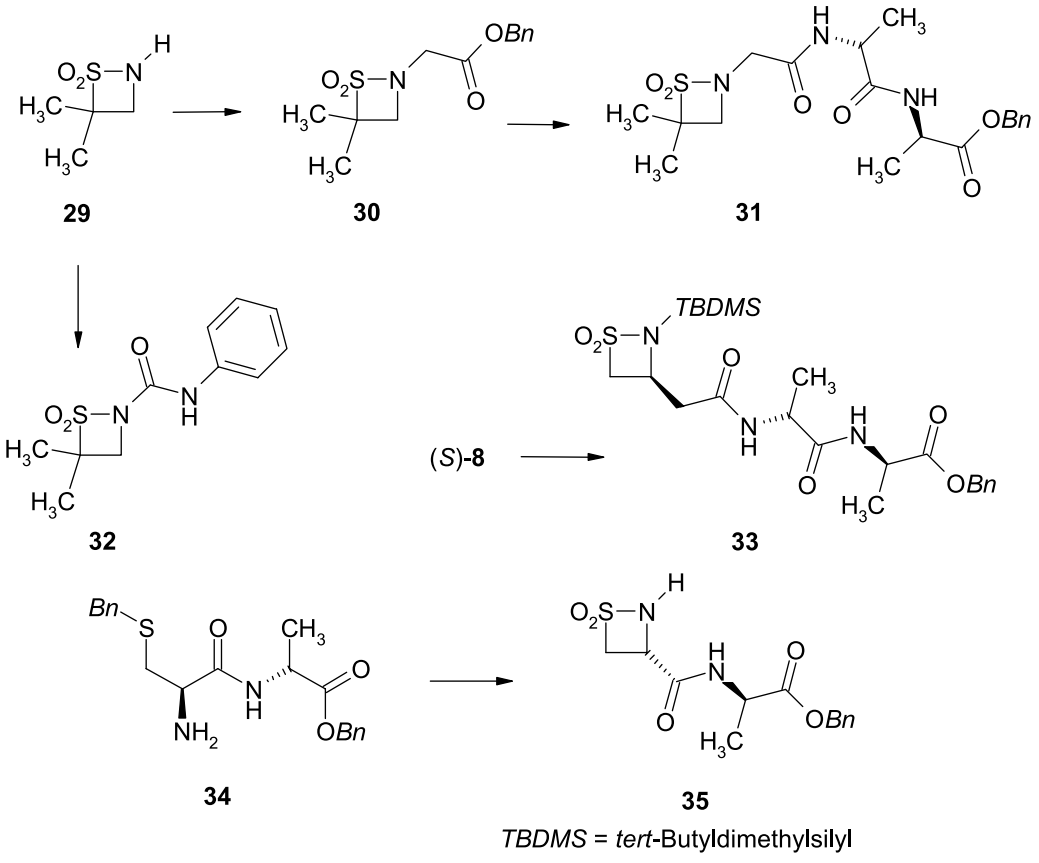
Scheme 5

Stereochemistry and Spectroscopy

The optical purity of the β-sultam **7** was checked using Pr(*hfc*)$_3$, and comparing the spectra of (*RS*)-**7** with those of (*S*)-**7** prepared *via* the brucine salt route (ee = 86%), and with those of (*S*)-**7** prepared from the aspartic ester **11** (ee > 95%). Furthermore, both compounds gave nearly identical CD spectra with a maximum at $\lambda = 244$ nm and minima at $\lambda = 241$ and 246 nm.

The optical purity of the β-sultam peptides was checked by HPLC using a ChiraSpher NT column. The diastereomeric mixtures of **15**, **18**, and **19** gave 2 peaks, ratio around 1:1, whereas from the compounds **20** and **22** only one peak was found establishing that only one enantiomer was formed (as expected). Therefore, we conclude the optical purity being about 95%.

All β-sultam peptides showed infrared absorptions of the sulfonyl group in the region of $\bar{\nu} = 1315$–1300 and 1160–$1140\,\mathrm{cm}^{-1}$. The absorptions near $3040\,\mathrm{cm}^{-1}$ are characteristic for 1,2-thiazetidine 1,1-dioxides, unsubstituted in position 4 [18]. In addition, there were found absorptions of the carbonyl groups from ester, acid, and amide at relevant positions. The IR spectra of free acids were characterized by



Scheme 6

carbonyl absorptions at $\bar{\nu} = 1740$ and $1630\,cm^{-1}$, and sulfonyl bands at $\bar{\nu} = 1300$ and $1160\,cm^{-1}$.

^1H NMR spectra of compounds **2**–**10** are characterized by the superposition of two ABX(M) systems. The first system originates from the protons 3-H, 4-H, and 4′-H, the second one belongs to the protons of the methylene group at C-3 (numbered as 5-H and 5′-H) and 3-H of the β-sultam ring. Characteristic coupling constants taken from the ^1H NMR spectra (300 MHz) of (*S*)-**7** with decoupling experiments were: $J_{5,5'} = 16.8$, $J_{4,4'} = 12.2$, $J_{3,4} = 5.5$, $J_{3,4'} = 7.0$, $J_{3,5} = 5.9$, and $J_{3,5'} = 7.6$ Hz.

Most ^1H and ^{13}C NMR spectra of the 1:1 mixtures of diastereomeric β-sultam peptides showed only one set of signals or small shift differences between 0 and 0.16 ppm of the two diastereomers. In some examples, the N–H (amide) showed for each diastereomer one separate proton signal, with differences in the shifts up to 0.2 ppm (**26**: $\delta = 6.32$ and 6.48 ppm, ratio 1:1). Furthermore, in some spectra we noticed differences in the shifts of 5-H and C-3/C-5 (**26**: $\delta = 2.55$ and 2.61 ppm, 5-H; $\delta = 37.70/37.89$ and 40.68/41.06 ppm, C-3 and C-5). In general, the ^1H NMR spectra included ABX patterns of the protons 3-H, 4-H, and 4′-H similar to those of other 2,3 disubstituted 1,2-thiazetidine 1,1-dioxides [3], sometimes with an additional coupling $^4J_{4'/N} = 3$ Hz [19]. Further characterization was done by ^{13}C and

^1H–^{13}C hetcor NMR spectra. As the R_f values of the diastereomers exhibited only very small differences, a separation by chromatographic methods was not successful. From the coupling constants, $J_{gem} = 12–13$, $J_{cis} = 8–9$, and $J_{trans} = 3–4.5$ Hz, we deduce in agreement with calculations (Hyperchem 5.0) that most of the β-sultam peptides exist with a slightly folded β-sultam ring and a more or less linear orientated peptide chain.

Some of the β-sultam peptides were tested by standard procedures as inhibitors of HLE or PPE but no remarkable effects were noticed.

Experimental

Melting points: *Linström* apparatus (uncorrected); IR spectra (KBr): Perkin-Elmer IR 1310, Beckman IR 4240, IR 33; ^1H NMR spectra: Varian T 60 (60 MHz), Bruker WP 80 (80 MHz), WP 250 (250 MHz), AM 400 (400 MHz), Varian U-300 (300 MHz), room temperature, internal *TMS*, values from 80 MHz spectra in $CDCl_3$, if not noted otherwise; MS spectra: Finnigan GC MS 4000, MAT 312, MAT 44 S; optical rotation: Polatronic D; CD spectra: Jasco spectropolarimeter J-710; elemental analyses: Institute of Pharmacy, or Chemisches Laboratorium, University of Freiburg or Greifswald: the results agreed with the calculated values within experimental error. Tetrahydrofuran (*THF*) was stored over $CaCl_2$ or KOH, then refluxed with Na and benzophenone, and distilled prior to use. Other solvents were dried/purified according to literature procedures. HPLC with Chiralpack AD, ChiraSpher NT, *n*-heptane/*Et*OH, 1 ml/min, room temperature, UV 260 nm.

Abbreviations: *Ac*O*Et* = Ethyl acetate; *Bu*Li = *n*-Butyllithium, 15% in hexane; CC = Column chromatography (Silica gel 60, Merck 7734, 0.063–0.200 mm); *DCC* = Dicyclohexyl carbodiimide; *DE* = Diethyl ether; *EDC* = *N*′-(3-Dimethylaminopropyl)-*N*-ethyl carbodiimide; *HMPT* = Hexamethylphosphortrisamide; *NHS* = *N*-Hydroxysuccinimide; *PE* = petroleum ether; *TBAF* = Tetrabutylammonium fluoride (1 *M* solution in *THF*), TLC = thin layer chromatography (DC Fertigplatten Silica gel 60 F_{254}, Merck 5549 or 5715).

For *(RS)-3-amino-4-(benzylthio)butyric acid* (**1**), *(RS)-benzyl 2-(tert-butyldimethylsilyl)-1,2-thiazetidine-3-acetate 1,1-dioxide* (**2**), *(RS)-2-(tert-butyldimethylsilyl)-1,2-thiazetidine-3-acetic acid 1,1-dioxide* (**3**), *and (RS)-4-(benzylthio)-3-(formylamino)butyric acid* (**4**) see Refs. [4], [3], [7] and [5].

(S)-4-(Benzylthio)-3-(formylamino)butyric acid brucine salt (**4a**) [5]

Compound **4** (12.6 g, 50 mmol), and brucine-dihydrate (23.0 g, 50 mmol) were dissolved in 100 cm^3 of warm acetone (40%), the solution was stored at 1–3°C for 24 h, and the precipitate was separated. Yield 12 g (35%); colorless crystals; mp 67–70°C (H_2O), (Ref. [5] 65–70°C); $[\alpha]_D^{20} = -15.2°\ cm^2\ g^{-1}$ ($c = 1.92$, *Et*OH), (Ref. [5] $[\alpha]_D^{20} = -16.3°\ cm^2\ g^{-1}$ ($c = 1.97$, *Et*OH)).

(S)-3-Amino-4-(benzylthio)butyric acid (**5**) [5]

From the brucine salt **4a**. Yield 2.5 g (72%); prismatic crystals; mp 195–196°C (*Et*OH/H_2O), (Ref. [5] 171–174°C); $[\alpha]_D^{20} = -59.2°\ cm^2\ g^{-1}$ ($c = 1.3$, 1 *N* HCl), (Ref. $[\alpha]_D^{20} = -64.0°\ cm^2\ g^{-1}$ ($c = 1.2$, 1 *N* HCl)).

The mother liquor of **4a** was evaporated, and the residue was purified as described. Yield 3.0 g (40%); mixture 60:40 of *R*:*S*; mp 195–197°C (H_2O); $[\alpha]_D^{20} = +24.5°\ cm^2\ g^{-1}$ ($c = 1.2$, 1 *N* HCl).

Benzyl (S)-3-amino-4-(benzylthio)butanoate tosylate (**6a**, $C_{25}H_{29}NO_5S_2$)

Compound **5** (5.1 g, 20 mmol), 4.5 g of p-toluenesulfonic acid monohydrate (24 mmol), and 12.19 g of benzylalcohol (113 mmol) in 150 cm^3 of $CHCl_3$ were refluxed for 20 h in a water separator. The solution was concentrated to 1/3, 200 cm^3 of *DE* were added, and after cooling to 3°C, the precipitate

was separated. Yield 6.3 g (88%); colorless crystals; mp 111–112°C ($CHCl_3$/*PE*); $[\alpha]_D^{20} = -4.5°\ cm^2\ g^{-1}$ ($c = 1.12$, $CHCl_3$).

Benzyl (S)-3-amino-4-(benzylthio)butanoate hydrochloride (**6b**, $C_{18}H_{22}ClNO_2S$)

a) Compound **6a** (6.39 g, 12.9 mmol) was dissolved in a solution of Na_2CO_3 (120 cm^3, 10%), the solution was extracted with 2 × 100 cm^3 of *DE*, the organic layer was dried (Na_2SO_4), and with cooling the solution was saturated with dry HCl. The precipitate was separated. b) Compound **14** (2.5 g, 6.0 mmol), 9.5 cm^3 of trifluoroacetic acid (120 mmol), and 3.5 cm^3 of propane-2-thiol (60 mmol) were stirred for 2 h at 0°C. The mixture was evaporated *in vacuo*, a solution of $NaCO_3$ (100 cm^3, 10%) was added, the mixture was extracted with 2 × 50 cm^3 of *DE*, and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in *DE* and saturated with HCl. After cooling to 0°C for 24 h, the precipitate was separated and dried *in vacuo*. Yield a) 3.9 g (86%); b) 2.1 g (99%); colorless crystals; mp 129–130°C ($CHCl_3$/*DE*); $[\alpha]_D^{20} = -11.7°\ cm^2\ g^{-1}$ ($c = 1.06$, $CHCl_3$); IR: $\bar{\nu} = 3412–3150$ (NH_3^+), 2915 (CH), 1714 (CO) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 2.79$ (dd, $J = 14.2$, 7.0 Hz, 2-H), 2.91 (dd, $J = 17.2$, 6.0 Hz, 4-H), 2.96 (dd, $J = 14.2$, 6.0 Hz, 2′-H), 3.03 (dd, $J = 17.2$, 6.4 Hz, 4′-H), 3.67 (quintet, $J = 6.6$ Hz, 3-H), 3.71 (s, SCH_2), 5.06, 5.11 (2d, each $J = 17.6$ Hz, OCH_2), 7.23 (m, 10arom H), 8.60 (s, NH_3^+) ppm.

Benzyl (S)-1,2-thiazetidine-3-acetate 1,1-dioxide (**7**, $C_{11}H_{13}NO_4S$)

Compound **6b** (5.0 g, 14.3 mmol) was dissolved in a mixture of 80 cm^3 of $CHCl_3$ and 60 cm^3 of *Et*OH (96%), At 0°C, the mixture was saturated with Cl_2, then, the solution was concentrated to 1/3, 200 cm^3 of *DE* were added, and the mixture was stored at −3°C for 24 h. The precipitate was separated and suspended in 200 cm^3 of $CHCl_3$, and at 0°C neutralized by stepwise addition of a satd. solution of NH_3 in $CHCl_3$. 100 cm^3 of *Ac*O*Et* were added, the organic layer was washed with H_2O, then dried (Na_2SO_4), and evaporated *in vacuo*. Yield 2.8 g (78%); colorless plats; mp 82–83°C (isopropanol/*DE*); $[\alpha]_D^{20} = +12.91°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR: $\bar{\nu} = 3318$ (NH), 3053, 2995 (CH), 1723 (CO), 1340, 1163 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 2.82$ (dd, $J = 5.9$, 16.8 Hz, 5-H), 2.89 (dd, $J = 7.6$, 16.8 Hz, 5′-H), 3.89–4.01 (ddd, $J = 0.7$, 4.9, 12.2 Hz, 4-H), 4.02 (m, 3-H), 4.36 (ddd, $J = 3.3$, 7.3, 12.2 Hz, 4′-H), 5.15 (s, OCH_2), 5.65 (s, N–H), 7.35 (m, 5arom H) ppm; ^{13}C NMR: $\delta = 37.25$ (C-5), 39.98 (C-3), 64.60 (C-4), 67.09 (OCH_2), 128.38, 128.63, 128.70, 135.07 (arom C), 169.86 (CO) ppm.

Benzyl (S)-2-(tert-butyldimethylsilyl)-1,2-thiazetidine-3-acetate 1,1-dioxide
(**8**, $C_{17}H_{27}NO_4SSi$)

At −78°C 9.1 cm^3 of *Bu*Li (14.56 mmol) were added to a solution of **7** (3.7 g, 14.5 mmol) in 150 cm^3 of *THF*. Then *tert*-butylchlorodimethylsilane (2.4 g, 16.0 mmol) in 20 cm^3 of *THF* was added. The mixture was stirred for 15 min at −78°C, and slowly warmed until the solution became clear. After cooling to 0°C, the mixture was hydrolyzed with a satd. solution of NH_4Cl, the organic layer was separated, and the aqueous layer was extracted with 2 × 100 cm^3 of *Ac*O*Et*. The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. Yield 2.4 g (49%); mp 78–79°C (cyclohexane:*n*-hexane = 1:1); $[\alpha]_D^{20} = -18.32°\ cm^2\ g^{-1}$ ($c = 1.0$, *Et*OH); IR: $\bar{\nu} = 1735$ (CO), 1306, 1152 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 0.28$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 2.81 (ddt, $J = 2.0$, 10.0, 16.4 Hz, 5-H), 2.94 (dd, $J = 3.9$, 16.4 Hz, 5′-H), 3.95 (dd, $J = 13.4$, 3.7 Hz, 4-H), 3.96 (m, 3-H), 4.39 (ddd, $J = 13.4$, 9.0, 1.5 Hz, 4′-H), 5.12 (s, OCH_2), 7.37 (m, 5arom H) ppm.

(S)-2-(tert-Butyldimethylsilyl)-1,2-thiazetidine-3-acetic acid 1,1-dioxide
(**9**, $C_{10}H_{21}NO_4SSi$)

From **8** (2.5 g, 7.1 mmol) in 250 cm^3 of *Et*OH and 0.4 g of Pd–C (10%) by hydrogenolysis. Yield 1.4 g (70%); colorless crystals; mp 113–114°C (*Et*OH); $[\alpha]_D^{20} = -19.42°\ cm^2\ g^{-1}$ ($c = 1.03$, *Et*OH);

IR: $\bar{\nu} = 3300–2800$ (OH), 1700 (CO), 1305, 1152 (SO_2) cm^{-1}; ^1H NMR (300 MHz, *Me*OH-d_4): $\delta = 0.28$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 2.72 (ddt, $J = 16.4$, 9.8, 3.4 Hz, 5-H), 2.91 (ddt, $J = 16.4$, 3.9, 1.8 Hz, 5′-H), 4.03 (dd, $J = 13.7$, 3.7 Hz, 3-H), 4.06 (dd, $J = 3.7$, 13.7 Hz, 4-H), 4.61 (dd, $J = 7.7$, 13.7 Hz, 4′-H) ppm.

(S)-2-Amino-4-oxo-4-benzoyloxybutane sulfonic acid (**10**, $C_{11}H_{15}NO_5S$)

From **7** (150 mg, 0.43 mmol) by hydrolysis with dil. HCl. Yield 100 mg (85%); colorless solid; mp 132–133°C (dec.); $[\alpha]_D^{20} = -8.6° \, cm^2 \, g^{-1}$ ($c = 0.35$, *DMSO*); $[\alpha]_D^{27} = +18.0° \, cm^2 \, g^{-1}$ ($c = 0.5$, 1 *N* HCl); IR: $\bar{\nu} = 3447$ (NH_2), 1728 (CO), 1207, 1152, 1043 (SO_2) cm^{-1}; ^1H NMR (300 MHz, *DMSO*-d_6, 50°C): $\delta = 2.74$ (dd, $J = 14.2$, 8.8 Hz, 3-H), 2.77 (dd, $J = 17.1$, 7.1 Hz, 1-H), 2.84 (dd, $J = 14.2$, 4.0 Hz, 3′-H), 2.92 (dd, $J = 17.1$, 6.4 Hz, 1′-H), 3.77 (m, 2-H), 5.12 (s, OCH_2), 7.32 (m, 5arom H), 7.88 (s, NH_2) ppm; MS(Fab-Gun Xe, 8 kV, 1 mA): $m/z = 274$ ($M^+ + 1$), 273 (M^+).

Boc-Asp(OBn)-OH (**11**)

Bachem A-1245.0100.

Benzyl (S)-3-(tert-butoxycarbonylamino)-4-hydroxybutanoate (**12**) [7]

From *Boc-Asp*(O*Bn*)OH (8 g, 24.8 mmol) in 30 cm^3 of *THF* by reduction with BH_3-*THF* (1 *N*) under N_2 at 0°C. The residue (6.3 g) was purified by FC (*Ac*O*Et*:cyclohexane = 1:1). Yield 3.6 g (47%); $R_f = 0.43$; colorless wax; mp 57°C (*Ac*O*Et*/cyclohexane); $[\alpha]_D^{22} = -4.77° \, cm^2 \, g^{-1}$ ($c = 6$, *Ac*O*Et*).

Benzyl (S)-3-(tert-butoxycarbonylamino)-4-bromobutanoate (**13**) [8]

From **12** (3.6 g, 11.6 mmol) by reaction with P(*Ph*)$_3$ (3.05 g, 11.6 mmol) and CBr_4 (5.8 g, 17.4 mmol). The residue was purified by FC (*Ac*O*Et*:cyclohexane = 1:4). Yield 2.7 g (63%); $R_f = 0.45$; colorless liquid; $[\alpha]_D^{24} = -0.80° \, cm^2 \, g^{-1}$ ($c = 6$, *Ac*O*Et*).

Benzyl (S)-3-(tert-butoxycarbonylamino)-4-(benzylthio)butanoate (**14**, $C_{23}H_{29}NO_4S$)

Under N_2 benzylmercaptan (1.1 cm^3, 9.4 mmol) was added with cooling to a suspension of NaH (350 mg, 8.7 mmol, 60%) in 2 cm^3 of *DMF*, then **13** (2.7 g, 7.25 mmol) dissolved in 6 cm^3 of *DMF* was added, the mixture was stirred for 3 h, 100 cm^3 of *Ac*O*Et* were added, and the mixture was washed with a satd. solution of NH_4Cl (2×50 cm^3). The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by FC (cyclohexane:*Ac*O*Et* = 4:1). Yield 2.7 g (89%); colorless viscous solid; mp 42°C (*Ac*O*Et*/cyclohexane); $[\alpha]_D^{26} = -7.58° \, cm^2 \, g^{-1}$ ($c = 6$, *Ac*O*Et*); $R_f = 0.45$; IR (film): $\bar{\nu} = 3450–3300$ (NH), 2978 (CH), 1750, 1680 (CO), 1246 (C–N) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.45$ [s, $C(CH_3)_3$], 2.55–2.76 (m, 2-H, 2′-H, 4-H, 4′-H), 3.72 (s, SCH_2), 4.10 (m, H-3), 5.07 (s, N–H), 5.10 (s, OCH_2), 7.21–7.38 (m, 10arom H) ppm.

General Procedure for the Reaction of **3** *with Esters of* L*-Amino Acids or Dipeptides*

Triethylamine (0.5 g, 5 mmol) was added to the amino acid ester/dipeptide ester salt (5 mmol) dissolved in 10 cm^3 of CH_2Cl_2, the mixture was stirred for 5 min, filtered, and then **3** (0.7 g, 2.5 mmol), and *NHS* (0.58 g, 5 mmol) dissolved in 50 cm^3 of CH_2Cl_2 were added. The mixture was cooled to −5°C, and *DCC* (0.65 g, 3.3 mmol) was added. After stirring for 20 h at −5°C, the precipitate was separated, and the organic layer was evaporated. The residue was dissolved in *DE*, and separated from insoluble precipitate. The solvent was evaporated, and the residue was purified by CC.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanine methyl ester (**15a**, $C_{20}H_{32}N_2O_5SSi$)

From L-*Phe*-O*Me*-HCl (1.02 g, 5 mmol). Yield 950 mg (86%); colorless liquid; $[\alpha]_D^{20} = +34.9^\circ\,cm^2\,g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3320$ (NH), 1730, 1650 (CO), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.23$ [s, $Si(CH_3)_2$], 0.93 [s, $C(CH_3)_3$], 2.53 (m, 5-H, 5′-H), 3.70 (s, OCH_3), 3.05 [m, 2β-H(*Phe*)], 3.95 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.04 (m, 3-H), 4.38 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.80 [m, α-H(*Phe*)], 6.49 (d, $J = 7.0$ Hz, N–H), 7.20 (m, 5arom H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine methyl ester (**15b**, $C_{13}H_{26}N_2O_5SSi$)

From *Gly*-O*Me*-HCl (1.12 g, 10 mmol). Yield 1.65 g (94%); colorless platelets; mp 126°C (*DE*); IR: $\bar{\nu} = 3360$ (NH), 3040, 2920, 2940, 2850 (CH), 1740, 1670 (CO), 1520 (amide), 1290, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.25$ [s, $Si(CH_3)_2$], 0.95 [s, $C(CH_3)_3$], 2.78 (m, 5-H, 5′-H), 3.68 (s, OCH_3), 4.00 [m, 2α-H(*Gly*), 4-H, 3-H], 4.50 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 6.33 (s, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-methionine methyl ester (**15c**, $C_{16}H_{32}N_2O_5S_2Si$)

From L-*Met*-O*Me*-HCl (0.86 g, 5 mmol). Yield 930 mg (87%); viscous liquid; $[\alpha]_D^{20} = +18.0^\circ\,cm^2\,g^{-1}$ ($c = 1.03$, $CHCl_3$); IR (film): $\bar{\nu} = 3325$ (NH), 3010, 2920, 2850 (CH), 1735, 1650 (CO), 1530 (amide), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.28$ [s, $Si(CH_3)_2$], 0.96 [s, $C(CH_3)_3$], 2.05 (s, SCH_3), 2.18 [m, 2γ-H(*Met*)], 2.50 [m, 2β-H(*Met*)], 2.83 (m, 5-H, 5′-H), 3.75 (s, OCH_3), 4.00 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.10 (m, 3-H), 4.52 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.65 [m, α-H(*Met*)], 6.80, 6.95 (d, $J = 7.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-leucine methyl ester (**15d**, $C_{17}H_{34}N_2O_5SSi$)

From L-*Leu*-O*Me*-HCl (0.84 g, 5 mmol). Yield 850 mg (86%); viscous liquid; $[\alpha]_D^{20} = +17.3^\circ\,cm^2\,g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3340$ (NH), 3030, 2920, 2950, 2850 (CH), 1740, 1650 (CO), 1530 (amide), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.30$ [s, $Si(CH_3)_2$], 0.95–1.00 [m, $C(CH_3)_3$, $CH(CH_3)_2$(*Leu*)], 1.63 [m 2β-H(*Leu*), γ-H(*Leu*)], 2.80 (m, 5-H, 5′-H), 3.73 (s, OCH_3), 4.02 (dd, 4-H), 4.10 (m, 3-H), 4.50 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.60 [m, α-H(*Leu*)], 6.60, 6.83 (d, $J = 7.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-glutamic acid dimethyl ester (**15e**, $C_{17}H_{32}N_2O_7SSi$)

From L-*Glu*-(O*Me*)$_2$-HCl (1.84 g, 10 mmol). Yield 1.7 g (78%); viscous liquid; $[\alpha]_D^{20} = +21.2^\circ\,cm^2\,g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3320$ (NH), 3030, 2920, 2950, 2850 (CH), 1740, 1665 (CO), 1530 (amide), 1305, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.30$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 2.15 [m, 2γ-H(*Glu*)], 2.33 [m, 2β-H(*Glu*)], 2.80 (m, 5-H, 5′-H), 3.58 [s, $OCH_3(\alpha)$], 3.75 [s, $OCH_3(\delta)$], 4.00 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.13 (m, 3-H), 4.52 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.60 [m, α-H(*Glu*)], 7.23, 7.33 (d, $J = 7.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-serine methyl ester (**15f**, $C_{14}H_{28}N_2O_6SSi$)

From L-*Ser*-O*Me*-HCl (1.42 g, 10 mmol). Yield 1.1 g (58%); colorless solid; mp 87°C (*DE*); $[\alpha]_D^{20} = +15^\circ\,cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); IR: $\bar{\nu} = 3341$ (NH), 3030, 2950, 2860 (CH), 1744, 1647 (CO), 1533 (amide), 1295, 1150, 1200 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.30$ [s, $Si(CH_3)_2$], 1.02 [s, $C(CH_3)_3$], 2.77 (dd, $J = 4.0$, 10.5 Hz, 5-H), 2.87 (dd, $J = 3.0$, 10.5 Hz, 5′-H), 3.02, 3.18 (t, $J = 5.0$ Hz, O–H), 3.80 (s, OCH_3),

3.88 [m, 2β-H(*Ser*)], 4.06 (m, 4-H, 3-H), 4.52 (m, 4′-H), 4.64 [m, α-H(*Ser*)], 6.91, 7.05 (d, $J = 8.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-cysteine ethyl ester (**15g**, $C_{15}H_{30}N_2O_5S_2Si$)

From L-*Cys*-O*Et*-HCl (1.58 g, 10 mmol). Yield 1.8 g (88%); viscous liquid; $[\alpha]_D^{20} = +20.5°\ cm^2\ g^{-1}$ ($c = 3.6$, $CHCl_3$); IR (film): $\bar{\nu} = 3340$ (NH), 3030, 2930, 2860 (CH), 1735, 1670 (CO), 1530 (amide), 1305, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.30$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 1.28 (t, $J = 7.0$ Hz, CH_3), 2.86 (m, 5-H, 5′-H), 2.98 [d, $J = 7.0$ Hz, 2β-H(*Cys*)], 3.13, 3.20 (2s, S–H), 4.05 (m, CH_2), 4.20 (m, 4-H), 4.38 (m, 3-H), 4.50 (dd, $J = 9.0$, 15.0 Hz, 4′-H), 4.75 [m, α-H(*Cys*)], 6.88, 7.00 (d, $J = 7.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanine benzyl ester (**15h**, $C_{26}H_{36}N_2O_5SSi$)

From L-*Phe*-O*Bn*-HCl (1.02 g, 5 mmol). Yield 950 mg (74%); viscous liquid; $[\alpha]_D^{20} = -7.8°\ cm^2\ g^{-1}$ ($c = 1.8$, $CHCl_3$); IR (film): $\bar{\nu} = 3340$ (NH), 3080, 3030, 2930, 2950, 2850 (CH), 1735, 1660 (CO), 1530 (amide), 1305, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.28$ [s, $Si(CH_3)_2$], 0.95 [s, $C(CH_3)_3$], 2.53 (m, 5-H, 5′-H), 3.08 [m, 2β-H(*Phe*)], 3.85 (dd, $J = 4.0$, 13.0 Hz, 4-H), 3.95 (m, 3-H), 4.18 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.90 [m, α-H(*Phe*)], 5.13 (s, OCH_2), 6.65, 6.75 (d, $J = 7.0$ Hz, N–H), 7.13, 7.25 (2s, 10arom H) ppm; MS (70 eV): m/z (%) = 518 (0.19, $M^+ + 1$), 460 (2.73), 91 (100).

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine benzyl ester (**15i**, $C_{19}H_{30}N_2O_5SSi$)

From *Gly*-O*Bn*-p-*Ts* (1.1 g, 3.27 mmol). Yield 980 mg (90%); colorless solid; mp 72°C (*DE*); IR: $\bar{\nu} = 3380$ (NH), 1740, 1670 (CO), 1525 (amide), 1300, 1145 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.27$ [s, $Si(CH_3)_2$], 0.98 [s, $C(CH_3)_3$], 2.70 (dd, $J = 9.75$, 15.0 Hz, 5-H), 2.84 (dd, $J = 4.5$, 15.0 Hz, 5′-H), 3.93 (dd, $J = 3.45$, 13.5 Hz, 4-H), 3.90 [dd, $J = 7.0$, 20.0 Hz, α-H(*Gly*)], 4.04 (m, 3-H), 4.20 [dd, $J = 7.0$, 20.0 Hz, α'-H(*Gly*)], 4.44 (dd, $J = 7.5$, 13.0 Hz, 4′-H), 5.15 (s, CH_2), 6.60 (d, $J = 7.0$ Hz, N–H), 7.30 (s, 5arom H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-O-benzyl-L-serine methyl ester (**15k**, $C_{21}H_{34}N_2O_6SSi$)

From O-*Bn*-L-*Ser*-O*Me*-HCl (1.72 g, 7 mmol). Yield 1.5 g (64%); colorless liquid; $[\alpha]_D^{20} = +12.9°\ cm^2\ g^{-1}$ ($c = 2.3$, *Ac*O*Et*); IR (film): $\bar{\nu} = 3349$ (NH), 3070, 3030, 2960, 2930, 2860 (CH), 1744, 1673 (CO), 1528 (amide), 1153, 1312 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.31$ [s, $Si(CH_3)_2$], 1.05 [s, $C(CH_3)_3$], 2.77 (dd, $J = 3.5$, 12.5 Hz, 5-H), 3.46–4.15 [m, 2β-H(*Ser*), 3-H, 4-H), 3.74 (s, OCH_3), 4.33–4.82 [m, α-H(*Ser*), 4′-H], 6.56, 6.64 (2d, $J = 7.0$ Hz, N–H), 7.33 (s, 5arom H) ppm; MS (70 eV): m/z (%) = 471 (7.65, M^+), 57 (100, $C(CH_3)_3^+$), 413 (22.95), 115 (13.91), 91 (94.43).

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}dicyclohexylurea (**16**, $C_{23}H_{43}N_3O_4SSi$)

As a by-product in reactions of **3** with esters of L-amino acids or dipeptides. Yield 10–30%; colorless crystals; mp 169°C (*DE*); IR: $\bar{\nu} = 3330$ (NH), 1700, 1650 (CO), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.28$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 1.27–1.77 (m, 22 cyclohexyl H), 2.78 (dd, $J = 11.0$, 15.0 Hz, 5-H), 3.03 (dd, $J = 5.0$, 15.0 Hz, 5′-H), 3.95 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.03 (m, 3-H), 4.53 (dd, $J = 13.0$, 9.0 Hz, 4′-H), 6.50 (d, $J = 7.0$ Hz, N–H) ppm.

2,5-Dioxopyrrolidinyl (RS)-2-(tert-butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-acetate (**17**, $C_{14}H_{24}N_2O_6SSi$)

See **21**.

*General Procedure for the Desilylation of **15***

Glacial acetic acid (0.075 g, 1.25 mmol) and 1.25 cm^3 of *TBAF* (1.25 mmol) were added to **15** (1.25 mmol) dissolved in 10–30 cm^3 of *THF* at 0°C. The mixture was stirred for 10 min, diluted with 20–30 cm^3 of *THF*, and then extracted with 30 cm^3 of a 1:1 mixture of a satd. NaCl- and a satd. $NaHCO_3$-solution. The organic layer was separated, dried (Na_2SO_4), evaporated, and the residue was purified by CC (silica gel) with *AcOEt*, if not noted otherwise.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-phenylalanine methyl ester (**18a**, $C_{14}H_{18}N_2O_5S$)

From **15a** (950 mg, 2.15 mmol). Yield 521 mg (78%); viscous liquid; $[\alpha]_D^{20} = +4.25°\ cm^2\ g^{-1}$ ($c = 1.2$, $CHCl_3$); IR (film): $\bar{\nu} = 3350$ (NH), 3060, 3030, 2970, 2880 (CH), 1745, 1660 (CO), 1540 (amide), 1310, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.58$ (m, 5-H, 5′-H), 3.03 [m, 2β-H(*Phe*)], 3.63 (s, OCH_3), 3.93 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.16 (m, 3-H), 4.28 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.73 [m, α-H(*Phe*)], 6.33 (d, $J = 13.0$ Hz, N–H), 7.03, 6.90 (2d, $J = 9.0$ Hz, N–H), 7.15 (m, 5arom H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]glycine methyl ester (**18b**, $C_7H_{12}N_2O_5S$)

From **15b** (1.0 g, 2.85 mmol), CC (*AcOEt:MeOH* = 1:1). Yield 150 mg (22%); colorless solid; mp 113°C ($CHCl_3$); IR: $\bar{\nu} = 3305$ (NH), 3080, 3040, 2960 (CH), 1753, 1643 (CO), 1547 (amide), 1323, 1165 (SO_2) cm^{-1}; ^1H NMR (100 MHz): $\delta = 2.72$, 2.78 (2dd, $J = 5.0$, 10.5 Hz, 5-H, 5′-H), 3.74 (s, OCH_3), 4.00 [m, 2α-H(*Gly*), 4-H, 3-H], 4.39 (dd, $J = 8.0$, 14.0 Hz, 4′-H), 6.88 (s, N–H), 7.63 (s, N–H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-methionine methyl ester (**18c**, $C_{10}H_{18}N_2O_5S_2$)

From **15c** (0.49 g, 1.25 mmol). Yield 220 mg (57%); viscous liquid; $[\alpha]_D^{20} = +11.3°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3400$ (NH), 2950, 2920, 2860 (CH), 1730, 1650 (CO), 1540 (amide), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.05$ (s, SCH_3), 2.18 [m, 2γ-H(*Met*)], 2.50 [m, 2β-H(*Met*)], 2.80 (d, $J = 7.0$ Hz, 5-H, 5′-H), 3.75 (s, OCH_3), 4.05 (m, 4-H), 4.27 (m, 3-H), 4.38 (m, 4′-H), 4.63 [m, α-H(*Met*)], 6.83 (s, N–H), 7.80 (d, $J = 9.0$ Hz, N–H) ppm; MS (70 eV): m/z (%) = 311 (4.99, $M^+ + 1$), 140 (11.92).

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-leucine methyl ester (**18d**, $C_{11}H_{20}N_2O_5S$)

From **15d** (0.53 g, 1.25 mmol), CC (acetone). Yield 250 mg (68%); viscous liquid; $[\alpha]_D^{20} = +7.52°\ cm^2\ g^{-1}$ ($c = 1.0$, $CHCl_3$); IR (film): $\bar{\nu} = 3300$ (NH), 3060, 3030, 2920, 2850 (CH), 1730, 1650 (CO), 1535 (amide), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.90$ (d, $2CH_3$), 1.66 [m, 2β-H(*Leu*), γ-H(*Leu*)], 2.70 (d, $J = 7.0$ Hz, 5-H, 5′-H), 3.63 (s, OCH_3), 4.03 (dd, $J = 4.0$, 13.0 Hz, 4-H), 4.03 (m, 3-H), 4.40 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.62 [m, α-H(*Leu*)], 6.88 (s, N–H), 7.00 (d, $J = 9.0$ Hz, N–H) ppm; MS (70 eV): m/z (%) = 293 (1.42, $M^+ + 1$), 140 (4.91).

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-glutamic acid dimethyl ester (**18e**, $C_{11}H_{18}N_2O_7S$)

From **15e** (1.5 g, 3.4 mmol). Yield 200 mg (18%); viscous liquid; $[\alpha]_D^{20} = +10.2°\ cm^2\ g^{-1}$ ($c = 1.0$, $CHCl_3$); IR (film): $\bar{\nu} = 3321$ (NH), 3040, 2960, 2850 (CH), 1740, 1658 (CO), 1544 (amide), 1320, 1156 (SO_2) cm^{-1}; ^1H NMR (100 MHz): $\delta = 2.07$, 2.20 [2m, 2β-H(*Glu*)], 2.42 [m, 2γ-H(*Glu*)], 2.70, 2.78 (2d, $J = 4.5$, 10.5 Hz, 5-H, 5′-H), 3.69, 3.68 [2s, $OCH_3(\alpha)$], 3.75, 3.77 [2s, $OCH_3(\delta)$], 4.06 (m, 3-H, 4-H), 4.57 (dd, $J = 8.0$, 14.0 Hz, 4′-H), 4.41 [m, α-H(*Glu*)], 6.37, 6.35 (2s, N–H), 7.00, 6.93 (2d, $J = 8.0$ Hz, N–H) ppm; MS (70 eV): m/z (%) = 323 (100, $M^+ + 1$), 291 (9.82), 259 (15.34).

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-cysteine ethyl ester (**18g**, $C_9H_{16}N_2O_5S_2$)

From **15g** (1.5 g, 3.65 mmol). Yield 700 mg (65%); colorless crystals; mp 112–114°C ($CHCl_3$/*DE*); $[\alpha]_D^{20} = +30.0°\ cm^2\ g^{-1}$ ($c = 1.6$, $CHCl_3$); IR: $\bar{\nu} = 3323$ (NH), 2555 (SH), 1746, 1649 (CO), 1534 (amide), 1310, 1155 (SO_2) cm^{-1}; ^1H NMR (100 MHz): $\delta = 1.31$ (t, $J = 5.5$ Hz, CH_3), 1.40 (t, $J = 5.5$ Hz, S–H), 2.79 (ddd, $J = 3.4$, 5.7, 10.5 Hz, 5-H, 5′-H), 3.01 [m, 2β-H(*Cys*)], 4.04 (m, CH_2), 4.25 (m, 3-H, 4-H), 4.42 (dd, $J = 8.0$, 14.0 Hz, 4′-H), 4.82 [m, α-H(*Cys*)], 6.13, 7.18 (s, N–H), 6.72, 6.76 (d, $J = 7.0$ Hz, N–H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-phenylalanine benzyl ester (**18h**, $C_{20}H_{22}N_2O_5S$)

From **15h** (1.9 g, 3.68 mmol). Yield 900 mg (61%); colorless solid; mp 91°C (*DE*/acetone); $[\alpha]_D^{20} = +10.71°\ cm^2\ g^{-1}$ ($c = 1.2$, $CHCl_3$); IR: $\bar{\nu} = 3320$ (NH), 3060, 3030, 2850 (CH), 1720, 1640 (CO), 1530 (amide), 1310, 1155 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 2.53$ (d, $J = 7.0$ Hz, 5-H, 5′-H), 3.08 [m, 2β-H(*Phe*)], 3.80 (m, 4-H), 3.93 (m, 3-H), 4.18 (m, 4′-H), 4.75 [m, α-H(*Phe*)], 5.08 (s, OCH_2), 6.83 (s, N–H), 7.18, 7.33 (2s, 10arom H), 7.63 (d, $J = 7.0$ Hz, N–H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]glycine benzyl ester (**18i**, $C_{13}H_{16}N_2O_5S$)

From **15i** (0.53 g, 1.25 mmol). Yield 0.23 g (76%); colorless solid; mp 132°C (*DE*); IR: $\bar{\nu} = 3320$ (NH), 3070, 3030, 2970, 2950, 2850 (CH), 1750, 1640 (CO), 1540 (amide), 1310, 1155 (SO_2) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.63$ (d, $J = 7.0$ Hz, 5-H, 5′-H), 3.90 [d, $J = 7.0$, 2α-H(*Gly*)], 4.02 (m, 3-H, 4-H), 4.33 (m, 4′-H), 5.08 (s, CH_2), 7.38 (s, 5arom H), 7.90 (s, N–H), 8.45, 8.55 (d, $J = 7.0$ Hz, N–H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-O-benzyl-L-serine methyl ester (**18k**, $C_{15}H_{20}N_2O_6S$)

From **15k** (1.0 g, 2.1 mmol). Yield 450 mg (60%); colorless solid; mp 144°C (*Ac*O*Et*); $[\alpha]_D^{20} = +19.7°\ cm^2\ g^{-1}$ ($c = 1.3$, *Ac*O*Et*); IR: $\bar{\nu} = 3412$ (NH), 3070, 3040, 3000, 2960, 2930, 2900, 2850 (CH), 1753, 1666, 1627 (CO), 1518 (amide), 1319, 1151 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.70$, 2.73 (d, $J = 6.0$ Hz, 5-H, 5′-H), 3.73 (s, OCH_3), 3.73 (m, 4-H), 3.87 (m, 3-H), 4.00 [m, 2β-H(*Ser*)], 4.25 (m, 4′-H), 4.25 [s, CH_2(*Bn*)], 4.70 [m, α-H(*Ser*)], 5.82, 6.06 (2s, N–H), 6.51 (m, N–H), 7.28 (s, 5arom H) ppm; MS (70 eV): m/z (%) = 356 (25.39, M^+), 91 (100), 65 (15.95).

General Procedure for the Hydrogenolysis of Benzyl Esters ***15***

The benzyl ester **15** (10 mmol) dissolved in 100 cm^3 of *Et*OH, and Pd–C (0.2 g, 10%) were hydrogenated at 100 kPa for 10–20 min. The catalyst was removed, and the solvent was evaporated *in vacuo*.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanine (**19h**, $C_{19}H_{30}N_2O_5SSi$)

From **15h** (0.39 g, 7.5 mmol). Yield 0.32 g (98%); colorless solid; mp 45°C; $[\alpha]_D^{20} = -29°\ cm^2\ g^{-1}$ ($c = 1.5$, $CHCl_3$); IR: $\bar{\nu} = 3400$ (NH, OH), 3030, 2920, 2950 (CH), 1735, 1650 (CO), 1550 (amide), 1305, 1150 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 0.25$ [s, $Si(CH_3)_2$], 0.95 [s, $C(CH_3)_3$], 2.75 (m, 5-H, 5′-H), 3.13 [m, 2β-H(*Phe*)], 3.95 (dd, $J = 4.0$, 13.0 Hz, 4-H), 3.98 (m, 3-H), 4.33 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.75 [m, α-H(*Phe*)], 5.20 (s, COOH), 7.2 (s, 5arom H), 7.65 (d, $J = 9.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine (**19i**, $C_{12}H_{24}N_2O_5SSi$)

From **15i** (0.32 g, 7.5 mmol). Yield 0.25 g (94%); colorless solid; mp 125°C (*DE*); IR: $\bar{\nu} = 3380$ (NH), 3050, 2930, 2950, 2870 (CH), 1770, 1660 (CO), 1570 (amide), 1300, 1155 (SO_2) cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 0.30$ [s, $Si(CH_3)_2$], 0.98 [s, $C(CH_3)_3$], 2.70 (dd, $J = 11.0$, 15.0 Hz, 5-H), 3.03 (dd, $J = 5.0$, 15.0 Hz, 5′-H), 3.95 [d, $J = 7.0$ Hz, 2α-H(*Gly*)], 3.95 (m, 4-H), 4.04 (m, 3-H), 4.50 (dd, $J = 13.0$, 9.0 Hz, 4′-H), 7.65 (s, N–H) ppm.

N-{2-[(S)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycyl-L-nitroarginine benzyl ester (**20a**, $C_{25}H_{41}N_7O_8SSi$)

Compound **21** (0.7 g, 2.0 mmol) dissolved in 100 cm^3 of *THF* was added to a mixture of 1.1 cm^3 of triethylamine (7.4 mmol) and *Boc-Gly-L-Arg*(NO_2)-O*Bn*-HCl (3.0 g, 7.4 mmol) in 150 cm^3 of *Me*CN at −10°C. After stirring for 3 days at room temperature, the mixture was filtered, the solvent evaporated, and the residue was purified by CC (*Ac*O*Et*:*Et*OH = 5:1, $R_f = 0.44$). Yield 350 mg (28%); colorless solid; mp 85–87°C; $[\alpha]_D^{20} = -18.6°\ cm^2\ g^{-1}$ ($c = 0.3$, *Et*OH); IR: $\bar{\nu} = 3320$ (NH), 2931, 2860 (CH), 1740, 1629 (CO), 1534 (NO_2), 1300, 1256, 1150 (SO_2) cm^{-1}; ^1H NMR (300 MHz, *Me*OH-d_4): $\delta = 0.22$ [s, $Si(CH_3)_2$], 1.01 [s, $C(CH_3)_3$], 1.6–1.95 [m, 2β-CH_2(*Arg*), 2δ-CH_2(*Arg*)], 2.60 (ddd, $J = 2.2$, 10.3, 14.7 Hz, 5-H), 2.90 (ddd, $J = 2.0$, 3.6, 14.7 Hz, 5′-H), 3.23 [m, 2γ-CH_2(*Arg*)], 3.84, 3.95 [dd, $J = 6.1$, 16.6 Hz, CH_2(*Gly*)], 4.06 (m, 3-H), 4.08 (dd, $J = 3.7$, 13.7 Hz, 4-H), 4.50 (dd, $J = 8.6$, 13.7 Hz, 4′-H), 4.52 [m, α-H(*Arg*)], 5.14, 5.20 (2d, $J = 12.2$ Hz, OCH_2), 7.38 (m, 5arom H) ppm; MS (FAB 26 kv 13): $m/z = 628$ ($M^+ + 1$), 570 (M^+-$C(CH_3)_3$), 154, 136, 107.

N-[(S)-(1,1-Dioxo-1,2-thiazetidene-3-yl)acetyl]-glycyl-L-nitroarginine benzyl ester (**20b**, $C_{19}H_{27}N_7O_8S$)

From **20a** (200 mg, 0.3 mmol) by desilylation, purification by CC (*Ac*O*Et*:*Et*OH = 5:1). Yield 100 mg (61%); colorless solid; mp 100°C (dec); $[\alpha]_D^{20} = -17.7°\ cm^2\ g^{-1}$ ($c = 0.4$, *Et*OH); IR: $\bar{\nu} = 3308$ (NH), 2940 (CH), 1740, 1654 (CO), 1534 (NO_2), 1290, 1264, 1041 (SO_2) cm^{-1}; ^1H NMR (300 MHz, 2D-Cosy, *Me*OH-d_4): $\delta = 1.62$ [m, 2γ-CH_2(*Arg*)], 1.76–1.92 [m, 2β-CH_2(*Arg*)], 2.69 (dd, $J = 6.3$, 17.0 Hz, 5-H), 2.75 (dd, $J = 6.8$, 17.0 Hz, 5′-H), 3.23 [m, 2δ-CH_2(*Arg*)], 3.86 [dd, $J = 6.0$, 16.6 Hz, α-CH(*Gly*)], 3.91 [dd, $J = 4.1$, 16.6 Hz, α-CH(*Gly*)], 3.95 (m, 3-H), 4.04 (dd, $J = 5.3$, 12.9 Hz, 4-H), 4.39 (dd, $J = 7.8$, 12.9 Hz, 4′-H), 4.53 [m, α-CH(*Arg*)], 5.14, 5.20 (2d, $J = 12.2$ Hz, OCH_2), 7.38 (m, 5arom H) ppm; MS (FAB 26 kv 3): $m/z = 532$ (M^++Na), 514 ($M^+ + 1$), 469 (M^+-NO_2), 107, 136, 154.

2,5-Dioxopyrrolidinyl (S)-2-(tert-butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-acetate (**21**, $C_{14}H_{24}N_2O_6SSi$)

DCC (0.60 g, 3.0 mmol) in 20 cm^3 of *THF* was added to a solution of (*S*)-**9** (0.70 g, 2.5 mmol) and *NHS* (0.71 g, 6.3 mmol) in 50 cm^3 of *THF* at −12°C. After stirring for 1 h, the mixture was filtered, the

solvent evaporated, the residue dissolved in *Ac*O*Et*, again filtered, and the solvent evaporated. Yield 0.90 g (96%); colorless solid; mp 151°C ($CHCl_3$/*PE*); $[\alpha]_D^{20} = -1.8°\ cm^2\ g^{-1}$ ($c = 1.1$, CH_2Cl_2); $R_f = 0.45$ ($CHCl_3$:*Me*OH = 1:1); IR: $\bar{\nu} = 3050$, 2950, 2920, 2850 (CH), 1810, 1785, 1730 (CO) 1306, 1152 (SO_2) cm^{-1}; ^1H NMR (300 MHz): $\delta = 0.28$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 2.82 (s, $2CH_2$), 3.16 (dd, $J = 4.0$, 16.1 Hz, 5-H), 3.10 (dd, $J = 9.8$, 16.1 Hz, 5′-H), 4.01 (m, 3-H), 4.06 (dd, $J = 3.7$, 13.7 Hz, 4-H), 4.61 (dd, $J = 8.1$, 13.7 Hz, 4′-H) ppm.

*N-{2-[(S)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-*L*-nitroarginylglycine benzyl ester* (**22a**, $C_{25}H_{41}N_7O_8SSi$)

From L-*Arg*(NO_2)-*Gly*-O*Bn*-HCl (2.17 g, 5.3 mmol) and **21** (1.02 g, 2.7 mmol) as described for **20**. CC ($CHCl_3$:*Me*CN:*Ac*O*Et* = 3:8:5, *Et*OH:*Ac*O*Et*:cyclohexane = 1:2:4, $CHCl_3$:*Me*OH = 12:1). Yield 250 mg (14.7%); colorless crystals; mp 94–95°C; $R_f = 0.35$ ($CHCl_3$:*Me*OH = 12:1); $[\alpha]_D^{20} = -33.7°\ cm^2\ g^{-1}$ ($c = 0.7$, *Et*OH); IR: $\bar{\nu} = 3419$ (NH), 2955, 2930 (CH), 1738, 1960, 1650 (CO), 1290, 1256, 1150 (SO_2) cm^{-1}; ^1H NMR (300 MHz, 2D-Cosy, acetone-d_6): $\delta = 0.25$ [s, $Si(CH_3)_2$], 0.97 [s, $C(CH_3)_3$], 1.70 [m, β-CH_2(*Arg*), δ-CH_2(*Arg*)], 2.73 (m, 5-H), 2.99 (ddd, $J = 3.9$, 8.7, 15.1 Hz, 5′-H), 3.37 [m, γ-CH_2(*Arg*)], 4.01 [m, 4-H, 3-H, CH_2(*Gly*)], 4.51 [m, 4′-H, α-CH(*Arg*)], 5.18 (s, OCH_2), 7.38 (m, 5arom H), 7.74–7.58 (m, 5N–H) ppm; MS (FAB 26 kv 3): $m/z = 628$ ($M^+ + 1$), 570 (M^+-$C(CH_3)_3$), 154, 136, 107.

*N-{2-[(S)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-*L*-nitroarginylglycine* (**22b**, $C_{18}H_{35}N_7O_8SSi$)

From **22a** (100 mg, 0.16 mmol) by hydrogenolysis. Yield 50 mg (59%); colorless solid; mp 145°C; $[\alpha]_D^{20} = -16.0°\ cm^2\ g^{-1}$ ($c = 0.12$, isopropanol); IR: $\bar{\nu} = 3428$ (OH, NH), 2935, 2925 (CH), 1720, 1660, 1648 (CO), 1535 (NO_2), 1288, 1152 (SO_2) cm^{-1}; ^1H-NMR (300 MHz, 2D-Cosy, *Me*OH-d_4): $\delta = 0.29$ [s, $Si(CH_3)_2$], 1.01 [s, $C(CH_3)_3$], 1.69 [m, 2β-CH_2(*Arg*)], 1.88 [m, 2γ-CH_2(*Arg*)], 2.6 (ddd, $J = 15.0$, 9.9, 2.4 Hz, 5-H), 2,96 (ddd, $J = 15.0$, 9.4, 3.8 Hz, 5′-H), 3.24 [m, 2δ-CH_2(*Arg*)], 3.87 [m, $J = 17.4$, 9.1 Hz, CH_2(*Gly*)], 4.04 (m, 3-H), 4.11 (dd, $J = 13.4$, 3.7 Hz, 4-H), 4.37 [m, α-CH(*Arg*)], 4.54 (ddd, $J = 13.4$, 7.7, 1.5 Hz, 4′-H) ppm.

*N-[(S)-(1,1-Dioxo-1,2-thiazetidene-3-yl)acetyl]-*L*-nitroarginylglycine benzyl ester* (**22c**, $C_{19}H_{27}N_7O_8S$)

From **22a** (200 mg, 0.3 mmol) by desilylation. CC ($CHCl_3$:*Me*OH = 12:1). Yield 100 mg (61%); mp 89–90°C; $[\alpha]_D^{20} = -18.0°\ cm^2\ g^{-1}$ ($c = 0.1$, isopropanol); IR: $\bar{\nu} = 3380$ (NH), 3035, 2949 (CH), 1734, 1647 (CO), 1534, 1400 (NO_2), 1300, 1291, 1157 (SO_2) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): $\delta = 1.7$ [m, 2β-CH_2(*Arg*), 2γ-CH_2(*Arg*)], 3.00 (m, 5-H, 5′-H), 3.34 [m, 2δ-CH_2(*Arg*)], 4.01 [m, 3-H, 4-H, CH_2(*Gly*)], 4.35 (ddd, $J = 1.7$, 7.6, 13.2 Hz, 4′-H), 4.54 [m, α-CH(*Arg*)], 5.18 (s, OCH_2), 7.00 (s, N–H), 7.36 (m, 5arom H), 7.32–8.0 (m, 5N–H) ppm.

*N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-*L*-alanylglycine benzyl ester* (**23a**, $C_{22}H_{35}N_3O_6SSi$)

From **3** and L-*Ala-Gly*-O*Bn*-HCl (1.86 g, 6 mmol) as described for **15**. Yield 0.52 g (42%); colorless liquid; $[\alpha]_D^{20} = +0.95°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3300$ (NH), 1740, 1650 (CO), 1530 (NH), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.28$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 1.37 (d, $J = 9.0$ Hz, CH_3), 2.75 (m, 5-H, 5′-H), 3.98 (dd, $J = 4.0$, 13.0 Hz, 4-H), 3.98 (m, 3-H), 4.11 [d, $J = 7.0$ Hz, 2α-H(*Gly*)], 4.53 (dd, $J = 9.0$, 13.0 Hz, 4′-H) 4.53 [m, α-H(*Ala*)], 5.18 (s, CH_2), 7.03 (m, 2N–H), 7.35 (s, 5arom H) ppm; MS: m/z (%) = 498 (3.56, $M^+ + 1$), 57 (17.12, $C(CH_3)_3^+$), 91 (100, benzyl).

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanylglycine methyl ester (**23b**, $C_{22}H_{35}N_3O_6SSi$)

From **3** and *L-Phe-Gly*-O*Me*-HCl (1.6 g, 6.8 mmol) as **23a**. Yield 1.3 g (52%); colorless crystals; mp 110°C (*DE*); $[\alpha]_D^{20} = -18.53°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR: $\bar{\nu} = 3301$ (NH), 1754, 1643 (CO), 1545 (NH), 1365, 1313, 1152 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.27$ [s, $Si(CH_3)_2$], 1.00 [s, $C(CH_3)_3$], 1.67 (m, 5-H, 5′-H), 3.05 [m, 2β-H(*Phe*)], 3.52 (dd, $J = 3.0$, 13.0 Hz, 4-H), 3.75 (s, OCH_3), 4.00 (m, 3-H), 4.00 [d, $J = 6.0$ Hz, 2α-H(*Gly*)], 4.30 [m, α-H(*Phe*)], 4.86 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 6.75, 6.87, 7.00 (3d, each $J = 7.0$ Hz, N–H), 7.22 (s, 5arom H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-alanyl-L-phenylalanine methyl ester (**23c**, $C_{23}H_{37}N_3O_6SSi$)

From **3** and *L-Ala-L-Phe*-O*Me*-HCl (2.87 g, 10 mmol) as **23a**. Yield 2.4 g (63%); colorless liquid; $[\alpha]_D^{20} = +21.5°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3332$ (NH), 1739, 1648 (CO), 1535 (amide), 1366, 1152 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.29$ [s, $Si(CH_3)_2$], 1.01 [s, $C(CH_3)_3$], 1.34 (d, $J = 7.0$ Hz, CH_3), 2.70 (m, 5-H, 5′-H), 3.12 [d, $J = 7.0$ Hz, 2β-H(*Phe*)], 3.75 (s, OCH_3), 3.97 (m, 3-H, 4-H), 4.43 [m, α-H(*Phe*), α-H(*Ala*)], 4.85 (dd, $J = 7.0$, 14.0 Hz, 4′-H), 6.63 (d, $J = 8.0$ Hz, 2N–H), 7.18 (s, 5arom H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-alanylglycine benzyl ester (**24a**, $C_{16}H_{21}N_3O_6S$)

From **23a** (1.9 g, 3.8 mmol) by desilylation. Yield 700 mg (48%); colorless crystals; mp 114°C ($CHCl_3$); $[\alpha]_D^{20} = -7.3°\ cm^2\ g^{-1}$ ($c = 1.2$, $CHCl_3$); IR: $\bar{\nu} = 3373$ (NH), 1744, 1650 (CO), 1534 (amide), 1308, 1156 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3/D_2O$): $\delta = 1.33$ (d, $J = 7.0$ Hz, CH_3), 2.69 (d, $J = 6.0$ Hz, 5-H, 5′-H), 3.97 [s, 2α-H(*Gly*)], 4.00–4.23 [m, α-H(*Ala*), 3-H, 4-H], 4.41 (dd, $J = 7.0$, 14.0 Hz, 4′-H), 5.10 (s, OCH_2), 7.26 (s, 5arom H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-phenylalanylglycine methyl ester (**24b**, $C_{16}H_{21}N_3O_6S$)

From **23b** (1.7 g, 3.4 mmol) by desilylation. Yield 1.1 g (85%); colorless crystals; mp 136°C (*Et*OH); $[\alpha]_D^{20} = -18.0°\ cm^2\ g^{-1}$ ($c = 1$, *Ac*O*Et*); IR: $\bar{\nu} = 3304$ (NH), 1746, 1638 (CO), 1551 (amide), 1314, 1156 (SO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/DMSO$-d_6): $\delta = 2.52$ (dd, $J = 6.0$, 15.0 Hz, 5-H), 2.67 (dd, $J = 7.5$, 15.0 Hz, 5′-H), 2.89 [d, $J = 7.5$ Hz, β-H(*Phe*)], 3.19 [d, $J = 5$ Hz, β'-H(*Phe*)], 3.70 (s, OCH_3), 3.80 (m, 3-H, 4-H), 3.96 [dd, $J = 6.0$, 18.0 Hz, CH_2(*Gly*)], 4.16 [m, α-H(*Phe*)], 4.77 (dd, $J = 9.0$, 13.5 Hz, 4′-H), 7.07 (m, N–H), 7.22 (s, 5arom H), 7.87 (d, $J = 9.0$ Hz, N–H), 8.04 (d, $J = 9.0$ Hz, N–H) ppm.

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-alanyl-L-phenylalanine methyl ester (**24c**, $C_{17}H_{23}N_3O_6S$)

From **23c** (1.74 g, 3.4 mmol) by desilylation. Yield 1.1 g (85%); colorless crystals; mp 165°C ($CHCl_3$); $[\alpha]_D^{20} = +10.4°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3/DMSO$); IR: $\bar{\nu} = 3373$, 3289 (NH), 1719, 1648 (CO), 1545 (amide), 1297, 1159 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3/DMSO$-d_6): $\delta = 1.32$ (d, $J = 7.5$ Hz, CH_3), 2.65 (d, $J = 6.0$ Hz, 5-H, 5′-H), 3.19, 3.00 [2dd, $J = 6.0$, 13.0 Hz, 2β-H(*Phe*)], 3.69 (s, OCH_3), 3.94 (dd, $J = 4.5$, 15.0 Hz, 4-H), 4.00 (m, 3-H), 4.32 [m, α-H(*Phe*), α-H(*Ala*)], 4.74 (dd, $J = 7.0$, 15.0 Hz, 4′-H), 7.05 (m, 2N–H), 7.21 (s, 5arom H), 7.60, 7.65 (d, $J = 7.0$ Hz, N–H) ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-alanyl-L-proline benzyl ester (**25**, $C_{25}H_{39}N_3O_6SSi$)

From **3** and L-*Ala*-L-*Pro*-O*Bn*-HCl (4.2 g, 13.4 mmol) as described for **15**. Yield 4.9 g (91%); colorless liquid; $[\alpha]_D^{20} = -47.77°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3300$ (NH), 1745, 1630 (CO), 1315, 1150

(SO_2) cm^{-1}; ^1H NMR: $\delta = 0.23$ [s, $Si(CH_3)_2$], 0.93 [s, $C(CH_3)_3$], 1.27 (d, $J = 9.0$ Hz, CH_3), 2.00 [m, 2β-H(*Pro*), 2γ-H(*Pro*)], 2.73 (m, 5-H, 5′-H), 3.63 [m, 2δ-H(*Pro*)], 3.96 (dd, $J = 4.0$, 13.0 Hz, 4-H), 3.96 (m, 3-H), 4.63 (dd, $J = 9.0$, 13.0 Hz, 4′-H), 4.63 [m, α-H(*Ala*), α-H(*Pro*)], 5.15 (s, OCH_2), 7.03 (d, $J = 9.0$ Hz, N–H), 7.30 (s, 5arom H) ppm; MS: m/z (%) = 538 (27.58, $M^+ + 1$), 57 (23.67, $C(CH_3)_3^+$), 91 (100, benzyl).

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-alanyl-L-proline benzyl ester (**26**, $C_{19}H_{25}N_3O_6S$)

From **25** (2.3 g, 4.3 mmol) by desilylation. Yield 500 mg (28%); colorless crystals; mp 130°C (*Et*OH); $[\alpha]_D^{20} = -70.6°\ cm^2\ g^{-1}$ ($c = 1.7$, $CHCl_3$); IR: $\bar{\nu} = 3285$ (NH), 1739, 1631 (CO), 1550 (NH), 1300, 1159 (SO_2) cm^{-1}; ^1H NMR (100 MHz): $\delta = 1.26$ (d, $J = 7.5$ Hz, CH_3), 1.97 [m, β-H(*Pro*), 2γ-H(*Pro*)], 2.20 [m, β-H(*Pro*)], 2.55, 2.61 (dd, $J = 5.5$, 15.0 Hz, 5-H), 2.65 (dd, $J = 7.5$, 17.5 Hz, 5′-H), 3.58, 3.70 [m, 2δ-H(*Pro*)], 3.88 (m, 3-H), 3.92 (dd, $J = 4.5$, 13.0 Hz, 4-H), 4.26 (dd, $J = 9.0$, 14.0 Hz, 4′-H), 4.49 [t, $J = 4.5$ Hz, α-H(*Pro*)], 4.72 [m, α-H(*Ala*)], 5.11 (dd, $J = 12.0$ Hz, OCH_2), 6.32, 6.48 (2s, N–H), 7.30 (s, 5arom H) ppm; ^{13}C-NMR: $\delta = 17.45$ (CH_3), 24.80 [C-γ(*Pro*)], 28.81 [C-β(*Pro*)], 37.70, 37.89 (C-3), 40.68, 41.06 (C-5), 46.37, 46.62 [C-α(*Ala*)], 46.92 [C-δ(*Pro*)], 59.07 [C-α(*Pro*)], 64.55 (C-4), 66.90 (OCH_2), 128.07, 128.35, 128.52, 135.36 (arom C), 168.74 [CO(ester)], 171.32 [CO(*Ala*)], 171.52 [CO(*Pro*)] ppm.

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-alanyl-L-proline (**27**, $C_{18}H_{33}N_3O_6SSi$)

From **25** (0.4 g, 0.74 mmol) by hydrogenolysis as **19**. Yield 0.31 g (90%); colorless liquid; $[\alpha]_D^{20} = -65.8°\ cm^2\ g^{-1}$ ($c = 1.2$, $CHCl_3$); IR (film): $\bar{\nu} = 3350$ (NH), 1750, 1640 (CO), 1315, 1160 (SO_2) cm^{-1}; ^1H NMR (250 MHz): $\delta = 0.24$ [s, $Si(CH_3)_2$], 0.97 [s, $C(CH_3)_3$], 1.28 (d, $J = 6.0$ Hz, CH_3), 2.04–2.43 [m, 2β-H(*Pro*), 2γ-H(*Pro*)], 2.63, 2.68 (dd, $J = 10.0$, 17.0 Hz, 5-H), 2.70, 2.81 (dd, $J = 4.0$, 17.0 Hz, 5′-H), 3.58–3.73 [m, 2δ-H(*Pro*)], 3.95 (dd, $J = 3.0$, 13.0 Hz, 4-H), 3.95 (m, 3-H), 3.96, 4.00 (dd, $J = 4.0$, 15.0 Hz, 4-H), 4.45 [m, α-H(*Pro*), α-H(*Ala*)], 4.47, 4.75 (dd, $J = 8.0$, 15.0 Hz, 4′-H), 5.78 (s, COOH), 7.54, 7.60 (2d, $J = 7.0$ Hz, N–H) ppm; MS: m/z (%) = 448 (1.16, $M^+ + 1$), 57 (41.27, $C(CH_3)_3^+$), 390 (2.05, M^+-isobutyl), 188 (1.88, M^+-*Ala-Pro*), 115 (14.5, *TBDMS*), 70 (100, pyrrolidene).

N-{2-[(RS)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-alanylglycine (**28**, $C_{15}H_{29}N_3O_6SSi$)

From **23a** (0.4 g, 0.8 mmol) by hydrogenolysis as **19**. Yield 0.29 g (90%); colorless liquid; $[\alpha]_D^{20} = +16.3°\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$); IR (film): $\bar{\nu} = 3330$ (NH), 1735, 1650 (CO), 1545 (amide), 1305, 1150, 1070 (SO_2) cm^{-1}; ^1H NMR: $\delta = 0.28$ [s, $Si(CH_3)_2$], 0.96 [s, $C(CH_3)_3$], 1.34 (d, $J = 9.0$ Hz, CH_3), 2.78 (m, 5-H, 5′-H), 3.94 [s, 2α-H(*Gly*)], 3.79–4.19 (m, 3-H, 4-H), 4.49 (dd, $J = 9.0$, 14.0 Hz, 4′-H), 4.49 [m, α-H(*Ala*)], 7.46 (s, COOH), 8.01 (s, 2N–H) ppm; MS: m/z (%) = 408 (1.89, $M^+ + 1$), 57 (15.36, $C(CH_3)_3^+$), 263 (1.26, M^+-*Ala-Gly*), 147 (100, M^+-*Ala-Gly-TBDMS*), 145 (12.52, *Ala-Gly*), 115 (5.43, *TBDMS*).

4,4-Dimethyl-1,2-thiazetidine 1,1-dioxide (**29**)

See Ref. [17].

Benzyl 4,4-dimethyl-1,2-thiazetidine-2-acetate 1,1-dioxide (**30**, $C_{13}H_{17}NO_4S$)

At −78°C under N_2 2.2 cm^3 of *Bu*Li (3.52 mmol) were added to a solution of **29** (470 mg, 3.48 mmol) in 30 cm^3 of *THF*. After 5 min 5 cm^3 of *HMPT*, and 0.66 cm^3 of benzyl bromoacetate (4.14 mmol) were

added. After stirring for 1 h, 100 cm^3 of *DE* were added, the mixture was washed with a satd. solution of NH_4Cl ($3 \times 100\ cm^3$), the organic layer was dried (Na_2SO_4), evaporated, and the residue was purified by FC (*DE*:cyclohexane = 1:1). Yield 770 mg (78%); colorless solid; mp 59.5–61°C; $R_f = 0.23$; IR (film): $\bar{\nu} = 2968$, 2932, 2878 (CH), 1746 (CO), 1309, 1129 (SO_2) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.60$ (s, $2CH_3$), 3.13 (s, 3-H, 3′-H), 3.80 (s, CH_2), 5.17 (s, OCH_2), 7.33 (s, 5arom H) ppm; ^{13}C NMR: $\delta = 21.9$ (CH_3), 46.5 (C-3), 52.5 (CH_2), 67.1 (OCH_2), 74.5 (C-4), 128.3, 128.5, 134.9 (arom C), 167.7 (CO) ppm; MS (CI/isobutane): m/z (%) = 322 (3.2), 284 (100, $M^+ + 1$), 260 (1.8), 256 (13.3), 220 (85.4).

[2-(4,4-Dimethyl-1,1-dioxo-1,2-thiazetidine-2-yl)acetyl]-D-alanyl-D-alanine benzyl ester (**31**, $C_{19}H_{27}N_3O_6S$)

Compound **30** (200 mg, 0.71 mmol) was hydrogenated as described for **19**. The residue was dissolved in 3 cm^3 of *DMF*, pentafluorophenol (155 mg, 0.84 mmol) was added, the mixture was cooled to −20°C, then *EDC* (135 mg, 0.71 mmol) was added, the mixture was stirred at room temperature for 12 h, 30 cm^3 of *Ac*O*Et* were added, the mixture was washed with a satd. solution of NH_4Cl ($3 \times 30\ cm^3$), the organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residue was dissolved in 3 cm^3 of CH_2Cl_2, and D-*Ala*-D-*Ala*-O*Bn*, prepared from *Boc*-D-*Ala*-D-*Ala*-O*Bn* (131 mg, 0.24 mmol), and triethylamine (50 mg, 0.50 mmol) were added. After stirring for 12 h, 50 cm^3 of *Ac*O*Et* were added, the mixture was washed with 50 cm^3 of a satd. solution of NH_4Cl, the organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified by FC (*Ac*O*Et*). Yield 47 mg (16%); yellow viscous liquid; $R_f = 0.4$ (*Ac*O*Et*); $[\alpha]_D^{27} = +30.2°\ cm^2\ g^{-1}$ ($c = 0.5$, *Ac*O*Et*); IR (film): $\bar{\nu} = 3423$ (NH), 1739, 1661 (CO), 1302, 1168 (SO_2) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.38$, 1.40 [2d, $J = 5.0$ Hz, $2CH_3$(*Ala*)], 1.65, 1.68 [2s, $2CH_3$(C-4)], 3.08 (dd, $J = 6.0$ Hz, 3-H, 3′-H), 3.69 [dd, $J = 17.0$ Hz, CH_2(N)], 4.42–4.61 [m, 2CH(*Ala*)], 5.15 (dd, $J = 12.0$ Hz, OCH_2), 6.53 (d, $J = 7.0$ Hz, N–H), 7.09 (d, $J = 8.0$ Hz, N–H), 7.26–7.38 (m, 5arom H) ppm; ^{13}C-NMR: $\delta = 17.4$, 17.5 [CH_3(*Ala*)], 21.3, 21.5 [CH_3(C-4)], 47.7 (C-3), 48.1, 48.5 [CH(*Ala*)], 52.5 (CH_2), 66.6 (OCH_2), 74.3 (C-4), 127.5, 127.8, 128.0, 134.6 (arom C), 166.4, 170.6 (CON), 171.7 (COO) ppm.

4,4-Dimethyl-N-phenyl-1,2-thiazetidine-2-carboxamide 1,1-dioxide (**32**, $C_{11}H_{14}N_2O_3S$)

Compound **29** (200 mg, 1.47 mmol), phenyl isocyanate (175 mg, 1.47 mmol), and dibutyltin dilaurate (3 drops) in 40 cm^3 of C_6H_6 were refluxed for 3 h. Then, the solvent was evaporated, and the residue was purified by FC (*Ac*O*Et*:cyclohexane = 1:1). Yield 227 mg (61%); colorless solid; mp 165–167°C; $R_f = 0.45$; IR: $\bar{\nu} = 3280$ (NH), 1664 (CO), 1320, 1176, 1122 (SO_2) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): $\delta = 1.69$ (s, $2CH_3$), 3.64 (s, 3-H, 3′-H), 7.07–7.56 (m, 5arom H), 8.23 (s, N–H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 21.9$ (CH_3), 49.6 (C-3), 75.2 (C-4), 120.9, 124.6, 129.5, 139.1 (arom C), 150.1 (CO) ppm.

2-[(S)-2-(tert-Butyldimethylsilyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl-D-alanyl-D-alanine benzyl ester (**33**, $C_{23}H_{37}N_3O_6SSi$)

From **8** (230 mg, 0.62 mmol), pentafluorophenol (140 mg, 0.74 mmol), *EDC* (118 mg, 0.62 mmol), and D-*Ala*-D-*Ala*-O*Bn*, prepared from *Boc*-D-*Ala*-D-*Ala*-O*Bn* (131 mg, 0.24 mmol), as described for **31**. Yield 90 mg (28.4%); yellow viscous liquid; ^1H NMR (300 MHz): $\delta = 0.26$, 0.28 [2s, $Si(CH_3)_2$], 0.98 [s, $C(CH_3)_3$], 1.37, 1.43 [2d, $J = 7.1$ Hz, $2CH_3$(*Ala*)], 2.67 (dd, $J = 10.0$, 15.0 Hz, 5-H), 2.83 (dd, $J = 4.0$, 15.0 Hz, 5′-H), 3.91–4.26 (m, 3-H, 4-H, 4′-H), 4.33–4.63 [m, 2CH(*Ala*)], 5.18 (dd, $J = 12.2$ Hz, OCH_2), 6.48, 6.50 (2s, 2N–H), 7.30–7.37 (m, 5arom H) ppm.

Boc-Cys(SBn)-D-Ala-OBn (**34**, $C_{25}H_{32}N_2O_5S$)

Boc-L-*Cys*(S*Bn*)-OH (2.0 g, 6.4 mmol), *NHS* (1.47 g, 7.0 mmol), D-*Ala*-O*Bn*-p-*Ts* (2.25 g, 6.4 mmol), and 0.9 cm^3 of triethylamine (6.4 mmol) were dissolved in 20 cm^3 of *DMF*, cooled to −20°C, and *DCC* (1.45 g,

7.0 mmol) was added. After stirring for 12 h, 100 cm^3 of *AcOEt* were added, the mixture was washed with a satd. solution of NH_4Cl ($2 \times 100\ cm^3$), the organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified by FC (*AcOEt*:cyclohexane = 1:2). Yield 2.15 g (71%); colorless solid; mp 74–76°C; $R_f = 0.55$; $[\alpha]_D^{27} = +21.8°\ cm^2\ g^{-1}$ ($c = 1$, *AcOEt*); IR: $\bar{\nu} = 3334$ (NH), 1730, 1689, 1652 (CO) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.41$ [d, $J = 7.0$ Hz, CH_3(*Ala*)], 1.46 [s, $C(CH_3)_3$], 2.75 [dd, $J = 7.0$, 14.0 Hz, β-H(*Cys*)], 2.86 [dd, $J = 6.0$, 14.0 Hz, β'-H(*Cys*)], 3.73 (dd, $J = 13.0$ Hz, SCH_2), 4.25 [m, α-H(*Cys*)], 4.55–4.65 [m, α-H(*Ala*)], 5.17 (dd, $J = 12.0$ Hz, OCH_2), 5.23 (s, NH_2), 6.73 (d, N–H), 7.27–7.40 (m, 10arom H) ppm.

N-[(R)-(1,1-Dioxo-1,2-thiazetidine-3-yl)carbonyl]-D-alanine benzyl ester
(**35**, $C_{13}H_{16}N_2O_5S$)

The mixture of **34** (2.15 g, 4.55 mmol), 15 cm^3 of *TFA*, and 4.2 cm^3 of propane-2-thiol was stirred at room temperature for 2 h. After evaporation *in vacuo*, 100 cm^3 of a solution of Na_2CO_3 (10%) were added, the mixture was extracted with $2 \times 100\ cm^3$ of *DE*, and a satd. solution of HCl was added to the combined organic layers. After storing for 24 h at 0°C, the solvent was separated, the residue was dried *in vacuo*, and dissolved in a mixture of 5 cm^3 of acetic acid and 0.7 cm^3 of H_2O. With cooling to <20°C, the mixture was saturated with Cl_2 for about 15 min, poured into 50 cm^3 of pentane, and stirred for 5 min. The organic layer was separated, the residue was dissolved in 50 cm^3 of *THF*, and triethylamine was added until the *pH* was alkaline. After stirring for 1 h, 100 cm^3 of *AcOEt* were added, the mixture was washed with 100 cm^3 of a satd. solution of NH_4Cl, the organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified by FC (*AcOEt*:cyclohexane = 2:1; then *AcOEt*). Yield 340 mg (24%); colorless solid; mp 117–119°C; $R_f = 0.33$ (*AcOEt*:cyclohexane = 2:1); $[\alpha]_D^{25} = -36.0°\ cm^2\ g^{-1}$ ($c = 0.05$, acetone); IR: $\bar{\nu} = 3324$, 3279 (NH), 1742, 1668 (CO), 1346, 1157 (SO_2) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): $\delta = 1.44$ (d, $J = 7.0$ Hz, CH_3), 4.14–4.21 (m, 3-H), 4.24 (dd, $J = 6.0$, 12.0 Hz, 4-H), 4.50–4.62 [m, α-H(*Ala*)], 4.62 (dd, $J = 3.0$, 12.0 Hz, 4′-H), 5.18 (dd, $J = 13.0$ Hz, OCH_2), 7.27–7.40 (m, 5arom H), 7.43, 7.66 (2s, 2N–H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 17.5$ (CH_3), 40.9 (C-3), 49.1 [CH(*Ala*)], 65.6 (C-4), 67.3 (OCH_2), 128.8, 128.9, 129.3, 137.0 (arom C), 169.5 (CON), 172.7 (COO) ppm.

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