Monatshefte für Chemie 135, 55–68 (2004)
DOI 10.1007/s00706-003-0105-2

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Substituted 1,2-Thiazetidine 1,1-Dioxides. Synthesis and Properties of N-Alkylated and N-Acylated Derivatives of 1,2-Thiazetidine-3-acetic Acid 1,1-Dioxide

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Received August 20, 2003; accepted August 25, 2003
Published online October 20, 2003

Summary. 1,2-Thiazetidine-3-acetic acid 1,1-dioxide was *N*-alkylated using bromoacetates, and *N*-acylated using either acyl chlorides, protected amino acid fluorides, or *N*-protected amino acid *NCA*, which seemed to be the most universal method. Most of the obtained "β-sultam peptides" were sensitive against humidity, they hydrolyzed forming sulfonic acids, and reactions with amines resulted in sulfonamides. Reactions of *N*-acylated products showed that the sulfonyl group was faster attacked than the imide structure.

Keywords. 1,2-Thiazetidine 1,1-dioxide; β-Sultam; β-Sultam peptide.

Introduction

1,2-Thiazetidine 1,1-dioxide (β-sultam) is the sulfone analogue of the β-lactam ring. Its reactivity is depending on the substituents usually higher than that of the analogue β-lactam system. Therefore, it should be highly interesting to replace the β-lactam ring in special compounds by the β-sultam moiety, and to study properties and specific reactivity. We have described a number of β-lactam peptides showing inhibitor activity against the serine protease elastase and/or the cysteine protease papain [1, 2]. In continuation of this project, we synthesized derivatives of 1,2-thiazetidine-3-acetic acid 1,1-dioxide (β-sultam-3-acetic acid) at the C-terminus with esters of amino acids or dipeptides [3]. Here we report about reactions at the nitrogen atom of **1**, and about the properties of those structures obtained by combination of both reactions.

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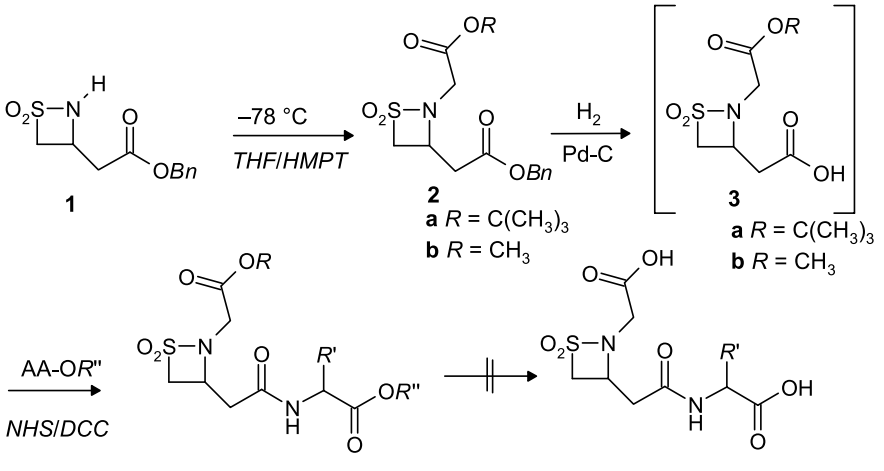
Results and Discussion

To explore the alkylation at the nitrogen atom of the β-sultam ring, we first studied the reaction between **1** and alkyl bromoacetates. The deprotonation was successful only with *Bu*Li. Using NaOH, KOH, or amines we observed always partial or complete ring opening. The alkylation finally was best done at $-78°C$ in *THF* in the presence of *HMPT* [4], whereby yields of up to 80% of **2a** or **2b** were isolated. Without *HMPT* the yields were completely unsatisfactory. After purification by CC, **2a** and **2b** were obtained as colourless viscous liquids, which had to be stored under N_2 at low temperature. By hydrogenolytic cleavage of the benzyl ester group at the *C*-terminus we obtained the carboxylic acids **3a** and **3b** as very unstable compounds. Therefore, they were immediately reacted with amino acid esters using the *NHS/DCC* methodology yielding the *N*-alkylated ''sultam peptides'' **4a**–**4e**. These compounds may be interpreted as peptide analogues with two protected *C*-terminals, as the substituent at the nitrogen can be seen as a built-in glycine. We tried different methods to obtain the free diacids, but all experiments failed completely until today. Probably, these diacids are much more sensitive than the acids **3**.

The structures of the diesters were confirmed by the characteristic C–H bands around $\bar{\nu} = 3020\,cm^{-1}$ of the protons in position 4 of the β-sultam ring [5], the SO_2 bands at $\bar{\nu} = 1320$ and $1150\,cm^{-1}$, and the bands of other functional groups in their IR spectra. The ^1H NMR spectra are characterized by the ABX system of the ring protons 3-H (A), 4-H_{trans} (B), and 4′-H_{cis} (X) with coupling constants, *e.g.* for **4b**, $J_{AB} = 6$, $J_{AX} = 8.25$, and $J_{BX} = 12.5$ Hz. The protons of the acetyl part at C-3 show a geminal coupling of $J = 15.8$ Hz, and couplings with 3-H of $J = 6$ and 7.5 Hz, while the coupling constant of the acetyl protons next to the nitrogen is 18 Hz. The protons of the fourth methylene group finally exhibit a clear doublet with $J = 6$ Hz. From these values one might deduce a pseudo equatorial orientation of the protons in the structure of **4b** (Fig. 1). It has to be noted that all



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a $R = CH_3$ $R' = H$ $R'' = Bn$ **b** $R = C(CH_3)_3$ $R' = H$ $R'' = CH_3$
c $R = C(CH_3)_3$ $R' = Bn$ $R'' = CH_3$ **d** $R = CH_3$ $R' = Bn$ $R'' = CH_3$
e $R = C(CH_3)_3$ $R' = (CH_2)_3NHC(=NNO_2)NH_2$ $R'' = CH_3$

Scheme 1

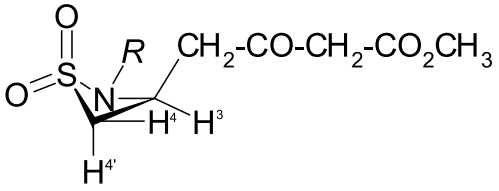
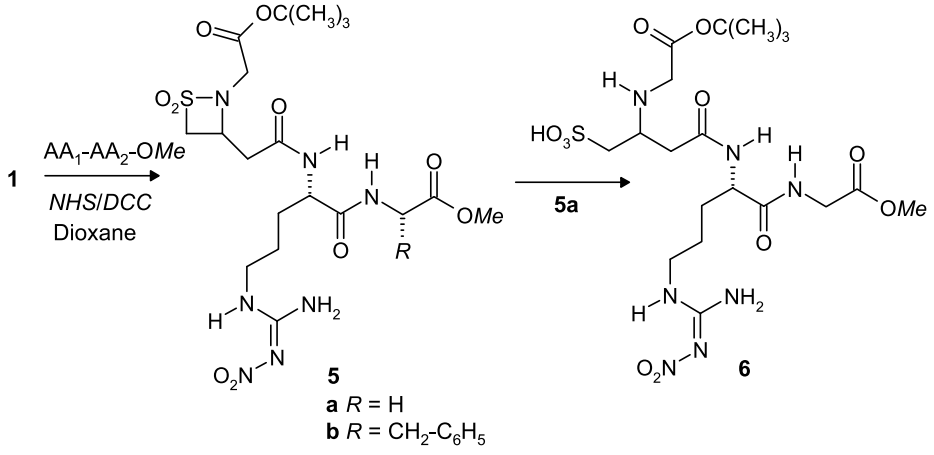


Fig. 1. Structure of **4b** ($R = CH_2CO_2C(CH_3)_3$) as deduced from ^1H NMR data

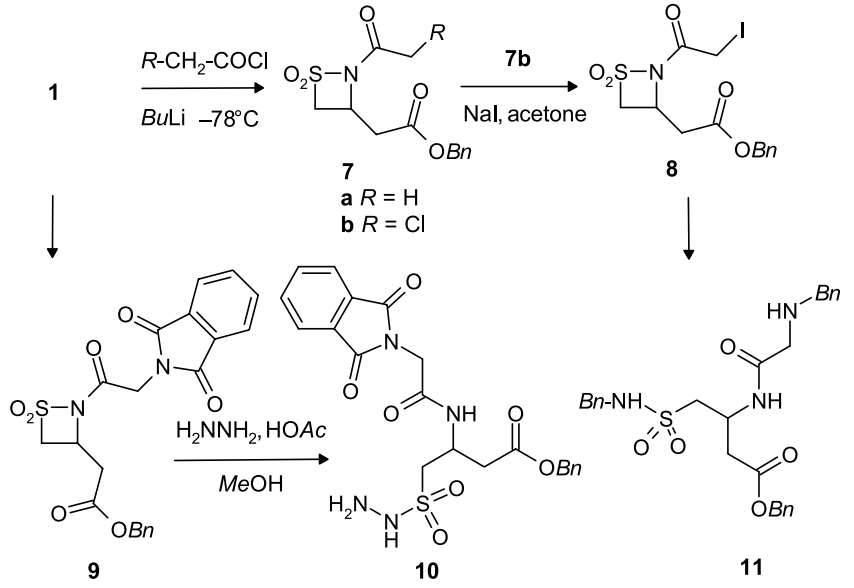


Scheme 2

compounds **4** were isolated as a mixture of two diastereomers as can be detected in the 300 MHz ^1H NMR spectra, and which is caused by the two possible configurations at C-3 of the β-sultam ring.

By analogous reactions between **1** and dipeptide esters compounds **5** were obtained, and the diester **5a** was hydrolyzed yielding the sulfonic acid **6**. Using a ChiraSpher NT column we could demonstrate in a HPLC experiment, that during the synthesis of **5a** no racemization had occurred in the peptide part. Only two lines were found.

Another possibility of substitution at the nitrogen is opened by acylation of the β-sultam. The success of these reactions depends very strongly on the reaction conditions [6]. Reactions between **1** and acyl chlorides in *THF* in the presence of triethylamine as reported for similar systems [7] or in the presence of NaH [8] failed. But, when the reactions were done at $-78°C$ using *Bu*Li, the *N*-acylated β-sultams **7a** and **7b** were isolated with yields of 60–70%. While **7a** is a stable solid compound, **7b** was obtained as an unstable viscous liquid, which after a short time, decomposed with release of chloroacetic acid. Nevertheless, we tried to use the reactive chlorine for substitution reactions by nucleophils. Reactions of **7b** with ammonia, phthalimide potassium in *DMF*, benzylamine, or sodium azide gave no isolable β-sultam derivatives. Only from the reaction with benzylamine we isolated *N*-benzylchloroacetamide [9]. However, the replacement of chlorine by iodine was successful, and **8** was obtained as a viscous liquid with 56% yield. When **8** was stirred with benzylamine the iodine was replaced by benzylamine, but the benzylamine also attacked the β-sultam ring yielding the open chain sulfonamide **11** as a



Scheme 3

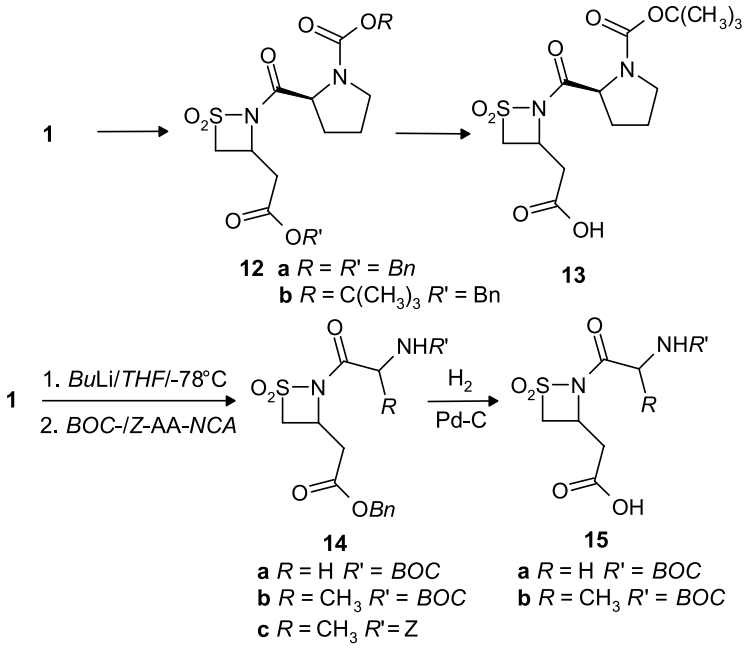
stable solid. An attack to the imide structure as in the reaction of **7b** with benzylamine was not observed.

Next we studied the acylation of **1** with *N*-protected amino acid halogenides. Phthaloylglycine [10] was transformed into the stable acid chloride with PCl_5 [11, 12], and reacted with **1** in an inverse reaction, the solution of **1** with *Bu*Li was added to the solution of the acyl chloride, yielding the *N*-(phthaloylglycyl)-β-sultam **9** with 44% yield. As deprotection of **9** with hydrazine was not successful, no defined product could be found, we tried the "soft method" of *Schwyzer et al.* [13] using hydrazine acetate in methanol. The obtained product **10** demonstrated once more that the β-sultam ring is much easier attacked by nucleophiles than the imide structure.

Reactions between **1** and *N*-protected amino acid fluorides [14, 15] failed with *Z-L-Ala*-F and *Boc-Gly*-F, probably caused by a base catalyzed intramolecular formation of oxazolinones [16], but were successful when we used *Boc*- or *Z-L-Pro*-F yielding **12a** and **12b**. The benzyl ester group of **12b** was hydrogenated giving the acid **13**, but deprotection of the proline nitrogen was not possible.

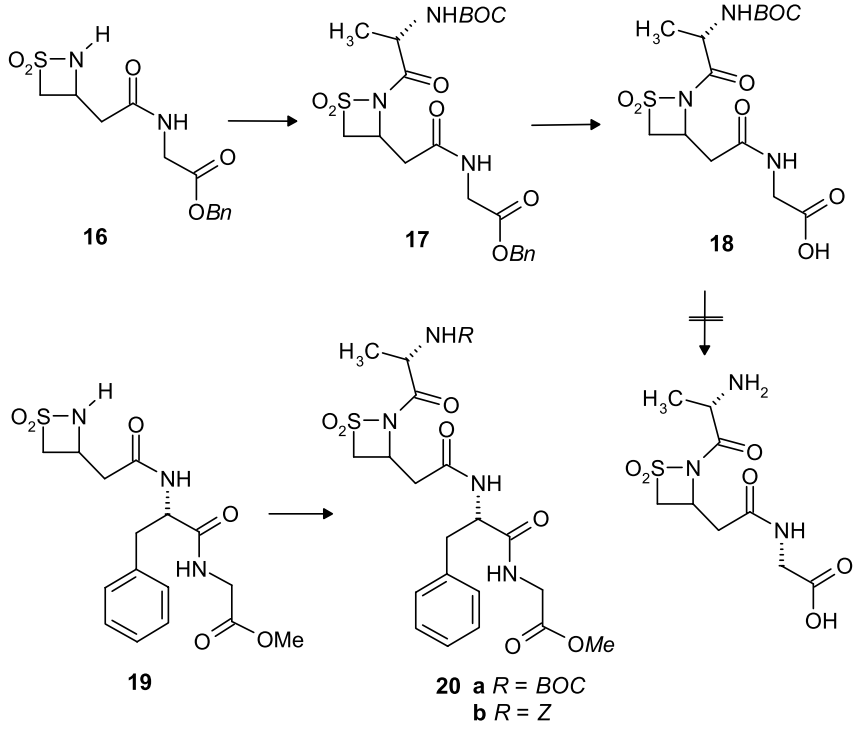
The most versatile method for the acylation of **1** with amino acid derivatives was the reaction with *Boc*- or *Z*-protected amino acid *N*-carboxyanhydrides (*NCA*) [17, 18] at $-78°C$ in *THF* in the presence of *Bu*Li. Using this method, we obtained the *N*-substituted β-sultams **14a**–**14c** as relatively stable compounds with yields about 60%. Compound **14c**, obtained from *Z-L-Ala-NCA* and **1** was partially hydrolyzed to the sulfonic acid during purification by CC. **14a** and **14b** were transformed into the acids **15a** and **15b** by hydrogenolysis in the presence of Pd-C.

The IR spectra of the *N*-acylated β-sultams show a shift of $20\,cm^{-1}$ to higher wave numbers for the sulfonyl bands. Furthermore, they are characterized by the C–H bands of the protons at C-4 of the β-sultam around $\bar{\nu} = 3040\,cm^{-1}$. In their ^1H NMR spectra we found the typical ABX system, 4-H (A), 3-



Scheme 4

H (B), and 4′-H (X) with the coupling constants $J_{cis} = 8$, $J_{trans} = 4$, and $J_{gem} = 13$ Hz (*e.g.* for **9**). The diastereotopic protons of the acetyl part at C-3 show the coupling constants $J_{gem} = 17$, $J_{cis} = 3.5$, and $J_{trans} = 10$ Hz.



Scheme 5

The reaction of **13**, **15b**, or **15a** with *L-Phe-OMe* or *Gly-OBn* using the *NHS/DCC* method gave no defined product. Therefore, we tried the opposite sequence starting with the "sultam peptides" **16** and **19** [2]. When these compounds were acylated with *Boc-* or *Z-L-Ala-NCA* we isolated the compounds **17**, **20a**, and **20b** as solid compounds with yields between 80 and 90%. By hydrogenation of **17** the acid **18** was accessible (yield 97%), but all experiments to deprotect the *N*-terminus were unsuccessful so for.

The reactivity against nucleophiles and thereby the stability of substituted β-sultams vary strongly with the substitution pattern at the nitrogen, as can be deduced from the described experiments. A big substituent like the *tert*-butyldimethylsilyl group inhibits the attack to the sulfonyl group [19], while smaller groups like alkyl or trimethylsilyl do not stabilize the system. Compounds **4** behave similar. *N*-Acylated products are much more reactive and sensitive. The β-sultam ring might be opened either by acid or by base catalyzed attack. This probably explains why we obtained free acids only in some special cases. The isolated products of hydrolysis are described in the experimental part, following the description of the parent β-sultam. Further experiments concerning stability and reactivity are under investigation.

Using standard procedures a selected number of compounds were tested as inhibitors of proteases and/or as antiinfectives, but no exciting biological activity was found.

Experimental

Melting points: *Linström* apparatus (uncorrected); IR spectra (KBr): Perkin-Elmer IR 1310, Beckman IR 4240, IR 33; ^{1}H 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, $CDCl_3$, if not noted otherwise, MS spectra: Finnigan GC MS 4000, MAT 312, MAT 44 S; elemental analyses: Institute of Pharmacy, or Chemisches Laboratorium, University of Freiburg: 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.

Abbreviations: *Bu*Li = *n*-Butyllithium, 15% in hexane; CC = Column chromatography (Silica gel 60, Merck 7734, 0.063–0.200 mm); *DCC* = Dicyclohexyl carbodiimide; *AcOEt* = Ethyl acetate; *HMPT* = Hexamethylphosphortrisamide; *NHS* = *N*-Hydroxysuccinimide; *TEA* = Triethylamine; TLC = thin layer chromatography (DC Fertigplatten Silica gel 60 F_{254}, Merck 5549 or 5715).

Benzyl (RS)-1,2-Thiazetidine-3-acetate 1,1-Dioxide (**1**)

See Ref. [7a].

General Procedure for the N-Alkylation of ***1***

At -78°C and under a N_2 atmosphere, 10 mmol of *Bu*Li were added to a solution of 2.55 g of **1** (10 mmol), and 3.6 g of *HMPT* (20 mmol) in 100 cm^3 of *THF*. After 2 min, 20 mmol of the bromoacetate in 20 cm^3 of *THF* were added dropwise. Stirring was continued for 15 min at -78°C, then the mixture was warmed to room temperature, and hydrolyzed with a satd. solution of NaCl (100 cm^3). The organic layer was dried (Na_2SO_4), and evaporated *in vacuo*. The residue was dissolved in 200 cm^3 of diethyl ether, it was washed with 3×100 cm^3 of H_2O, dried (Na_2SO_4), and the solvent was evaporated.

tert-Butyl (RS)-3-(Benzyloxycarbonylmethyl)-1,2-thiazetidine-2-acetate 1,1-Dioxide (**2a**)

See Ref. [7a].

Methyl (RS)-3-(Benzyloxycarbonylmethyl)-1,2-thiazetidine-2-acetate 1,1-Dioxide (**2b**, $C_{14}H_{17}NO_6S$)

From 3.06 g (20 mmol) of methyl bromoacetate. Purification by CC ($CHCl_3$:*Ac*O*Et* = 9:1). Yield 2.9 g (87%); colourless viscous liquid; IR (Film): $\bar{\nu} = 3030$, 2960 (CH), 1495, 750 (*ar*), 1735 (CO), 1325, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.85$ (m, 5-H, 5-H′), 3.83 (s, NCH_2), 3.88 (m, 3-H), 3.90 (m, 4-H), 4.35 (dd, $J = 15$, 9 Hz, 4-H′), 5.05 (s, CH_2), 7.25 (s, 5arom H) ppm.

General Procedure for the Hydrogenolysis of the Benzyl Ester

The benzyl ester (5 mmol) was dissolved in 50 cm^3 of *THF*, 0.3 g of Pd-C (10%) were added, and the mixture was hydrogenated (1 atm) at room temperature until the ester was completely converted (TLC control, ~2 h). The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was dried for 1 h at 0.3 Torr.

General Procedure for the Reaction with Amino Acid or Dipeptide Ester

The residue of the hydrogenolysis or 5 mmol of the isolated acid **3** was dissolved in 50 cm^3 of CH_2Cl_2, 1.16 g of *NHS* (10 mmol), a suspension of 8 mmol of the ester salt, and 0.8 mmol of *TEA* in 20 cm^3 of CH_2Cl_2 were added. The mixture was cooled to −10°C, and 10 mmol of *DCC* in CH_2Cl_2 were added. After 3 h at −10°C and 12 h stirring at room temperature, the mixture was filtered, and the solvent was evaporated *in vacuo*.

N-{2-[(RS)-2-(Methoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine Benzyl Ester (**4a**, $C_{16}H_{20}N_2O_7S$)

From **2b** (0.83 g, 2.5 mmol), *Gly*-O*Bn*-tosylate (1.35 g, 0.4 mmol), *NHS* (0.58 g, 5 mmol), *TEA* (0.4 g, 0.4 mmol), and *DCC* (0.65 g, 3.3 mmol). Purification by CC (*Ac*O*Et*). Yield 750 mg (78%); viscous liquid; IR (Film): $\bar{\nu} = 3380$ (NH), 3020, 2950 (CH), 1740, 1660 (CO), 1540 (Amide), 1320, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.80$ (d, $J = 7$ Hz, 5-H, 5-H′), 3.73 (s, OCH_3), 4.00 (s, 2H, 1-H′), 4.08 (s, 2α-H), 3.80–4.23 (m, 4-H, 4-H′, 3-H), 5.15 (s, CH_2), 6.93 (m, NH), 7.24 (s, 5arom H) ppm.

N-{2-[(RS)-2-(tert-Butoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-glycine Methyl Ester (**4b**, $C_{13}H_{22}N_2O_7S$)

From **2a** (1.85 g, 5 mmol), *NHS* (1.16 g, 10 mmol), *Gly*-O*Me*-HCl (1.06 g, 10 mmol), *TEA* (1.0 g, 10 mmol), and *DCC* (1.3 g, 6.6 mmol). Purification by CC (*Ac*O*Et*). Yield 1.35 g (77%); colourless solid; mp 105°C (diethyl ether); IR: $\bar{\nu} = 3330$ (NH), 3080, 3040, 2980, 2930, 2850 (CH), 1760, 1745, 1675 (CO), 1550 (Amide), 1320, 1165, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.48$ [s, $C(CH_3)_3$], 2.80 (dd, $J = 6$, 15.8 Hz, 5-H), 2.90 (dd, $J = 7.5$, 15.8 Hz, 5-H′), 3.72 (s, OCH_3), 3.88 (AB, $J = 18$ Hz, 2H, 1-H′), 3.95, 4.05 (d, $J = 6$ Hz, 2α-H), 4.15 (dd, $J = 6$, 12.7 Hz, 4-H), 4.35 (dd, $J = 8.25$, 12.7 Hz, 4-H′), 7.25, 7.35 (d, $J = 6$ Hz, NH) ppm.

(RS)-5-Aza-2-[(tert-butoxycarbonylmethyl)amino]-4,7-dioxo-7-methoxyheptane-1-sulfonic Acid ($C_{13}H_{24}N_2O_8S$, *Product of Hydrolysis*)

Colorless solid; mp 141°C (dec); IR: $\bar{\nu} = 1741$, 1673 (CO), 1558 (Amide), 1230, 1158, 1033 (SO_3H) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.47$ [s, $C(CH_3)_3$], 2.74 (d, $J = 6$ Hz, 2H, 3-H), 2.89 (d, $J = 6$ Hz, 2H,

1-H), 3.62 (s, OCH_3), 3.87 (d, $J = 6$ Hz, 2H, 2-H′), 3.95 (d, $J = 6$ Hz, 2H, 6-H), 3.87 (m, 2-H), 8.60 (t, $J = 6$ Hz, NH), 9.08 (s, NH_2^+) ppm.

N-{2-[(RS)-2-(tert-Butoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanine Methyl Ester (**4c**, $C_{20}H_{28}N_2O_7S$)

From **2a** (0.7 g, 2 mmol), *L-Phe*-O*Me*-HCl (0.8 g, 0.4 mmol), *NHS* (0.58 g, 5 mmol), *TEA* (0.8 g, 4 mmol), and *DCC* (0.5 g). Purification by CC (*Ac*O*Et*:$CHCl_3 = 1:1$). Yield 630 mg (72%); viscous liquid; IR (Film): $\bar{\nu} = 3360$ (NH), 3030, 2980, 2940, 2860 (CH), 1745, 1670 (CO), 1535 (Amide), 1330, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.40$ [s, $C(CH_3)_3$], 2.68 (d, $J = 7$ Hz, 2H, 5-H), 3.08 (m, 2β-H), 3.68 (s, OCH_3), 3.80 (s, 2H, 1-H′), 4.79 (m, α-H), 3.90–4.40 (m, 4-H, 4-H′, 3-H), 6.65 (d, $J = 9$ Hz, NH), 7.23 (m, 5arom H) ppm; $[\alpha]_D^{25} = +27 \cdot 10^{-10}\ cm^2\ g^{-1}$ ($c = 1$, $CHCl_3$).

N-{2-[(RS)-2-(Methoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanine Methyl Ester (**4d**, $C_{17}H_{22}N_2O_7S$)

From **2b** (1.6 g, 5 mmol), *L-Phe*-O*Me*-HCl (1.6 g, 0.8 mmol), *TEA* (0.8 g, 0.8 mmol), and *DCC* (1.3 g). Purification by CC (*Ac*O*Et*:$CHCl_3 = 1:1$). Yield 1.45 g (73%); colourless solid; mp 74°C (*n*-hexane/$CHCl_3$); IR: $\bar{\nu} = 3320$ (NH), 3050, 3030, 2950, 2930, 2850 (CH), 1740, 1640 (CO), 1530 (Amide), 13150, 1150 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.70$ (d, $J = 7$ Hz, 2H, 5-H), 3.08 (m, 2β-H), 3.68 (s, 2OCH_3), 3.80 (s, 2H, 1-H′), 4.73 (m, α-H), 3.90–4.40 (m, 4-H, 4-H′, 3-H), 6.60 (s, NH), 7.25 (m, 5arom H) ppm; $[\alpha]_D^{25} = +25 \cdot 10^{-10}\ cm^2\ g^{-1}$ ($c = 1.1$, $CHCl_3$).

N-{2-[(RS)-2-(tert-Butoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-nitroarginine Methyl Ester (**4e**, $C_{17}H_{30}N_6O_9S$)

From **3a** (0.88 g, 3.2 mmol), nitro-*Arg*-O*Me*-HCl (1.35 g, 5 mmol), *NHS* (0.72 g, 6.3 mmol), *TEA* (0.75 ml, 5 mmol), and *DCC* (0.71 g, 3.5 mmol). Purification by CC (*Ac*O*Et*:*Et*OH = 5:1). $R_f = 0.43$; yield 0.8 g (51%); mp 91°C (dec); $[\alpha]_D^{20} = -5.04 \cdot 10^{-10}\ cm^2\ g^{-1}$ ($c = 0.83$, *Me*OH); IR: $\bar{\nu} = 3328$ (NH), 2928, 2851 (CH), 1738, 1624 (CO), 1534 (NO_2), 1320, 1156 (SO_2) cm^{-1}; ^1H NMR (300 MHz, 2D-COSY, CD_3OD, 27°C): $\delta = 1.42$ [s, $C(CH_3)_3$], 2.79 (2dd, $J = 15.4$, 6.4 Hz, 5-H, 5-H′), 3.28 [m, 2δ-H(Arg)], 3.73, 3.74* (2s, CH_3O), 3.76 (dd, $J = 17.8$, 3.4 Hz, CHN), 3.91 (dd, $J = 17.8$, 5.6 Hz, CNH′), 3.85 (m, 3-H), 4.07 (ddd, $J = 13.9$, 5.8, 2.4 Hz, 4-H), 4.39 (ddd, $J = 13.9$, 8.3, 1.0 Hz, 4-H′), 4.41 [m, α-H(Arg)] ppm; MS (Fab 26 kV 3): *m/z* = 541 $[M+Na]^+$, 517 $[M+1]^+$, 394 $[M-Boc]^+$, 154 [*p*-O_2N-Ph-$CH_2OH]^+$, 136 [O = C-CH_2-Ph]$^+$. *Ratio of diastereomers = 1:1 (from NMR).

N-{2-[(RS)-2-(tert-Butoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-nitroarginylglycine Methyl Ester (**5a**, $C_{19}H_{33}N_7O_{10}S$)

Compound **3a** (1.5 g, 5.4 mmol), and 1.2 g of *NHS* (10.8 mmol) were dissolved in 100 cm^3 of dioxane, a solution of 3.0 g of nitro-*Arg-Gly*-O*Me*-HCl (6 mmol) and 0.8 cm^3 of *TEA* (6 mmol) in 200 cm^3 of dioxane was added, and the mixture was cooled to −10°C. Then, *DCC* (1.2 g, 6 mmol) dissolved in 20 cm^3 of dioxane was added, and the mixture was stirred for 12–15 h. The mixture was filtered, and the solvent was evaporated *in vacuo*. Purification of the residue by CC (*Ac*O*Et*:*Et*OH = 5:1). Yield 350 mg (18%); colourless solid; mp 86°C (dec); $[\alpha]_D^{20} = -5.83 \cdot 10^{-10}\ cm^2\ g^{-1}$ ($c = 0.6$, *Me*OH); IR: $\bar{\nu} = 3364$ (NH), 2980, 2951 (CH), 1739, 1654 (CO), 1536 (NO_2), 1320, 1300, 1264, 1154 (SO_2) cm^{-1}; ^1H NMR (300 MHz, 2D-COSY, CD_3OD, 27°C): $\delta = 1.45$ [s, $C(CH_3)_3$], 1.72–1.91 [m, 2β-H(Arg), 2γ-H(Arg)], 2.77 (2dd, $J = 17.0$, 5.3 Hz, 5-H, 5-H′), 3.23 [m, 2δ-H(Arg)], 3.71, 3,72* (2s, CH_3O), 3.76 (dd, $J = 17.6$, 2.4 Hz, CHN), 3.91 (m, CH′N), 3.83 (m, 3-H), 4.02 [m, 2α-H(Gly)], 4.19 (dd, $J = 12.9$, 5.9 Hz, 4-H), 4.39 (dd, $J = 12.9$, 8.3 Hz, 4-H′), 4.43 [m, α-H(Arg)] ppm; MS (FAB 26 kV

3): $m/z = 574$ $[M+Na]^+$, 552 $[M]^+$, 496 $[M^+\text{-}NO_2]$, 153 [*p*-O_2N-Ph-$CH_2OH]^+$, 150 [*p*-O_2N-Ph-C=O]$^+$, 136 [O=C-CH_2-Ph]$^+$, 107 $[PhCH_2O]^+$; HPLC: $t_1 = 14.00$, $t_2 = 15.15$ min, ChiraSpher NT, *n*-hexane:EtOH = 1:1.

N-{2-[(RS)-2-(tert-Butoxycarbonylmethyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-nitroarginyl-phenylalanine Methyl Ester (**5b**, $C_{26}H_{39}N_7O_{10}S$)

From **3a** (1.3 g, 4.5 mmol), *NHS* (1.0 g, 9.0 mmol), nitro-*Arg-Phe*-O*Me*-HCl (2.2 g, 5.2 mmol), *TEA* (0.8 ml, 5.2 mmol), and *DCC* (1.2 g, 6 mmol) as described for **5a**. Yield 150 mg (5.2%); mp 80°C (dec); $[\alpha]_D^{20} = -5.19 \cdot 10^{-10}$ cm^2 g^{-1} ($c = 0.27$, *Et*OH); IR: $\bar{\nu} = 3318$ (NH), 2934 (CH), 1740, 1657 (CO), 1535 (NO_2), 1321, 1290, 1264, 1153 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD, 27°C): $\delta = 1.42$ [s, $C(CH_3)_3$], 1.62–1.95 [m, 2β-H(Arg), 2γ-H(Arg)], 2.73 (m, 5-H, 5-H′), 2.86 (2dd, $J = 15.0$, 8.8 Hz, CH-Ph), 3.14–3.25 [m, 2δ-H(Arg), CH′-Ph], 3.71, 3.73* (2s, CH_3O), 3.74–3.96 (m, CH_2N, 3-H), 4.09 (m, 4-H), 4.29–4.39 [m, α-H(Arg)], 4.71 [m, α-H(Phe)], 7.24 (m, 5arom H) ppm; MS (FAB 26 kV 3): $m/z = 688$ $[M+2Na]^+$, 642 $[M]^+$, 597 $[M\text{-}NO_2+1]^+$, 586 $[M\text{-Boc}+1]^+$, 153 [*p*-O_2N-Ph-$CH_2OH]^+$, 150 [*p*-O_2N-Ph-C=O]$^+$, 136 [O=C-CH_2-Ph]$^+$, 107 $[PhCH_2O]^+$.

(RS)-5,8-Diaza-2-[(tert-butoxycarbonylmethyl)amino]-4,7,10-trioxo-6-[3-(nitroguanidyl)propyl]-10-methoxydecane-1-sulfonic Acid (**6**, $C_{19}H_{35}N_7O_{11}S$)

From **5a** (50 mg, 0.09 mmol) by hydrolysis. Yield 30 mg (58%); colourless solid; mp 112–114°C (dec); $[\alpha]_D^{27} = -21.5 \cdot 10^{-10}$ cm^2 g^{-1} ($c = 0.55$, 1 *N* HCl); IR: $\bar{\nu} = 3371$ (NH), 2985, 2950 (CH), 1738, 1638 (CO), 1544 (NO_2), 1256, 1220, 1154, 1038 (SO_3^-) cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6, 50°C): $\delta = 1.46$ [s, $C(CH_3)_3$], 1.55 [m, 2γ-H(Arg)], 1.72 [m, 2β-H(Arg)], 2.76 (dd, $J = 5.9$, 17.3 Hz, 3-H), 2.79 (dd, $J = 5.9$, 17.3 Hz, 3-H), 2.88 (dd, $J = 4.7$, 14.0 Hz, 1-H), 2.93 (dd, $J = 7.0$, 14.0 Hz, 1-H), 3.15 [m, 2δ-H(Arg)], 3.62 (s, CH_3O), 3.74–3.84 (m, NCH_2, 2-H), 3.90 [dd, $J = 8.8$, 16.9 Hz, α-H(Gly)], 3.99 [dd, $J = 7.1$, 16.9 Hz, α-H′(Gly)], 4.27 [m, α-H(Arg)], 7.81 (s, NH_2), 8.34 (m, 3NH), 9.00 (s, SO_3H) ppm; MS FAB-Gun (Xe, 8 kV, 1 mA), 3 kV: $m/z = 570$ $[M]^+$, 154 [*p*-O_2N-Ph-$CH_2OH+1]^+$, 150 [*p*-O_2N-Ph-C=O]$^+$, 136 [O=C-CH_2-Ph]$^+$, 107 $[PhCH_2O]^+$.

*General Procedure for the Acylation of **1** with Acyl Chlorides*

At −78°C and under a N_2 atmosphere, 3.9 mmol of *Bu*Li were added to a solution of 1.0 g of **1** (3.9 mmol) in 50 cm^3 of *THF*. After 5 min stirring 3.9 mmol of the acyl chloride in 10 cm^3 of *THF* were added dropwise. Stirring was continued for 15 min at −78°C, and after warming to room temperature, the mixture was hydrolyzed with a satd. solution of NaCl (100 cm^3), the organic layer was dried (Na_2SO_4), and the solvent was evaporated *in vacuo*.

Benzyl (RS)-(2-Acetyl-1,2-thiazetidine-3-yl)acetate 1,1-Dioxide (**7a**, $C_{13}H_{15}NO_5S$)

From **1** (1.0 g, 3.9 mmol), *Bu*Li (3.9 mmol), and acetyl chloride (3.5 g, 3.9 mmol). Yield 0.81 g (70%); colourless solid; mp 51°C; IR (Film): $\bar{\nu} = 3040$, 2970 (CH), 1735, 1690 (CO), 1310, 1340, 1160 (SO_2) cm^{-1}; ^{1}H NMR: $\delta = 2.25$ (s, CH_3), 2.71 (dd, 2H, 5-H), 4.26 (m, 3-H), 4.06 (dd, $J = 13$, 3 Hz, 4-H), 4.42 (dd, $J = 13$, 9 Hz, 4-H′), 5.14 (s, CH_2), 7.34 (s, 5arom H) ppm.

(RS)-2-Amino-4-oxo-4-benzyloxybutane-1-sulfonic Acid ($C_{11}H_{15}NO_5S$, *Product of Hydrolysis*)

Colourless solid; mp 145°C (dec); IR: $\bar{\nu} = 1732$ (CO), 1236, 1041 (SO_3H) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.72$ (dd, $J = 3.8$, 11 Hz, 3-H), 2.76 (dd, $J = 2.3$, 11 Hz, 3-H′), 2.85 (dd, $J = 4.5$, 15.8 Hz, 1-H), 2.94 (dd, $J = 6$, 15.8 Hz, 1-H′), 3.75 (m, 2-H), 5.13 (s, CH_2), 7.37 (s, 5arom H), 7.92 (s, NH_3^+) ppm.

Benzyl (RS)-(2-Chloroacetyl-1,2-thiazetidine-3-yl)acetate 1,1-Dioxide (**7b**, $C_{13}H_{14}ClNO_5S$)

From **1** (1.0 g, 3.9 mmol), *Bu*Li (3.9 mmol), and chloroacetyl chloride (0.44 g, 3.9 mmol). Yield 0.74 g (57%); viscous liquid; IR (Film): $\bar{\nu} = 3040$, 2960, 2940, 2870 (CH), 1740 (CO), 1360, 1170, 1190 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.63$ (dd, $J = 10$, 17 Hz, 5-H), 3.38 (dd, $J = 5$, 17 Hz, 5-H′), 4.01 (dd, $J = 13$, 3 Hz, 4-H), 4.03 (m, 3-H), 4.19 (s, CH_2Cl), 4.52 (dd, $J = 13$, 9 Hz, 4-H′), 5.11 (s, CH_2), 7.30 (s, 5arom H) ppm; MS (70 eV): m/z (%) = 270 (2.43) [M-SO_2], 242 (16.09) [M-Benzyl], 65 (9.75) [SO_2^+], 77 (22.92) [$COCH_2Cl$], 91 (100) [Benzyl].

Benzyl (RS)-(2-Iodoacetyl-1,2-thiazetidine-3-yl)acetate 1,1-Dioxide (**8**, $C_{13}H_{14}INO_5S$)

Compound **7b** (0.7 g, 2.1 mmol), and 0.639 of NaI (4.2 mmol) in 30 cm^3 of acetone were refluxed for 2 h. After cooling to room temperature, the mixture was filtered, and the solvent was evaporated *in vacuo*. Purification by CC (*Ac*O*Et*). Yield 0.5 g (56%); yellow viscous liquid; IR (Film): $\bar{\nu} = 3040$, 2960, 2870 (CH), 1740, 1700 (CO), 1350, 1165 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.55$ (dd, $J = 9$, 17 Hz, 5-H), 3.28 (dd, $J = 4$, 17 Hz, 5-H′), 3.78 (s, CH_2I), 4.08 (m, 3-H), 4.10 (dd, $J = 4$, 13 Hz, 4-H), 4.45 (dd, $J = 13$, 9 Hz, 4-H′), 5.05 (s, CH_2), 7.20 (s, 5arom H) ppm; MS (70 eV): m/z (%) = 423 (4.24) [M^+], 254 (3.12) [M-Iodoacetyl], 91 (100) [Benzyl], 107 (37.22) [O-Benzyl], 127 (5.26) [Iodine], 169 (1.21) [Iodoacetyl], 254 (3.12) [PS-58-H].

General Procedure for the Acylation of ß-Sultams with Boc-/Z-L-Amino Acid N-Carboxyanhydrides (NCA) or Amino Acid Fluorides

At −78°C and under a N_2 atmosphere, 3.9 mmol of *Bu*Li were added with stirring to a solution of 1.0 g of **1** (3.9 mmol) in 50 cm^3 of *THF*, and after 3 min 3.9 mmol of the acylation reagent in 10 cm^3 of *THF* were dropwise added. Stirring was continued for 15 min at −78°C, then the mixture was warmed to room temperature, and hydrolyzed with a satd. solution of NaCl. The aqueous layer was twice extracted with *Ac*O*Et*, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. Purification by CC (cyclohexane:*Ac*O*Et* = 1:1), if not noted otherwise.

Benzyl (RS)-2-(Phthaloylglycyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**9**, $C_{21}H_{18}N_2O_7S$)

From **1** and phthalylglycyl chloride (0.87 g, 3.9 mmol). Yield 750 mg (44%); colourless crystals; mp 125°C (*Me*OH); IR: $\bar{\nu} = 3040$, 2980, 2930 (CH), 1774, 1725 (CO), 1365, 1345, 1300, 1163 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.74$ (dd, $J = 10$, 17 Hz, 5-H), 3.35 (dd, $J = 3.5$, 17 Hz, 5-H′), 4.05 (dd, $J = 4$, 13 Hz, 4-H), 4.34–4.43 (m, 3-H), 4.50 (dd, $J = 8$, 13 Hz, 4-H′), 4.59, 4.60 [s, 2α-H(Gly)], 5.06 (s, CH_2), 7.28 (s, 5arom H), 7.82/7.83, 7.68/7.69 (AB, $J = 5.5$ Hz, 4arom H) ppm; MS (70 eV): m/z (%) = 442 (0.49) [$M^+ + 1$], 255 (0.82) [PS-58], 160 (78.42) [Phthalimide].

Benzyl (RS)-4-(Hydrazinosulfonyl)-3-[2-(phthalimido)acetylamino]butanoate (**10**, $C_{21}H_{22}N_4O_7S$)

2.5 cm^3 of a 1 *M* solution of hydrazine acetate in *Me*OH were added with stirring to a suspension of 1.0 g of **9** (2.26 mmol) in 25 cm^3 of MeOH. After 1 h of stirring, the precipitate was separated. Yield 0.9 g (84%); mp 132°C ($CHCl_3$); IR: $\bar{\nu} = 3070$, 3040, 2980, 2930 (CH), 1777, 1725, 1677 (CO), 1371, 1346, 1321, 1172 (SO_2) cm^{-1}; ^1H NMR: $\delta = 2.86$ (dd, $J = 5$, 10.5 Hz, 2-H), 3.08 (dd, $J = 4.5$, 10.5 Hz, 2-H′), 3.50 (dd, $J = 5.5$, 15 Hz, 4-H), 3.70 (dd, $J = 7$, 15 Hz, 4-H′), 3.80 (m, NH), 3.80 (s, NH_2), 4.30 (s, 2α-H), 4.65 (m, 3-H), 5.13 (s, CH_2), 6.83, 7.08 (d, $J = 9$ Hz, NH), 7.33 (s, 5arom H), 7.80 (m, 4arom H) ppm; MS (70 eV): m/z (%) = 474 (0.24) [$M^+ + 1$], 160, 161 (100) [$C_9H_6NO_2^+$], 91 (100) [C_7H_7], 77 (100) [C_6H_5], 104 (100) [C_8H_8].

Benzyl (RS)-4-(Benzylaminosulfonyl)-3-[2-(benzylamino)acetylamino]butanoate (**11**, $C_{27}H_{31}N_3O_5S$)

A mixture of 0.5 g of **8** (1.2 mmol) and 2 cm^3 of freshly distilled benzylamine was stirred at room temperature for 30 min. Purification by CC (CH_2Cl_2:*Ac*O*Et* = 8:2). Yield 350 mg (57%); colourless solid; mp 87°C (CH_2Cl_2/diethyl ether); IR (Film): $\bar{\nu}$ = 3150–2850 (CH), 1735, 1650 (CO), 1320, 1140 (SO_2) cm^{-1}; ^1H NMR: δ = 1.83 (s, NH), 2.50 (dd, J = 6, 17.5 Hz, 2-H), 2.55 (dd, J = 6, 17.5 Hz, 2-H′), 2.98 (dd, J = 4.5, 15 Hz, 4-H), 3.20 (AB, J = 17.3 Hz, 2α-H), 3.28 (dd, J = 9.75, 15 Hz, 4-H′), 3.69 (AB, J = 13 Hz, CH_2), 4.23 (s, CH_2), 4.55 (m, 3-H), 5.10 (s, CH_2), 5.90 (t, J = 4.5 Hz, NH), 7.28 (s, 15arom H), 7.98 (d, J = 13 Hz, NH) ppm; MS (70 eV): m/z (%) = 601 (0.69) [M^++1], 235 (1.41) [M − 3Benzyl], 106 (77.7) [C_7H_8N], 91 (100) [C_7H_7], 77 (13.51) [C_6H_5], 65 (30.99) [C_5H_5].

Benzyl (RS)-2-(Z-L-Prolyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**12a**, $C_{24}H_{26}N_2O_7S$)

From **1** (0.77 g, 3 mmol), and *Z-L-Pro*-F (3 mmol). CC (*n*-hexane:*Ac*O*Et* = 1:1). Yield 0.4 g (27%); viscous liquid; IR (Film): $\bar{\nu}$ = 3060, 3030, 2960, 2880 (CH), 1710 (CO), 1352, 1166 (SO_2) cm^{-1}; ^1H NMR: δ = 1.79–2.06 (m, β-H, 2γ-H), 2.30 (m, β-H), 2.77, 2.81 (dd, J = 10, 17 Hz, 5-H), 3.03, 3.12 (dd, J = 3.5, 17 Hz, 5-H′), 3.59 (m, 2δ-H), 3.82, 3.87 (dd, J = 4.5, 13 Hz, 4-H), 4.22–4.36 (m, 3-H), 4.22, 4.36 (dd, J = 7, 13 Hz, 4-H′), 4.40–4.53 (m, α-H), 4.95–5.20 (m, 2CH_2), 7.33 (s, 10arom H) ppm; $[\alpha]_D^{23} = -20.3 \cdot 10^{-10}\,cm^2\,g^{-1}$ (c = 1, *Ac*O*Et*:$CHCl_3$ = 1:1); MS (70 eV): m/z (%) = 486 (5.04) [M^+], 351 (44.27) [M–Z], 205/204 (100) [$C_{12}H_{14}NO_3^+$], 91/92 (100) [$C_7H_7^+$], 70 (100) [$C_4H_8N^+$], 65 (100) [SO_2H].

Benzyl (RS)-2-(Boc-L-Prolyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**12b**, $C_{21}H_{28}N_2O_7S$)

From **1** (0.94 g, 3.69 mmol), and *Boc-L-Pro*-F (0.8 g, 3.7 mmol). CC (diethyl ether). Yield 1.15 g (66%); light yellow viscous liquid; IR: $\bar{\nu}$ = 3030, 2980, 2930, 2880 (CH), 1705, 1695 (CO), 1351, 1163 (SO_2) cm^{-1}; ^1H NMR: δ = 1.39, 1.42 [s, $C(CH_3)_3$], 1.73–2.08 (m, β-H, 2γ-H), 2.26 (m, β-H), 2.66, 2.70 (dd, J = 9, 17 Hz, 5-H), 3.34, 3.36 (dd, J = 4, 17 Hz, 5-H′), 3.50 (m, 2δ-H), 3.99, 3.95 (dd, J = 4, 16 Hz, 4-H), 4.38 (m, α-H, 3-H), 4.33, 4.43 (dd, J = 9, 16 Hz, 4-H′), 5.10, 5.11 (m, CH_2), 7.31, 7.32 (s, 5arom H) ppm; $[\alpha]_D^{23} = -38.43 \cdot 10^{-10}\,cm^2\,g^{-1}$ (c = 2.61, $CHCl_3$); MS (70 eV): m/z (%) = 453 (1.73) [M^+], 523 (2.88) [M+$C_4H_8N^+$], 361 (1.2) [M–Benzyl], 170 (66.79) [Boc-Pro], 91 (70.58) [$C_7H_7^+$], 70 (100) [$C_4H_8N^+$].

(RS)-2-(Boc-L-Prolyl)-1,2-thiazetidine-3-acetic Acid 1,1-Dioxide (**13**, $C_{14}H_{22}N_2O_7S$)

From **12a** (0.7 g, 1.5 mmol) according to the general procedure. Purification by CC (diethyl ether). Yield 350 mg (65%); viscous liquid; IR (Film): $\bar{\nu}$ = 2980, 2930 (CH), 1707 (CO), 1367, 1352, 1164 (SO_2) cm^{-1}; ^1H NMR: δ = 1.38, 1.41 [s, $C(CH_3)_3$], 1.83–2.18 (m, β-H, 2γ-H), 2.34 (m, β-H), 2.68, 2.72 (dd, J = 9, 17 Hz, 5-H), 3.41, 3.43 (dd, J = 4, 17 Hz, 5-H′), 3.50 (m, 2δ-H), 4.03, 4.07 (dd, J = 4, 17 Hz, 4-H), 4.44 (m, α-H, 3-H), 4.39, 4.55 (dd, J = 9, 16 Hz, 4-H′), 8.77 (s, OH) ppm; $[\alpha]_D^{23} = -60.0 \cdot 10^{-10}\,cm^2\,g^{-1}$ (c = 2.61, $CHCl_3$); MS (70 eV): m/z (%) = 363 (3.91) [M^++1], 432 (0.67) [M+$C_4H_8N^+$], 292 (2.01) [M–$C_4H_8N^+$], 170 (48.59) [Boc-Pro], 70 (100) [$C_4H_8N^+$].

Benzyl (RS)-2-(Boc-Glycyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**14a**, $C_{18}H_{24}N_2O_7S$)

From **1** (1.0 g, 3.9 mmol, *Bu*Li (3.9 mmol), and *Boc-Gly-NCA* (0.78 g, 3.9 mmol). Yield 1.0 g (62%); colourless solid; mp 102°C (*Et*OH); IR: $\bar{\nu}$ = 3324 (NH), 3070, 3040, 2980, 2940 (CH), 1708, 1683 (CO), 1367, 1335, 1161 (SO_2) cm^{-1}; ^1H NMR: δ = 1.40 [s, $C(CH_3)_3$], 2.71 (dd, J = 9, 17 Hz, 5-H),

3.38 (dd, $J = 4.5$, 17 Hz, 5-H′), 4.03 [d, $J = 7$ Hz, 2α-H(Gly)], 4.03 (m, 4-H), 4.38 (m, 3-H), 4.46 (dd, $J = 9$, 15 Hz, 4-H′), 5.10 (s, CH_2), 5.10 (s, NH), 7.30 (s, 5arom H) ppm.

Benzyl (RS)-2-(Boc-L-Alanyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**14b**, $C_{19}H_{26}N_2O_7S$)

From **1** (1.0 g, 3.9 mmol), *Bu*Li (3.9 mmol), and *Boc-L-Ala-NCA* (0.84 g, 3.9 mmol). Yield 1.1 g (65%); viscous liquid; IR (Film): $\bar{\nu} = 3370$ (NH), 3040, 2980, 2940, 2880 (CH), 1708 (CO), 1367, 1351, 1165 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.43$ [m, $C(CH_3)_3$, β-H(Ala)], 2.74, 2.88 (dd, $J = 9$, 16 Hz, 5-H), 3.34, 3.44 (dd, $J = 4$, 16 Hz, 5-H′), 4.00 (dd, $J = 4$, 12.5 Hz, 4-H), 4.41 (m, α-H, 4-H′, 3-H), 5.13 (s, CH_2), 5.27, 5.22 (d, $J = 7$ Hz, NH), 7.41 (s, 5arom H) ppm; $[\alpha]_D^{23} = +2.08 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1.5$, $CHCl_3$); MS (70 eV): m/z (%) = 427 (0.52) [$M^+ + 1$], 371 (5.45) [M-$C_4H_9^+$], 327 (8.52) [M-Boc], 167 (1.67) [Boc-Ala], 91 (68.39) [C_7H_7], 44 (100).

Benzyl (RS)-2-(Z-L-Alanyl)-1,2-thiazetidine-3-acetate 1,1-Dioxide (**14c**, $C_{22}H_{24}N_2O_7S$)

From **1** (1.0 g, 3.9 mmol), *Bu*Li (3.9 mmol), and *Z-L-Ala-NCA* (0.97 g, 3.9 mmol). Yield 750 mg (43%); colourless solid; mp 84°C; IR: $\bar{\nu} = 1720$ (CO), 1355, 1155 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.43$ (d, $J = 10$ Hz, CH_3), 2.75 (dd, $J = 10$, 17 Hz, 5-H), 3.34, 3.45 (dd, $J = 5$, 17 Hz, 5-H′), 3.98 (m, 4-H), 4.36 (m, α-H, 3-H), 4.48, 4.35 (dd, $J = 7$, 15 Hz, 4-H′), 5.11 (s, $2CH_2$), 5.39 (d, $J = 7$ Hz, NH) 7.33 (s, 10arom H) ppm; $[\alpha]_D^{23} = +1.3 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); MS (70 eV): m/z (%) = 460 (9.03) [M^+], 324 (28.33) [M–Z], 91/92 (100) [C_7H_7], 65 (100) [SO_2H].

(RS)-2-[(Z-L-Alanyl)amino]-4-benzyloxy-4-oxobutane-1-sulfonic Acid ($C_{22}H_{26}N_2O_8S$, *Product of Hydrolysis*)

Colourless solid; mp 117°C (dec); IR: $\bar{\nu} = 3380$ (NH), 3070, 3040, 2970, 2960 (CH), 1731, 1711 (CO), 1530 (Amide), 1332, 1166 (SO_3H) cm^{-1}; ^1H NMR: $\delta = 1.24$, 1.26 (d, $J = 7.5$ Hz, CH_3), 2.79 (d, $J = 7$ Hz, 2H, 3-H), 3.43, 3.38 (dd, $J = 7$, 10 Hz, 2H, 1-H), 4.08 [m, α-H(Ala)], 4.60 (m, 2-H), 5.06 (s, $2CH_2$), 5.22 (s, NH, SO_3H), 6.91 (d, $J = 9$ Hz, NH), 7.29 (s, 5arom H) ppm; MS (70 eV): m/z (%) = 385 (2.10) [$M^+ + 1 - C_7H_7$], 296 (0.26) [$M^+ - 2 \times C_7H_7$], 179 (39.82), 91 (100) $[C_7H_7]^+$.

(RS)-2-(Boc-Glycyl)-1,2-thiazetidine-3-acetic Acid 1,1-Dioxide (**15a**, $C_{11}H_{18}N_2O_7S$)

From **14a** (1.4 g, 3.5 mmol) by hydrogenolysis according to the general procedure. Yield 700 mg (62%); colourless solid; mp 53°C; IR: $\bar{\nu} = 3410$ (OH), 1719 (CO), 1513 (Amide), 1368, 1350, 1163 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.34$ [s, $C(CH_3)_3$], 2.71 (dd, $J = 10$, 19 Hz, 5-H), 3.30 (dd, $J = 3$, 19 Hz, 5-H′), 4.01 [d, $J = 7$ Hz, 2H, α-H(Gly)], 4.01 (m, 4-H), 4.48 (m, 3-H), 4.53 (dd, $J = 8$, 16 Hz, 4-H′), 5.28 (s, NH), 8.55 (s, OH) ppm.

(RS)-2-(Boc-L-Alanyl)-1,2-thiazetidine-3-acetic Acid 1,1-Dioxide (**15b**, $C_{12}H_{20}N_2O_7S$)

From **14b** (1.5 g, 3.5 mmol) by hydrogenolysis according to the general procedure. Yield 900 mg (76%); colourless solid; mp 45°C; IR: $\bar{\nu} = 3376$ (NH), 3050, 2980, 2940, 2880 (CH), 1713 (CO), 1509 (Amide), 1394, 1354, 1162 (SO_2) cm^{-1}; ^1H NMR: $\delta = 1.46$ [s, $C(CH_3)_3$, β-H(Ala)], 2.63, 2.68 (dd, $J = 9$, 17 Hz, 5-H), 3.30, 3.40 (dd, $J = 4$, 17 Hz, 5-H′), 4.00–4.63 (m, 3-H, 4-H, 4-H′, α-H), 5.22 (m, NH), 7.90 (s, OH) ppm; $[\alpha]_D^{23} = +11.9 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1.45$, $CHCl_3$).

(RS)-N-[(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]glycine Benzyl Ester (**16**)

See Ref. [3].

(RS)-N-{[2-(Boc-L-Alanyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine Benzyl Ester (**17**, $C_{21}H_{29}N_3O_8S$)

From **16** (620 mg, 2 mmol), *Bu*Li (1.25 cm^3, 2 mmol), and *Boc-Ala-NCA* (0.43 g, 2 mmol). Yield 800 mg (83%); colourless solid; mp 45°C; IR: $\bar{\nu} = 3377$ (NH), 3040, 2980, 2960 (CH), 1750, 1711 (CO), 1520 (Amide), 1353, 1163 (SO_2) cm^{-1}; ^{1}H NMR: $\delta = 1.39$ [s, $C(CH_3)_3$, β-H(Ala)], 2.62 (dd, $J = 9$, 16 Hz, 5-H), 2.75 (dd, $J = 6$, 16 Hz, 5-H), 3.12, 3.19 (d, $J = 16$ Hz, 5-H′), 3.96, 4.05 [dd, $J = 6$, 18 Hz, 2α-H(Gly)], 4.18 (dd, $J = 6$, 13.5 Hz, 4-H), 4.20 (m, 3-H), 4.35 (dd, $J = 9$, 13.5 Hz, 4-H′), 4.38 [m, α-H(Ala)], 5.11 (s, CH_2), 5.35, 5.23 (d, $J = 6$ Hz, NH), 6.98 [s, NH(Boc)], 7.31 (s, 5arom H) ppm; $[\alpha]_D^{23} = +7.74 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$).

(RS)-N-{[2-(Boc-L-Alanyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}glycine (**18**, $C_{14}H_{23}N_3O_8S$)

From **17** (800 mg, 1.65 mmol) by hydrogenolysis according to the general procedure. Yield 630 mg (97%); colourless solid; mp 79°C; IR: $\bar{\nu} = 3367$ (OH), 3040, 2980, 2940 (CH), 1706 (CO), 1534 (Amide), 1349, 1164 (SO_2) cm^{-1}; ^{1}H NMR: $\delta = 1.38$ [s, $C(CH_3)_3$, β-H(Ala)], 2.67 (m, 5-H), 3.21 (m, 5-H′), 3.96 [s, 2α-H(Gly)], 4.21 (m, 4-H, 3-H), 4.40 [m, 4-H′, α-H(Ala)], 5.39, 5.47 (s, NH), 7.32 [s, NH(Boc)] ppm; $[\alpha]_D^{23} = +4.2 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1{,}1$, $CHCl_3$); MS (70 eV): m/z (%) = 292 (0.23) [M^++1-Boc].

N-[(RS)-(1,1-Dioxo-1,2-thiazetidine-3-yl)acetyl]-L-phenylalanylglycine Methyl Ester (**19**)

See Ref. [3].

N-{[(RS)-2-(Boc-L-Alanyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanyl-glycine Methyl Ester (**20a**, $C_{24}H_{34}N_4O_9S$)

From **19** (500 mg, 1.3 mmol), *Bu*Li (0.81 cm^3, 1.3 mmol), and *Boc-L-Ala-NCA* (0.28 g, 1.3 mmol) by acylation. Yield 650 mg (90%); colourless solid; mp 83°C ($CHCl_3$/CCl_4); IR: $\bar{\nu} = 3309$ (NH), 3070, 3030, 2980, 2940 (CH), 1750, 1700, 1660 (CO), 1528 (Amide), 1350, 1162 (SO_2) cm^{-1}; ^{1}H NMR: $\delta = 1.38$ [m, β-H(Ala)], 1.40 [s, $C(CH_3)_3$], 2.47 (dd, $J = 9$, 15 Hz, 5-H), 2.87 (dd, $J = 9$, 14 Hz, β-H), 3.02 (dd, $J = 4.5$, 15 Hz, 5-H′), 3.18 (dd, $J = 6$, 14 Hz, β-H′), 3.69 (s, OCH_3), 3.86, 4.10 (dd, $J = 4.5$, 13.5 Hz, 4-H), 3.90 [dd, $J = 6$, 18 Hz, α-H(Gly)], 3.93 [dd, $J = 6$, 18 Hz, α-H′ (Gly)], 4.20 (m, 3-H), 4.35 [m, α-H(Ala)], 4.30, 4.40 (dd, $J = 7.5$, 13.5 Hz, 4-H′), 4.63 [m, α-H(Phe)], 5.46 (s, NH), 6.86 (d, $J = 7$ Hz, NH), 7.00 (s, NH), 7.25 (m, 5arom H) ppm; $[\alpha]_D^{23} = -28.6 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1.1$, *AcOEt*); MS (70 eV): m/z (%) = 492 (21.09) [M^++1–SO_2], 57 (100) [$C_4H_9^+$].

N-{[(RS)-2-(Z-L-Alanyl)-1,1-dioxo-1,2-thiazetidine-3-yl]acetyl}-L-phenylalanyl-glycine Methyl Ester (**20b**, $C_{27}H_{32}N_4O_9S$)

From **19** (500 mg, 1.3 mmol), *Bu*Li (0.81 cm^3, 1.3 mmol), and *Z-L-Ala-NCA* (0.33 g, 1.3 mmol) by acylation. Yield 600 mg (78%); colourless solid; mp 105°C ($CHCl_3$/CCl_4); IR: $\bar{\nu} = 3323$ (NH), 3060, 3030, 2960 (CH), 1700, 1639 (CO), 1534 (Amide), 1351, 1162 (SO_2) cm^{-1}; ^{1}H NMR: $\delta = 1.42$ [d, $J = 7.5$ Hz, β-H(Ala)], 2.43 (dd, $J = 7.5$, 15 Hz, 5-H), 3.06 (m, 5-H′), 2.90, 2.96 (d, $J = 7$ Hz, β-H), 3.11, 3.18 (d, $J = 7$ Hz, β-H′), 3.64 (s, OCH_3), 3.82 (m, 3-H), 3.82, 4.03 [dd, $J = 6$, 18 Hz, 2α-H(Gly)], 4.35 [m, 4-H, 4-H′, α-H(Ala)], 4.71 [m, α-H(Phe)], 5.04 (AB, $J = 9$, 15 Hz, CH_2), 5.57, 6.90 (d, $J = 6$ Hz, NH), 6.93 (m, 2NH), 7.17 (m, 5arom H), 7.25 (s, 5arom H) ppm; $[\alpha]_D^{23} = -28.6 \cdot 10^{-10}\,cm^2\,g^{-1}$ ($c = 1.1$, $CHCl_3$).

Acknowledgments

We thank Dr. *J. Loose*, Department of Pharmaceutical/Medicinal Chemistry (PMC), University of Greifswald, for the inhibition tests. Furthermore, we wish to thank Degussa AG, for generous support with chemicals, E. Merck KGaG, Darmstadt, for a general biological screening, for support with chromatography materials, and the HPLC experiments, and we thank the "Fonds der Chemischen Industrie" for financial support. *B.A.T.* thanks the DAAD for a study (Ph.D.) grant.

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