Synthesis of the First Penicillin Derivatives with Medium-Sized Lactam Ring and of Related Thiazolidines

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The novel concept of penicillin derivatives **4** with a medium-sized instead of a β-lactam ring is presented. Two synthetic paths were invented, resulting in the evaluation of the synthetic potential in the succinic, glutaric, and adipic acid series. A number of novel penicillin-derived thiazolidines were prepared, notably the derivatives **16** and **22** with anellated 7- and 13-membered lactam ring.

Synthesewege zu Penicillinderivaten mit mittelgroßem Lactamring und zu verwandten Thiazolidinen

Das neue Konzept von Penicillinderivaten **4** mit einem mittelgroßen anstelle eines β-Lactamringes wird vorgestellt. Zwei Synthesewege wurden entworfen, die zur Beurteilung der synthetischen Möglichkeiten bei entspr. Bernstein-, Glutar- und Adipinsäurederivaten führten. Eine Reihe neuer Thiazolidine wurde hergestellt, insbesondere die Derivate **16** und **22** mit anelliertem 7- und 13-gliedrigem Lactamring.

Penicillins, cephalosporins, and related β-lactam antibiotics are milestones of the pharmaceutical development in the 20th century. The story of their discovery has been recounted many times[1], and the number of semisynthetic derivatives with improved activity and stability is countless. Despite of more than 30 years of successful research in this field, much remains to be done, and the challenge of growing bacterial resistance - a threat of immediate interest[2] - forces us to ever invent new tools in this life-prolonging chemical warfare.

β-Lactams kill bacteria by acylating proteins that catalyze the construction of the bacterial cell wall[3]. Since the β-lactam ring is responsible for this, *Christensen*[4] reduced the minimal requirements for antibacterial activity to a core (**1**). Optimal activity, of course, requires side chains for binding to the target enzymes. However, the introduction only of a γ- instead of the β-lactam ring indeed decreases the activity drastically[5]. This is undoubtedly due to the increased hydrolytic stability of the pyrrolidinone moiety, resulting in too low a (or no) degree of acylation of the catalytic serine hydroxyl group of the bacterial target enzymes. In lactivicin[6] **2**, a lactam antibiotic isolated from soil bacteria, and in the synthetic γ-lactams[7] **3**, the five-membered ring is rendered more labile by the introduction of another heteroatom, and the antibiotic activity approaches that of β-lactams.

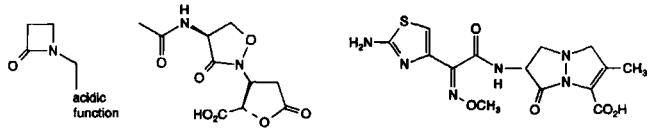

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Figure 1

Medium-sized rings, *i.e.* rings with about 7 to 13 members depending on the type of ring, are known to be less stable and to form more reluctantly than 'ordinary' or large rings[8][9]. With this in mind, we developed a new concept: to substitute the β-lactam ring of β-lactam antibiotics by a medium-sized lactam ring of suitable hydrolytic stability - that is to say, of suitable *in*stability -, comparable to that of a β-lactam, so that it will on the one hand not be hydrolyzed until it reaches the target enzymes, and on the other hand be able to acylate the crucial serine hydroxyl group and thereby inhibit these enzymes. This might result in substances of equal activity to the classical antibiotics of this family. To our knowledge, it is a structural variation that has not been considered as yet. In the penicillin series, our target molecules are represented by formula **4**. We decided to integrate the N-acyl sidechain of penicillins in the medium-sized ring. The optimum conformation of that sidechain is not known[10]. Since the exact conformation of the antibiotic-enzyme complexes is also not known exactly[3], our molecules are designed to provide structure-activity information through the possibilities the medium-sized ring offers in variation of substituent positioning.

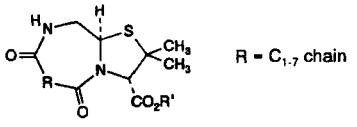

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Figure 2

The investigations were also inspired by the fact that in recent years, several other thiazolidines with pronounced pharmacological profile were found[11]. We consequently intended to get novel penicillin-derived thiazolidines for further testing.

We designed two synthetic ways to elucidate the accessibility of different ring sizes: 1) a stepwise pathway; 2) a building block procedure.

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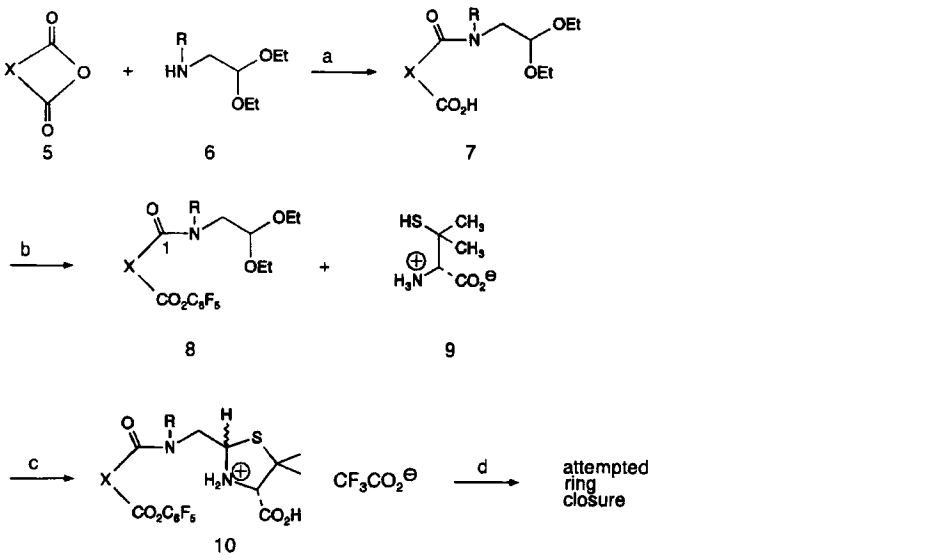
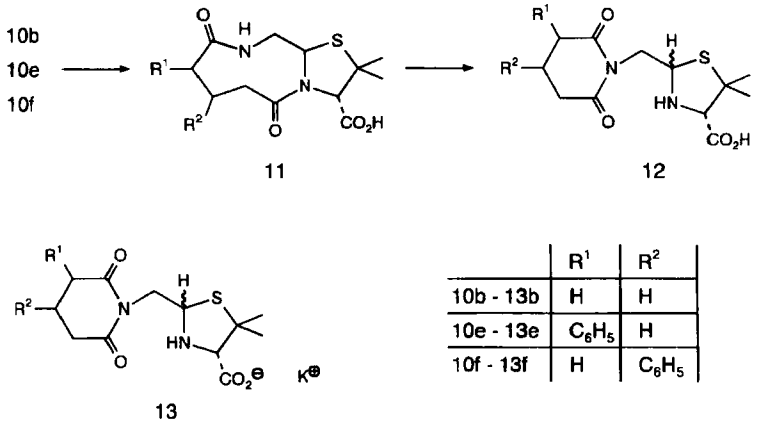


X	$(CH_2)_2$	$(CH_2)_3$		$(CH_2)_4$	$^2CH(C_6H_5)^3CH_2{}^4CH_2$	$^2CH_2{}^3CH(C_6H_5)^4CH_2$	$^2CH_2{}^3CH_2{}^4CH(C_6H_5)$
R	CH_3	H	CH_3	H	H	H	H
	7a	7b	7c	7d	7e	7f	7g
	8a	8b	8c	8d	8e	8f	8g
	10a	10b	10c	10d	10e	10f	10g

Scheme 1: a: EtOH, r.t.- b: C_6F_5OH, DCC, 0°C.- c: CF_3CO_2H, THF, 37-41°C, 24 h.- d: PPY, dioxane-tBuOH 15:1, 98°C.-



	R^1	R^2
10b - 13b	H	H
10e - 13e	C_6H_5	H
10f - 13f	H	C_6H_5

Figure 3

Stepwise Pathway

The stepwise pathway is delineated in Scheme 1. The amides **7** had been prepared by us through the reaction of succinic, glutaric, and adipic anhydrides **5** with aminoacetaldehyde diethylacetal and (in two cases) methylaminoacetaldehyde diethylacetal, and they had been activated by transformation to pentafluorophenylesters (**8**)[12]. The subsequent conversion of the *O,O*- to an *N,S*-acetal with D(-)-penicillamine **9** required the use of an anhydrous, polar, acidic solvent so as to prevent undesired solvolyses or ester and amide formations. When penicillamine was dissolved in a mixture of trifluoroacetic acid and tetrahydrofuran, added to a solution of the acetal **8**, and stirred at about 40°C overnight, the reaction proceeded as desired. The resulting thiazolidinium trifluoroacetates **10** were isolated as sticky oils that slowly solidified in the refrigerator. They were used without extensive purification for the subsequent ring closure reactions. In the Experimental Part, the isolation and analytical and spectroscopic characterization of one of them (**10d**) is given.

The ring closure reactions were attempted under high-dilution conditions[13] by slowly introducing a solution of the thiazolidinium salts **10** in dioxan into a boiling mixture

of dioxan and t-butanol (15:1) containing 2-3 molar equivalents of pyrrolidinopyridine (PPY).

Since we did not expect the eight-membered dilactam to form because of the ease of formation of a succinimide (see also below, building-block procedure), we tried the reaction on the *N*-methyl derivative **10a**. But in several different runs we failed to perceive the formation of an eight-membered ring; only oligomeric gums were isolated.

The *N*-methyl glutarate **10c** and the adipate **10d** also failed to give a perhydrodiazoninedione and a perhydrodiazecinedione, respectively.

The glutaric acid derivatives **10e** and **10f** were also subjected to the aforementioned cyclization conditions. The solvent was evaporated, and the residue partitioned between ether and aqueous bicarbonate. Work-up afforded, a white powder that was recrystallized from ethanol. After solidification or crystallization, the material was soluble in hydrochloric acid - though it had been extracted with ether from hydrochloric acid (cf. Exper. Part). In summary, we interpret the chemical and spectroscopic evidence as follows: the initially formed nine-membered rings (**11**) during solidification undergo rearrangement to the isomeric glutarimides (**12**). Since there is one case of a pH-dependent glutarimide-perhydrodiazecinedione equilibrium in the lit.[14] (Figure 4), we tried several methods to rearrange the glutar-

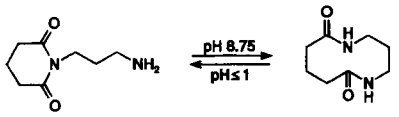


Figure 4

imides back to the nine-membered dilactams. For instance, we converted them to the potassium salts **13** by reaction with potassium 2-ethylhexanoate in a standard procedure for the preparation of the potassium salts of sensitive cephalosporins (Exper. Part), but the spectra invariably indicated the presence of the epimeric glutarimides. The spectroscopic evidence points towards a glutarimide structure: In the IR spectra, there are bands at about 1720 and 1670 cm^{-1}. The former is not due solely to the carboxylic group, as proven by the spectra of the potassium salts that also show these glutarimide bands plus another one at 1600 cm^{-1} of the carboxylate. In [D_6]DMSO we observed a doublet for the proton C<u>H</u>-COOH due to coupling with the NH group. Finally, the ^1H- and ^{13}C-NMR spectra of the unsubstituted glutarimide **12b** unequivocally show the presence of a symmetrical glutarate moiety. These data were confirmed when we had prepared and characterized the diphenylmethylester glutarimides (see below).

We obtained a chemical proof for the glutarimide structure, too: the 2-phenyl- (**10e**) and the 4-phenyl-thiazolidiniumglutarate (**10g**) gave an identical cyclization product (**12e**). The unsubstituted derivative **12b** was also obtained more simply by stirring a solution of the trifluoroacetate **10b** in diethyl ether that precipitated the glutarimide after some time.

The glutarimides are subject to 2-epimerization in solution, most likely by ring opening of the *N,S*-acetal. The ratio of the 2-epimers is dependent on the substitutent and on the solvent; in [D_6]DMSO solution, according to the NMR spectra the equilibrium is on the side of one epimer only. For a discussion of the stereochemistry, see below.

The thiazolidines **12b** and **12f** are presently under pharmacological testing in a pharmaceutical company; results cannot yet be disclosed.

Building Block Procedure

Our second approach to medium-sized dilactams, the building block procedure, is delineated in Scheme 2.

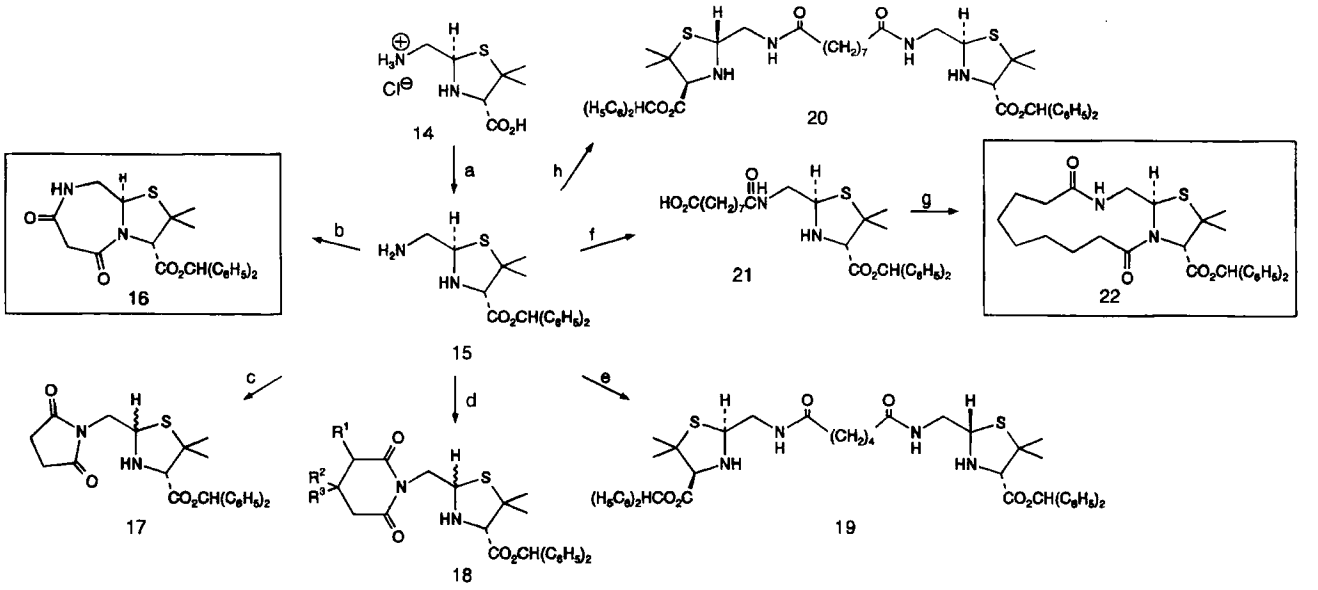
The thiazolidine **14** - easily obtainable from natural penicillins - and its diastereomerically pure diphenylmethyl ester **15** had been prepared by us[11]. **15** served as the diamine building block in the one-pot, two-step or two-pot, two-step ring closure reactions depicted.

We tried three derivatives of malonic acid to get the diazacycloheptanedione **16**. Carbon suboxide[15] with **15** only gave oligomers of a molecular mass of about 1000-2000, and malonic dichloride gave polymeric tars. But malonic acid itself coupled with **15** in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to give the desired dilactam **16**. The low yield is certainly to be explained with the low stability of this compound - it quickly oligomerizes both in solution and in substance. The spectroscopic data and assignments of this and the following new compounds are compiled in the Exper. Part. Assignments of individual NMR signals to certain groups and respective epimers are based on correlation and DEPT spectra, on the comparison of the various products among themselves, and - importantly - on the spectroscopic and stereochemical investigation we published[11] on the penicillin-derived thiazolidines **14** and **15**. For further discussion, see below.

Succinic anhydride was reacted with **15** in two steps. The intermediate amide was not isolated, but condensated intramolecularly with dicyclohexylcarbodiimide and pentafluorophenol to yield the expected succinimide **17**. Again, the introduction of an N-methyl group in the diamine building block (2-*N*-methylaminomethyl-3,3-dimethyl-1,3-thiazolidine-4-carboxylic acid[16]), so as to prevent succinimide formation, did not lead to the isolation of a monomeric product.

Likewise, glutaric, 2-phenyl-, 3-phenyl-, and 3,3-diphenylglutaric anhydride were reacted with **15** in two steps to give the glutarimides **18a-d**. The succinimide and glutarimides were stable, crystalline compounds that could be purified by cc. Their spectra resembled very well those of the corresponding acids (see above).

Adipic anhydride was reacted with the penicillin derivative **15** as described for the glutaric anhydrides, but it only gave oligomeric gums. Adipic acid itself, when subjected to a two-step condensation reaction with **15**, in contrast to



	R^1	R^2	R^3
18a	H	H	H
18b	C_6H_5	H	H
18c	H	C_6H_5	H
18d	H	C_6H_5	C_6H_5

Scheme 2: a: $(C_6H_5)_2CN_2$, DMF, 50°C; 1 M NaOH, ether.- b: 1) $CH_2(CO_2H)_2$, DCC (1 eq.), HOBt (1 eq.), THF.- 2) DCC (1 eq.), HOBt (1 eq.).- c: 1) succinic anhydride, THF, r.t. 12 h; 2) C_6F_5OH, DCC, N-Et-morpholine, 0°C, 12 h.- d: 1) glutaric anhydride, THF, r.t. 15 min; 2) HOBt, DCC, N-Et-morpholine, 0°C, 1 h, r.t., 5 h.- e: 1) $HO_2C(CH_2)_4CO_2H$, DCC (1 eq.), HOBt (1 eq.), THF; 2.) DCC (1 eq.), HOBt (1 eq.).- f: $HO_2C(CH_2)_7CO_2C_6F_5$, CH_2Cl_2, r.t., 16 h.- g: DCC, HOBt, EA, 0°C, 56 h.- h: $HO_2C(CH_2)_7CO_2H$, 1.) DCC (1 eq.), HOBt (1 eq.), THF; 2.) DCC (1 eq.), HOBt (1 eq.).

malonic acid failed to cyclize, but gave the bisamide **19** by a 2:1 reaction. The constitution of this product was further supported by its $M^{+\bullet}$.

So again, our investigations show the 8-10-membered, and also the 7-membered, dilactam systems not being stable enough for the formation of the target penicillin derivatives. We also did not yet succeed in preparing the 11- and 12-membered dilactams of this series. These systems are too prone to imide, polyamide, or amide formation. Our results render the preparation of a derivative of this ring size very unlikely that would be stable enough so as to become pharmacologically relevant.

Nonanedioic (azelaic) acid showed the same behaviour as adipic acid when it was condensated with **15** in a one-pot, two-step procedure: the 2:1 bisamide product **20** was formed. Since a monomeric anhydride of this acid is not known[19], we made use of its pentafluorophenyl half-ester - recently prepared by us[12] - that also has just one activated carboxyl group. Through this, we were able to perform the cyclization in two steps - a procedure always to be preferred because it gives rise to less side reactions and products. The first step yielded the amide **21** in 90% yield after chromatographical purification and recrystallization. The spectroscopic data unequivocally prove the presence of only this constitutional isomer, formed by the reaction of the primary amino group of **15** with the activated ester. In the ^{1}H-NMR spectrum, for instance, we clearly see the coupling between the amide-NH and the neighbouring NCH_2 protons (Exper. Part). This compound was handled with much care, avoiding contact with protic or wet solvents and prolonged storage in dilute solutions, since all this promotes epimerization at C-2 of our thiazolidines.

The cyclization to the 13-membered dilactam **22** was achieved through the intramolecular condensation reaction of the amino acid **21** with the standard reagents dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The isolated yield was 48% though the reaction went rather sluggish. We explain this both with a reluctance of the medium-sized ring to form and a certain extent of steric hindrance from the neighbouring diphenylmethyl ester group. The latter probably had already been responsible for the exclusive acylation of the primary amino group in the previous step. Structure and diastereoisomeric purity of **22** follow from the analytical and spectroscopic data, see also the discussion of the stereochemistry below. The NMR spectra are fairly similar to those of the educt **21**. This is not very surprising because there is just one additional covalent bond in **22**. But the IR-, ^{1}H- and ^{13}C-NMR spectra and the chromatographical behaviour all prove the disappearance of the sec. amino and carboxylic acid groups in lieu of a tert. amide. The precautions against 2-epimerization mentioned above for the amino acid **21** also had to be taken for **22**.

The diazacyclotridecanothiazolidine **22** and the (much less stable) diazacycloheptanedione **16** are the first derivatives of penicillin with medium-sized lactam rings: a λ-lactam and an ε-lactam instead of a β-lactam. We think that they represent the beginning of an 'expanded' view on lactam antibiotics. According to the present state of our investigations, the thirteen-membered lactam ring is the most likely one to substitute the 'classical' four-membered ring of penicillins. The synthetic way that led us to it has several advantages: cheap, readily obtainable, stereochemically defined, starting materials (**15**, to be produced readily from penicillin G[11]; dicarboxylic acids); variable, peptide-synthesis derived methodology; convergent building-block approach.

Our future interest, apart from pharmacological investigations, will center on the preparation of derivatives of the thirteen-membered ring compound **22** with substituents derived from the N-acyl side chains of broad-spectrum penicillins and cephalosporins.

Stereochemistry

As mentioned above, the thiazolidines with a glutarimide sidechain are able to undergo 2-epimerization. Several mechanisms for this epimerization of thiazolidines have been discussed. We addressed this matter in the case of the penicillin-derived thiazolidines **14** and **15**[11]: the dihydrochloride **14** quickly epimerized in dilute aqueous solution by a hydrolytical mechanism, whereas the diphenylmethyl ester derivative **15** was configurationally stable, due to the bulkiness of the ester group and to the insolubility of **15** in water, chloroform, and in many other solvents that promote acid-catalyzed epimerizations. Our stereochemical assignments had rested on two observations mainly: firstly, the methylene carbon (bound to C-2 of the thiazolidine ring) that resonated at lower field was assigned to the *E*-epimer (2R,4S) by comparison with the relative shift of the penicilline methyl groups[11]. Secondly, the coupling constants of the sec. amine proton with 2- and 4-H in [D_6]DMSO solution had clarified the relative configuration of the two centers[11]. An NMR study[17] had shown that in 2-carboxythiazolidine-4-carboxylic acids 4-H resonates at lower field when *cis* to the carboxy-substituent at C-2, as compared to *trans* position. But this finding cannot be generalized because the reverse was observed with some closely related benzylpenicilloates[18], so we did not rest our assignments on it. Unfortunately, that NMR study also contains an inconsistency: the crucial educt, penicillamine, is said to have R-configuration, but in the formula schemes S-penicillamine (penicillin configuration) is shown.

These previous findings and considerations helped analyze the situation with the molecules described in this report. Again, the N$\underline{C}H_2$ resonating at lower field was assigned to the *E*-epimer (2R,4S). Parallely, 2-H and 4-H of the same epimer were almost always observed at lower field, as the above-mentioned NMR study[17] had found for their derivatives. Also the difference in chemical shift of the methyl groups was always larger for this isomer. In most of the cases, the NMR signal sets could easily be distinguished because the epimers were not in a 1:1 equilibrium. If there were just one epimer detectable - as several times in [D_6]DMSO solution -, or if they were present in about equal amounts, the addition of a small amount of chloroform to DMSO shifted the equilibrium so that the signal sets became distinguishable. The Table lists the chemical shifts of $\underline{C}H_2N$, 2-H and 4-H, the difference in chemical shift of the α- and β-methyl groups, and the ratio of the epimers in the solvent used. Inspection of the table shows that the trends are almost completely consistent. On this basis we assigned *Z*-configuration to the only isomer of **19** detectable in [D_6]DMSO although we were not able to unequivocally distinguish the signals of the three isomers present in $CDCl_3$. In the case of the azelaic acid derivatives **20** and **21**, the relative shift of 4-H was reversed, but the remaining three criteria were consistent. We regard the ^{13}C shift of $\underline{C}H_2N$ as most reliable by comparison with the behaviour of the methyl groups of penicillins (see above).

Table. Significant NMR data of the thiazolidines in this report

	E-Epimer				Z-Epimer				E:Z
	$\underline{C}H_2N$ ppm	$\Delta\delta CH_3$	2-H	4-H	$\underline{C}H_2N$ ppm	$\Delta\delta CH_3$	2-H	4-H	(solvent)
10d	/	0.23	5.22	4.29	/	0.18	5.13	4.27	~1:1 ($CDCl_3$)
12b	43.3	0.44	4.87	3.77	41.7	0.34	4.80	3.50	1:15 ($CDCl_3$ - D_6-DMSO 3:1)
13b	/	0.36	4.93	3.68	/	0.32	4.69	3.40	1:2 (D_2O)
12e	/	0.38	4.96	3.72	/	0.34	4.87	3.58	1:10 ($CDCl_3$ - CD_3OD 5:1)
12f	43.9	0.43	4.97	3.91	42.7	0.26	4.71	3.74	~1:1 ($CDCl_3$)
13f	/	0.46	4.76	3.25	/	0.36	4.62	cov'd	6:1 (D_6-DMSO) (1:1 D_2O)
17	44.0	0.71	4.96	3.97	42.4	0.60	4.84	3.64	10:1 ($CDCl_3$)
18a	43.9	0.72	4.93	3.99	42.9	0.59	4.85	3.62	4:1 ($CDCl_3$) (1:0, D_6-DMSO)
18b	44.5	0.70	4.99	4.02	44.4	0.68	cov'd	4.01	~1:1 ($CDCl_3$)
18c	44.2	0.72	4.95	4.02	43.3	0.58	4.87	3.64	2:1 ($CDCl_3$)
18d	43.8	0.74	4.62	3.93	43.0	0.56	4.69	cov'd	10:1 ($CDCl_3$) (1:0, D_6-DMSO)
19	/	/	/	/	/	0.56	4.63	3.56	0:1 (D_6-DMSO) ($CDCl_3$: 3 isomers)
20	45.3	0.63	4.65	3.79	42.3	0.62	4.78	3.73	2:1 ($CDCl_3$, after some days) (1:0, $CDCl_3$)
21	44.9	0.60	4.70	3.85	42.5	0.60	4.80	3.82	2:1 ($CDCl_3$, after some days) (1:0, $CDCl_3$)
22	45.2	0.62	4.64	3.77	42.2	0.63	4.71	3.66	2:1 ($CDCl_3$, after some days) (1:0, $CDCl_3$)

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Experimental Part

M.p. (uncorr.): Dr. Tottoli apparatus (Büchi).- IR: Perkin Elmer 398.- ^{1}H-NMR: Varian T-60 (60 MHz), Jeol JNM-FX-100 (100 MHz) and Jeol JNM-GX-400 (400 MHz). Aqueous samples were referenced against water as an internal standard at 4.63 ppm.- ^{13}C-NMR: Jeol JNM-FX-100 (25 MHz) and Jeol JNM-GX-400 (100 MHz); aqueous samples were referenced against dioxan (69.0 ppm) as an external standard.- Mass spectra: Vacuum Generators 7070.

2-[N-(5'-Pentafluorophenyloxycarbonyl-1'-pentanoyl)]aminomethyl-5,5-dimethyl-1,3-thiazolinium-4-carboxylic acid trifluoroacetate (**10d**)

2.31 g (5.4 mmol) of **8d**[12] were dissolved in 40 ml of dry tetrahydrofuran. A solution of 0.81 g (5.4 mmol) of D(-)-penicillamine in 4.0 ml of tetrahydrofuran and 4.0 ml of trifluoroacetic acid was added and the clear solution stirred at 30-40°C for 36 h. The solvent was evaporated, adding three 5-ml portions of toluene at the end of the evaporation to remove the excess of trifluoroacetic acid. Diethyl ether (50 ml) precipitated a white powder (consisting of the 2-epimers) on keeping the mixture at 0°C for two weeks; yield 2.81 g (87%), m.p. 89-91°C.- IR (KBr): $\tilde{\nu}$ = 3500-2300; 3340; 1786; 1724; 1667; 1634; 1520; 1200 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.47, 1.51 (br s, 2 x 3H, CH_3), 1.69, 1.70 (br s, 2 x 3H, CH_3), 1.75 (m, 2 x 4H, CH_2CH_2), 2.32 (m, 2 x 2H, CH_2CON), 2.68 (2t, J = 7 Hz, 2 x 2H, CH_2COO), 3.65 (m, 2 x 1H, CH_2N), 3.82 (m, 2 x 1H, CH_2N), 4.27/4.29 (s, 2 x 1H, CHCOO), 5.13 (dd, J = 3 and 7 Hz, 1H, CHNS), 5.22 (dd, J = 4 and 7 Hz, 1H, CHNS), 7.68 (br t, 1H, NH), 7.76 (br t, 1H, NH), 9.40 (br s, 3H, OH, NH_2).- $C_{21}H_{22}F_8N_2O_7S$ (598.5) Calcd. C 42.14 H 3.71 N 4.68 Found C 41.93 H 3.73 N 4.71.

2-(N,N-1',5'-Pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (**12b**)

2.52 g (6.1 mmol) of **8b**[12] were dissolved in 60 ml of dry tetrahydrofuran. A solution of 0.91 g (6.1 mmol) of D(-)-penicillamine in 4.0 ml of tetrahydrofuran and 4.4 ml of trifluoroacetic acid was added and the clear solution stirred at 30-40°C for 24 h. Work-up as described for **10d**. The two epimers, after recrystallization from ethanol, were isolated as a mixture, ratio 1:15 (*E*:*Z*) in $CDCl_3$-[D_6]DMSO (3:1) solution. White crystals, yield 1.17 g (67%), m.p. 182/8°C.- IR (KBr): $\tilde{\nu}$ = 3300-2700; 3260; 1723; 1670 cm^{-1}.- ^{1}H-NMR ($CDCl_3$-[D_6]DMSO 3:1): *Z*-epimer: δ = 1.28 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.97 (quint, J = 6.5 Hz, 2H, CH_2), 2.69 (t, J = 6.5 Hz, 4H, CH_2CO), 3.50 (s, 1H, CHCOO), 4.03 (dd, J = 3.2 and 13.6 Hz, 1H, CH_2N), 4.16 (dd, J = 9.0 and 13.6 Hz, 1H, CH_2N), 4.80 (dd, J = 3.4 and 9.2 Hz, 1H, NCHS); second small (see above) signal set of *E*-epimer.- ^{13}C-NMR ($CDCl_3$-[D_6]DMSO 1:4): δ = 16.5 ($CH_2\underline{C}H_2CH_2$); 25.8, 27.2, 27.9, 28.3 (CH_3); 32.1 ($\underline{C}H_2CH_2\underline{C}H_2$); 41.7, 43.3 ($CH_2N$); 57.5, 58.6 ($CMe_2$); 63.4, 64.6 (<u>C</u>HCOOH); 71.1, 73.6 (NCHS); 169.5, 170.2 (acid-CO); 172.1, 172.6 (imide-CO); some signals of epimers coincide.- MS (70 eV): m/e (%) 267 (2) (M - 19)$^+$, 160 (100) (dimethylthiazoliniumcarboxylic acid).- $C_{12}H_{18}N_2O_4S$ (286.4) Calcd. C 50.32 H 6.35 N 9.78 Found C 50.28 H 6.09 N 9.75.

Potassium 2-(N,N-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**13b**)

69 mg (0.24 mmol) of **12b** were dissolved in 3.2 ml of a 0.077 M solution of potassium 2-ethylhexanoate (= 0.25 mmol) in acetone. The solvent was allowed to evaporate, and the residue redissolved in 5 ml of dichloromethane. Diethyl ether precipitated a white powder; yield 61 mg (78%). The ratio of the 2-epimers was 1:2 (*E*:*Z*) in D_2O solution.- IR (KBr): $\tilde{\nu}$ = 3600-3200; 1720; 1668; 1600 cm^{-1}.- ^{1}H-NMR (D_2O): *Z*-epimer: δ = 1.20 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.89 (quint, J = 6.5 Hz, 2H, 3'-CH_2), 2.68 (t, J = 6.5 Hz, 4H, CH_2CO), 3.40 (s, 1H, CHCOO), 4.02 (dd, J = 4 and 14 Hz, 1H, CH_2N), 4.11 (dd, J = 8 and 14 Hz, 1H, CH_2N), 4.69 (dd, J = 4 and 8 Hz, 1H, NCHS). *E*-epimer: 1.19 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.75 (quint, J = 6.5 Hz, 2H, 3'-CH_2), 2.64 (t, J = 6.5 Hz, 4H, CH_2CO), 3.68 (s, 1H, CHCOO), 3.79 (dd, J = 6 and 13 Hz, 1H, CH_2N; second proton covered), 4.93 (dd, J = 6 and 8 Hz, 1H, NCHS).- $C_{12}H_{17}KN_2O_4S$ (324.5).

2-(N,N-2'-Phenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (**12e**)

1.) 1.31 g (2.7 mmol) of *N*-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-2-phenyl-1-butyramide[12] (**8e**) were dissolved in 30 ml of dry tetrahydrofuran, and 0.40 g (2.7 mmol) of D(-)-penicillamine in 2.0 ml tetrahydrofuran and 2.0 ml of trifluoroacetic acid were added. The solution was stirred at 35-40°C for 30 h. The solvent was evaporated, adding three 5-ml portions of toluene at the end of evaporation to remove excess trifluoroacetic acid. The residual viscous yellow oil was dissolved in 150 ml of dry dioxan and added to a refluxing solution of 444 mg (3.0 mmol) of pyrrolidinopyridin in dry dioxan (1500 ml) and t-butanol (100 ml) within 4 h. It was refluxed for another 15 min, allowed to reach room temp., and filtered. The solvent was evaporated at reduced pressure. The residue was partitioned between 100 ml of diethyl ether and 100 ml of sat. Na_2CO_3 solution, and filtered. (During the following operations, the solutions were kept at about 10°C.) The aqueous phase was acidified to pH 3-4 with 2M HCl and extracted with three 10-ml portions of diethyl ether. Drying over Na_2SO_4 and evaporation left 800 mg of a colourless solid that was suspended in 8 ml of boiling benzene (became gelatinous) and dissolved by addition of 6 ml of chloroform. A second crystallization from ethanol (96%) yielded white crystals, 587 mg (60%), m.p. 146°C (dec.). They consisted of the mixture of the 2-epimers; in $CDCl_3$/CD_3OD (5:1) solution, their ratio was 1:10 (*E*:*Z*).

2.) The same procedure, starting from *N-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-4-phenyl-1-butyramide*[12] (**8g**) gave an identical substance.- IR (KBr): $\tilde{\nu}$ = 3390, 1720, 1668 cm^{-1}.- ^{1}H-NMR ($CDCl_3$/CD_3OD 5:1): *Z*-epimer: δ = 1.33 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.27 (mc, 2H, $C\underline{H}_2CH_2CO$), 2.83 (t, J = 5.5 Hz, 2H, CH_2CO), 3.58 (s, 1H, CHCOO), 3.91 (t, J = 8 Hz, 1H, CHPh), 4.14 (dd, J = 3.5 and 14 Hz, 1H, CH_2N), 4.28 (dd, J = 9.5 and 14 Hz, 1H, CH_2N), 4.87 (dd, J = 3.5 and 9.5 Hz, 1H, NCHS), 7.21-7.39 (m, 5H, Ar-H). Second small set of signals of *E*-epimer.- MS (70 eV): m/z (%) 362 (4) ($M^{+\cdot}$), 160 (100) (dimethylthiazoliniumcarboxylic acid).- $C_{18}H_{22}N_2O_4S \cdot 0.5\ H_2O$ (371.5) (from ethanol 96%) Calcd. C 58.19 H 6.25 N 7.54 Found C 58.06 H 6.03 N 7.56.

2-(N,N-3'-Phenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid (**12f**)

It was prepared from 1.31 g (2.7 mmol) of **8f**[12] and 0.40 g (2.7 mmol) of D(-)-penicillamine as described for **12e**. The 2-epimers were isolated in a yield of 779 mg (80%), m.p. 168°C (dec.; benzene/chloroform). In $CDCl_3$ solution, their ratio was 1:1.- IR (KBr): $\tilde{\nu}$ = 3260; 1716; 1665 cm^{-1}.- ^{1}H-NMR ($CDCl_3$) (double signal set of equal intensity): δ = 1.21 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.74-3.05 (m, 8H, CH_2CO), 3.39 (mc, 2H, CHPh), 3.74 (s, 1H, CHCOO), 3.76 (dd, partly covered by previous signal, J = 5 and 14 Hz, 1H, CH_2N), 3.91 (s, 1H, CHCOO), 4.07 (dd, J = 3 and 13.5 Hz, 1H, CH_2N), 4.21 (mc, 2H, CH_2N), 4.71 (dd, J = 3 and 10 Hz, 1H, CHN), 4.97 (dd, J = 5 and 10 Hz, 1H, CHN), 7.18-7.37 (m, 5H, Ar-H), 7.74 (br, 1H, NH).- ^{13}C-NMR ($CDCl_3$): (double signal set): δ = 27.4, 27.9, 28.6, 28.8 (CH_3); 34.4, 34.5 (CHPh); 39.5, 39.8 ($\underline{C}H_2CO$); 42.7, 43.9 (CH_2N); 57.0, 58.8 (CMe_2); 62.5, 63.3

(CHCOO); 71.4, 73.4 (NCHS); 126.4, 127.5, 129.1 (Ar-CH); 140.6, 140.8 (Ar-C); 170.8, 172.3, 172.6, 172.8 (CO).- MS (70 eV): m/z (%) 330 (0.9), 160 (100) (dimethylthiazoliniumcarboxylic acid).- Mol. mass determination: calcd. 362; found 376 (vapour pressure osmometry, chloroform solution).- $C_{18}H_{22}N_2O_4S$ (362.5) Calcd. C 59.65 H 6.12 N 7.73 Found C 59.63 H 6.05 N 7.74.

Potassium 2-(N,N-3'-phenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**13f**)

79 mg (0.22 mmol) of **12f** were dissolved in 3.0 ml of a 0.077 M solution of potassium 2-ethylhexanoate (= 0.23 mmol) in acetone. On concentrating the solution to half of its initial volume and keeping it at 0°C for a few days, colourless needles precipitated; yield 77 mg (80%). The ratio of the 2-epimers was 1:1 in D_2O solution, and 6:1 (*E*:*Z*) in [D_6]DMSO solution.- IR (KBr): $\tilde{\nu}$ = 3400 (br); 3305; 1722; 1668; 1594 cm^{-1}.- ^{1}H-NMR ([D_6]DMSO): *E*-epimer: δ = 1.11 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.88 (mc, 4H, CH_2CO), 3.25 (s, 1H, CHCOO), 3.43 (dd, J = 5.5 and 13 Hz, 1H, CH_2N), 4.02 (dd, J = 10 and 13 Hz, 1H, CH_2N), 4.76 (dd, J = 5.5 and 10 Hz, 1H, NCHS). 7.24 (mc, 1H, NH), 7.34 (s, 5H, Ar-H).- *Z*-epimer: δ = 1.17 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.88 (mc, 4H, CH_2CO), (CHCOO covered by OH signal), 3.90 (dd, J = 4 and 14 Hz, 1H, CH_2N; other proton covered), 4.62 (dd, J = 4 and 10 Hz, 1H, NCHS), 7.33 (s, 5H, Ar-H).- $C_{18}H_{21}KN_2O_4S \cdot 2\ H_2O$ (436.6) Calcd. C 49.51 H 5.78 N 6.41 Found C 49.30 H 5.69 N 6.71.

(3S,8aR)-2,2-Dimethyl-4,6-dioxo-3-diphenylmethyloxycarbonyl-1,4-diazacycloheptano[3,4-b]1,3-thiazolidine (**16**)

406 mg (1.14 mmol) of **15**[11] were dissolved in 20 ml of dry tetrahydrofuran. 119 mg (1.14 mmol) of malonic acid and 308 mg (2.28 mmol) of 1-hydroxybenzotriazole were added, and the solution was cooled to 0°C, followed by the addition of 470 mg (2.28 mmol) of dicyclohexylcarbodiimide. It was stirred at 0°C for 1 h and at room temp. for 6 h, filtered, and the solvent evaporated at reduced pressure. The residue was purified by cc on silica gel/acetone, to give a white powder after precipitation from ethyl acetate with hexane, yield 111 mg (26%), m.p. 120-130°C.- IR (KBr): $\tilde{\nu}$ = 3320; 1738; 1660 cm^{-1} (br).- ^{1}H-NMR ($CDCl_3$): δ = 1.32 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 3.15 (br s, 2H, $COCH_2CO$), 3.40 (mc, 1H, CH_2N), 3.66 (s, 1H, CHCOO), 3.70 (mc, 1H, CH_2N), 5.34 (mc, 1H, NCHS), 6.96 (s, 1H, $CHPh_2$), 7.30 (mc, 10 H, Ar-H).- **16** quickly oligomerizes in solution, esp. if concentrated.- MS (70 eV): m/z (%) 424 (0.2%) ($M^{+\cdot}$), 167 (100) ($CHPh_2^+$).- $C_{23}H_{24}N_2O_4S$ (424.6) Calcd. C 65.06 H 5.71 N 6.60 Found C 64.87 H 5.92 N 6.44.

Diphenylmethyl 2-(N,N-1',4'-butanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**17**)

116 mg (1.16 mmol) of succinic anhydride were dissolved in 10 ml of dry tetrahydrofuran. A solution of 415 mg (1.16 mmol) of **15**[11] in 10 ml of tetrahydrofuran was added dropwise, and the mixture stirred for 12 h. 220 mg (1.2 mmol) of pentafluorophenol were added, followed by cooling to 0°C, and the addition of 240 mg (1.2 mmol) of dicyclohexylcarbodiimide and 0.305 ml (2.4 mmol) of *N*-ethylmorpholine. The mixture was kept at 0°C for 12 h, filtered and evaporated. Purification by flash chromatography on silical gel/t-butylmethyl ether yielded 303 mg (63%) of white crystals, m.p. 134°C. The ratio of the 2-epimers was 10:1 (*E*:*Z*) in $CDCl_3$ solution.- IR (KBr): $\tilde{\nu}$ = 3325; 1770 (w); 1736 (m); 1700 cm^{-1} (s).- ^{1}H-NMR ($CDCl_3$): *E*-epimer: δ = 0.94 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.68 (s, 4H, CH_2CH_2), 3.43 (dd, J = 5.5 and 13.5 Hz, 1H, CH_2N), 3.80 (dd, J = 11 and 13.5 Hz, 1H, CH_2N), 3.97 (s, 1H, CHCOO), 4.96 (dd, J = 5.5 and 11 Hz, 1H, NCHS), 6.93 (s, 1H, COOCH), 7.31 (mc, 10 H, Ar-H).- *Z*-epimer: δ = 1.00 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.73 (s, 4H, CH_2CH_2), 3.64 (s, 1H, CHCOO), 3.87 (dd, partly covered, CH_2N), 4.84 (dd, J = 5 and 12 Hz, 1H, NCHS), 6.95 (s, 1H, COOCH), remaining signals covered or coincide with signals of the *E*-epimer.- ^{13}C-NMR ($CDCl_3$): *E*-epimer: δ = 27.4 (CH_3), 28.1 (CH_2CH_2), 28.6 (CH_3), 44.0 (CH_2N), 60.1 (CMe_2), 63.0 (NCHS), 71.1 (CHCOO), 78.1 ($CHPh_2$); 126.7, 128.1, 128.8, 128.9, 139.3, 139.4 (Ar-C), 168.7 (ester-CO), 177.1, 177.2 (imide-CO). Second very small set of signals of Z-epimer.- MS (70 eV): m/z (%) 339 (1) (M - succinimide)$^+$, 167 (100).- $C_{24}H_{26}N_2O_4S$ (438.6) Calcd. C 65.72 H 5.99 N 6.39 Found C 65.46 H 5.89 N 6.37.

Diphenylmethyl 2-(N,N-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**18a**)

163 mg (1.43 mmol) of glutaric anhydride and 510 mg (1.43 mmol) of **15**[11] were dissolved in 10 ml of dry tetrahydrofuran. The mixture was stirred for 15 min, then cooled to 0°C. 193 mg (1.43 mmol) of 1-hydroxybenzotriazole, 0.182 ml (1.43 mmol) of *N*-ethylmorpholine and 339 mg (1.65 mmol) of dicyclohexylcarbodiimide were added. It was stirred at 0°C for 1 h and at room temp. for 5 h. After filtration and evaporation, the residue was purified by cc on silica gel, eluting with a gradient from hexane-ethyl acetate (6 + 4) to ethyl acetate. Colourless crystals, yield 143 mg (23%), m.p. 154-6°C (hexane/ethyl acetate). The ratio of the 2-epimers was 4:1 (*E*:*Z*) in $CDCl_3$ and 2:1 in [D_5]pyridine and [D_3]nitromethane solution; in [D_6]DMSO solution, only the signals of the *E*-epimer were detectable.- IR (KBr): $\tilde{\nu}$ = 3301; 1744; 1721; 1673 cm^{-1}.- ^{1}H-NMR ([D_6]DMSO): δ = 0.94 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.78 (quint, 6.5 Hz, 2H, 3'-CH_2), 2.57 (t, J = 6.5 Hz, 4H, CH_2CO), 3.47 (dd, J = 5 and 13 Hz, 1H, CH_2N), 3.79 (d, J = 13.5 Hz, 1H, CHCOO), 3.97 (dd, J = 10 and 13 Hz, 1H, CH_2N), 4.16 (dd, J = 7 and 13.5 Hz, 1H, NH), 4.78 (mc, 1H, NCHS), 6.89 (s, 1H, COOCH), 7.36 (mc, 10 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 16.9 (C-3'); 27.2, 27.4, 28.0, 28.2, 28.6, 32.6; 42.9, 43.9 (CH_2N); 59.1, 59.7 (CMe_2); 63.7, 65.3 (NCHS); 71.3, 74.4 (CHCOO), 77.8 ($CHPh_2$); two sp^3-signals covered; 126.6, 126.9, 127.5, 127.8, 128.1, 128.4, 139.4, 167.8, 168.7, 172,4, 172.8.- CI-MS (NH_3): m/z (%) 453 (12) (M + H)$^+$, 167 (100).- $C_{25}H_{28}N_2O_4S$ (452.5) Calcd. C 66.35 H 6.24 N 6.19 Found C 66.27 H 6.19 N 6.26.

Diphenylmethyl 2-(N,N-2'-phenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**18b**)

It was prepared from 725 mg (2.00 mmol) of **15** and 380 mg (2.00 mmol) of 2-phenylglutaric anhydride[20] as described for **18a**. Purification by flash chromatography on silica gel/hexane/ethyl acetate 1+1, and recrystallization from t-butylmethyl ether gave 240 mg (23%) of colourless needles, m.p. 52°C. The ratio of the 2-epimers was 1:1 in $CDCl_3$ solution.- IR (KBr): $\tilde{\nu}$ = 3310; 1730; 1670 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 0.95, 0.96 (2s, 6H, 2 x CH_3), 1.64, 1.65 (2s, 6H, 2 x CH_3), 2.21 (mc, 4H, 2 x CH_2), 2.68 (mc, 6H, 2 x CH_2CH), 3.74 (mc, 1H, CH_2N), 3.84 (mc, 1H, CH_2N), 4.01 (s, 1H, CHCOO), 4.02 (s, 1H, CHCOO), 4.27 (mc, 2H, CH_2N), 4.99 (mc, 2H, NCHS), 6.927 (s, 1H, CHPh), 6.932 (s, 1H, CHPh), 7.29 (mc, 30 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 25.4, 25.8, 27.6, 28.7, 28.8, 31.2, 31.5, 44.4, 44.5, 48.7, 48.8, 59.9, 60.0, 63.6, 63.8, 71.3, 71.4, 78.0 (two sp^3 signals covered or isochronous), 125.8, 126.6, 127.5, 127.8, 127.9, 128.3, 128.5, 128.7, 129.0, 138.3, 138.4, 139.4, 139.5, 168.9, 169.0, 172.3, 173.4, 173.7.- MS (70 eV): m/z (%) 510 (0.3) (M - 18)$^{+\cdot}$, 167 (100).- $C_{31}H_{32}N_2O_4S$ (528.7) Calcd. C 70.43 H 6.10 N 5.30 Found C 70.29 H 6.15 N 5.48.

Diphenymethyl 2-(N,N-3'-phenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**18c**)

It was prepared from 580 mg (1.60 mmol) of **15** and 304 mg (1.60 mmol) of 3-phenylglutaric anhydride[21], cf. **18a**. Purification was achieved by flash chromatography on silica gel/hexane/ethyl acetate 1+1, and

recrystallization from t-butylmethyl ether to give 348 mg (41%) of colourless needles, m.p. 162°C. The ratio of the 3-epimers was 2:1 (*E*:*Z*) in $CDCl_3$ solution.- IR (KBr): $\tilde{\nu}$ = 3230; 1728; 1667 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): *E*-epimer: δ = 0.95 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.78 (mc, 2H, CH_2CO), 2.97 (mc, 2H, CH_2CO), 3.44 (mc, 1H, CHPh), 3.69 (dd, J = 5 and 13 Hz, 1H, CH_2N), 4.02 (s, 1H, CHCOO), 4.20 (dd, J = 10 and 13 Hz, 1H, CH_2N), 4.95 (dd, J = 5 and 10 Hz, 1H, NCHS), 6.94 (s, 1H, COOCH), 7.35 (mc, 15 H, Ar-H).- *Z*-epimer: δ = 1.03 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), CH_2CO- and CHPh-signals isochronous with *E*-epimer and covered, 3.64 (s, 1H, CHCOO), 4.12 (dd, J = 3.5 and 13.5 Hz, 1H, CH_2N; second proton covered), 4.87 (dd, J = 3.5 and 9.5 Hz, 1H, NCHS), 6.95 (s, 1H, COOCH), Ar-H isochronous with *E*-epimer.- ^{13}C-NMR ($CDCl_3$): δ = 27.5, 28.2, 28.3, 28.7 (CH_3); 34.59, 34.61 (CHPh); 39.6, 39.9 ($\underline{C}H_2CO$); 43.3, 44.2 (CH_2N); 59.3, 59.9 (CMe_2); 63.7, 65.1 (NCHS); 71.3, 74.4 ($\underline{C}HCOO$); 78.0, 78.1 ($\underline{C}HPh_2$); 126.4, 126.6, 127.5, 127.9, 128.0, 128.2, 128.6, 129.0, 139.4, 140.5, 140.7 (Ar-C); 167.8, 168.9, 171.8, 172.1 (CO). Assignments are based on an ^{1}H/^{13}C correlation spectrum.- MS (70 eV): m/z (%) 510 (1) $(M - 18)^{+\cdot}$, 167 (100).- Mol. mass determin.: calcd. 529; found 516 (*Rast* method, camphor).- $C_{31}H_{32}N_2O_4S$ (528.7) Calcd. C 70.43 H 6.10 N 5.30 Found C 70.51 H 5.99 N 5.44.

Diphenylmethyl 2-(N,N-3',3'-diphenyl-1',5'-pentanedioyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**18d**)

533 mg (2.0 mmol) of 3,3-diphenylglutaric anhydride[22] and 786 mg (2.0 mmol) of **15**[11] were dissolved in 15 ml of dry tetrahydrofuran. The mixture was refluxed for a few min, then cooled to 0°C. 270 mg (2.0 mmol) of 1-hydroxybenzotriazole, 0.380 ml (3.0 mmol) of *N*-ethylmorpholine and 615 mg (3.0 mmol) of dicyclohexylcarbodiimide were added. It was stirred at 0°C for 1 h, and at room temp. for 2 h. Acetic acid (30%, 1 ml) was added to destroy excess dicyclohexylcarbodiimide. After filtration and evaporation, the residue was purified by cc on silica gel/hexane-ethylacetate (4+6). Colourless crystals, yield 346 mg (29%), m.p. 162/3°C (hexane/t-butylmethylether).- IR (KBr): $\tilde{\nu}$ = 3240; 1726; 1665 cm^{-1}.- ^{1}H-NMR ([D_6]DMSO): δ = 0.90 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.37 (dd, J = 5 and 13 Hz, 1H, CH_2N), 3.47 (d, J = 17 Hz, 2H, CH_2CO), 3.54 (d, J = 16.5 Hz, 2H, CH_2CO), 3.77 (s, 1H, CHCOO), 3.84 (dd, J = 10 and 13 Hz, 1H, CH_2N), 4.58 (m, 1H, NCHS), 6.91 (s, 1H, $CHPh_2$), 7.1-7.5 (m, 20 H, Ar-H).- ^{13}C-NMR ([D_6]DMSO): δ = 27.2 (CH_3), 28.5 (CH_3), 43.8 (CH_2N), 43.9 (CH_2CO), 59.7 (CMe_2), 63.9 (NCHS), 71.3 ($\underline{C}HCOO$), 77.3 ($CHPh_2$), 126.4, 126.8, 127.3, 128.0, 128.3, 128.7, 140.1, 144.7 (Ar), 168.1 (COO), 171.5 (CON).- MS (70 eV): m/z (%) 605 (0.4) $(M + H)^+$, 167 (100) ($CHPh_2^+$).- $C_{37}H_{36}N_2O_4S$ (604.8) Calcd. C 73.47 H 6.01 N 4.63 Found C 73.35 H 5.99 N 4.61.

(2S,4S)-Bis(diphenylmethyl)N,N',-6-hexanedioylbis(2-aminomethyl-3,3-dimethyl-1,3-thiazolidine-4-carboxylate) (**19**)

786 mg (2.0 mmol) of the hydrochloride of **15**[11], 270 mg (2.0 mmol) of 1-hydroxybenzotriazole and 292 mg (2.0 mmol) of adipic acid were suspended in 10 ml of dry tetrahydrofuran. 0.240 ml (2.0 mmol) of *N*-ethylmorpholine were added and, after cooling to 0°C, 412 mg (2.0 mmol) of dicyclohexylcarbodiimide. It was stirred at this temp. for 3 h. The cooling bath was removed, and another 270 mg (2.0 mmol) of 1-hydroxybenzotriazole and 0.240 ml (2.0 mmol) of *N*-ethylmorpholine were added. The temp. was again lowered to 0°C, followed by addition of 412 mg (2.0 mmol) of dicyclohexylcarbodiimide and 6 ml of tetrahydrofuran. It was stirred at room temp. overnight, filtered, and the solvent evaporated at reduced pressure. The residue was partitioned between 30 ml of ethyl acetate and 30 ml of 2M HCl. The phases were separated and the org. layer washed with 30-ml-portions each of 2M HCl and brine. Finally, the residue from the ethyl acetate phase was purified by cc on silica gel/chloroform-methanol (9+1), to give a white powder, yield 500 mg (61%), m.p. 48-53°C.- IR (KBr): $\tilde{\nu}$ = 3300; 1734; 1650; 1535 cm^{-1}.- ^{1}H-NMR ([D_6]DMSO): δ = 0.98 (s, 6H, CH_3), 1.45 (m, 4H, CH_2CH_2), 1.54 (s, 6H, CH_3), 2.04 (m, 4H, CH_2CO), 3.10 (m, 2H, CH_2N), second CH_2N-proton covered by water signal, 3.56 (s, 2H, CHCOO), 4.63 (br t, 2H, NCHS), 6.91 (s, 2H, $CHPh_2$), 7.20-7.35 (m, 20 H, Ar-H), 7.95 (m, 2H, NH). The substance slowly epimerizes in chloroform solution, giving a triple set of signals.- Mol. mass: calcd. 823.2, found 855.5 (vapour pressure osmometry, benzene solution).- $C_{46}H_{54}N_4O_6S_2 \cdot H_2O$ (841.2) Calcd. C 65.68 H 6.48 N 6.66 S 7.62 Found C 65.53 H 6.61 N 6.67 S 7.35.

(2R,4S)-Bis(diphenylmethyl)N,N'-1',9'-nonanedioylbis(2-aminomethyl-3,3-dimethyl-1,3-thiazolidine-4-carboxylate) (**20**)

620 mg (1.6 mmol) of the hydrochloride of **15**[11], 210 mg (1.6 mmol) of 1-hydroxybenzotriazole and 301 mg (1.6 mmol) of 1,9-nonanedioic acid were suspended in 10 ml of dry tetrahydrofuran. 0.408 ml (3.2 mmol) of *N*-ethylmorpholine were added, the mixture was cooled to 0°C, and 330 mg (1.6 mmol) of dicyclohexylcarbodiimide were added. After stirring at this temp. for 1 h, another 210 mg (1.6 mmol) of 1-hydroxybenzotriazole, 0.408 ml (3.2 mmol) of *N*-ethylmorpholine and 330 mg (1.6 mmol) of dicyclohexylcarbodiimide were added. The mixture was allowed to warm up overnight, filtered, and evaporated at reduced pressure. The residue was purified by cc on silica gel/chloroform-methanol (9+1), to give a white powder, yield 362 mg (51%), m.p. 104-6°C. The substance slowly epimerizes in chloroform solution.- IR (KBr): $\tilde{\nu}$ = 3300; 1733; 1645 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 0.98 (s, 6H, CH_3), 1.28 (br s, 6H, 4'-, 5'-, 6'-CH_2), 1.60 (br s, 10 H, CH_3, 3'- and 7'-CH_2), 2.12 (t, J = 7.5 Hz, 4H, CH_2CO), 3.10 (ddd, J = 4; 9.5 and 14 Hz, 2H, CH_2N), 3.44 (br s, 2H, NH), 3.55 (ddd, J = 5; 8 and 14 Hz, 2H, CH_2N), 3.77 (br s, 2H, CHCOO), 4.64 (br s, 2H, NCHS), 6.10 (br dd, J = 4 and 8 Hz, 2H, HNCO), 6.98 (s, 2H, COOCH), 7.35 (mc, 20 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 25.5, 27.1, 28.0, 28.8 (CH_2 and CH_3); 36.5 ($\underline{C}H_2CO$); 45.3 (CH_2N); 59.3 (CMe_2); 65.2 (NCHS); 71.2 ($\underline{C}HCOO$); 78.6 ($CHPh_2$); 126.9, 127.7, 128.1, 128.5, 139.2 (Ar-C); 168.6 (ester-CO), 172.9 (amide-CO).- MS (70 eV): m/z (%) 326 (1.4) (diphenylmethyl dimethylthiazoliniumcarboxylate), 167 (100).- $C_{49}H_{60}N_4O_6S_2 \cdot H_2O$ (883.3) Calcd. C 66.63 H 7.09 N 6.34 Found C 66.31 H 7.10 N 6.57.

(2R,4S)-Diphenylmethyl 2-(N-8'-hydroxycarbonyl-1'-octanoyl)aminomethyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (**21**)

1.78 g (5.0 mmol) of **15**[11] and 1.71 g (4.8 mmol) of 1,9-nonanedioic acid pentafluorophenyl ester[12] were dissolved in 16 ml of dry, ethanol-free dichloromethane and stirred for 16 h. The solvent was evaporated and the residue purified chromatographically on silica gel/t-butylmethyl ether to give 2.28 g (90%) of a white powder, m.p. 90-2°C (diisopropyl ether/ethyl acetate).- IR (KBr): $\tilde{\nu}$ = 3329 (NH); 3241 (NH); 3200-2400 (acid-OH); 1737 (ester-CO); 1685 (acid-CO); 1650 (amide-CO); 1530 (HNCO comb.) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 0.99 (s, 3H, CH_3), 1.30 (br s, 6H, 4'-, 5'-, 6'-CH_2), 1.60 (br s, 7H, CH_3, 3'- and 7'-CH_2), 2.15 (t, J = 8 Hz, 2H, CH_2CON), 2.29 (t, J = 8 Hz, 2H, CH_2COO), 3.09 (ddd, J = 4; 10 and 13 Hz, 1H, CH_2N), 3.58 (ddd, J = 5; 8 and 13 Hz, 1H, CH_2N), 3.79 (s, 1H, CHCOO), 4.65 (dd, J = 5 and 10 Hz, 1H, NCHS), 6.20 (br dd, J = 4 and 8 Hz, 2H, CONH; NH [broad]), 6.98 (s, 1H, COOCH), 7.32 (mc, 10 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 24.5, 25.4 (CH_2); 26.8, 27.8 (CH_3); 28.7, 28.8, 33.8, 36.2, 36.3 (CH_2); 45.2 (CH_2N); 58.9 (CMe_2); 64.7 (NCHS); 71.0 ($\underline{C}HCOO$); 78.1 ($\underline{C}HPh_2$); 126.7, 127.6, 128.3, 128.4, 128.5 (Ar-CH); 139.1 (Ar-C); 168.4 (ester-CO), 173.3 (amide-CO); 177.7 (acid-CO). Assignments on the basis of a DEPT spectrum and by comparison with related compounds.- CI-MS (isobutane): m/z (%) 493 (0.15) $(M - S - H)^+$, 167 (100).- $C_{29}H_{38}N_2O_5S \cdot 0.5\ H_2O$ (535.8) Calcd. C 65.01 H 7.35 N 5.23 S 5.98 Found C 64.95 H 7.15 N 5.30 S 6.04.

(3S,14aR)-2,2-Dimethyl-4,12-dioxo-3-(diphenylmethyloxycarbonyl)-1,4-diazacyclotridecano[3,4-b]1,3-thiazolidine **(22)**

417 mg (0.79 mmol) of **21** and 97 mg (0.72 mmol) of 1-hydroxybenzotriazol were dissolved in 10 ml of ethyl acetate. The solution was cooled to 0°C, and 154 mg (0.75 mmol) of dicyclohexylcarbodiimide in 2 ml of ethyl acetate were added. It was kept at this temp. for 56 h. The solvent was evaporated, and the residue purified by cc on silica gel/chloroform-methanol (97+3), to yield 192 mg (48%) of a colourless oil.- IR (KBr): $\tilde{\nu}$ = 3320 (NH); 1733 (ester-CO); 1650 (br; amide-CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 0.99 (s, 3H, CH_3), 1.30 (br, 6H, $CH_2CH_2CH_2$), 1.61 (br, 7H, CH_3, $C\underline{H}CH_2CO$), 2.14 (t, J = 7.5 Hz, 2H, CH_2CO), 2.29 (t, J = 7.5 Hz, 2H, CH_2CO); 3.09 (ddd, J = 4; 9.5 Hz and 14 Hz, 1H, CH_2N); 3.58 (ddd, J = 5; 8 and 14 Hz, 1H, CH_2N), 3.77 (s, 1H, CHCOO), 4.64 (dd, J = 5 and 9.5 Hz, 1H, NCHS), 5.95 (br dd, J = 4 and 8 Hz, 1H, NH), 6.98 (s, 1H, $CHPh_2$), 7.35 (m, 10 H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 24.8, 25.5, 27.1 (CH_2); 27.9 (CH_3); 28.7, 28.9 (CH_2); 29.1 (CH_3); 34.0, 36.6 ($\underline{C}H_2CO$); 45.2 (CH_2N), 59.3 (CMe_2); 65.1 ($C\underline{H}COO$); 71.2 (NCHS); 78.1 ($CHPh_2$); 126.9, 127.7, 128.3, 128.4, 128.6 (Ar-CH), 139.2 (Ar-C); 168.5 (ester-CO), 172.8 (CONH), 174.2 (CON).- MS (70 eV): m/e (%) 509 (0.1) $(M + H)^+$, 167 (100) ($CHPh_2^+$).- $C_{29}H_{36}N_2O_4S$ (508.7) Calcd. C 68.46 H 7.15 N 5.51 Found C 68.54 H 7.17 N 5.61.

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