Synthesis and Biological Evaluation of Integrin Antagonists Containing *trans*- and *cis*-2,5-Disubstituted THF Rings

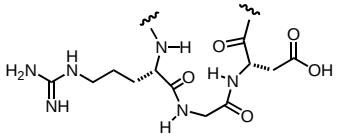
Frank Osterkamp,[a] Burkhard Ziemer,[a] Ulrich Koert,*[a] Matthias Wiesner,[b] Peter Raddatz,[b] and Simon L. Goodman[b]

Abstract: The synthesis of a series of RGD mimetics is described. All compounds consist of a central 2,5-disubstituted tetrahydrofuran core, a variable linker to a guanidino group, and a β-amino alanine unit to mimic the carboxylic acid. Three types of linkers were investigated: a simple four-atom methylene chain (type A, compounds **14**, **15**, **16**, and **17**), a four-atom methylene chain with an additional chiral center, and a nitrogen substituent (type B, compounds **38**, **39**, and **40**), and an amide linker of different length with an additional chiral center (type C, compounds **59**, **60**, **61**, and **62**). A variety of compounds were tested as potential integrin antagonists in a receptor binding assay ($\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$). The relative and absolute configuration of the chiral centers at the THF ring had a pronounced effect on the binding activity and selectivity. Compound **14** proved to be a selective inhibitor of $\alpha_{IIb}\beta_3$ ($IC_{50} = 20$ nM), whereas compound **40** exhibited high activity for binding of $\alpha_{IIb}\beta_3$ ($IC_{50} = 67$ nM) and $\alpha_v\beta_3$ ($IC_{50} = 52$ nM).

Keywords: β-turn · integrin antagonists · peptidomimetics · synthesis design

Introduction

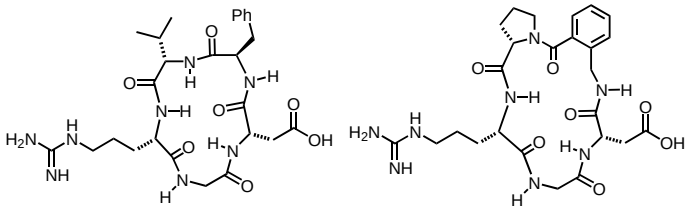
Cell-cell and cell-matrix adhesion processes are controlled by four classes of cell-surface proteins: cadherins, selectins, receptors of the immunoglobulin family, and integrins.[1] The integrins are cell-surface receptors consisting of heterodimeric glycoproteins (GPs) with different numbers and types of α and β subunits. They bind to extracellular matrix adhesive proteins such as fibrinogen, fibronectin, vitronectin, and VCAM-1 (vascular cell adhesion molecule-1). Within the integrin receptor family, the $\alpha_v\beta_3$-integrin and the $\alpha_{IIb}\beta_3$-integrin receptor (also called GPIIb/IIIa) have gained particular importance in medicinal chemistry. The $\alpha_v\beta_3$ integrin binds the natural ligands fibrinogen and vitronectin and is involved in many pathological processes such as angiogenesis, platelet aggregation, and tumor growth.[2] $\alpha_v\beta_3$-Antagonists are therefore promising drug candidates for different diseases such as cancer and osteoporosis. The $\alpha_{IIb}\beta_3$ integrin is involved in blood platelet aggregation and its blocking has been investigated in the context of thrombosis therapy.[3] The RGD motif is common for the ligands found in the adhesive interactions with the $\alpha_{IIb}\beta_3$- and the $\alpha_v\beta_3$-type integrins (Figure 1). Intensive efforts have been made to find selective $\alpha_{IIb}\beta_3$- and the $\alpha_v\beta_3$-type antagonists by structural variation of the RGD motif.[4, 5]



R G D

Figure 1. The RGD motif which is essential for most binding sites of naturally occurring integrin ligands.

Cyclic RGD peptides such as **2**[6] or **3**[7] were developed by different groups (see Figure 2).[8, 9, 10] Their advantage is the conformational constraint of the cyclic system, which allows a



2: *cyclo*(-RGDfV-)
Kessler and Merck KGaA[6]

3: *cyclo*(-RGD-Mamb-P-)
Dupont-Merck[7]

Figure 2. Cyclic peptide integrin antagonists.

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good design of the bioactive conformation leading to high selectivities for the different integrin receptors. However, as with all peptide drugs, the potential immunogenicity and low bioavailibility may cause problems.

Highly potent non-peptide integrin antagonists are presently being developed. Prominent examples are summarized in Figure 3 ($\alpha_v\beta_3$-selective[11–16]) and Figure 4 ($\alpha_{IIb}\beta_3$-selective[17–22]). The underlying design principles for all these compounds are quite similar. They consist of a rigid preferably achiral core unit which links a guanidine-type functionality (or secondary amine functionality in **9**) and a carboxylic acid moiety. Efforts to use a carbohydrate framework as central template led to a rather low receptor affinity.[15]

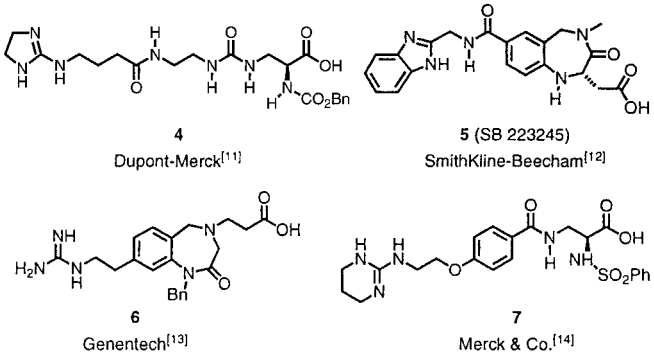


Figure 3. Examples for non-peptide $\alpha_v\beta_3$ antagonists.

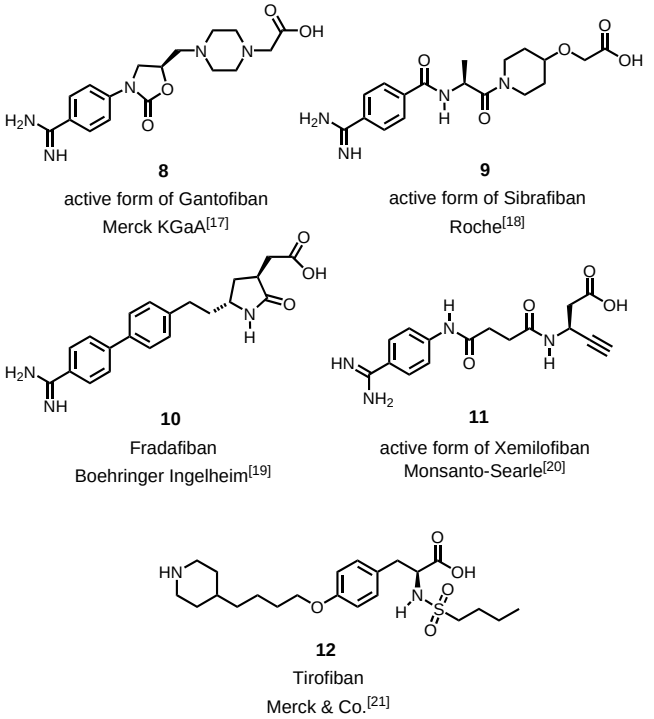


Figure 4. Examples for non-peptide $\alpha_{IIb}\beta_3$ antagonists.

In this paper we describe the synthesis and biological evaluation of a series of tetrahydrofuran (THF)-based integrin antagonists. The aim of our work was first of all to investigate the potential of 2,5-disubstituted THFs[23] as chiral core units in RGD mimics. The THF ring as the general structure **13** (Figure 5) in our RGD mimics is located at the conformationally sensitive glycine position of the original RGD sequence. We anticipated that the variation of the absolute and relative configuration at the stereogenic centers C-2 and C-5 of the THF ring offers the opportunity to tune the

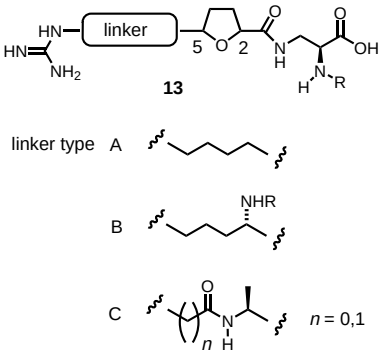


Figure 5. Potential integrin antagonists of type **13** with a 2,5-disubstituted THF core unit, a variable linker to the guanidino function, and a constant (*S*)-β-amino-alanine side chain.

receptor activity and selectivity. Our simple initial hypothesis was that *trans* THFs should lead to more extended conformations of the RGD mimics and therefore to compounds which are more active towards the $\alpha_{IIb}\beta_3$ integrin. Whereas by the use of *cis* THFs preferably bent conformations of the RGD mimics should be induced, hence some $\alpha_v\beta_3$ selectivity was expected. This hypothesis was based on the results from the cyclic RGD peptides in which very potent $\alpha_v\beta_3$-type antagonists display a "glycine centered in a γ-turn" conformation, while the most active $\alpha_{IIb}\beta_3$ inhibitors exhibit a "turn–extended-turn" conformation.[3] While the (*S*)-β-amino-alanine side chain had been proven to be a useful aspartic acid mimic,[11] we decided to work with this subunit and concentrate on target structures of type **13**. Three types of linkers between the THF unit and the guanidino function were investigated: a simple four atom methylene chain (type A), a four atom methylene chain with an additional chiral center and a nitrogen substituent (type B), and an amide linker of different length with an additional chiral center (type C).

Results and Discussion

Synthesis: The synthesis of all four stereoisomers of the type A linked target structures **14**, **15**, **16**, and **17** (Figure 6) used one common stereocenter from the chiral pool as starting point for the THF-ring construction. The (*S*)-acetonide bromide **20** is readily available from L-malic acid[24] and has recently been used as a valuable building block for the stereoselective synthesis of 2,5-disubstituted THFs.[25, 26] It was converted into the corresponding organomagnesium compound and allowed to react with the aldehyde **19**,[27] which is accessible by Swern oxidation[29] of the alcohol **18**. Thus, the secondary alcohol **21** was obtained in good yield as a 1:1 epimeric mixture.

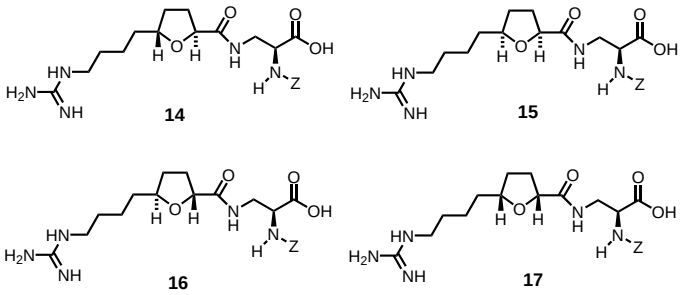
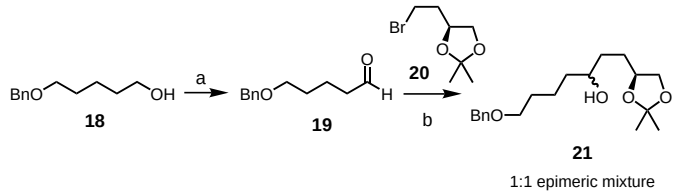
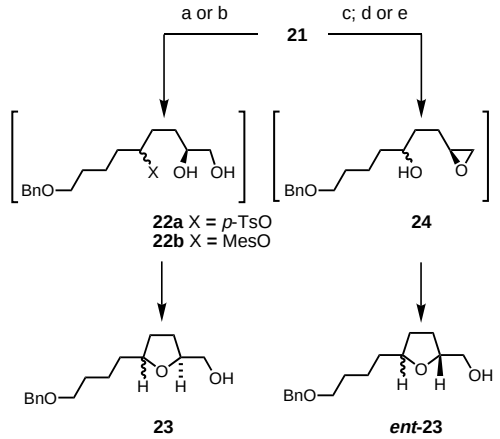


Figure 6. THF-based RGD mimetics **14**, **15**, **16**, and **17** with type A linker.



Scheme 1. Preparation of the alcohol **21**: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-60 \rightarrow 0\,^{\circ}C$, 30 min, 98%; b) Mg, THF, 0 °C, 20 min, 80%.

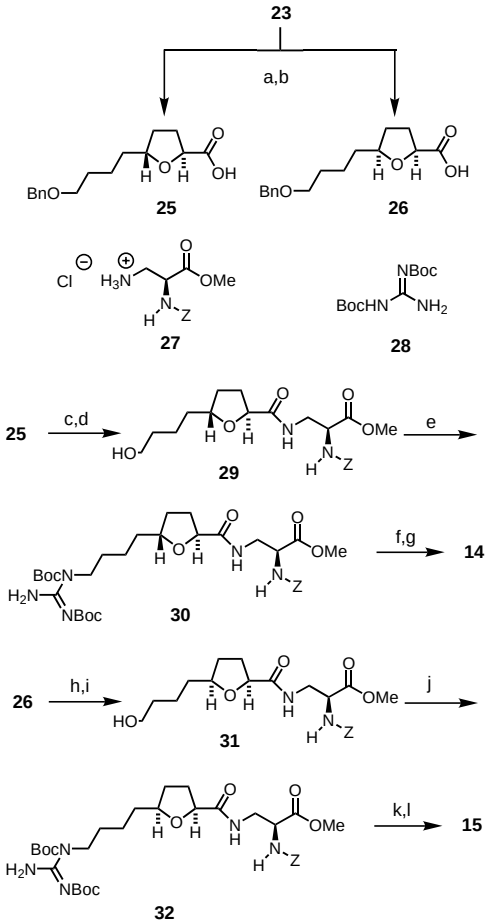
Two stereochemical complementary pathways for closing the THF ring were established. After conversion of the hydroxy function of **21** into a leaving group (tosylate or mesylate), the cleavage of the acetonide provided the diols **22a** and **22b**, which reacted in an intramolecular Williamson reaction to yield the THF alcohol **23** (retention at C2, inversion at C5).[25] In the case of the mesylate **22b** the THF-ring closure occurred directly under the acidic conditions of the acetonide cleavage (see Scheme 2). The second



Scheme 2. Stereocomplementary routes to the THF alcohols **23** and ***ent*-23**: a) i) *p*-TsCl, pyridine, CH_2Cl_2, rt, 2 h; ii) HOAc, H_2O, rt, 13 h; iii) NaH, THF/DMSO, 40 °C, 4 h, 63% from **21**; b) i) MesCl, Et_3N, CH_2Cl_2, $-15\,^{\circ}C$, 1 h; ii) 1N HCl, THF, rt, 2 h, 77% from **21**; c) 1N HCl, THF, rt, 2 h, 90%; d) i) mesitylenesulfonyl chloride, pyridine, CH_2Cl_2, 0 °C, 36 h; ii) K_2CO_3, MeOH, rt, 2 h; iii) HOAc, CH_2Cl_2, rt, 2 h, 48%; e) NaH, tosylimidazole, THF, rt, 45 min, 77%. *p*-Ts = *para*-toluenesulfonyl, Mes = methanesulfonyl, DMSO = dimethyl sulfoxide.

route started with the cleavage of the acetonide in **21** to the corresponding triol. A subsequent stereocontrolled conversion of the 1,2-diol group into an epoxide function (**21** → **24**) followed by an intramolecular 5-exo opening of the epoxide by the OH group gave the THF alcohol ***ent*-23** (inversion at C2, retention at C5).[26] A one-step procedure using 4 equiv NaH and 1.2 equiv tosylimidazole[28] gave a higher yield than the three-step route via the mesitylene sulfonate. However, the stereocontrol of the tosylimidazole procedure was not complete. Due to the formation of the secondary tosylate as a minor by-product, only a 9:1 selectivity was achieved.

A two-step oxidation (Swern[29]+$NaClO_2$[30]) of the alcohol **23** led to the THF carboxylic acids **25** and **26** after chromatographic separation of the *trans* and *cis* isomers (Scheme 3).



Scheme 3. Synthesis of the RGD-mimetics **14** and **15**: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-60 \rightarrow 0\,^{\circ}C$, 30 min; b) $NaClO_2$, NaH_2PO_4, amylene, *t*-BuOH, rt, 12 h, 77%; 40% of **25** and 21% of **26** after chromatography; c) H_2, 10% Pd/C, THF/MeOH/H_2O 4:2:1, rt, 18 h; d) **27**, BOP, EtN(iPr)$_2$, MeCN, rt, 16 h, 89% from **25**; e) **28**, PPh_3, diisopropyl azodicarboxylate, THF, rt, 16 h, 62%; f) LiOH, THF, H_2O, rt, 20 min; g) TFA, CH_2Cl_2, rt, 2 h, 85% from **30**; h) and i) see c) and d), 62% from **26**; j) see e), 74%; k) and l) see f) and g), 79% from **32**. BOP = 1-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, TFA = trifluoroacetic acid.

The stereochemical assignment of the relative configuration at the THF ring was possible by NMR spectroscopy. Evaluation of the NOESY spectrum from **26** showed 2-H/5-H and 3-H/5-H cross peaks for the *cis* isomer (Figure 7), which were absent in the case of the *trans*-isomer **25**.

Hydrolytic cleavage of the benzylether in **25** and coupling (BOP/EtN(iPr)$_2$)[31] of the resulting hydroxycarboxylic acid

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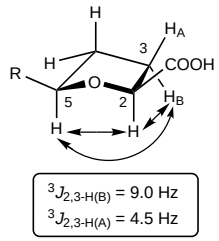
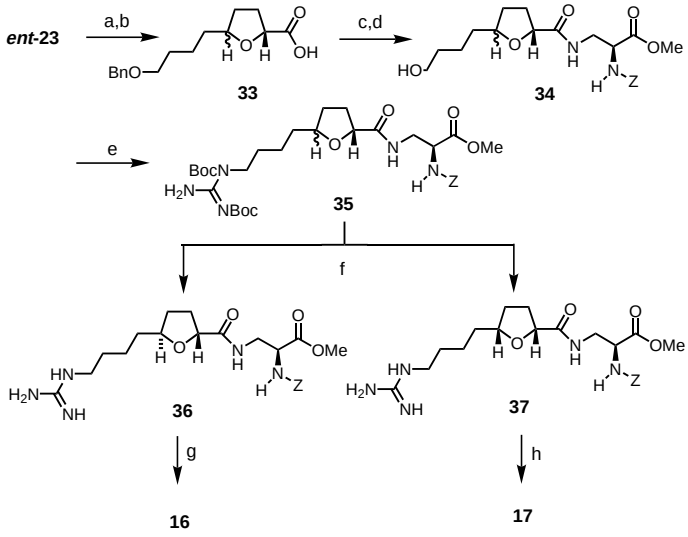


Figure 7. Sterochemical assignment of the *cis* configuration of **26** from NMR data.

with the amine component **27** delivered the amide **29** in 89% yield. The amine component is available via Hofmann degradation and esterfication of Z-protected L-asparagine.[32] Using the guanidine reagent **28** the introduction of the Boc-protected guanidino group (**29** → **30**) was achieved by a Mitsunobu reaction.[33] Hydrolysis of the methyl ester, *N*-Boc deprotection, and RP-HPLC purification gave the free *trans*-THF guanidine carboxylic acid **14**. Along the same route the *cis*-THF guanidine carboxylic acid **15** was prepared from the *cis*-THF carboxylic acid **26**.

For the synthesis of the two other type-A linked stereoisomers **16** and **17**, the separation of the *trans* and *cis* isomers was performed in a later stage of the guanidine methyl esters **36** and **37** (Scheme 4). Thus, the THF alcohol ***ent*-23** was



Scheme 4. Synthesis of the RGD-mimetics **16** and **17**: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-60 \rightarrow 0\,^\circ C$, 30 min; b) $NaClO_2$, NaH_2PO_4, amylene, *t*-BuOH, rt, 12 h; 64%; c) H_2, 10% Pd/C, THF/MeOH/H_2O 4:2:1, rt, 18 h; d) **27**, BOP, EtN(*i*Pr)$_2$, MeCN, rt, 16 h, 75% from **34**; e) **28**, PPh_3, diisopropyl azodicarboxylate, THF, rt, 16 h, 78%; f) TFA, CH_2Cl_2, rt, 2 h, HPLC separation of the *trans* and *cis* isomer; g) LiOH, THF, H_2O, rt, 20 min, 10% from **35**; h) LiOH, THF, H_2O, rt, 2 h 6% from **35**. BOP = 1-Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, TFA = trifluoroacetic acid.

oxidized to the carboxylic acid **33**, which was coupled with the amine unit **27** to yield the amide **34**. The latter was transformed into the *N*-Boc-protected guanidine **35**. After *N*-Boc deprotection the *trans*-THF **36** and the *cis*-THF **37** were separated by RP-HPLC. Hydrolysis of the methyl ester group gave the final RGD-mimetics **16** and **17**.

The stereochemical assignment of the relative configuration in **16** and **17** was achieved by NMR spectroscopy. The NOESY spectrum of **16** and **17** showed 2′-H/3′-H and 3′-H/5′-H cross peaks for the *trans*-isomer **16** and 2′-H/5′-H and 3′-H/5′-H cross peaks for the *cis*-isomer **17** (Figure 8).

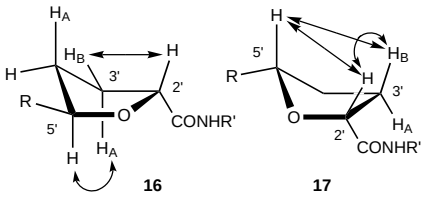


Figure 8. Sterochemical assignment of the *trans* configuration of **16** and the *cis* configuration of **17** from depicted NOESY data.

Three THF-RGD mimetics **38**, **39**, and **40** of type B linker were accessible from the *N*-protected ornithine derivative **41** (Figure 9).

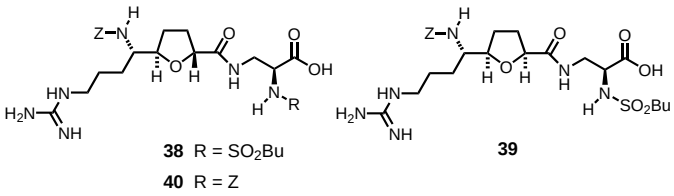


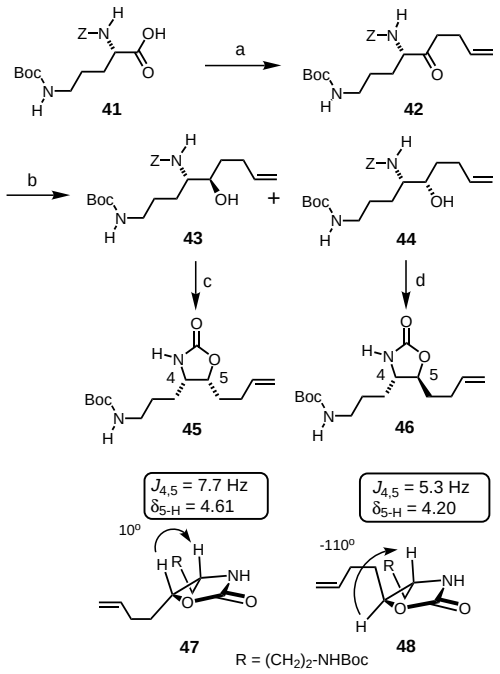
Figure 9. THF-based RGD mimetics **38**, **39**, and **40** with type B linker.

The acylation the bis-*N*-protected carboxylic acid **41** to the ketone **42** required some effort. Acylation of the lithium salt or the acid chloride failed.[34] The two *N*-protecting groups (Boc and Z) with their free NH groups were not compatible with these reaction conditions. A successful conversion of **41** to **42** was possible via the thiopyridine ester of **41**.[35] Reaction of the thiopyridine ester with the butenyl Grignard reagent in THF at $-78\,^\circ C$ afforded 27% of the desired product **42** (Scheme 2). The yield could be improved to 92% by transmetallation of the Grignard reagent with CuCN/2 LiCl at $-40\,^\circ C$ and subsequent addition of the thiopyridine ester. Reduction of the ketone **42** with L-selectride gave the two epimeric alcohols **43** and **44** in a 3:1 ratio. The stereochemical assignment of compounds **43** and **44** was possible by NMR studies of the corresponding oxazolidinones **45** and **46**. In the case of the *cis* oxazolidinone a preferred conformer **47** exhibits a $J_{4,5} = 7.7$ Hz, while the preferred conformer of the *trans* oxazolidinone **48** exhibits a $J_{4,5} = 5.3$ Hz.[36]

In order to support this assignment, an X-ray crystal structure analysis of the *p*-nitrobenzoate **49**, a crystalline derivative of the main reduction epimer **43**, was done. (Figure 10). The results from the NMR studies and from the X-ray crystal structure analysis were consistent.

The stereochemical outcome of the L-selectride reduction deserves some comments. In related reductions of for example the alanine-derived ketones the opposite selectivity is observed.[37] An explanation for the non-Felkin–Anh selectivity observed in the reduction of **42** may be a chelating effect of the *N*-Boc group.

The terminal alkene **43** was epoxidized with MCPBA to a 1:1 epimeric mixture of epoxy alcohols, which by treatment with PPTS underwent an intramolecular epoxide opening to give the THF alcohol **50** as a 1:1 mixture at C-2 (Scheme 6).



Scheme 5. Acylation of **41** and stereoselective reduction of ketone **42**: a) i) 2-mercaptopyridine, *N*,*N*′-diisopropylcarbodiimide, CH_2Cl_2, 94%; i) 2.4 equiv CuCN × 2 LiCl, 2.4 equiv $BrMgCH_2CH_2CH{=}CH_2$, THF, $-78 \rightarrow -5\,^{\circ}C$, 30 min, 92%; b) L-selectride, THF, $-100 \rightarrow -70\,^{\circ}C$, 30 min; 46% of pure **43** after crystallisation; c) NaH, THF, rt, 18 h, 90%; d) NaH, THF, rt, 18 h, chromatography, 15%. L-selectride = Lithium-tri-*sec*-butylborohydride.

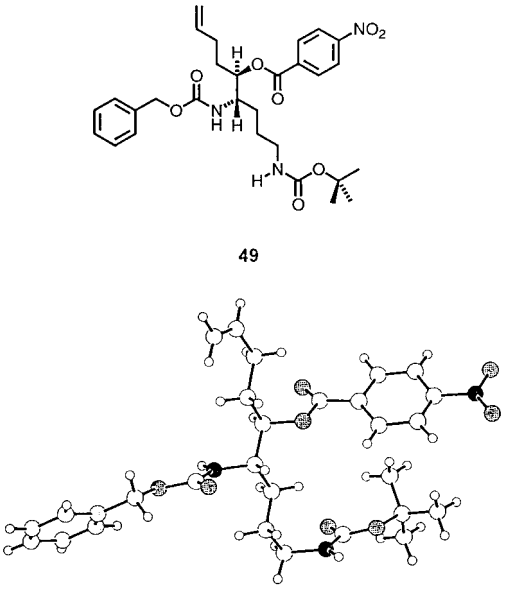
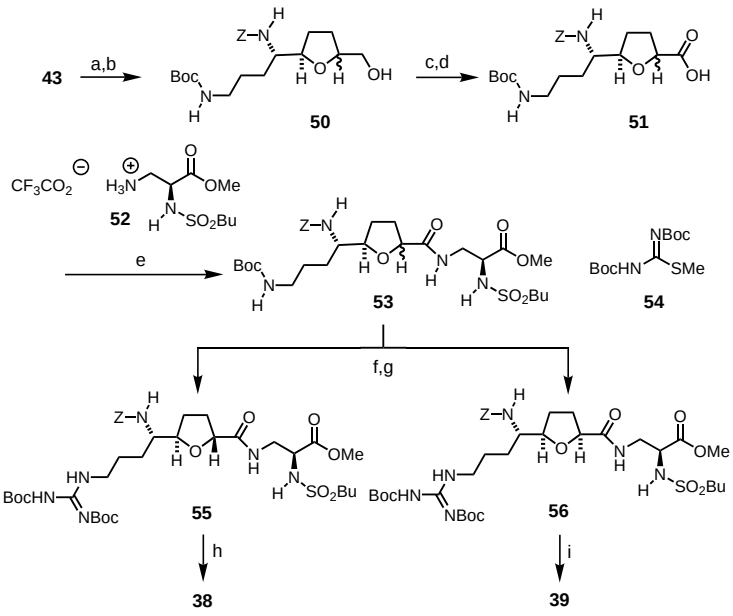


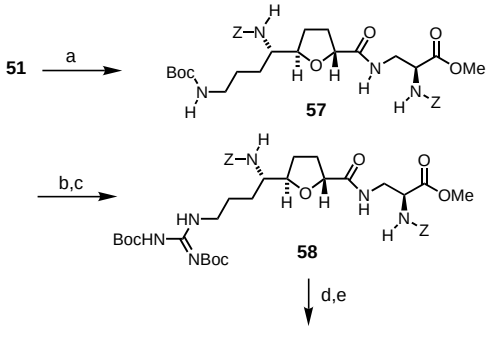
Figure 10. X-ray crystal structure of the *p*-nitrobenzoate **49**.

Oxidation of **50** yielded the carboxylic acid **51**. Coupling of **51** with the β-amino alanine derivative **52**[32] resulted in the amide **53**. After Boc deprotection an primary amine was obtained, which was allowed to react with the iso-thiourea **54**[38] to produce after chromatographic (HPLC) diastereomer separation the *trans*-THF compound **55** and the *cis*-THF compound **56**. Cleavage of the guanidine protecting groups and hydrolysis of the methyl ester yielded the RGD-mimetics **38** and **39**.



Scheme 6. Synthesis of the RGD-mimetics **38** and **39**: a) MCPBA, CH_2Cl_2, rt, 12 h; b) PPTS, CH_2Cl_2, rt, 12 h; 90% from **43**; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-60 \rightarrow 0\,^{\circ}C$, 30 min; d) $NaClO_2$, NaH_2PO_4, amylene, *t*-BuOH, rt, 12 h; 64% from **50**; e) **52**, HOBt, EDC, $EtN(iPr)_2$, THF, rt, 16 h, 61%; f) TFA, CH_2Cl_2, rt, 2 h; g) **54**, $HgCl_2$, Et_3N, DMF, rt, 3 h, HPLC separation of the *cis* and *trans* isomers, 38% of **55** and 13% of **56**; h) i) LiOH, THF, H_2O, rt, 20 min; ii) TFA, CH_2Cl_2, rt, 2 h, 66%; i) see h, 43%. MCPBA = *meta*-chloroperoxybenzoic acid, PPTS = pyridinium *para*-toluenesulfonate, HOBt = 1-Hydroxy-1*H*-benzotriazole, EDC = N′-(3′-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride.

In order to evaluate the effect of the butylsulfonyl group versus the Z group on receptor binding the *trans*-THF RGD mimetic[32] **40** containing a Z-group was synthesized analogous to the route for compounds **38** and **39** (Scheme 7). In the case



Scheme 7. Synthesis of the RGD-mimetic **40**: a) **27**, HOBt, EDC, Et-$N(iPr)_2$, THF, rt, 16 h, crystallization of the *trans* isomer, 37%; b) TFA, CH_2Cl_2, rt, 2 h; c) **54**, $HgCl_2$, Et_3N, DMF, rt, 3 h, 73% from **57**; d) i) LiOH, THF, H_2O, rt, 20 min; ii) TFA, CH_2Cl_2, rt, 2 h, 46% from **58**.

of **40**, the isomerically pure *trans*-THF epimer could be separated by crystallization after the coupling reaction of the carboxylic acid **51** with amine component **27**.

The stereochemical assignment of compounds **38**, **39**, and **40** was possible by NMR studies. The results from the evaluation of the corresponding NOESY spectra are summarized in Figure 11.

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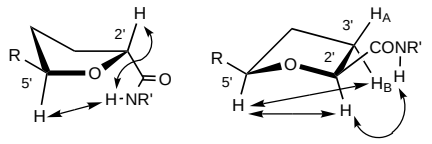


Figure 11. Sterochemical assignment of the relative configuration at the THF rings of **38**, **39**, and **40** from NOESY data.

The third group of RGD mimetics (type C) with an amide linker of different length and an additional chiral center was addressed next. Four target structures **59**, **60**, **61**, and **62** were chosen (Figure 12).

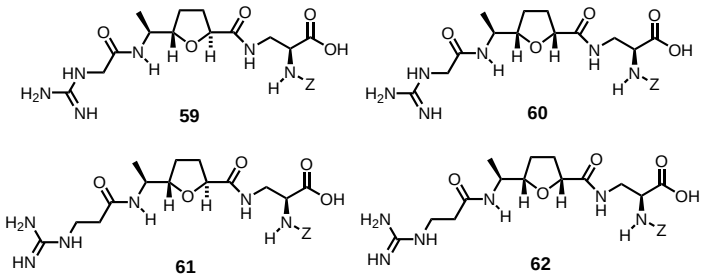
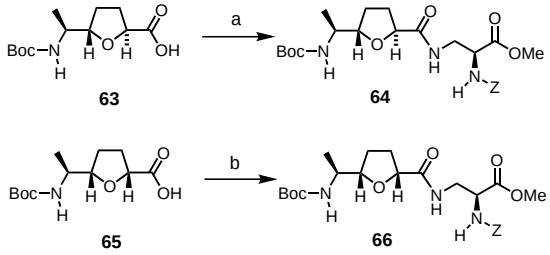


Figure 12. THF-based RGD mimetics **59**, **60**, **61**, and **62** with type C linker.

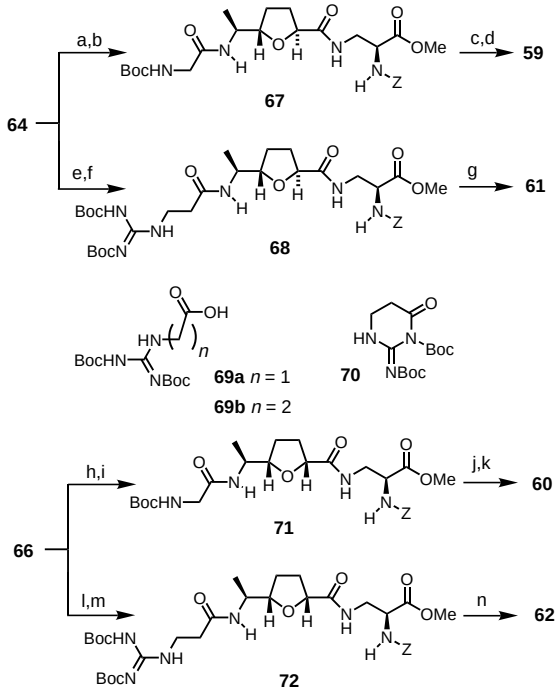
Starting point for the synthesis of the four type C linked target structures were the *N*-Boc-protected THF amino acids **63** and **65** (Scheme 8).[34] The *trans*-THF configuration of **63**



Scheme 8. Synthesis of compounds **64** and **66**: a) **27**, HOBt, EDC, $EtN(iPr)_2$, THF, rt, 16 h, 81 %; b) see a) 84 %.

and the *cis*-THF configuration of **65** have been established by X-ray crystal structure analysis.[34] Coupling (HOBt/EDC) of the Boc-protected THF amino acids with the amine component **27** gave the two amides **64** and **66**.

The *trans*-THF amide **64** was *N*-Boc deprotected and allowed to react with *N*-Boc-glycine to yield the diamide **67** (Scheme 9). After conversion of the *N*-Boc group in **67** into a guanidino function the completion of the carbon skeleton of the RGD mimetic was obtained. All attempts to use building block **69a** for the combined introduction of the linker and the guanidino function failed, as a result of the easy formation of the five-membered creatinine-like heterocycle. Deprotection of the guanidino function in **67** and hydrolysis of the methyl ester provided the target compound **59**. The tripeptide **68** with an additional carbon atom in the linker chain was synthesized from the *N*-Boc deprotected form of **64** by coupling with building block **69b**.[39] This time, the formation of the six-membered ring **70**, which occurred initially as major product, could be suppressed to some extend by optimized reaction conditions. Deprotection of the guanidino function and hydrolysis of the methyl ester gave access to the RGD-mimetic **61**. Along the same routes the *cis*-THF derivative **66** was converted via the diamides **71** and **72** into the two *cis*-THF RGD mimetics **60** and **62**.



Scheme 9. Synthesis of the RGD-mimetics **59**, **60**, **61**, and **62**: a) TFA, CH_2Cl_2, rt, 2 h; b) *N*-Boc-glycine, HOBt, EDC, $EtN(iPr)_2$, THF, rt, 18 h, 94 % from **64**; c) i) TFA, CH_2Cl_2, rt, 2 h; ii) **54**, $HgCl_2$, Et_3N, DMF, rt, 2.5 h, 93 %; d) i) LiOH, THF, H_2O, rt, 20 min; ii) TFA, CH_2Cl_2, rt, 2 h, 60 %; e) TFA, CH_2Cl_2, rt, 2 h; f) **69b**, HOBt, EDC, $EtN(iPr)_2$, THF, 0 °C → rt, 3 h, rt, 3 h, 75 % from **64**; g) see d), 72 %; h) and i): see a) and b), 81 %; j) and k): see c) and d), 67 %; l) and m): see e) and f) 35 % **72** and 29 % **70**; n) see d), 79 %.

Biological evaluation: The RGD mimetics were tested for their biological activity in a receptor binding assay.[41] All three types of linkers led to receptor antagonists with submicromolar activity on $\alpha_{IIb}\beta_3$ or on $\alpha_v\beta_3$ (Table 1) integrin receptor. The linker type and the relative configuration of the THF ring had a pronounced effect on the receptor activity and selectivity. All compounds were essentially inactive on $\alpha_v\beta_5$, probably as a result of the β-amino alanine side chain which is known to be specific for the β_3-integrin.[11]

All four compounds with the flexible type A linker (**14**, **15**, **16**, and **17**) showed a stronger binding with the $\alpha_{IIb}\beta_3$ than with the $\alpha_v\beta_3$-type receptor. Compound **14** exhibited a high activity and selectivity for $\alpha_{IIb}\beta_3$ ($IC_{50} = 20$ nM, IC_{50} ($\alpha_v\beta_3$) = 3.5 μM) and may be a good candidate for further delevopment. The relative and absolute configuration of the THF ring in this series has a remarkable influence on the binding to the $\alpha_{IIb}\beta_3$ receptor: The *trans* compounds are more active than the *cis* compounds, the most potent is the 2′*S*,5′*S*-stereoisomer **14**.

The three compounds **38**, **39**, and **40** with type B linker were found to be active in the nanomolar range for binding with the

Table 1. Effect of compounds (**14**–**17**, **38**–**40**, and **59**–**62**) on ligand interaction with integrins.[a]

Linker type	Compound	IC_{50} [μM] $\alpha_v\beta_3$	IC_{50} [μM] $\alpha_{IIb}\beta_3$	IC_{50} [μM] $\alpha_V\beta_5$
A	**14**	3.5	0.02	> 10
A	**15**	1.8	0.39	> 10
A	**16**	7.1	0.21	8.8
A	**17**	5.9	2.7	> 10
B	**38**	0.20	0.24	> 10
B	**39**	0.41	1.82	> 10
B	**40**	0.052	0.067	> 10
C	**59**	4.8	0.32	> 10
C	**60**	> 10	> 10	> 10
C	**61**	0.71	0.29	> 10
C	**62**	> 10	> 10	> 10
	2	0.003	6.4	1.8
	GRGDSPK	0.32	6.0	> 10

[a] Biotinylated ligands vitronectin ($\alpha_v\beta_3$ and $\alpha_v\beta_5$) or fibrinogen ($\alpha_{IIb}\beta_3$) were allowed to bind to immobilized integrins in the presence of the compounds **14**–**17**, **38**–**40**, and **59**–**62**. The concentration necessary for half-maximum inhibition of ligand binding is shown. The peptide GRGDSPK and compound **2** were included for reference. The sign > indicates that the IC_{50} had not been reached at the maximum concentration tested (10 μM).[41]

$\alpha_{IIb}\beta_3$ and with the $\alpha_v\beta_3$ receptor. This time, the *trans*-THF compound was more active than its *cis* counterpart at the $\alpha_{IIb}\beta_3$ and the $\alpha_v\beta_3$ integrin. The comparison between compounds **38** and **40** allowed the evaluation of the N-substituent of the β-amino alanine part: The benzyloxycarbonyl (Z) group led to 3–4 times stronger binding than the butylsulfonyl group. By comparison of **40** and **16** the beneficial effect of the type B linker for $\alpha_v\beta_3$ binding can be clearly seen (enhancement of $\alpha_v\beta_3$ binding by factor 140 versus 3 for $\alpha_{IIb}\beta_3$ binding).

In the type C linker series the *trans*–*cis* effect was most pronounced: Both *cis*-compounds **60** and **62** showed no activity. The central *cis*-THF amino acid in **60** and **62** was recently recognized as β-turn mimic.[34] Analogy of the NMR parameters in the THF part indicated that an energetically favorable hydrogen bond also fixed **60** and **62** in a β-turn like conformation. This β-turn like conformation leads to a collapse of the RGD motif and a complete loss of binding. The *trans*-THF compounds **59** and **61**, which cannot adopt a β-turn like conformation, showed activity for both receptors with some selectivity in favor of the $\alpha_{IIb}\beta_3$ receptor. The effect of the linker length on receptor binding is seen in the comparison between both compounds: In the $\alpha_v\beta_3$ case the longer linker **61** resulted in a higher activity, whereas no substantial effect of the linker length was found for the $\alpha_{IIb}\beta_3$ receptor affinity.

Additionally performed molecular modeling studies on all RGD mimics were of limited validity due to the inherent flexibility of these compounds. Only in the case of **60** and **62** and the type B linker structures **38**, **39**, and **40** we were able to locate pronounced minimum conformers. Representative overlays of the calculated minimum conformers of **62** and **40** our most active compound on the $\alpha_v\beta_3$ integrin are displayed in Figure 13.

The tight arrangement of the pharmacophoric groups in Figure 13, bottom is presumably the reason for the inactivity

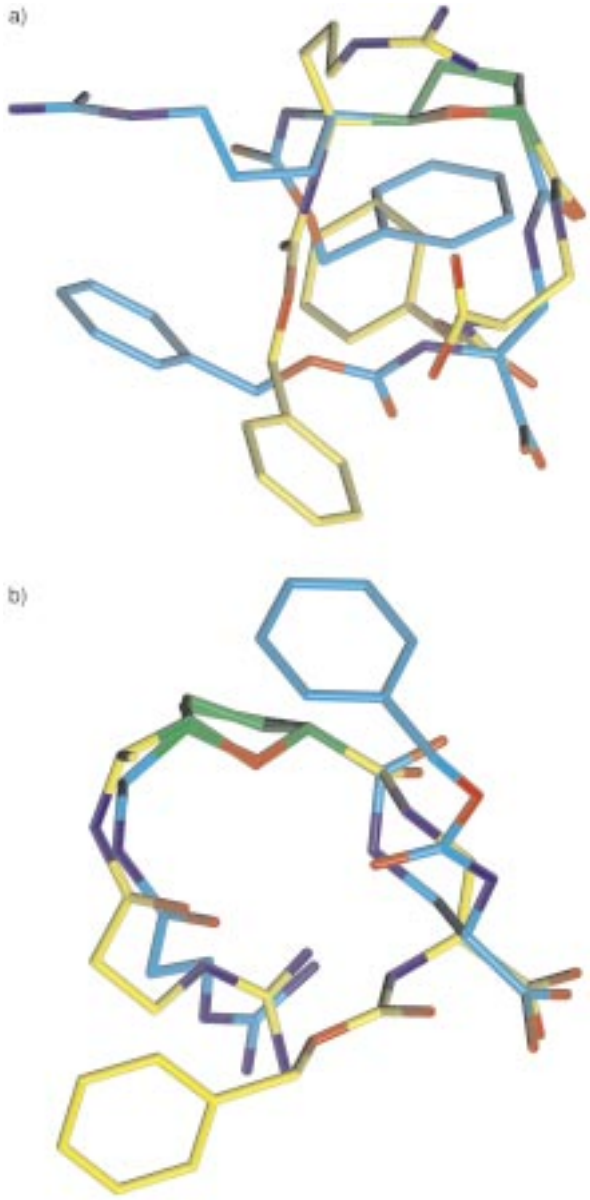


Figure 13. Overlay of low energy conformations of THF-based RGD mimetics, THF ring in green; top: **40** (yellow 83% and blue 15% populated at 298 K); bottom: **62** (yellow 87% and blue 8% populated at 298 K).

of **62**. Interestingly an anologous hydrogen-bonded motif of **39** was not observed either by molecular modeling nor by NMR techniques. The benzyloxycarbonylamino substituent adjacent to the THF in **40** (Figure 13, top) obviously forces the guanidino side chain into a direction appropiate for $\alpha_v\beta_3$ (and $\alpha_{IIb}\beta_3$) binding far away from the carboxylic acid moiety.

Conclusion

The work presented here shows that 2,5-disubstituted tetrahydrofurans are well suited as a new core unit for RGD mimetics. The activity and selectivity of the receptor binding can be addressed by choosing the relative and absolute configuration of the stereocenters at the THF ring and the linker type. Synthetic routes to the different stereoisomers

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were successfully established. In agreement with our initial hypothesis all RGD mimics possessing a *trans*-THF unit were considerably more active on the $\alpha_{IIb}\beta_3$ integrin than their comparable *cis*-THF counterparts. A good selectivity and activity for $\alpha_{IIb}\beta_3$ was observed for compound **14** with type A linker. The use of *cis*-THF compounds did not automatically generate $\alpha_v\beta_3$ activity or selectivity. Although our best RGD mimic in terms of $\alpha_v\beta_3$ selectivity **39** (factor 4.4) was *cis* configured, the *trans*-THF compound **40** was the best in terms of $\alpha_v\beta_3$ activity. In order to achieve higher activity towards the $\alpha_v\beta_3$ receptor the use of the type B linker seems to be more important than the THF configuration. The β-turn imitating *cis*-THF amino acid as central core (in **60** and **62**) is not suitable for integrin binding.

The present work focuses on selected stereoisomers for each linker type. From the results obtained the investigation of further stereoisomers are promising. In particular the type B linker, where only two stereoisomers were tested, should be explored in future work. General conclusions on structure–activity relationships can only be given after the biological data of these compounds are available.

The new synthetic routes to THF-integrin antagonists presented herein and the promising biological evaluation of these new class of compounds should encourage further efforts to develop prospective drug candidates for the therapy of thrombosis, angiogenesis, and tumor metastasis.

Experimental Section

General: All b.p.'s and m.p.'s are uncorrected. IR: Bruker IFS 88. NMR: Bruker AC-300, DPX-300, AMX-500, and AMX-600. For ^{1}H NMR: $CDCl_3$ as solvent $\delta_H = 7.25$, [D$_6$]DMSO as solvent $\delta_H = 2.50$, [D$_4$]MeOH as solvent $\delta_H = 4.78$; for ^{13}C NMR: $CDCl_3$ as solvent $\delta_C = 77.0$, [D$_6$]DMSO as solvent $\delta_C = 39.5$, [D$_4$]MeOH as solvent $\delta_C = 49.0$. Elemental analysis: CHN Rapid (Heraeus), CHNS-932 Analysator (Leco). HRMS: Finnigan MAT 95. All reactions were performed under an inert atmosphere of argon in oven- or flame-dried glassware. Dry solvents: THF, Et_2O, benzene, and toluene were distilled from sodium benzophenone. All commercially available reagents were used without purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck F-254 silica glass plates visualized with UV light and/or heat-gun treatment with 5% phosphomolybdic acid in ethanol or 1.2% anisaldehyde in ethanol and 2.20% H_2SO_4. Column chromatography (CC) was performed with Merck silica gel 60 (70–200 mesh and 230–400 mesh). PE: light petroleum ether, b.p. 40–60 °C. MTBE: methyl *tert*-butyl ether, DIAD: diisopropyl azodicarboxylate.

5-Benzyloxypentanal (19): A solution of DMSO (14.4 mL, 15.9 g, 201 mmol) in CH_2Cl_2 (100 mL) was added dropwise over a period of 20 min at −60 °C to a solution of oxalyl chloride (10.8 mL, 15.7 g, 124 mmol) in CH_2Cl_2 (400 mL). After the reaction mixture was stirred at this temperature for 5 min, a solution of the alcohol **18** (20.0 g, 103 mmol) in CH_2Cl_2 (100 mL) was added dropwise, and the reaction mixture was stirred for an additional 15 min. NEt_3 (60.0 mL, 43.8 g, 433 mmol) was added and the solution was stirred for further 5 min at −60 °C. The reaction mixture was allowed to warm to 0 °C within 30 min. The reaction was quenched by the addition of sat. aqueous $NaHCO_3$ (400 mL). After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with sat. aqueous NaCl (300 mL) and dried with $MgSO_4$. After removal of the solvent in vacuo and azeotropical distillation with toluene (50 mL), the crude product was purified by CC (100 g, PE/Et_2O 1:1) to yield aldehyde **19** (19.5 g, 98%) as a slightly yellow liquid. $R_f = 0.60$ (PE/Et_2O 1:1); IR (neat): $\tilde{\nu} = 3030$m (ArH), 2940/2865s (CH), 2740w (CHO), 1725s (C=O), 1455m, 1365w, 1205w, 1100s, 740m, 700m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.58–1.81$ (m, 4H, 3-H$_2$, 4-H$_2$), 2.44 (td, $J = 7.1$, 1.4 Hz, 2H, 2-H$_2$), 3.48 (t, $J = 6.0$ Hz, 2H, 5-H$_2$), 4.49 (s, 2H, CH_2-Ph), 7.25–7.38 (m, 5H, Ph), 9.74 (t, $J = 1.5$ Hz, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.9$ (C-3), 29.0 (C-4), 43.5 (C-2), 69.7 (C-5), 72.8 (CH_2-Ph), 127.48, 127.54, 128.3, 138.4 (Ph), 202.4 (C-1).

(2*S*,5*RS*)-9-Benzyloxy-1,2-*O*-isopropyliden-nonane-1,2,5-triol (21): After Mg turnings (182 mg, 7.50 mmol) in THF (3 mL) were activated with some drops of dibromoethane, a solution of bromide **20** (1.04 g, 5.00 mmol, filtered through 5 g silica gel prior to use with PE/Et_2O 5:1) in THF (5 mL) was added dropwise in a manner that the internal temperature did not exceed 40 °C. After additional stirring for 1 h at room temperature, the Grignard solution was cooled to 0 °C and a solution of aldehyde **19** (460 mg, 2.39 mmol) in THF (5 mL) was added within 10 min. After 20 min at room temperature, sat. aqueous NH_4Cl (20 mL) was added, and the two-phase system was stirred for additional 1 h. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aqueous NaCl (30 mL) and dried with $MgSO_4$. Removal of the solvents in vacuo and purification by CC (30 g, PE/Et_2O 1:1) afforded the epimeric alcohol **21** (620 mg, 80%) as a colorless oil. $R_f =$ 0.30 (PE/Et_2O 1:2); IR (neat): $\tilde{\nu} = 3445$m (OH), 3030w (ArH), 2985m/2935s/2860s (CH), 1455m, 1370s, 1255m, 1215m, 1155m, 1100s, 1060s, 1030m, 855w, 735m, 700m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$, 1.41 (2s, 6H, 2CH$_3$) superimposed by 1.35–1.74 (m, 10H, 3-H$_2$, 4-H$_2$, 6-H$_2$, 7-H$_2$, 8-H$_2$), 1.90–2.69 (m, 1H, OH), 3.47 (t, $J = 6.4$ Hz, 2H, 9-H$_2$), superimposed by 3.46–3.66 (m, 2H, 1-H$_A$, 5-H), 3.98–4.13 (m, 2H, 1-H$_B$, 2-H), 4.49 (s, 2H, CH_2-Ph), 7.22–7.35 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$ (C-7), 25.6, 26.9 (2CH_3), 29.6 (C-8), 29.5 and 30.0, 33.5 and 33.7, 37.1 and 37.2 [C-3, C-4, C-6 (two epimers each)], 69.4 (C-1), 70.2 (C-9), 71.1, 71.4 [C-5 (two epimers)], 72.8 (CH_2-Ph), 76.1 (C-2), 108.8 (C$_q$, ketal), 127.4, 127.5, 128.2, 138.4 (Ph); $C_{19}H_{30}O_4$ (322.45): calcd C 70.78, H 9.38; found C 71.05, H 9.09.

(2*S*,5*RS*)-5-(4′-Benzyloxybutyl)-2-hydroxymethyl-tetrahydrofuran (23) via tosylation: Pyridine (1.5 mL) and *p*-toluene sulfonyl chloride (750 mg, 3.93 mmol) were added at 0 °C to a solution of alcohol **21** (322 mg, 1.00 mmol) in CH_2Cl_2 (5 mL). After the solution was stirred for 4 h at room temperature, water (5 mL) was added, and the stirring was continued until excess *p*-toluene sulfonyl chloride was destroyed. The mixture was adjusted to pH 2 with 1N aqueous HCl. After separation of the layers, the aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organic layers were washed with sat. aqueous $NaHCO_3$ (10 mL) and sat. aqueous NaCl (10 mL). Drying with $MgSO_4$, removal of the solvents in vacuo, and subsequent CC (20 g, PE/Et_2O 1:1) yielded tosylate **22a** (428 mg, 90%) as a colorless oil. $R_f = 0.59$ (PE/Et_2O 1:1). Tosylate **22a** (290 mg, 0.608 mmol) was dissolved in HOAc (10 mL) and H_2O (2 mL). After the solution was stirred at room temperature for 13 h, the solvents were removed in vacuo at room temperature. Toluene (10 mL) was added and subsequently removed in vacuo (2×). The obtained crude product was used without further purification for the following cyclization step. $R_f = 0.07$ (Et_2O). After the crude product was dissolved in THF (10 mL), NaH (95%, 100 mg, 3.96 mmol) and four drops of DMSO were added. The reaction mixture was allowed to stir for 4 h at 40 °C. At 0 °C HOAc (8 mL) was added carefully and the solvents were removed in vacuo. The crude product was partitioned between H_2O (10 mL) and Et_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (30 mL). The organic layers were washed with sat. aqueous $NaHCO_3$ (15 mL) and sat. aqueous NaCl (10 mL). After drying with $MgSO_4$ and removal of the solvents under reduced pressure, purification with CC (15 g, Et_2O) yielded the title compounds as a colorless oil (125 mg, 78% based on tosylate **22a**, 63% based on the alcohol **21**). $R_f = 0.50$ (Et_2O); HPLC: $t_R = 27.5$ and 30.3 min (Si 60; 4% isopropyl alcohol in *n*-hexane); IR (neat): $\tilde{\nu} = 3425$m (OH), 3030w (ArH), 2930/2860s (CH), 1455m, 1360w, 1100s, 1045m, 735m, 700m, 665m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32–1.75$ and 1.80–2.06 (m, 8H; m, 2H, 3-H$_2$, 4-H$_2$, 1′-H$_2$, 2′-H$_2$, 3′-H$_2$), 2.59 (br s, 1H, OH), 3.40–3.69 (m, 4H, 4′-H$_2$, 1″-H$_2$), 3.80–4.13 (m, 2H, 2-H, 5-H), 4.49 (s, 2H, CH_2-Ph), 7.23–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.7$ (C-3′), 29.6 (C-2′), 26.9 and 27.4, 31.1 and 31.8, 35.4 and 35.5 [C-3, C-4 and C-1′ (two epimers each)], 64.8, 65.0 [C-1″ (two epimers)], 70.0 (C-4′), 72.7 (CH_2-Ph), 78.8 [C-2 (one epimer)], 79.1 [C-2 (one epimer), C-5 (one epimer)], 79.8 [C-5 (one epimer)], 127.3, 127.5, 128.2, 138.4 (Ph); $C_{16}H_{24}O_3$ (264.36): calcd C 72.69, H 9.15; found C 72.75, H 9.08.

Preparation of THF derivative 23 via mesylation: A solution of alcohol **21** (17.6 g, 54.6 mmol) in CH_2Cl_2 (220 mL) was treated with NEt_3 (30.3 mL,

22.1 g, 218 mmol) at −40 °C and methanesulfonyl chloride (8.53 mL, 12.5 g, 109 mmol) was added dropwise within 10 min. The reaction mixture was allowed to warm to −15 °C and was stirred for 1 h at this temperature. Sat. aqueous $NaHCO_3$ (200 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (200 mL). The combined organic layers were washed with sat. aqueous NaCl (100 mL). After the organic layer was dried with $MgSO_4$, the solvent was removed in vacuo. Toluene (50 mL) was added and subsequently removed in vacuo. The obtained crude product **22b** was used without further purification for the following steps. $R_f = 0.47$ (PE/Et_2O 1:1). Crude mesylate **22b** was dissolved in THF (100 mL) and aqueous 1N HCl (120 mL). After the solution was stirred for 4 h at room temperature, the reaction mixture was extracted with EtOAc (3 × 100 mL). The organic layers were washed with sat. aqueous NaCl (2 × 50 mL), and after separation dried with Na_2SO_4, the solvents were removed in vacuo. CC (300 g, PE/Et_2O 1:3) afforded THF alcohol **23** as a colorless (11.1 g, 77 % based on the alcohol **21**).

(2*R*,5*RS*)-5-(4′-Benzyloxybutyl)-2-hydroxymethyl-tetrahydrofuran (*ent*-23): A solution of alcohol **21** (1.12 g, 3.47 mmol) in THF (10 mL) and 1N aqueous HCl (6 mL) was stirred for 2 h at room temperature. The reaction mixture was then extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed successively with sat. aqueous $NaHCO_3$ (20 mL) and sat. aqueous NaCl (15 mL). After the organic phase was dried with Na_2SO_4, the solvents were removed under reduced pressure. CC (20 g, EtOAc) gave the triol (885 mg, 3.13 mmol, 90 %) as a colorless oil. $R_f = 0.25$ (EtOAc); IR (neat): $\tilde{\nu} = 3360$ br s (OH), 2935/2865s (CH), 1455m, 1365m, 1315w, 1275m, 1200w, 1100s, 1070s, 1030m, 735m, 715m, 700m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35-1.68$ (m, 10H, 3-H_2, 4-H_2, 6-H_2, 7-H_2, 8-H_2), 3.46 (t, $J = 6.4$ Hz, 2H, 9-H_2), superimposed by 3.34–3.71 (m, 4H, 1-H_2, 2-H, 5-H), 4.48 (s, 2H, CH_2-Ph), 4.67 (br s, 3H, 3OH), 7.22–7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$ (C-7), 29.5 (C-8), 28.8, 29.7, 32.8, 33.6, 36.9, 37.2 [C-3, C-4, C-6 (two epimers each)], 66.2, 66.6 [C-1 (two epimers)], 70.3 (C-9), 71.3, 71.7, 72.1, 72.4 [C-2, C-5 (two epimers each)], 72.8 (CH_2-Ph), 127.5, 127.6, 128.3, 138.3 (Ph).

Pyridine (3.5 mL, 3.4 g, 43 mmol) and mesitylene sulfonyl chloride (358 mg, 1.64 mmol) were added sequentially at 0 °C to a solution of this triol (420 mg, 1.49 mmol) in CH_2Cl_2 (10 mL). After the solution was stirred for 36 h at 0 °C, water (10 mL) was added, and the stirring was continued for additional 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were washed successively with 1N aqueous HCl (20 mL), sat. aqueous $NaHCO_3$ (10 mL) and sat. aqueous NaCl (10 mL). Subsequent drying with Na_2SO_4 and removal of the solvents in vacuo yielded an oily residue which was dissolved in MeOH (15 mL). After addition of solid K_2CO_3 (1.00 g, 7.24 mmol), the reaction mixture was stirred for 2 h. The solvent was removed in vacuo at room temperature. The residual oil was dissolved in Et_2O (30 mL) and washed with water (2 × 10 mL), and then with sat. aqueous NaCl (20 mL). After removal of the solvent in vacuo, the residue (crude epoxide **24**) was dissolved in CH_2Cl_2 (10 mL) and treated with HOAc (1 mL). The reaction mixture was again stirred for 2 h at room temperature. After addition of water (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (10 mL) and sat. aqueous NaCl (10 mL), and dried with Na_2SO_4. Removal of the solvent in vacuo and purification with CC (20 g, PE/Et_2O 1:3) afforded alcohol ***ent*-23** (188 mg, 48 % based on the corresponding triol) as a colorless oil. This epimeric mixture was almost identical to the enantiomeric mixture **23** in all spectroscopic respects apart from optical rotation.

Preparation of THF alcohol *ent*-23 via epoxide formation by tosyl imidazole: A solution of the triol prepared from **21** (2.75 g, 8.53 mmol) in THF (30 mL) was treated with NaH (95 %, 861 mg, 34.1 mmol). After the visible gas evolution stopped, the solution was stirred for further 15 min at room temperature and then cooled to 0 °C. *p*-Toluene sulfonyl imidazole (2.28 g, 10.2 mmol) was added in one portion and the stirring was continued for 45 min at room temperature. The reaction was quenched by careful addition of sat. aqueous NH_4Cl (20 mL). The reaction mixture was extracted with MTBE (3 × 25 mL) and the organic layers were washed with sat. aqueous NaCl (20 mL). After the organic layers were dried with Na_2SO_4, evaporation of the solvents and purification with CC (100 g, MTBE/CH_2Cl_2 4:1) yielded alcohol ***ent*-23** (1.73 g, 77 %) as a colorless oil.

(2*S*,5*R*)-5-(4′-Benzyloxybutyl)-tetrahydrofuran-2-carboxylic acid (25) and **(2*S*,5*S*)-5-(4′-benzyloxybutyl)-tetrahydrofuran-2-carboxylic acid (26)**: Alcohol **23** (5.00 g, 18.9 mmol) was subjected to Swern-oxidation conditions already described for the preparation of **19** with the following amounts of reagents: oxalyl chloride (2.48 mL, 3.60 g, 28.4 mmol) in CH_2Cl_2 (100 mL), DMSO (2.95 mL, 3.25 g, 41.6 mmol) in CH_2Cl_2 (10 mL) and NEt_3 (11.9 mL, 8.61 g, 85.1 mmol). Without purification by CC we obtained the crude aldehyde (5.10 g) as a slightly yellow oil. $R_f = 0.37$ (PE/MTBE 1:1). This product was subsequently further oxidized to the corresponding carboxylic acid: The crude aldehyde was dissolved in a mixture of *t*-BuOH (24 mL) und amylene (12 mL). At 0 °C a solution of $NaClO_2$ (80 %, 2.72 g, 24.1 mmol) and $NaH_2PO_4 \times H_2O$ (3.33 g, 24.1 mmol) in water (12 mL) was added over a period of 20 min. The mixture was allowed to stir for 12 h at room temperature. After removal of the organic solvents in vacuo, 0.4M aqueous NaOH (40 mL) was added. The aqueous layer was extracted with MTBE (2 × 20 mL) before the aqueous layer was adjusted to pH 2 by the addition of 2M aqueous HCl solution. The obtained suspension was extracted with EtOAc (3 × 30 mL) and the organic layers were washed with sat. aqueous NaCl (2 × 10 mL). The organic layers were dried with Na_2SO_4, and the solvents removed in vacuo, and the epimers then purified by CC (2 × 300 g, MTBE/CH_2Cl_2 1:1 + 1 % HOAc). Epimer **26** was separated (1.09 g, 21 % based on **23**) from epimer **25** (2.10 g, 40 % based on **23**), which solidified after several days of storage. In addition, an unseparated epimeric mixture of **25**/**26** was obtained (860 mg, 16 % based on **23**). Thus, the combined yield for the two-step oxidation **23** to **25**/**26** was 77 %. Epimeric mixture **25**/**26** as dicyclohexyl ammonium salt: $C_{28}H_{45}NO_4$ (459.67) calcd C 73.16, H 9.86, N 3.05; found C 73.15, H 9.88, N 2.96. THF carboxylic acid **25**: $R_f = 0.45$ (MTBE + 1 % HOAc); $[\alpha]_D = -28.8$, $[\alpha]_{578} = -30.1$, $[\alpha]_{546} = -34.7$, $[\alpha]_{436} = -61.5$, $[\alpha]_{365} = -101.7$ ($c = 1.06$, $CHCl_3$, $T = 20$ °C); IR (neat): $\tilde{\nu} = 2500-3500$ br s (COOH), 3085/3060/3030m (ArH), 2940/2865s (CH), 2640w, 1745s (C=O), 1495w, 1455m, 1360m, 1275m, 1205m, 1095s, 1030m, 740m, 700m, 665w; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.38-1.72$ (m, 7H, 4-H_A, 1′-H_2, 2′-H_2, 3′-H_2), 2.03–2.11 (m, 2H, 3-H_A, 4-H_B), 2.08 (m, 1H, 3-H_B), 3.48 (t, $J = 6.4$ Hz, 2H, 4′-H_2), 4.08–4.17 (m, 1H, 5-H), 4.46–4.56 (m, 1H, 2-H), superimposed by 4.50 (s, 2H, CH_2-Ph), ca. 6.0 (br s, 1H, COOH), 7.26–7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.5$ (C-2′), 29.5, 29.9, 30.9 (C-4, C-1′, C-3′), 34.9 (C-3), 70.0 (C-4′), 72.7 (CH_2-Ph), 76.1 (C-2), 80.9 (C-5), 127.4, 127.5, 128.2, 138.3 (Ph), 177.4 (COOH).

THF carboxylic acid **26**: m.p. 50 °C; $R_f = 0.64$ (MTBE + 1 % HOAc); $[\alpha]_D = -28.1$, $[\alpha]_{578} = -29.3$, $[\alpha]_{546} = -33.2$, $[\alpha]_{436} = -55.6$, $[\alpha]_{365} = -85.1$ ($c = 1.00$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 2600-3600$ br s (COOH), 2975m/2940s/2885s/2865s (CH), 1760s (C=O), 1455m, 1365m, 1205s, 1185m, 1125s, 1105s, 1085s, 1070s, 1050m, 1030m, 845w, 830w, 750m, 700w; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.40-1.60$ (m, 4H, 4-H_A, 1′-H_A, 2′-H_2), 1.66 (m, 2H, 3′-H_2), 1.69–1.77 (m, 1H, 1′-H_B), 2.02 (dddd, $J = 13.3$, 7.7, 5.7, 3.6 Hz, 1H, 4-H_B), 2.19 (dddd, $J = 12.7$, 8.4, 4.3, 4.3 Hz, 1H, 3-H_A), 2.30 (dddd, $J = 13.0$, 9.8, 9.1, 7.7 Hz, 1H, 3-H_B), 3.48 (t, $J = 6.4$ Hz, 2H, 4′-H_2), 4.02 (m, 1H, 5-H), 4.45 (dd, $J = 9.0$, 4.5 Hz, 1H, 2-H), 4.50 (s, 2H, CH_2-Ph), 7.25–7.30 (m, 5H, Ph), 9.30 (br s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.9$ (C-2′), 29.5, 30.2, 30.8 (C-4, C-1′, C-3′), 35.1 (C-3), 70.0 (C-4′), 72.8 (CH_2-Ph), 76.4 (C-2), 82.0 (C-5), 127.5, 127.6, 128.3, 138.4 (Ph), 176.4 (COOH). The *cis* vs. *trans* assignment was done unambiguously by interpretation of 600 MHz NOESY spectra of both epimers.

(2*S*,2′*S*,5′*R*)-3-[5′-(4″-Hydroxybutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino methyl propionate (29): A solution of carboxylic acid **25** (1.57 g, 5.61 mmol) in THF (26 mL), MeOH (13 mL), and water (6.5 mL) was hydrogenated under vigorous stirring for 18 h at atmospheric pressure in the presence of Pd on charcoal (10 %, 140 mg). The catalyst was removed by filtration from a pad of Celite which was washed with MeOH (50 mL). The solvents were removed in vacuo and residual water was removed by azeotropic distillation with toluene (2 × 10 mL). CC (30 g, EtOAc) yielded the unprotected carboxylic acid (1.05 g, 95 %) which was directly used in the following peptide coupling. $R_f = 0.22$ (MTBE + 1 % HOAc). This hydroxy acid, amine hydrochloride **27** (1.70 g, 5.89 mmol), and BOP (2.61 g, 5.89 mmol) were dissolved in acetonitrile (70 mL), and treated with EtN(*i*Pr)$_2$ (2.04 mL, 1.52 g, 11.8 mmol) at room temperature. After the solution was stirred for 16 h, the solvent was removed in vacuo, and the residue was diluted with EtOAc (300 mL). This solution was washed successively with 2N aqueous HCl (2 × 50 mL), sat. aqueous $NaHCO_3$ (2 × 50 mL), sat. aqueous NaCl (100 mL), and was dried with Na_2SO_4. After removal of the solvent in vacuo, purification with CC [65 g, EtOAc/CH_2Cl_2 1:1 (600 mL), then EtOAc/CH_2Cl_2 3:1 (600 mL)] gave

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amide **29** (2.11 g, 89% based on **25**) as a colorless oil. $R_f = 0.33$ (EtOAc); HPLC: $t_R = 50.4$ min (Si 60, 1.5 mL min^{-1}; 15% isopropyl alcohol in *n*-hexane); $[\alpha]_D = +4.1$, $[\alpha]_{578} = +4.4$, $[\alpha]_{546} = +5.1$, $[\alpha]_{436} = +9.9$, $[\alpha]_{365} = +19.4$ ($c = 1.05$, $CHCl_3$, $T = 20\,^\circ C$); IR (neat): $\tilde{\nu} = 3350$ br s (OH/NH), 3065/3035w (ArH), 2940s/2865m (CH), 1725s (C=O), 1660s (carbamate C=O), 1530s, 1455m, 1440m, 1345m, 1265s, 1215s, 1070s, 1030m, 845w, 740m, 700m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37-2.09$ (m, 10H, 3′-H_A, 4′-H_2, 1″-H_2, 2″-H_2, 3″-H_2, OH), 2.31 (m, 1H, 3′-H_B), AB signal ($\delta_A = 3.55$, $\delta_B = 3.80$, $J_{AB} = 13.9$ Hz additionally split by $J_A = 4.5$, 4.5 Hz; $J_B = 7.6$, 6.4 Hz, 2H, 3-H_2), 3.65 (t, $J = 6.2$ Hz, 2H, 4″-H_2), 3.76 (s, 3H, OCH_3), 3.95 (m, 1H, 5′-H), 4.36 (t, $J = 7.2$ Hz, 1H, 2′-H), 4.41–4.54 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 5.88 (br d, $J = 7.0$ Hz, 1H, NHZ), 7.09 (br t, $J = 5.3$ Hz, 1H, N^3H), 7.25–7.45 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$ (C-2″), 30.1 (C-3′), 31.2 (C-4′), 32.4, 34.9 (C-1″, C-3″), 40.4 (C-3), 52.8 (OCH_3), 54.4 (C-2), 62.6 (C-4″), 67.1 (*C*H_2-Ph), 77.9 (C-2′), 80.8 (C-5′), 128.1, 128.2, 128.5, 136.0 (Ph), 156.0 (Z-CO), 170.7 (CONH), 174.7 (COO); ESI-MS: $[C_{21}H_{30}N_2O_7+H]^+$ calcd 423.21; found 423.14.

(2*S*,2′*S*,5′*R*)-3-(5′-{4″-[*N*$^{1'''}$,*N*$^{2'''}$-Bis-(*tert*-butoxycarbonyl)-guanidino]-butyl}-tetrahydrofuran-2′-carbamoyl)-2-benzyloxycarbonylamino methyl propionate (30): Amide **29** (800 mg, 1.90 mmol), guanidine derivative **28** (983 mg, 3.79 mmol), and PPh_3 (746 mg, 2.84 mmol) were dissolved in THF (14 mL) and cooled to 0 °C. DIAD (0.74 mL, 0.77 g, 3.8 mmol) was added dropwise. After 16 h at room temperature, water (10 drops) was added and the solvent was removed in vacuo. Filtration (10 g, PE/MTBE 1:2) and purification with CC (40 g, PE/MTBE 1:1) gave compound **30** (783 mg, 62%) as a colorless oil. $R_f = 0.38$ (PE/MTBE 1:2); $[\alpha]_D = -13.0$, $[\alpha]_{578} = -13.8$, $[\alpha]_{546} = -15.5$, $[\alpha]_{436} = -27.5$, $[\alpha]_{365} = -44.8$ ($c = 0.40$, $CHCl_3$, $T = 20\,^\circ C$); IR (neat): $\tilde{\nu} = 3380$m (NH), 2975m/2935m/2865w (CH), 1715s (C=O), 1675m, 1645m, 1610s, 1515s, 1455m, 1435m, 1390m, 1370m, 1345m, 1280s, 1250s, 1150s, 1100s, 980w, 915w, 890w, 780w, 735m, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$, 1.52 (2s, 2*t*Bu), 1.23–1.70 (m, 7H; m, 2H, 3′-H_A, 4′-H_2, 1″-H_2, 2″-H_2, 3″-H_2), 2.22–2.40 (m, 1H, 3′-H_B), 3.48–4.01 (m, 8H, 5′-H, 3-H_2, 4″-H_2, OCH_3), 4.33 (br t, $J = 7.1$ Hz, 1H, 2′-H), 4.40–4.49 (m, 1H, 2-H), 5.10 (s, 2H, CH_2-Ph), 5.98, 6.08 (2 br d, $J = 7.5$ Hz each, 1H, NHZ rotamers), 7.10 (br s, 1H, N^3H), 7.27–7.40 (m, 5H, Ph), 9.29 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.0$ (C-2″), 27.9, 28.1 [2 C(*C*H_3)$_3$], 28.6, 30.0, 31.0 (C-4′, C-1″, C-3″), 34.8 (C-3′), 40.2 (C-3), 44.3 (C-4″), 52.6 (OCH_3), 54.4 (C-2), 66.9 (*C*H_2-Ph), 77.8 (C-2′), 78.5, 83.4 [2 *C*(CH$_3$)$_3$], 80.8 (C-5′), 127.9, 128.1, 128.4, 136.2 (Ph), 155.4 (C=N), 156.6 (Z-CO), 160.5, 163.7 (2 Boc-CO), 170.6 (CONH), 174.7 (COO); ESI-MS: $[C_{32}H_{49}N_5O_{10}+H]^+$ calcd 664.36; found 664.37.

(2*S*,2′*S*,5′*R*)-3-[5′-(4″-Guanidinobutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino propionic acid (14, as trifluoroacetate): A solution of THF derivative **30** (90 mg, 0.14 mmol) in THF (3 mL) was treated at room temperature with LiOH (1.0 mL of a 0.3 M aqueous solution, 0.30 mmol). After 20 min the reaction mixture was adjusted to pH 3 by the addition of 5% aqueous citric acid. The solvent was removed in vacuo and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were washed with sat. aqueous NaCl (10 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (4 mL), and treated with TFA (1.5 mL). After the solution was stirred for 2 h, the reaction mixture was codistilled with toluene (2 × 5 mL). The residue was purified by preparative HPLC [41 mm ID, Rainin, RP 18, 40 mL min^{-1}, 77% (water + 0.2% TFA) and 23% (acetonitrile + 0.2% TFA)] to yield the trifluoracetate **14** (65 mg, 85%). HPLC: $t_R = 12.8$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN + 10% D_2O): $\delta = 1.24-1.65$ (m, 7H, 4′-H_A, 1″-H_2, 2″-H_2, 3″-H_2), 1.72–1.79 (m, 1H, 3′-H_A), 1.83–1.90 (m, 1H, 4′-H_B), 2.21 (m, 1H, 3′-H_B), 3.03–3.08 (m, 2H, 4″-H_2), AB signal ($\delta_A = 3.48$, $\delta_B = 3.52$, $J_{AB} = 13.8$, additionally split by $J_A = 5.1$ Hz; $J_B = 7.9$ Hz, 2H, 3-H_2), 3.94 (dddd, all $J_{vic} \approx 6.6$ Hz, 1H, 5′-H), 4.22–4.28 (m, 2H, 2-H, 2′-H), AB signal ($\delta_A = 5.02$, $\delta_B = 5.03$, $J_{AB} = 12.6$ Hz, 2H, CH_2-Ph), 7.26–7.37 (m, 5H, Ph); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 23.5$ (C-2″), 29.2, 31.1, 31.4, 35.2 (C-3′, C-4′, C-1″, C-3″), 41.8 (C-4″), 54.7 (br, C-2), 67.3 (*C*H_2-Ph), 78.4 (C-2′), 81.6 (C-5′), 128.8, 129.4, 129.7, 137.5 (Ph), 157.5, 157.8 (C=N, Z-CO), 176.3 (CONH, COO); the signal of C-3 at approx. $\delta = 40$ was superimposed by the solvent signals; HRMS (FAB): $[C_{21}H_{32}N_5O_6]^+$ calcd 450.2353; found 450.2347.

(2*S*,2′*S*,5′*S*)-3-[5′-(4″-Hydroxybutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino methyl propionate (31): The amide **31** was prepared analogously to the amide **29** using the following amounts of substrate and reagents: carboxylic acid **26** (980 mg, 3.50 mmol) and Pd/C (10%, 100 mg) to yield the unprotected carboxylic acid (660 mg, quant.). $R_f = 0.24$ (MTBE + 1% HOAc). Amine hydrochloride **27** (1.11 g, 3.85 mmol), BOP (1.70 g, 3.85 mmol), and EtN(*i*Pr)$_2$ (1.33 mL, 995 mg, 7.70 mmol) to yield amide **31** (919 mg, 62% based on **26**) as colorless oil. $R_f = 0.33$ (EtOAc); HPLC: $t_R = 44.5$ min (Si 60, 1.5 mL min^{-1}; 15% isopropyl alcohol in *n*-hexane); $[\alpha]_D = +1.1$, $[\alpha]_{578} = +1.4$, $[\alpha]_{546} = +1.9$, $[\alpha]_{436} = +7.0$, $[\alpha]_{365} = +19.9$ ($c = 0.80$, $CHCl_3$, $T = 20\,^\circ C$); IR (neat): $\tilde{\nu} = 3400$ br s (OH/NH), 3065/3035w (ArH), 2940s/2865m (CH), 1725s (C=O), 1660s (carbamate C=O), 1530s, 1455m, 1440m, 1365m, 1345m, 1215s, 1180m, 1070s, 845s, 775w,740m, 700m, 665m; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32-1.77$ (m, 7H, 4′-H_A, 1″-H_2, 2″-H_2, 3″-H_2), 1.84–2.10 (m, 3H, 3′-H_A, 4′-H_B, OH), 2.15–2.31 (m, 1H, 3′-H_B), AB signal ($\delta_A = 3.65$, $\delta_B = 3.91$, $J_{AB} = 14.0$ Hz additionally split by $J_A = 4.8$, 4.8 Hz; $J_B = 7.0$, 7.0 Hz, 2H, 3-H_2), 3.64 (t, $J = 5.9$ Hz, 2H, 4″-H_2), 3.75 (s, 3H, OCH_3), 3.97 (m, 1H, 5′-H), 4.29 (dd, $J = 8.7$, 4.9 Hz, 1H, 2′-H), 4.44 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 5.94 (br d, $J = 7.0$ Hz, 1H, NHZ), 7.10 (br t, $J = 4.9$ Hz, 1H, N^3H), 7.28–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.3$ (C-2″), 30.3, 30.4 (C-3′, C-4′), 32.3, 35.1 (C-1″, C-3″), 40.2 (C-3), 52.8 (OCH_3), 54.5 (C-2), 62.3 (C-4″), 67.1 (*C*H_2Ph), 78.2 (C-2′), 81.5 (C-5′), 128.1, 128.2, 128.5, 136.0 (Ph), 156.0 (Z-CO), 170.7 (CONH), 174.5 (COO); ESI-MS: $[C_{21}H_{30}N_2O_7+Na]^+$ calcd 445.20; found 445.14.

(2*S*,2′*S*,5′*S*)-3-(5′-{4″-[*N*$^{1'''}$,*N*$^{2'''}$-Bis-(*tert*-butoxycarbonyl)-guanidino]-butyl}-tetrahydrofuran-2′-carbamoyl)-2-benzyloxycarbonylamino methyl propionate (32): The guanidine derivative **32** was prepared as described for **30** using the following amounts of substrate and reagents: amide **31** (600 mg, 1.42 mmol), guanidine derivative **28** (735 mg, 2.83 mmol), PPh_3 (558 mg, 2.13 mmol), and DIAD (0.55 mL, 0.57 g, 2.8 mmol). Title compound **32** (693 mg, 74%) was obtained as a colorless oil. $R_f = 0.38$ (PE/MTBE 1:2); $[\alpha]_D = -3.1$, $[\alpha]_{578} = -3.3$, $[\alpha]_{546} = -3.5$, $[\alpha]_{436} = -4.5$, $[\alpha]_{365} = -3.3$ ($c = 0.85$, $CHCl_3$, $T = 20\,^\circ C$); IR (neat): $\tilde{\nu} = 3380$m (NH), 2975m/2935m/2865w (CH), 1715s (C=O), 1680m, 1640m, 1610s, 1515s, 1455m, 1440m, 1390m, 1370m, 1345w, 1280s, 1250s, 1210m, 1150s, 1105m, 980w, 890w, 780w, 735w, 700w, 665w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$, 1.52 (2s, 18H, 2*t*Bu), 1.21–2.32 (m, 10H, 3′-H_2, 4′-H_2, 1″-H_2, 2″-H_2, 3″-H_2), 3.52–4.00 (m, 8H, 3-H_2, 5′-H, 4″-H_2, OCH_3), 4.22–4.33 (m, 1H, 2′-H), 4.39–4.50 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 5.82, 5.97 (2 br d, $J = 7.5$ Hz each, 1H, NHZ rotamers), 7.02 (br s, N^3H), 7.28–7.40 (m, 5H, Ph), 9.29 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$ (C-2″), 28.0, 28.3 [2 C(*C*H_3)$_3$], 28.5, 30.3, 30.6 (C-4′, C-1″, C-3″), 35.2 (C-3′), 40.3 (C-3), 44.4 (C-4″), 52.8 (OCH_3), 54.6 (C-2), 67.0 (*C*H_2Ph), 78.0 (C-2′), 78.7, 83.6 [2 *C*(CH$_3$)$_3$], 81.4 (C-5′), 128.1, 128.2, 128.5 (Ph), 155.0 (C=N), 170.7 (CONH), 174.5 (COO); the signals with low intensity (Z-CO, Boc-CO and Ar_q) were not detected; ESI-MS: $[C_{32}H_{49}N_5O_{10}+H]^+$ calcd 664.36; found 664.36.

(2*S*,2′*S*,5′*S*)-3-[5′-(4″-Guanidinobutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino propionic acid (15, as trifluoroacetate): The preparation and purification was done as described for **14** starting from THF derivative **32** (86 mg, 0.13 mmol). After lyophylization, trifluoroacetate **15** (58 mg, 79%) was obtained as a white solid. HPLC: $t_R = 12.7$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN + 5% D_2O): $\delta = 1.26-1.63$ (m, 7H, 4′-H_A, 1″-H_2, 2″-H_2, 3″-H_2), 1.86–1.94 (m, 2H, 3′-H_A, 4′-H_B), 2.16 (m, 1H, 3′-H_B), 3.08 (t, $J = 6.8$ Hz, 2H, 4″-H_2), 3.35–3.65 (m, 2H, 3-H_2)*, 3.90 (m, 1H, 5′-H), 4.22 (dd, J = 8.7, 4.3 Hz, 1H, 2′-H), 4.29 (dd, $J = 7.5$ and 2.5 Hz, 1H, 2-H), 5.05 (m, 2H, CH_2-Ph), 7.26–7.38 (m, 5H, Ph); *superimposed by HOD signal; ^{13}C NMR (150 MHz, CD_3CN + 33% D_2O): $\delta =$ 22.8 (C-2″), 28.0, 30.0, 30.3, 34.4 (C-3′, C-4′, C-1″, C-3″), 39.5 (C-3), 41.2 (C-4″), 53.9 (C-2), 67.4 (*C*H_2-Ph), 77.7 (C-2′), 82.4 (C-5′), 127.8, 128.6, 129.0 (Ph), 176.7, 177.2 (CONH, COO); the signals with low intensity (Z-CO, guanidine-C and Ar_q) were not detected; HRMS (FAB): $[C_{21}H_{32}N_5O_6]^+$ calcd 450.2353; found 450.2358.

(2*R*,5*RS*)-5-(4′-Benzyloxybutyl)-tetrahydrofuran-2-carboxylic acid (33): The two-step oxidation was performed analogous to the preparation of the carboxylic acids **25**/**26** starting from the alcohol ***ent*-23** (5.00 g, 18.9 mmol). The following amounts of reagents were used: oxalyl chloride (3.30 mL, 4.80 g, 37.8 mmol) in CH_2Cl_2 (150 mL), DMSO (4.10 mL, 4.51 g, 57.0 mmol) in CH_2Cl_2 (20 mL), and NEt_3 (15.7 mL, 11.4 g, 113 mmol). Without purification by CC the corresponding crude aldehyde (5.03 g) was obtained as yellow oil. $R_f = 0.37$ (PE/MTBE 1:1). Subsequent Pinnick-oxidation using *t*-BuOH (24 mL), amylene (12 mL), $NaClO_2$ (80%, 2.72 g,

24.1 mmol), and $NaH_2PO_4 \times H_2O$ (3.33 g, 24.1 mmol) in water (12 mL) yielded after usual work-up a slightly yellow crude product. This was further purified by means of the dicyclohexyl ammonium salt: The crude carboxylic acid was dissolved in MTBE (100 mL) and treated with dicyclohexyl amine (4.98 mL, 4.53 g, 25 mmol). After removal of the solvent in vacuo, the remaining solid was recrystallized from MTBE/PE 2:1. The obtained ammonium salt was dissolved in MTBE (300 mL) and the free acid was liberated by washing with 1N aqueous HCl (2×100 mL). After drying of the organic layer with Na_2SO_4 and removal of the solvent the title compound (3.37 g, 64%) was obtained as an epimeric mixture. $R_f = 0.40 - 0.65$ (MTBE + 1% HOAc); IR (neat): $\tilde{\nu} = 2500 - 3500$ brs (COOH), 3085/3060/3030m (ArH), 2940/2865s (CH), 1750brs (C=O), 1495w, 1455m, 1365m, 1280m, 1205m, 1100s, 1030w, 740m, 700m, 665w; **33** as dicyclohexyl ammonium salt: $C_{28}H_{45}NO_4$ (459.67) calcd C 73.16, H 9.86, N 3.05; found C 72.79, H 9.76, N 3.02; ^{1}H and ^{13}C NMR spectra of **33** were a correct superimposition of the spectra for the separated epimers **25**/**26**.

(2*S*,2′*R*,5′*RS*)-3-[5′-(4″-Hydroxybutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino methyl propionate (34): The amide **34** was prepared as described for the amide **29** using the following amounts of substrate and reagents: carboxylic acid **33** (1.93 g, 6.93 mmol) and Pd/C (10%, 180 mg) to yield the unprotected carboxylic acid (1.21 g, 93%). $R_f = 0.12 - 0.24$ (MTBE + 1% HOAc). Amine hydrochloride **27** (1.92 g, 6.64 mmol), BOP (2.95 g, 6.67 mmol), and NEt_3 (1.97 mL, 1.43 g, 14.1 mmol) instead of $EtN(iPr)_2$ yielded amide **34** (2.20 g, 5.21 mmol, 75% based on **33**) as a colorless oil. $R_f = 0.33$ (EtOAc); HPLC: $t_R = 49.0$ and 52.7 min (Si 60, 1.5 mL min^{-1}; 15% isopropyl alcohol in *n*-hexane); IR (neat): $\tilde{\nu} = 3360$ brm (OH/NH), 3065/3035w (ArH), 2940m/2865w (CH), 1720s (C=O), 1660s (carbamate C=O), 1530s, 1455m, 1440m, 1345w, 1300m, 1260m, 1215m, 1070s, 1055m, 700w, 645w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.37 – 1.71, 1.80 – 2.36 (m, 7H; m, 4H, 3′-H_2, 4′-H_2, 1″-H_2, 2″-H_2, 3″-H_2, OH), 3.48 – 3.82 (m, 7H, 3-H_2, 4″-H_2, OCH_3), 3.88 – 4.01 (m, 1H, 5′-H), 4.26 – 4.50 (m, 2H, 2-H, 2′-H), 5.11 (s, 2H, CH_2-Ph), 6.02 [brd, $J = 7.7$ Hz, 0.5H, NHZ (one epimer)], 6.06 [brd, $J = 7.5$ Hz, 0.5H, NHZ (one epimer)], 7.12, 7.14 [2brs, 1H, N^{3}H (two epimers)], 7.28 – 7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.4$ (C-2″), 30.0, 30.2, 30.6, 31.3, 32.2, 32.4, 34.9, 35.1 [C-3′, C-4′, C-1″, C-3″ (two epimers each)], 40.7 (C-3), 52.7 (OCH_3), 54.5 (C-2), 62.2 and 62.5 (C-4″), 67.0 (CH_2-Ph), 77.4 and 77.9 (C-2′), 80.8 and 81.5 (C-5′), 128.0, 128.1, 128.5, 136.1 (Ph), 156.2 (Z-CO), 170.7 (CONH), 174.8 (COO); ESI-MS: $[C_{21}H_{30}N_2O_7+H]^+$ calcd 423.21; found 423.12.

(2*S*,2′*R*,5′*RS*)-3-(5′-{4″-[$N^{1‴}$,$N^{2‴}$-Bis-(*tert*-butoxycarbonyl)-guanidino]-butyl}-tetrahydrofuran-2′-carbamoyl)-2-benzyloxycarbonylamino methyl propionate (35): The guanidine derivative **35** was prepared as described for **30** using the following amounts of substrate and reagents: amide **34** (930 mg, 2.21 mmol), guanidine derivative **28** (1.15 g, 4.42 mmol), PPh_3 (868 mg, 3.31 mmol), and DIAD (0.65 mL, 0.67 g, 4.4 mmol); title compound **35** (1.14 g, 78%) was obtained as a colorless oil. $R_f = 0.38$ (PE/MTBE 1:2); IR (neat): $\tilde{\nu} = 3390$ brs (NH/OH), 2980/2940 (CH), 1715s (C=O), 1680m, 1640m, 1610s, 1515s, 1455m, 1440m, 1390m, 1370m, 1280s, 1250s, 1150s, 1100s, 980m, 885w, 850w, 780w, 745w, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$, 1.52 (2s, 2*t*Bu), 1.20 – 1.77, 1.87 – 2.40 (m, 7H; m, 3H, 3′-H_2, 4′-H_2, 1″-H_2, 2″-H_2, 3″-H_2), 3.52 – 4.03 (m, 8H, 5′-H, 3-H_2, 4″-H_2, OCH_3), 4.27 – 4.52 (m, 2H, 2-H, 2′-H), 5.11 (s, 2H, CH_2-Ph), 5.93 – 6.09 (m, 1H, NHZ), 7.05 (brs, 1H, N^{3}H), 7.26 – 7.38 (m, 5H, Ph), 9.28 (brs, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.1$ and 23.4 (C-2″), 28.2, 28.5 [2C(CH_3)$_3$], 28.7, 30.0, 30.2, 30.6, 31.1 [C-4′, C-1″, C-3″ (two epimers each)], 34.9 and 35.1 (C-3′), 40.6 (C-3), 44.3 (C-4″), 52.6 (OCH_3), 54.7 (br, C-2), 67.0 (CH_2-Ph), 78.0 (C-2′), 78.7, 83.5 [2*C*(CH_3)$_3$], 80.9 and 81.7 (C-5′), 128.0, 128.1, 128.4, 136.1 (Ph), 155.0 (C=N), 156.7 (Z-CO), 160.6, 163.8 (2 Boc-CO), 170.6 (CONH), 174.7 (COO); ESI-MS: $[C_{32}H_{49}N_5O_{10}+H]^+$ calcd 664.36; found 664.37.

(2*S*,2′*R*,5′*S*)-3-[5′-(4″-Guanidinobutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino propionic acid (16, as trifluoroacetate) and **(2*S*,2′*R*,5′*R*)-3-[5′-(4″-guanidinobutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino propionic acid (17, as trifluoroacetate)**: A solution of **35** (515 mg, 0.776 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (6 mL) at room temperature. After the solution was stirred for 2 h, the solvents were removed in vacuo, and the residue was azeotropically distilled with toluene (20 mL). The crude guanidinium salt was divided in 10 portions which were partially separated by preparative HPLC [41 mm ID, 40 mL min^{-1}, 74% (water + 0.2% TFA + 0.2% NEt_3) and 26% (acetonitrile + 0.2% TFA + 0.2% NEt_3)]. The yield of this Boc deprotection and isomer separation could not be determined due to the presence of excess buffer salt from HPLC. Only pure diastereomers were used for subsequent ester hydrolysis, mixed fractions were not used further. HPLC: $t_R = 11.7$ min (**37**) and 12.4 min (**36**) (Rainin, RP 18, 1.5 mL min^{-1}, 23% to 30% B within 15 min, A: water + 0.1% TFA + 0.1% NEt_3; B: acetonitrile + 0.1% TFA + 0.1% NEt_3). Each separated isomer was dissolved in THF (5 mL) and treated with 0.3N aqueous LiOH (10 mL). After 2 h, the reaction mixture was acidified with TFA. After concentration in vacuo to about 6 mL, the crude material was purified by preparative HPLC [3 runs, 41 mm ID, Rainin, RP 18, 40 mL min^{-1}, 77% (water + 0.2% TFA) and 23% (acetonitrile + 0.2% TFA)]. After lyophylization, the trifluoroacetate of **17** (28 mg, 6%) and **16** (42 mg, 10%) was obtained as a white solids. Trifluoroacetate of **16**: HPLC: $t_R = 12.8$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN + 10% D_2O): $\delta = 1.32 - 1.59$ (m, 7H, 4′-H_A, 1″-H_2, 2″-H_2, 3″-H_2), 1.78 – 1.87 (m, 1H, 3′-H_A), 1.87 – 1.94 (m, 1H, 4′-H_B), 2.22 (m, 1H, 3′-H_B), 3.04 – 3.09 (m, 2H, 4″-H_2), AB signal ($\delta_A = 3.41$, $\delta_B = 3.62$, $J_{AB} = 13.9$ Hz, additionally split by $J_A = 7.5$ Hz, $J_B =$ 4.6 Hz, 2H, 3-H_2), 3.87 – 3.97 (m, 1H, 5′-H), 4.23 – 4.29 (m, 2H, 2-H, 2′-H), AB signal ($\delta_A = 5.03$, $\delta_B = 5.07$, $J_{AB} = 12.6$ Hz, 2H, CH_2-Ph), 7.31 – 7.37 (m, 5H, Ph); ^{13}C NMR (75 MHz, [D$_6$]DMSO + 2% D_2O): $\delta = 23.0$ (C-2″), 28.8 (C-3″), 30.2, 30.6 (C-3′, C-4′), 34.9 (C-1″), 41.0 (C-4″), 53.9 (C-2), 66.1 (CH_2-Ph), 77.8 (C-2′), 80.4 (C-5′), 128.1, 128.4, 128.9, 137.2 (Ph), 156.6, 156.9 (C=N, Z-CO), 172.3, 174.2 (CONH, COO); the signal of C-3 at approx. $\delta =$ 40 was superimposed by the solvent signals. HRMS (FAB): $[C_{21}H_{32}N_5O_6]^+$ calcd 450.2353; found 450.2353. Trifluoroacetate of **17**: HPLC: $t_R =$ 12.6 min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN + 5% D_2O): $\delta = 1.26 - 1.63$ (m, 7H, 4′-H_A, 1″-H_2, 2″-H_2, 3″-H_2), 1.86 – 1.97 (m, 2H, 3′-H_A, 4′-H_B), 2.16 (m, 1H, 3′-H_B), 3.08 (t, $J = 7.1$ Hz, 2H, 4″-H_2), 3.41 (dd, $J = 14.0$, 8.0 Hz, 1H, 3-H_A), 3.71 (dd, $J = 14.0$, 5.0 Hz, 1H, 3-H_B), 3.90 (m, 1H, 5′-H), 4.23 (dd, $J = 8.8$, 4.5 Hz, 1H, 2′-H), 4.32 (dd, $J = 8.0$, 5.1 Hz, 1H, 2-H), 5.05 (m, 2H, CH_2-Ph), 7.28 – 7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, CD_3CN + 10% D_2O): $\delta = 24.0$ (C-2″), 29.0 (C-3″), 31.0, 31.1 (C-3′, C-4′), 35.5 (C-1″), 40.6 (C-3), 42.0 (C-4″), 54.7 (C-2), 67.5 (CH_2-Ph), 78.7 (C-2′), 82.4 (C-5′), 128.7, 129.1, 129.5, 137.5 (Ph), 157.7 (Z-CO, C=N), 173.3, 176.4 (CONH, COO); HRMS (FAB): $[C_{21}H_{32}N_5O_6]^+$ calcd 450.2353; found 450.2351. The *cis* vs. *trans* assignment was done unambiguously by interpretation of 600 MHz NOESY spectra of both epimers.

(4*S*)-4-Benzyloxycarbonylamino-1-*tert*-butoxycarbonylamino-8-nonene-5-one (42): A solution of 4-bromo-1-butene (7.34 g, 54.4 mmol) in Et_2O (65 mL) was added dropwise to Mg turnings (1.98 g, 81.6 mmol) covered with Et_2O (14 mL) in a manner that the reaction gently refluxed. After cooling to room temperature, the reaction mixture was diluted with Et_2O (60 mL) and refluxed for 1 h. The Grignard solution was cooled to room temperature again and transferred to a 250 mL dropping funnel via a double ended needle. Ornithine derivative **41** (5.00 g, 13.6 mmol) was dissolved in a 1 L three-necked flask in Et_2O (280 mL), and cooled to $-78\,^\circ$C. *n*-BuLi (1.7M in hexanes, 16.0 mL, 27.2 mmol) was added dropwise and a white precipitate soon formed. After 15 min at this temperature, the reaction mixture was allowed to warm to $0\,^\circ$C and the Grignard solution was added within 1 h. The reaction mixture was stirred overnight at room temperature. The reaction was quenched at $0\,^\circ$C by careful addition of sat. aqueous NH_4Cl (120 mL). After separation of the layers, the aqueous layer was extracted with MTBE (3×150 mL). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (2×100 mL) and sat. aqueous NaCl (200 mL). After the organic phases were dried with Na_2SO_4, the solvents were removed in vacuo. CC (50 g, PE/MTBE 2:1) and recrystallization from MTBE (5 mL) yielded ketone **42** (730 mg, 13%) as a white solid. M.p. 75 – 76 °C (MTBE); $R_f = 0.48$ (PE/MTBE 1:1); $[\alpha]_D = +40.1$, $[\alpha]_{578} = +42.2$, $[\alpha]_{546} = +49.4$, $[\alpha]_{436} = +106.3$, $[\alpha]_{365} = +225.5$ ($c = 0.98$, $CHCl_3$, $T = 20\,^\circ$C); IR (neat): $\tilde{\nu} = 3355$m (NH), 3065w (CH olef.), 3035w (ArH), 2960w/2930w (CH aliph.), 1715s (CO), 1680s (carbamate C=O), 1525s, 1455w, 1390w, 1365m, 1350w, 1285m, 1235m, 1165m, 1060w, 695w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (s, 9H, *t*Bu), superimposed by 1.34 – 1.52 (m, 3H, 2-H_2, 3-H_A), 1.74 – 1.88 (m, 1H, 3-H_B), 2.24 (ddd, all $J_{vic} \approx 6.9$ Hz, 2H, 7-H_2), 2.35 – 2.58 (m, 2H, 6-H_2), 2.96 – 3.12 (m, 2H, 1-H_2), 4.20 – 4.38 (m, 1H, 4-H), 4.68 (brs, 1H, BocNH), 4.84 – 5.03 (m, 4H, 9-H_2, Ph-CH_2), 5.56 – 5.78 (m, 2H, 8-H, NH), 7.18 – 7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.8$ (C-2), 27.3 (C-7), 28.3 [C(CH_3)$_3$], 28.5 (C-3),

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38.7 (C-6), 39.8 (C-1), 59.2 (C-4), 66.8 (Ph-CH_2), 79.0 [$C(CH_3)_3$], 115.5 (C-9), 127.9, 128.0, 128.4, 136.2 (Ph), 136.5 (C-8), 155.9 (Boc-, Z-C=O), 208.2 (C-5).

Preparation of the ketone 42 via cuprate addition to 41 activated as 2-thiopyridine ester: Diisopropyl carbodiimide (4.05 mL, 3.48 g, 27.6 mmol) was added within 5 min at 0 °C to a solution of ornithine derivative **41** (10.1 g, 27.6 mmol) and 2-mercapto pyridine (3.07 g, 27.6 mmol) in CH_2Cl_2 (30 mL). After additional 5 min, the ice bath was removed and the reaction mixture was stirred for 4 h at room temperature. The precipitated urea was removed by filtration after cooling to 0 °C and washed with cool CH_2Cl_2 (10 mL). The filtrate was washed with 0.4 M aqueous NaOH (10 mL) and sat. aqueous NaCl (20 mL). After drying with Na_2SO_4 and removal of the solvent in vacuo the corresponding thioester (12.1 g, approx. 94 %) was obtained as a yellow oil which contained little diisopropyl urea. It was not possible to remove this impurity by CC (300 g, PE/MTBE 1:3). Thus, this slightly impurified materials was used for further transformations. $R_f = 0.52$ (MTBE); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (s, 9H, *t*Bu), superimposed by 1.38–1.78 (m, 3H, 3-H_A, 4-H_2), 1.82–2.04 (m, 1H, 3-H_B), 3.07 (m, 2H, 5-H_2), 4.59 (m, 1H, 2-H), 4.74 (br s, 1H, NH), 5.12 (s, 2H, Ph-CH_2), 6.02 (br s, 1H, NH), 7.20–7.39 (m, 6H, Ph, 5′-H), 7.54 (d, $J = 7.8$ Hz, 1H, 3′-H), 7.69 (t, $J = 7.6$ Hz, 1H, 4′-H), 8.57 (m, 1H, 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.1$ (C-4), 28.3 [C(CH_3)$_3$], 29.4 (C-3), 39.8 (C-5), 61.1 (C-2), 67.2 (Ph-CH_2), 79.2 [$C(CH_3)_3$], 123.5 (C-5′), 128.0, 128.1, 128.4, 136.0 (Ph), 130.3 (C-3′), 137.1 (C-4′), 150.3 (C-6′), 151.0 (C-2′), 156.0 (Boc-, Z-C=O), 198.4 (C-1). A solution of 4-bromo-1-butene (2.34 mL, 3.24 g, 24.0 mmol) in THF (14 mL) was added dropwise to Mg turnings (0.73 g, 30 mmol) covered with THF (7 mL). The solution of the bromide was added in a manner that the reaction mixture gently refluxed and was refluxed for additional 1 h at the end of the addition. A solution of dry LiCl (2.03 g, 48.0 mmol) and CuCN (2.12 g, 24.0 mmol) in THF (30 mL) was prepared at room temperature in a separate flask. The cold grignard solution was added −40 °C within 10 min to this greenish solution. After 15 min at this temperature, the reaction mixture was cooled to −78 °C and and a solution of the thiopyridine ester (4.60 g, 10.0 mmol) in THF (20 mL) was added dropwise within 10 min. After 10 min the reaction mixture was allowed to warm to −5 °C within 30 min. The reaction was quenched by careful addition of sat. aqueous NH_4Cl (30 mL). The orange precipitate was removed by filtration through a pad of Celite and was washed with MTBE (300 mL). The layers were separated and the aqueous layer was extracted with MTBE (3 × 30 mL). The combined organic layers were washed with sat. aqueous NaCl (40 mL) and dried with Na_2SO_4. The solvents were removed in vacuo and recrystallization from MTBE (40 mL) yielded ketone **42** (3.72 g, 9.20 mmol, 92 %).

(4*S*,5*R*)-4-Benzyloxycarbonylamino-1-*tert*-butoxycarbonylamino-8-non-ene-5-ol (43): Ketone **42** (1.59 g, 3.94 mmol) was dissolved in THF (40 mL) and cooled to −100 °C. L-Selectride (11.8 mL of a 1 M solution in THF precooled to −78 °C, 11.8 mmol) was added dropwise. This mixture was allowed to warm to −70 °C within 1 h and the reaction was quenched by careful addition of water (20 mL). At 0 °C 15 % aqueous NaOH (10 mL) and 30 % aqueous H_2O_2 (3.0 mL) were added carefully. After 90 min at 0 °C a mixture of sat. aqueous $NaHCO_3$ (60 mL) and MTBE (60 mL) was added. The aqueous layer was extracted with MTBE (3 × 40 mL) and the combined organic layers were washed with sat. aqueous NaCl (50 mL). After drying with $MgSO_4$ the solvents were removed in vacuo and the residue was purified by CC (70 g, PE/MTBE 1:1). The title compound was obtained as a diastereomeric mixture (1.30 g, 81 %), ds ≈ 3:1 according to the ^{13}C-NMR spectrum. The minor diastereomer could be removed by fractional crystallization from MTBE. Isomerically pure alcohol **43** (742 mg, 46 %) was obtained as white crystals. M.p. 123 °C; $R_f = 0.22$ (PE/MTBE 1:1); $[\alpha]_D = -16.3$, $[\alpha]_{578} = -17.3$, $[\alpha]_{546} = -19.7$, $[\alpha]_{436} = -33.7$, $[\alpha]_{365} = -51.9$ ($c = 0.77$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3355/3330$s (NH, OH), 2945m/2910w/2870w (CH), 1685s (C=O), 1535s, 1365w, 1330m, 1285m, 1170m, 1055m, 1015w, 740w, 695m; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H, *t*Bu), superimposed by 1.30–1.60 (m, 6H, 2-H_2, 3-H_2, 6-H_2), 1.95–2.35 (m, 2H, 7-H_2), 2.87 (br d, $J = 5.8$ Hz, 1H, OH), 3.04 (br s, 2H, 1-H_2), 3.60 (m, 2H, 4-H, 5-H), 4.68 (br t, $J = 5.5$ Hz, 1H, BocNH), 4.90–5.05 (m, 4H, 9-H_2, Ph-CH_2), 5.33 (br d, $J = 8.8$ Hz, 1H, NHZ), 5.78 (m, 1H, 8-H), 7.28 (s, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.1$, 26.7 (C-2, C-7), 28.3 [C(CH_3)$_3$], 30.2, 32.3 (C-3, C-6), 40.2 (C-1), 55.5 (C-4), 66.7 (Ph-CH_2), 73.8 (C-5), 79.1 [$C(CH_3)_3$], 115.0 (C-9), 127.98, 128.03, 128.4, 136.3 (Ph), 138.1 (C-8), 156.1, 156.7 (Boc-, Z-C=O); $C_{22}H_{34}N_2O_5$ (406.52): calcd C 65.00, H 8.43, N 6.89; found C 65.20, H 8.20, N 6.81.

(4*S*,5*R*)-5-(But-3′-ene-1′-yl)-4-(3″-*tert*-butoxycarbonylamino-prop-1″-yl)-1,3-oxazolidin-2-one (45): A solution of alcohol **43** (150 mg, 0.369 mmol) in THF (5 mL) was treated with NaH (95 %, 14 mg, 0.58 mmol) at 0 °C. After stirring for 18 h at room temperature, water (5 mL) was added. The mixture was extracted with MTBE (3 × 10 mL), and the organic layers were washed with sat. aqueous NaCl (10 mL). After drying with Na_2SO_4 the solvents were removed in vacuo. CC (20 g, MTBE) yielded compound **45** (100 mg, 90 %) as a slightly yellow oil. $R_f = 0.60$ (EtOAc); $[\alpha]_D = -10.3$, $[\alpha]_{578} = -11.1$, $[\alpha]_{546} = -12.4$, $[\alpha]_{436} = -22.8$, $[\alpha]_{365} = -38.1$ ($c = 0.52$, $CHCl_3$, $T = 20$ °C); IR (neat): $\tilde{\nu} = 3315$m (NH), 2975m/2930m (CH), 1750s (C=O), 1700s (C=O), 1640w, 1520m, 1455w, 1390m, 1365m, 1250m, 1170m, 1100w, 1040w, 915w; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.42$ (s, 9H, *t*Bu), superimposed by 1.38–1.68 (m, 6H, 1′-H_2, 1″-H_2, 2″-H_2), 2.08–2.35 (m, 2H, 2′-H_2), 3.06 (br t, $J = 5.6$ Hz, 2H, 3″-H_2), 3.79 (ddd, $J = 8.0$, 8.0, 3.5 Hz, 1H, 4-H), 4.61 (ddd, $J = 9.8$, 7.7, 4.0 Hz, 1H, 5-H)*, 5.01 (d m, $J = 10.2$ Hz, 1H, 4′-H_E), 5.07 (dq, $J = 17.1$, 1.7 Hz, 1H, 4′-H_Z), 5.85 (ddt, $J = 17.1$, 10.2, 6.8 Hz, 1H, 3′-H); *two homonuclear decoupling experiments verified $J_{4,5} = 7.7$ Hz; ^{13}C NMR (75 MHz, CD_3OD): $\delta = 27.5$, 28.3, 29.6, 31.2 (C-1′, C-2′, C-1″, C-2″), 28.8 [C(CH_3)$_3$], 40.8 (C-3″), 56.4 (C-4), 79.9 [$C(CH_3)_3$], 81.1 (C-5), 116.0 (C-4′), 138.5 (C-3′), 158.5 (Boc-CO), 161.7 (CO).

(4*S*,5*S*)-5-(But-3′-ene-1′-yl)-4-(3″-*tert*-butoxycarbonylamino-prop-1″-yl)-1,3-oxazolidin-2-one (46): A solution of alcohol **44** (ds ≈ 3:1) in THF (7 mL) was treated with NaH (95 %, 30 mg, 1.25 mmol) at 0 °C. After 18 h at room temperature the reaction was quenched by the addition of half sat. aqueous NaCl (20 mL) at 0 °C. This mixture was extracted with EtOAc (30 mL), the organic layers were washed with sat. aqueous NaCl (10 mL) and dried with $MgSO_4$. Removal of the solvents in vacuo and separation by CC (20 g, MTBE) yielded compound **46** (32 mg, 15 %) as a colorless oil. $R_f = 0.32$ (MTBE); $[\alpha]_D = -50.3$, $[\alpha]_{578} = -52.6$, $[\alpha]_{546} = -61.4$, $[\alpha]_{436} = -105.2$, $[\alpha]_{365} = -163.8$ ($c = 0.58$, $CHCl_3$, $T = 20$ °C); IR (neat): $\tilde{\nu} = 3315$m (NH), 3080w, 2975/2935m (CH), 1750s (C=O), 1710s (C=O), 1520m, 1455m, 1390s, 1365m, 1250s, 1170s; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.42$ (s, 9H, *t*Bu), superimposed by 1.40–1.60, 1.70–1.80 (m, 4H; m, 2H, 1′-H_2, 1″-H_2, 2″-H_2), 2.19 (m, 2H, 2′-H_2), 3.04 (br t, $J = 6.0$ Hz, 2H, 3″-H_2), 3.48 (br ddd, all $J \approx 5.5$ Hz, 1H, 4-H), 4.20 (ddd, $J = 7.4$, 5.3, 5.3 Hz, 1H, 5-H)*, 4.99 (d m, $J = 10.4$ Hz, 1H, 4′-H_E), 5.06 (dq, $J = 17.1$, 1.7 Hz, 1H, 4′-H_Z), 5.84 (ddt, $J = 17.0$, 10.3, 6.6 Hz, 1H, 3′-H); *two homonuclear decoupling experiments verified $J_{4,5} = 5.3$ Hz; ^{13}C NMR (75 MHz, CD_3OD): $\delta = 26.6$, 30.1, 33.5, 35.2 (C-1′, C-2′, C-1″, C-2″), 28.8 [C(CH_3)$_3$], 40.8 (C-3″), 58.7 (C-4), 79.9 [$C(CH_3)_3$], 83.1 (C-5), 116.0 (C-4′), 138.5 (C-3′), 158.6 (Boc-CO), 161.5 (CO).

(4*S*,5*R*)-4-Benzyloxycarbonylamino-1-*tert*-butoxycarbonylamino-8-non-ene-5-yl-p-nitrobenzoate (49): A solution of alcohol **43** (300 mg, 0.738 mmol) in CH_2Cl_2 (5 mL) and pyridine (1.0 mL) was treated with *p*-nitro-benzoyl chloride (405 mg, 1.48 mmol) at 0 °C. After the addition of catalytic amounts of DMAP the reaction mixture was allowed to stir for 18 h at room temperature. Water (10 mL) was added followed by extraction with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with 0.5 M aqueous $CuSO_4$ (2 × 10 mL), half sat. aqueous NaCl (10 mL), and dried with $MgSO_4$. After removal of the solvent and CC (20 g, MTBE/PE 2:1) the title compound (348 mg, 85 %) was obtained as colorless crystals. Crystals suitable for X-ray crystal structural analysis were obtained from a solution of **49** in wet acetone. M.p. 112–114 °C (acetone/water); $R_f = 0.70$ (MTBE/PE 1:1); $[\alpha]_D = -3.5$, $[\alpha]_{578} = -4.3$, $[\alpha]_{546} = -5.0$, $[\alpha]_{436} = -7.8$; ($c = 0.46$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3370$m (NH), 2930m (CH), 1720s (C=O), 1690s (C=O), 1610w, 1530m, 1455m, 1385m, 1350m, 1280s, 1170m, 1120m, 1105m, 1015w, 915w, 720w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H, *t*Bu), superimposed by 1.35–1.84 (m, 6H, 2-H_2, 3-H_2, 6-H_2), 2.00–2.27 (m, 2H, 7-H_2), 3.14 (br s, 2H, 1-H_2), 4.03 (m, 1H, 4-H), 4.63 (m, 1H, 5-H), 4.92–5.24 (m, 6H, 9-H_2, CH_2-Ph, 2NH), 5.78 (m, 1H, 8-H), 7.20–7.42 (m, 5H, Ph), 8.03–8.29 (m, 4H, Ar-NO_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.0$, 27.3, 29.1, 29.7 (C-2, C-3, C-6, C-7), 28.3 [C(CH_3)$_3$], 39.8 (C-1), 53.3 (C-4), 66.7 (CH_2-Ph), 77.1 (C-5), 79.6 [$C(CH_3)_3$], 115.7 (C-9), 123.5, 127.9, 128.1, 128.5, 130.7, 135.4, 136.4 (Ar-NO_2, Ph), 136.9 (C-8), 156.2 (Boc-CO), 164.3 (CO); $C_{29}H_{37}N_3O_8$ (555.62): calcd C 62.69, H 6.71, N 7.56; found C 62.59, H 6.53, N 7.46.

Crystal data of **49**: 0.48 × 0.20 × 0.01 mm, monoclinic, *P*21, $a = 19.127$ (8), $b = 5.1311$ (13), $c = 30.102$ (11) pm, $\beta = 99.19$ (5), $V = 2916.3$ (18) 10^{-30} m^3, $Z = 4$, $\rho_{calcd} = 1.265$ Mg m^{-3}, $2\Theta_{max} = 48.00°$, $Mo_{K\alpha}$, 71.073 pm, φ-rotation,

180 K, reflections: measured 15328, independent 9090, LP-correction, no absorption correction ($\mu = 0.087\ mm^{-1}$), structure solution by direct methods (SHELX-97) (Sheldrick 1997), structure refinement by full-matrix least squares with 9090 F^2 data, 698 free parameters, H atoms geometrically generated and refined with the corresponding C atoms (riding model), $R_1 = 0.1224$ [2925 reflections with $I > 2\,\sigma(I)$], $wR_2 = 0.326$ (all data), residual electron density: -0.473 to $0.499 \times 10^{30}\ e\,m^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116712. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

(2*RS*,5*R*,1′*S*)-5-(1′-Benzyloxycarbonylamino-4′-*tert*-butoxycarbonylamino-butyl)-2-hydroxymethylene-tetrahydrofuran (50): A solution of MCPBA (60%, 1.06 g, 3.7 mmol) in CH_2Cl_2 (15 mL) was added within 10 min to a solution of alcohol **43** (715 mg, 1.76 mmol) in CH_2Cl_2 (15 mL). After stirring at room temperature for 3.5 h the reaction mixture was poored on sat. aqueous Na_2SO_3 (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (15 mL) and sat. aqueous NaCl (50 mL). The solvents were removed in vacuo after drying with $MgSO_4$ and the residual oil was dissolved in CH_2Cl_2 (10 mL) and treated with PPTS (20 mg). After 12 h sat. aqueous $NaHCO_3$ (15 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with sat. aqueous NaCl (30 mL). After the organic phase was dried with Na_2SO_4, the solvent was removed in vacuo and the residue was purified by CC [50 g, PE/MTBE 1:2 (400 mL), then MTBE]. Compound **50** (670 mg, 90%) was obtained as a white foam. The diasteromeric ratio was approx. 1:1 as determined by ^{13}C NMR. M.p. 80 °C; $R_f = 0.30$ (MTBE); $[\alpha]_D = -15.6$, $[\alpha]_{578} = -16.2$, $[\alpha]_{546} = -18.4$, $[\alpha]_{436} = -29.7$, $[\alpha]_{365} = -42.3$ ($c = 1.48$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3360$m (NH, OH), 3035w (ArH), 2960m/2940m/2875w (CH), 1685s (C=O), 1530s, 1455w, 1365w, 1280m, 1240m, 1175m, 1085w, 1045m, 1020w, 695w; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H, *t*Bu), superimposed by 1.20–1.78, 1.80–2.05 (m, 6H; m, 2H, 3-H_2, 4-H_2, 2′-H_2, 3′-H_2), 2.61 (br s, 1H, OH), 3.11 (m, 2H, 4′-H_2), 3.45 (dd, $J = 11.7$, 6.0 Hz, 1H, 1″-H_A), 3.62 [dd, $J = 12.4$, 3.2 Hz, ca. 0.5H, 1″-H_B (one epimer)], superimposed partially by 3.65 [dd, $J = 11.9$, 3.2 Hz, 1″-H_B (one epimer)], superimposed by 3.62–3.78 (m, 1H, 1′-H), 3.83–4.07 (m, 2H, 2-H, 5-H), 4.70 (m, 1H, NH), 5.08 (s, 2H, Ph-CH_2), superimposed by 5.02–5.13 (m, 1H, NH), 7.26–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.6$ (br), 26.8, 27.2, 27.9, 28.5 (C-3, C-4, C-2′, C-3′), 28.3 [C(CH_3)$_3$], 40.2 (C-4′), 54.0, 54.3 [C-1′ (two epimers)], 64.7, 64.9 [C-1″ (two epimers)], 66.7 (Ph-CH_2), 79.1 [$C(CH_3)_3$], 80.0, 81.7, 82.0 [C-2, C-5 (two epimers)], 128.0, 128.4, 136.4 (Ph), 156.0, 156.4, 156.5 [Boc-, Z-C=O (two epimers)]; $C_{22}H_{34}N_2O_6$ (422.52): calcd C 62.54, H 8.11, N 6.63; found C 62.32, H 8.21, N 6.49.

(2*RS*,5*R*,1′*S*)-5-(1′-Benzyloxycarbonylamino-4′-*tert*-butoxycarbonylamino-butyl)-tetrahydrofuran-2-carboxylic acid (51): Starting from the alcohol **50** (3.58 g, 8.47 mmol) this two-step oxidation was performed analogous to the preparation of the carboxylic acids **25**/**26**. The following amounts of reagents were used: oxalyl chloride (1.45 mL, 2.14 g, 16.9 mmol) in CH_2Cl_2 (60 mL), DMSO (1.80 mL, 1.98 g, 25.4 mmol) in CH_2Cl_2 (10 mL), and NEt_3 (14.1 mL, 10.3 g, 101 mmol). Without purification by CC the corresponding crude aldehyde (3.65 g) was obtained as a yellow oil. $R_f = 0.38$ (MTBE). Subsequent Pinnick-oxidation using *t*-BuOH (12 mL), amylene (6 mL), $NaClO_2$ (80%, 1.24 g, 11.0 mmol) and $NaH_2PO_4 \times H_2O$ (1.51 g, 11.0 mmol) in water (6 mL) yielded a slightly yellow crude product after usual work-up. This was further purified as the dicyclohexyl ammonium salt analogous to the preparation of carboxylic acids **25**/**26** using dicyclohexyl amine (2.49 mL, 2.27 g, 12.5 mmol). After liberation of the free acids with the aid of 5% aqueous citric acid (2×100 mL) instead of aqueous HCl, the acid **51** (3.37 g, 64%) was obtained as an epimeric mixture. M.p. 69–74 °C; $R_f = 0.05$–0.24 (MTBE); IR (KBr): $\tilde{\nu} = 3345$ br m (NH, COOH), 3035w (ArH), 2975m/2935m (CH), 1695s (C=O), 1635m, 1530s, 1455m, 1390w, 1365m, 1340m, 1250m, 1170m, 1080m, 1015w, 740w, 700w; ^1H NMR (300 MHz, CD_3OD): $\delta = 1.42$ (s, 9H, *t*Bu), superimposed by 1.27–2.12 (m, 7H, 3-H_A, 4-H_2, 2′-H_2, 3′-H_2), 2.18–2.36 (m, 1H, 3-H_B), 2.99–3.09 (m, 2H, 4′-H_2), 3.54–3.71 (m, 1H, 1′-H), 3.89 [dt, $J = 7.0$, 7.0 Hz, 5-H (epimer A)], 4.04 [dt, $J = 6.8$, 6.8 Hz, 5-H (epimer B)], 4.42 [dd, $J = 8.0$, 5.9 Hz, 2-H (epimer B)], 4.47 [dd, $J = 7.9$, 5.5 Hz, 2-H (epimer A)], 5.08 (br s, 2H, Ph-CH_2), 7.26–7.39 (m, 5H, Ph); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 27.5$, 28.2, 29.7 (C-4, C-2′, C-3′), 28.8 [C(CH_3)$_3$], 31.0 (C-3), 40.8 (C-4′), 55.5 (C-1′), 67.4 (Ph-CH_2), 78.2, 78.5 [C-2 (two epimers)], 79.8 [$C(CH_3)_3$], 84.1, 84.6 [C-5 (two epimers)], 128.7, 128.9, 129.5, 138.5 (Ph), 176.6, 177.0 [COOH (two epimers)]; $C_{22}H_{32}N_2O_5$ (436.50): calcd C 60.54, H 7.39, N 6.42; found C 60.11, H 7.45, N 6.15.

(2*S*,2′*RS*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-*tert*-butoxycarbonyl-aminobutyl)-tetrahydrofuran-2′-carbamoyl]-2-butylsulfonylamino-methyl propionate (53): $EtN(iPr)_2$ (1.98 mL, 1.47 g, 11.3 mmol) and EDC (728 mg, 3.80 mmol) were added subsequently to a solution of carboxylic acid **51** (1.65 g, 3.78 mmol), trifluoroacetate **52** (1.73 g, 4.90 mmol), and HOBt (868 mg, 5.70 mmol) in THF (15 mL). After the solution was stirred at room temperature for 18 h, the solvent was removed in vacuo, and the residue dissolved in EtOAc (50 mL). After successive washings with 5% aqueous citric acid (2×10 mL), sat. aqueous $NaHCO_3$ (20 mL), and sat. aqueous NaCl (20 mL) the organic layer was dried with Na_2SO_4. Removal of the solvent in vacuo and CC (200 g, MTBE/PE 5:1) afforded amide **53** (1.51 g, 61%) as a white solid. M.p. 57–58 °C; $R_f = 0.52$ (MTBE); HPLC: $t_R = 13.7$ min (Si 60; 1.5 mL min^{-1}, 10% isopropyl alcohol in *n*-hexane); 14.5 and 15.3 min (Rainin, RP 18, 1 mL min^{-1}, 40% to 80% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); IR (KBr): $\tilde{\nu} = 3420$ br s (NH), 2960m/2875w (CH), 1685 br s (C=O), 1525w, 1455m, 1425s, 1365m, 1330m, 1250w, 1215m, 1150m, 1080w; ^1H NMR (300 MHz, CD_3OD): $\delta = 0.95$, 0.96 (2t, $J = 7.3$ Hz each, 3H, CH_3), 1.43 (s, 9H, *t*Bu), superimposed by 1.28–1.97 (m, 9H, 2CH_2CH_2, 4′-H_A), 1.88–2.07 (m, 2H, 3′-H_A, 4′-H_B) 2.16–2.36 (m, 1H, 3′-H_B), 3.04 (m, 4H, 4″-H_2, SO_2CH_2), 3.75 (s, 3H, OMe), superimposed by 3.26–3.86 (m, 3H, 3-H_2, 1″-H), 3.96 [ddd, all $J_{vic} \approx 6.0$ Hz, 5′-H (one epimer)], 4.08 [ddd, all $J_{vic} = 6.5$ Hz, 5′-H (one epimer)], 4.21–4.37 (m, 2H, 2-H, 2′-H), 5.03–5.17 (m, 2H, PhCH_2), 7.23–7.43 (m, 5H, Ph); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 14.0$ (CH_3), 22.5, 26.7, 27.7, 28.1, 29.7, 29.9, 30.9, 31.2 (2CH_2CH_2, C-3′, C-4′), 28.8 [C(CH_3)$_3$], 41.2, 41.4, 42.0 (C-3, C-4″), 53.2 (OMe), 54.2 (SO_2CH_2), 55.2, 55.4 [C-1″ (two epimers)], 56.6, 56.7 [C-2 (two epimers)], 67.4 (CH_2-Ph), 79.8 [C-2′, $C(CH_3)_3$], 84.3, 84.8 [C-5′ (two epimers)], 128.6, 128.7, 129.0, 129.5, 138.0 (Ph), 158.5, 159.1 (Z-CO, Boc-CO), 172.2 (CONH), 176.1, 176.5 [COO (two epimers)]; $C_{30}H_{48}N_4O_{10}S$ (656.79): calcd C 54.86, H 7.37, N 8.53, S 4.88; found C 55.23, H 7.44, N 8.04, S 4.55; HRMS (FAB): $[C_{30}H_{48}N_4O_{10}S+H]^+$ calcd 657.3169; found 657.337.

(2*S*,2′*R*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-[$N^{2'''}$,$N^{3'''}$-bis-(*tert*-butoxycarbonyl)-guanidino]-butyl)-tetrahydrofuran-2′-carbamoyl]-2-butylsulfonyl-amino-methyl propionate (55) and **(2*S*,2′*S*,5′*R*,1″*S*)-3-[5′-(1″-benzyloxy-carbonylamino-4″-[$N^{2'''}$,$N^{3'''}$-bis-(*tert*-butoxycarbonyl)-guanidino]-butyl)-tetrahydrofuran-2′-carbamoyl]-2-butylsulfonylamino methyl propionate (56)**: A solution of protected amine **53** (480 mg, 0.731 mmol) in CH_2Cl_2 (15 mL) was treated with TFA (3 mL). After 4 h at room temperature the solvents were removed under reduced pressure. Azeotropic distillation with toluene (2×5 mL) yielded a slightly brownish oil which was used without further purification in the guanylation. This residue, isothiourea **54** (233 mg, 0.800 mmol), and NEt_3 (0.41 mL, 0.30 g, 2.9 mmol) were dissolved in DMF (7 mL). After addition of $HgCl_2$ (228 mg, 0.840 mmol) the reaction mixture was stirred for 2.5 h at room temperature. It was diluted with EtOAc (30 mL) and filtered with the aid of Celite. The filtrate was washed with 5% aqueous citric acid (2×7 mL), sat. aqueous $NaHCO_3$ (7 mL), sat. aqueous NaCl (7 mL). The organic phase was dried with Na_2SO_4. Removal of the solvents in vacuo and subsequent CC (60 g, MTBE) afforded the guanidine derivatives **55**/**56** (395 mg, 68% based on **53**) as a colorless solid. This approx. 2:1 mixture of C-2′-epimers was separated by preparative HPLC (6 runs, 21 mm ID, Rainin, Si 60, 21.6 mL min^{-1}, 15% isopropyl alcohol in *n*-hexane). In addition to the diastereomerically pure **56** (220 mg, 0.275 mmol, 38%)* and **55** (75 mg, 0.094 mmol, 13%)* an epimeric mixture (50 mg, 0.063 mmol, 9%) was obtained; *the *cis* vs. *trans* assignment was done unambiguously by interpretation of 600 MHz NOESY spectra of both separated epimers after transformation to **38** and **39** (see below). Analytical data of the epimeric mixture: $R_f = 0.32$ (MTBE); IR (KBr): $\tilde{\nu} = 3335$w (NH), 2960w (CH), 1720s (CO), 1640s, 1530w, 1455w, 1415w, 1370m, 1330s, 1230w, 1135s, 1055w, 1025w; $C_{36}H_{58}N_6O_{12}S$ (798.94): calcd C 54.12, H 7.32, N 10.52, S 4.01; found C 54.01, H 7.61, N 9.99, S 3.57. Guanidine derivative **55**: m.p. 67–68 °C; $[\alpha]_D = +12.6$, $[\alpha]_{578} = +13.5$, $[\alpha]_{546} = +15.7$, $[\alpha]_{436} = +29.2$, $[\alpha]_{365} = +52.0$ ($c = 0.65$, $CHCl_3$, $T = 20$ °C); HPLC: $t_R = 15.6$ min (Si 60; 1.5 mL min^{-1},

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15% isopropyl alcohol in *n*-hexane); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.46, 1.52 (2s, 18H, 2*t*Bu), superimposed by 1.22–1.90 (m, 9H, 2CH_2CH_2, 4′-H_A), 1.90–2.07 (m, 2H, 3′-H_A, 4′-H_B) 2.20–2.36 (m, 1H, 3′-H_B), 3.04 (t, J = 7.9 Hz, 2H, SO_2CH_2), 3.25–3.43 (m, 3H, 3-H_A, 4″-H_2), 3.75 (s, 3H, OMe), superimposed by 3.62–3.79 (m, 2H, 3-H_B, 1″-H), 4.09 (ddd, all J_{vic} = 6.5 Hz, 1H, 5′-H), 4.23 (dd, J = 8.3, 5.3 Hz, 1H, 2-H), 4.35 (dd, J = 7.9, 6.0 Hz, 1H, 2′-H), 5.09 (s, 2H, Ph-CH_2), 7.22–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, CD_3OD): δ = 14.0 (CH_3), 22.5, 26.7, 26.9, 29.4 (2CH_2CH_2), 28.2 (C-4′), 28.3, 28.6 [2C(CH_3)$_3$], 30.9 (C-3′), 41.6, 41.9 (C-3, C-4″), 53.1 (OMe), 54.2 (SO_2CH_2), 55.1 (C-1″), 56.6 (C-2), 67.4 (CH_2-Ph), 79.8, 84.2 [2C(CH_3)$_3$], 80.3 (C-2′), 84.4 (C-5′), 128.7, 128.9, 129.4, 138.5 (Ph), 154.2 (C=N), 157.6, 159.0 (Z-CO, Boc-CO), 164.6 (Boc-CO), 172.2 (CONH), 176.5 (COO). Guanidine derivative **56**: m.p. 59 °C; $[\alpha]_D$ = +6.9, $[\alpha]_{578}$ = +7.2, $[\alpha]_{546}$ = +8.1, $[\alpha]_{436}$ = +16.7, $[\alpha]_{365}$ = +30.4 (c = 0.90, $CHCl_3$, T = 20 °C); HPLC: t_R = 12.5 min (Si 60; 1.5 mL min^{-1}, 15% isopropyl alcohol in *n*-hexane); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.94 (t, J = 7.3 Hz, 3H, CH_3), 1.47 and 1.53 (2s, 18H, 2*t*Bu), superimposed by 1.21–1.85 (m, 9H, 2CH_2CH_2, 4′-H_A), 1.95 (m, 2H, 3′-H_A, 4′-H_B) 2.23 (m, 1H, 3′-H_B), 3.04 (t, J = 7.9 Hz, 2H, SO_2CH_2), 3.31–3.61 (m, 4H, 3-H_2, 4″-H_2), 3.74 (s, 3H, OMe), 3.75–3.86 (m, 1H, 1″-H), 3.91–4.02 (m, 1H, 5′-H), 4.20–4.23 (m, 2H, 2-H, 2′-H), 5.05–5.18 (m, 2H, Ph-CH_2), 7.22–7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, CD_3OD): δ = 14.0 (CH_3), 22.5, 26.6, 27.0, 29.7 (2CH_2CH_2), 27.7 (C-4′), 28.3, 28.6 [2C(CH_3)$_3$], 31.2 (C-3′), 41.5, 41.9 (C-3, C-4″), 53.2 (OMe), 54.2 (SO_2CH_2), 55.5 (C-1″), 56.5 (C-2), 67.4 (CH_2-Ph), 79.8, 84.7 [2C(CH_3)$_3$], 80.3 (C-2′), 84.4 (C-5′), 128.5, 128.9, 129.5, 138.0 (Ph), 154.1 (C=N), 158.0, 159.3 (Z-CO, Boc-CO), 164.5 (Boc-CO), 172.1 (CONH), 176.9 (COO).

(2*S*,2′*R*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-guanidino-butyl)-tetrahydrofuran-2′-carbamoyl]-2-butylsulfonylamino propionic acid (38, as trifluoroacetate): The preparation was done as described for **14** starting from THF derivative **55** (42 mg, 0.052 mmol). Purification by preparative HPLC [3 runs, 21 mm ID, Rainin, RP 18, 21.6 mL min^{-1}, 70% (water + 0.2% TFA) and 30% (acetonitrile + 0.2% TFA)] yielded trifluoroacetate **38** (16 mg, 43%) as a colorless oil; HPLC: t_R = 6.7 min (MN, RP 18, 1 mL min^{-1}, 1% to 40% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); t_R = 17.3 min (MN, RP 18, 1 mL min^{-1}, 20% to 80% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN): δ = 0.91 (t, J = 7.4 Hz, 3H, CH_3), 1.40 (m, 3H, 2″-H_A, CH_2-CH_3), 1.49–1.60 (m, 1H, 3″-H_A), 1.60–1.78 (m, 5H, 4′-H_A, 2″-H_B, 3″-H_B, SO_2CH_2-CH_2), 1.89–1.97 (m, 2H, 3′-H_A, 4′-H_B), 2.18–2.29 (m, 1H, 3′-H_B), 3.03 (t, J = 6.4 Hz, 2H, SO_2CH_2), 3.06–3.14, 3.12–3.22 (2m, 1H each, 4″-H_2), 3.39 (ddd, J = 13.2, 6.6, 6.6 Hz, 1H, 3-H_A), 3.59–3.69 (m, 2H, 3-H_B, 1″-H), 3.99 (m, 1H, 5′-H), 4.13 (m, 1H, 2-H), 4.34 (m, 1H, 2′-H), 5.07 (s, 2H, PhCH_2), 5.78 (d, J = 9.7 Hz, 0.6H, NHZ), 6.02 (d, J = 8.3 Hz, $NHSO_2$), 6.36 (brs, 1.8H, $2NH_2$), 7.08 (brs, N$^{4''}$H), 7.29–7.38 (m, 5H, Ph), 7.40 (m, N^{3}H); the sample still contained 13 mass-% water which was explicit substracted from the yield; due to recording the spectrum with presaturation of the HOD signal the integral size of some exchangeable protons is too small; in addition a second conformer/epimer (approx. 10 mol-%) was detected, but these signals were not reported above; ^{13}C NMR (75 MHz, CD_3CN): δ = 14.0 (CH_3), 22.2 (CH_2-CH_3), 25.4 (C-3″), 26.4 (SO_2CH_2-CH_2), 28.5 (C-4′), 29.3 (C-2″), 30.7 (C-3′), 42.2 (C-3, C-4″), 53.8 (SO_2CH_2), 54.8 (C-1″), 56.0 (C-2), 67.2 (CH_2-Ph), 79.6 (C-2′), 83.7 (C-5′), 128.6, 129.0, 129.6 (Ph), 158.1 (presumably C=N); the CO-signals as well as the signal for C_q of Ph were not detected. FAB-MS: $[C_{25}H_{41}N_6O_8S]^+$ calcd 585.3; found 585.4.

(2*S*,2′*S*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-guanidino-butyl)-tetrahydrofuran-2′-carbamoyl]-2-butylsulfonylamino propionic acid (39, as a trifluoroacetate): The preparation and purification was done as described for **38** starting from THF derivative **56** (73 mg, 0.091 mmol) and afforded **39** (42 mg, 66%) as a colorless oil. HPLC: t_R = 16.7 min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN): δ = 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.32–1.42 (m, 3H, 2″-H_A, CH_2-CH_3), 1.49–1.59 (m, 1H, 3″-H_A), 1.59–1.76 (m, 5H, 4′-H_A, 2″-H_B, 3″-H_B, SO_2CH_2-CH_2), 1.86–1.93 (m, 2H, 3′-H_A, 4′-H_B) 2.19 (m, 1H, 3′-H_B), 3.01 (t, J = 8.0 Hz, 2H, SO_2CH_2), 3.06–3.13, 3.11–3.21 (2m, 1H each, 4″-H_2), 3.48 (m, 2H, 3-H_2), 3.69 (m, 1H, 1″-H), 3.92 (m, 1H, 5′-H), 4.13 (m, 1H, 2-H), 4.28 (m, 1H, 2′-H), AB signal (δ_A = 5.06, δ_B = 5.09, J_{AB} = 12.6 Hz, 2H, Ph-CH_2), 6.10 (d, J = 9.2 Hz, 0.7H, NHZ), 6.17 (d, J = 8.7 Hz, 0.7H, $NHSO_2$), 6.47, 6.57 (2brs, 3H, $2NH_2$), 7.28–7.37 (m, 5H, Ph), 7.39 (brt, J = 5.9 Hz, 1H, N^{3}H), 7.43 (brs, 1H, N$^{4''}$H); the sample still contained 6 mass-% water which was explicit substracted from the yield; due to recording the spectrum with presaturation of the HOD signal the integral size of some exchangeable protons was too small; ^{13}C NMR (75 MHz, CD_3CN): δ = 13.9 (CH_3), 21.4 (CH_2-CH_3), 25.7 (C-3″), 26.3 (SO_2CH_2-CH_2), 27.7 (C-4′), 29.0 (C-2″), 30.8 (C-3′), 42.0, 42.1 (C-3, C-4″), 53.6 (SO_2CH_2), 54.9 (C-1″), 56.4 (C-2), 67.2 (CH_2-Ph), 79.6 (C-2′), 84.1 (C-5′), 128.5, 128.9, 129.5, 138.1 (Ph), 158.1 (presumably C=N), 175.0 (COO); some CO-signals were not detected. FAB-MS: $[C_{25}H_{41}N_6O_8S]^+$ calcd 585.3; found 585.5.

(2*S*,2′*R*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-*tert*-butoxycarbonyl-aminobutyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino-methyl propionate (57): The preparation was done analogous to the amide **53** using the following amounts of substrate and reagents: carboxylic acid **51** (535 mg, 1.23 mmol), amine hydrochloride **27** (391 mg, 1.35 mmol), HOBt (282 mg, 1.84 mmol), EtN(*i*Pr)$_2$ (0.47 mL, 0.35 g, 2.7 mmol), and EDC (236 mg, 1.23 mmol). CC (100 g, EtOAc/PE 1:1) yielded the product (651 mg, 79%) as a mixture of C-2′-epimers. Crystallization from Et_2O (40 mL) afforded the pure *trans*-isomer **57** (302 mg, 0.450 mmol, 37%) as a white solid. M.p. 104 °C; R_f = 0.74 (EtOAc); $[\alpha]_D$ = +10.4, $[\alpha]_{578}$ = +11.3, $[\alpha]_{546}$ = +13.3, $[\alpha]_{436}$ = +25.2, $[\alpha]_{365}$ = +48.9 (c = 0.89, $CHCl_3$, T = 20 °C); IR (KBr): $\tilde{\nu}$ = 3335 brm (NH), 2950w/2935m (CH), 1705s (C=O), 1685s (C=O), 1530s, 1435m, 1365w, 1340w, 1250m, 1170w, 1070w, 700w; ^{1}H NMR (300 MHz, CD_3OD): δ = 1.42 (s, 9H, *t*Bu), superimposed by 1.24–1.97 (m, 7H, 3′-H_A, 4′-H_2, 2″-H_2, 3″-H_2), 2.16–2.33 (m, 1H, 3′-H_B), 3.01 (brt, J = 6.4 Hz, 2H, 4″-H_2), 3.46 (dd, J = 13.7, 7.4 Hz, 1H, 3-H_A), 3.72 (s, 3H, OMe), superimposed by 3.58–3.75 (m, 2H, 3-H_B, 1″-H), 3.98 (dt, J = 6.5, 6.5 Hz, 1H, 5′-H), 4.31 (dd, J = 7.5, 6.2 Hz, 1H, 2′-H), 4.38 (dd, J = 7.3, 5.2 Hz, 1H, 2-H), 5.02–5.15 (m, 4H, 2Ph-CH_2), 7.23–7.39 (m, 10H, 2Ph); ^{13}C NMR (75 MHz, CD_3OD): δ = 27.6, 28.0, 29.3 (C-4′, C-2″, C-3″), 28.8 [C(CH_3)$_3$], 31.0 (C-3′), 41.0 (C-3, C-4″), 53.0 (OMe), 55.0 (C-1″), 55.3 (C-2), 67.4, 67.8 (2CH_2-Ph), 79.8 [C-2′, C(CH_3)$_3$], 84.3 (C-5′), 128.7, 128.9, 129.0, 129.5, 138.0, 138.4 (2Ph), 158.4, 159.0 (2Z-CO, Boc-CO), 172.4 (CONH), 176.6 (COO); $C_{34}H_{46}N_4O_{10}$ (670.75): calcd C 60.88, H 6.91, N 8.35; found C 60.93, H 7.00, N 8.18. Epimeric mixture (strongly enriched by the *cis* isomer): ^{1}H NMR (300 MHz, CD_3OD): δ = 1.41 (s, 9H, *t*Bu), superimposed by 1.23–1.95 (m, 7H, 3′-H_A, 4′-H_2, 2″-H_2, 3″-H_2), 2.11–2.30 (m, 1H, 3′-H_B), 2.90–3.14 (m, 2H, 4″-H_2), 3.40–3.80 (m, 3H, 3-H_2, 1″-H), 3.70 (s, 3H, OMe), 3.85–4.02 (m, 1H, 5′-H), 4.23 (m, 1H, 2′-H), 4.30–4.44 (m, 1H, 2-H), 5.02–5.17 (m, 4H, 2Ph-CH_2), 7.20–7.39 (m, 10H, 2Ph); ^{13}C NMR (75 MHz, CD_3OD): δ = 27.7 (double intensity), 29.7, 31.4 (C-3′, C-4′, C-2″, C-3″), 28.9 [C(CH_3)$_3$], 40.9 (C-3, C-4″), 53.1 (OMe), 55.3 (C-2, C-1″), 67.5, 67.9 (2CH_2-Ph), 79.8 [C(CH_3)$_3$], 79.9 (C-2′), 84.9 (C-5′), 128.7, 128.9, 129.0, 129.1, 129.5, 138.1, 138.5 (2Ph), 158.4, 158.6 (2Z-CO, Boc-CO), 172.3 (CONH), 176.1 (COO).

(2*S*,2′*R*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-[*N*$^{2'''}$,*N*$^{3'''}$-bis-(*tert*-butoxycarbonyl)-guanidino]-butyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxy-carbonylamino methyl propionate (58): The preparation was done analogous to the preparation of the guanidine derivatives **55**/**56** using the following amounts of substrate and reagents: Boc-protected amine **57** (104 mg, 0.155 mmol), TFA (1 mL), then isothiourea **54** (48 mg, 0.17 mmol), NEt_3 (0.10 mL, 73 mg, 0.72 mmol) and $HgCl_2$ (46 mg, 0.17 mmol). CC (15 g, MTBE) yielded the guanidine derivative **58** (92 mg, 0.11 mmol, 73%) as a colorless solid. M.p. 68–69 °C; R_f = 0.40 (MTBE); $[\alpha]_D$ = +16.9, $[\alpha]_{578}$ = +17.7, $[\alpha]_{546}$ = +20.0, $[\alpha]_{436}$ = +36.3, $[\alpha]_{365}$ = +62.1 (c = 0.70, $CHCl_3$, T = 20 °C); IR (KBr): $\tilde{\nu}$ = 3335 brm (NH), 2950w/2930w (CH), 1720s (C=O), 1640s, 1525m, 1455m, 1415m, 1370m, 1335m, 1230m, 1155m, 1135m, 1055m, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47, 1.49 (2s, 18H, 2*t*Bu), 1.30–2.08 (m, 7H, 3′-H_A, 4′-H_2, 2″-H_2, 3″-H_2), 2.22–2.39 (m, 1H, 3′-H_B), 3.27–3.41, 3.44–3.60, 3.61–3.80 (3m, 1H, 2H, 2H, 3-H_2, 1″-H, 4″-H_2), 3.73 (s, 3H, OMe), 3.94 (ddd, all $J_{vic} \approx$ 6.0 Hz, 1H, 5′-H), 4.34 (dd, J = 6.9, 6.9 Hz, 1H, 2′-H), 4.44 (m, 1H, 2′-H), 5.09 (m, 4H, 2CH_2-Ph), 5.53 (d, J = 7.4 Hz, 1H, NHZ), 6.06 (d, J = 7.2 Hz, 1H, NHZ), 7.15 (brs, 1H, N^{3}H), 7.22–7.30 (m, 10H, 2Ph), 8.34 (brs, 1H, N$^{1'''}$H), 11.49 (s, 1H, NHBoc); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 27.3, 27.6, 29.3 (C-3′, C-4′, C-2″, C-3″), 28.1 [C(CH_3)$_3$], 40.3, 40.8 (C-3, C-4″), 52.6 (OMe), 53.9, 54.5 (C-2, C-1″), 66.6, 66.9 (2CH_2-Ph), 78.7, 79.1 [C-2′, C(CH_3)$_3$], 82.9, 83.0 [C-5′, C(CH_3)$_3$], 127.9, 128.0, 128.4, 136.0, 136.4 (2Ph), 156.1, 156.3, 156.4 (2Z-CO, Boc-CO, C=N), 163.3 (Boc-CO), 170.5 (CONH), 174.1 (COO); $C_{40}H_{56}N_6O_{12}$ (812.91): calcd C 59.10, H 6.94, N 10.34; found C 58.86, H 7.47, N 10.11.

(2*S*,2′*R*,5′*R*,1″*S*)-3-[5′-(1″-Benzyloxycarbonylamino-4″-guanidino-butyl)-tetrahydrofuran-2′-carbamoyl]-2-benzyloxycarbonylamino propionic acid

(40, as trifluoroacetate): The preparation and purification was done as described for **38**. Starting from THF derivative **58** (35 mg, 0.043 mmol) **40** (14 mg, 46%) was obtained as a white solid after lyophylization. HPLC: $t_R = 19.5$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (300 MHz, CD_3CN): $\delta = 1.34-1.76$ (m, 5H, 2″-H_2, 3″-H_2, 4′-H_A), 1.80–1.92 (m, 2H, 3′-H_A, 4′-H_B), 2.15–2.27 (m, 1H, 3′-H_B), 3.05–3.17 (m, 2H, 4″-H_2)*, 3.43 (ddd, $J = 13.4$, 6.6, 6.6 Hz, 1H, 3-H_A), 3.51–3.69 (m, 2H, 3-H_B, 1″-H), 3.85–3.95 (m, 1H, 5′-H), 4.23–4.33 (m, 2H, 2-H, 2′-H), 5.06 (s, 4H, 2Ph-CH_2), 5.83 (d, $J = 9.4$ Hz, 1H, NHZ), 6.39 (d, $J = 7.5$ Hz, 1H, NHZ), 6.63 (br s, 4H, 2NH_2), 7.26–7.42 (m, 11H, 2 × Ph, NH), 7.60 (m, 1H, NH); the sample still contained approx. 10 mass-% water which was explicit substracted from the yield; *this signal was superimposed by the HOD signal. ^{13}C NMR (75 MHz, CD_3CN): $\delta = 25.5$, 28.4, 29.3, 30.6 (C-3′, C-4′, C-2″, C-3″), 41.4, 42.0 (C-3, C-4″), 54.4 (C-2, C-1″), 66.9, 67.2 (2CH_2-Ph), 79.5 (C-2′), 83.6 (C-5′), 128.5, 128.9, 129.0, 129.5 (Ph), 157.9 and 158.4 (C=N and Z-CO), 173.0 and 175.5; some CO-signals as well as the signal for C_q of Ph were not detected; HRMS (FAB): $[C_{29}H_{39}N_6O_8]^+$ calcd 599.2829; found 599.2865.

(2*S*,2′*S*,5′*S*,1″*S*)-2-Benzyloxycarbonylamino-3-[5′-(1″-*tert*-butoxycarbonylaminoethyl)-tetrahydrofuran-2′-carbamoyl] methyl propionate (64): The preparation was done analogous to amide **53** using the following amounts of substrate and reagents: carboxylic acid **63** (1.00 g, 3.86 mmol), amine hydrochloride **27** (1.10 g, 4.24 mmol), HOBt (886 mg, 5.78 mmol), Et-N(*i*Pr)$_2$ (0.74 mL, 0.55 g, 4.2 mmol), and EDC (799 mg, 4.17 mmol). The amide **64** (1.54 g, 81%) was obtained as a white foam. M.p. 53 °C; $R_f = 0.44$ (MTBE); $[\alpha]_D = -11.5$, $[\alpha]_{578} = -12.2$, $[\alpha]_{546} = -13.7$, $[\alpha]_{436} = -22.2$, $[\alpha]_{365} = -31.6$ ($c = 0.96$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3385$ br s, 3120m, 2980m (CH), 1715 br s (COOR), 1525s, 1455m, 1400s, 1365m, 1250m, 1170m, 1060m, 780w, 740w, 700w, 615w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 6.4$ Hz, 3H, 2″-H_3), 1.44 (s, 9H, *t*Bu), 1.71–1.78 (m, 1H, 4′-H_A), 1.81–1.89 (m, 2H, 3′-H_A, 4′-H_B), 2.24–2.39 (m, 1H, 3′-H_B), 3.50–3.82 (m, 6H, 3-H_2, 1″-H, OCH_3), 3.82–3.96 (m, 1H, 5′-H), 4.38 (t, $J =$ 6.9 Hz, 1H, 2′-H), 4.42 (m, 1H, 2-H), 4.64 (br s, 1H, NHBoc), 5.12 (s, 2H, CH_2-Ph), 5.80 (d, $J = 6.8$ Hz, 1H, NHZ), 7.07 (br s, 1H, N^{3}H), 7.28–7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.9$ (C-2″), 28.2 (C-4′), 28.4 [C(CH_3)$_3$], 30.2 (C-3′), 40.8 (C-3), approx. 49 (br, low intensity, C-1″), 52.8 (OCH_3), 54.4 (C-2), 67.1 (*C*H_2-Ph), 78.7 (C-2′), 79.4 [*C*(CH_3)$_3$], 83.4 (C-5′), 128.1, 128.3, 128.5, 136.0 (Ph), 155.7 (Z-CO, Boc-CO), 170.6 (CONH), 174.0 (COO); $C_{24}H_{35}N_3O_8$ (493.55): calcd C 58.41, H 7.15, N 8.51; found C 58.49, H 6.84, N 8.17.

(2*S*,2′*R*,5′*S*,1″*S*)-2-Benzyloxycarbonylamino-3-[5′-(1″-*tert*-butoxycarbonylaminoethyl)-tetrahydrofuran-2′-carbamoyl] methyl propionate (66): The preparation was done analogous to the preparation of amide **53** using the following amounts of substrate and reagents: carboxylic acid **65** (1.30 g, 5.00 mmol), amine hydrochloride **27** (1.59 g, 5.50 mmol), HOBt (1.15 g, 7.50 mmol), Et*N*(*i*Pr)$_2$ (0.96 mL, 0.71 g, 5.5 mmol), and EDC (1.01 g, 5.25 mmol) to yield amide **66** (2.07 g, 84%) as a white solid. M.p. 60 °C; $R_f = 0.44$ (MTBE); $[\alpha]_D = +29.8$, $[\alpha]_{578} = +31.1$, $[\alpha]_{546} = +35.5$, $[\alpha]_{436} = +61.8$, $[\alpha]_{365} = +101.6$ ($c = 1.03$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} =$ 3360 br s, 2980m (CH), 1725/1695s (4 × C=O), 1535s, 1455m, 1400m, 1365m, 1340m, 1250m, 1210m, 1170m, 1085m, 1060m, 775w, 700w, 610w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 5.4$ Hz, 3H, 2″-H_3), 1.41 (s, 9H, *t*Bu), superimposed by 1.30–1.55 (m, 1H, 4′-H_A), 1.82–1.95, 2.07–2.25 (m, 1H; m, 1H, 3′-H_A, 4′-H_B), 2.27–2.42 (m, 1H, 3′-H_B), 3.48–3.89 (m, 7H, 3-H_2, 5′-H, 1″-H, OCH_3), 4.38 (br d, $J = 8.0$ Hz, 1H, 2′-H), 4.48 (br s, 1H, 2-H), 5.00–5.19 (m, 3H, CH_2-Ph, NHBoc), 6.61 (d, $J = 7.0$ Hz, 1H, NHZ), 7.22–7.42 (m, 5H, Ph), 8.66 (br s, 1H, N^{3}H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.2$ (C-2″), 28.1 [C(CH_3)$_3$], 28.3 (C-4′), 31.1 (C-3′), 40.3 (C-3), 51.1 (C-1″), 52.1 (OCH_3), 55.0 (C-2), 66.5 (*C*H_2-Ph), 78.7 (C-2′), 79.5 [*C*(CH_3)$_3$], 85.9 (C-5′), 127.7, 127.8, 128.1, 136.2 (Ph), 156.1, 156.8 (Z-CO, Boc-CO), 170.6 (CONH), 175.2 (COO); $C_{24}H_{35}N_3O_8$ (493.55): calcd C 58.41, H 7.15, N 8.51; found C 58.38, H 7.05, N 8.25.

{*N*-(*tert*-Butoxycarbonyl)-glycyl}-{(2′*S*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino methyl propionate (67): The preparation was done analogous to amide **53** using the following amounts of substrate and reagents: crude deprotected amine **64** (422 mg, approx. 1.07 mmol), Boc-glycine (234 mg, 1.33 mmol), HOBt (298 mg, 1.95 mmol), EDC (255 mg, 1.54 mmol), and Et*N*(*i*Pr)$_2$ (0.21 mL, 0.16 g, 1.2 mmol). After CC (50 g, EtOAc followed by acetone/CH_2Cl_2 1:1) amide **67** (553 mg, 94%) was obtained as a white solid. M.p. 61 °C; $R_f = 0.06$ (EtOAc); $[\alpha]_D = -7.1$, $[\alpha]_{578} = -7.3$, $[\alpha]_{546} = -8.3$, $[\alpha]_{436} = -13.9$, $[\alpha]_{365} = -19.8$ ($c = 1.02$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3400$ br s, 2980w (CH), 1720s (COOR), 1665s, 1525s, 1455w, 1400s, 1370m, 1250m, 1230m, 1170m, 1050w, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.44 (s, 9H, *t*Bu), 1.52–1.67 (m, 1H, 4′-H_A), 1.80–2.02 (m, 2H, 3′-H_A, 4′-H_B), 2.31 (m, 1H, 3′-H_B), 3.46–3.60 (m, 1H, 3-H_A), 3.52–3.82 (m, 7H, 3-H_B, 5′-H, 2‴-H_2, OCH_3), 4.07 (m, 1H, 1″-H), 4.37 (t, $J = 7.3$ Hz, 1H, 2′-H), 4.51 (m, 1H, 2-H), 5.12 (s, 2H, CH_2-Ph), 5.30 (br s, NHBoc), 6.05 (br d, $J = 7.2$ Hz, 1H, NHZ), 6.44 (br d, $J = 8.5$ Hz, 1H, N$^{1''}$H), 7.22 (br s, 1H, N^{3}H), 7.28–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$ (C-2″), 28.2 [C(CH_3)$_3$], 28.6 (C-4′), 29.8 (C-3′), 41.0 (C-3), 44.5 (br C-2‴), 47.7 (C-1″), 52.8 (OCH_3), 54.2 (C-2), 67.1 (*C*H_2-Ph), 78.3 (C-2′), 80.3 [*C*(CH_3)$_3$], 83.0 (C-5′), 127.9, 128.3, 128.5, 135.9 (Ph), 156.3 (Z-CO, Boc-CO), 169.3, 170.6 (2 CONH), 173.9 (COO); $C_{26}H_{38}N_4O_9$ (550.60): calcd C 56.72, H 6.96, N 10.18; found C 56.20, H 7.22, N 10.40.

{2‴-Guanidino-acetyl}-{(2′*S*,5′*S*,1″*S*)-5′-(1″-amino-ethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino propionic acid} (59, as trifluoroacetate) via guanylation and deprotection: The guanylation was done analogous to the guanidine derivatives **55**/**56** using the following amounts of substrate and reagents: Boc-protected amine **67** (523 mg, 0.950 mmol), TFA (3 mL); then isothiourea **54** (296 mg, 1.02 mmol), NEt_3 (0.40 mL, 0.29 g, 2.9 mmol), and $HgCl_2$ (290 mg, 1.07 mmol). CC (2 × 40 g, EtOAc) gave the corresponding guanidine derivative (615 mg, 93% based on **67**) as a white solid. M.p. 90–92 °C; $R_f = 0.32$ (EtOAc); $[\alpha]_D = -6.4$, $[\alpha]_{578} = -6.6$, $[\alpha]_{546} = -7.6$, $[\alpha]_{436} = -12.7$, $[\alpha]_{365} = -17.2$ ($c = 0.86$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3100-3400$s, 2980m (CH), 1725s (COOR), 1645s, 1620s, 1530m, 1400s, 1370m, 1310s, 1255m, 1230m, 1145s, 1100m, 1060w, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.47, 1.50 (2s, 18H, 2*t*Bu), approx. 1.47–1.73 (m, 1H, 4′-H_A), 1.82–2.00 (m, 2H, 3′-H_A, 4′-H_B), 2.19–2.38 (m, 1H, 3′-H_B), 3.50–3.83 (m, 5H, 3-H_2, OCH_3), 3.89 (m, 1H, 5′-H), 3.98–4.11 (m, 3H, 1″-H, 2‴-H_2), 4.38 (t, $J = 7.2$ Hz, 1H, 2′-H), 4.47 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 5.92 (d, $J = 7.2$ Hz, 1H, NHZ), 6.61 (d, $J = 8.7$ Hz, 1H, N$^{1''}$H), 7.16 (m, 1H, N^{3}H), 7.30–7.38 (m, 5H, Ph), 8.91 (m, 1H, N$^{1'''}$H), 11.37 (s, 1H, NHBoc); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$ (C-2″), 27.9, 28.1 [2 C(*C*H_3)$_3$, C-4′], 30.0 (C-3′), 41.0 (C-3), 44.8 (C-2‴), 47.6 (C-1″), 52.8 (OCH_3), 54.2 (C-2), 67.1 (*C*H_2-Ph), 78.6, 82.8 [2 *C*(CH_3)$_3$], 79.5 (C-2′), 83.5 (C-5′), 127.9, 128.2, 128.5, 135.9 (Ph), 152.7 (C=N), 156.1 (Z-CO, Boc-CO), 162.9 (Boc-CO), 168.0, 170.5 (2 CONH), 173.8 (COO); $C_{32}H_{48}N_6O_{11}$ (692.76): calcd C 55.48, H 6.98, N 12.13; found C 55.38, H 7.12, N 11.54. The deprotection was done analogous to amide **14** starting from the corresponding guanidine derivative (300 mg, 0.433 mmol). After purification by preparative HPLC (6 runs, 21 mm ID, Rainin, RP 18, 21.6 mL min^{-1}, 20% to 40% B within 20 min A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) and lyophylization the trifluoracetate of **59** (155 mg, 60%) was obtained as a white solid. HPLC: $t_R =$ 9.3 min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); IR (neat): $\tilde{\nu} = 2800-$ 3700s (NH; COOH), 1660 br s (C=O, C=N), 1535m, 1400m, 1205m, 1135m, 1070w, 725w, 700w; ^{1}H NMR (300 MHz, CD_3CN): $\delta = 1.06$ (br d, $J = 6.4$ Hz, 3H, 2″-H_3), 1.42–1.60 (m, 1H, 4′-H_A), 1.69–1.89 (m, 2H, 3′-H_A, 4′-H_B), 2.09–2.23 (m, 1H, 3′-H_B), 3.40–3.64 (m, 2H, 3-H_2), 3.79–3.99 (m, 4H, 5′-H, 1″-H, 2‴-H_2), 4.20–4.35 (m, 2H, 2-H, 2′-H), 5.01 (s, 2H, CH_2-Ph), 6.45 (d, $J = 7.5$ Hz, 1H, NHZ), 6.71 (br s, 4H*, two exchangeable H's), 7.04–7.33 (m, 7H, N$^{1''}$H, N$^{1''''}$H, Ph), 7.54 (br s, 1H, N^{3}H), 9.30 (br s, 3H, three exchangeable H's); *this integral size was too large because the sample contained approx. 1 equiv water. ^{13}C NMR (75 MHz, CD_3CN): $\delta =$ 17.7 (C-2″), 28.9 (C-4′), 31.1 (C-3′), 40.9 (C-3), 45.0 (C-2‴), 49.3 (C-1″), 55.0 (C-2), 67.4 (CH_2-Ph), 79.1 (C-2′), 83.6 (C-5′), 128.6, 128.9, 129.4, 137.6 (Ph), 157.4, 158.7 (Z-CO, C=N), 168.4, 172.9 (2 CONH), 176.1 (COO); ESI-MS: $[C_{22}H_{33}N_6O_7]^+$ calcd 479.23; found 479.19.

{3‴-[*N*$^{2''''}$,*N*$^{3''''}$-Bis-(*tert*-Butoxycarbonyl)-guanidino]-propionyl}-{(2′*S*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino methyl propionate} (68): A solution of dipeptide **64** (305 mg, 0.608 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (0.5 mL). After 4 h at room temperature the solvents were removed in vacuo and the residue was codistilled with toluene (2 × 5 mL). Sat. aqueous $NaHCO_3$ (6 mL) was added and extraction with EtOAc (2 × 15 mL) followed. The organic layer was washed with sat. aqueous NaCl (10 mL) and dried with Na_2SO_4. After removal of the solvent in vacuo, the free amine (240 mg, approx. 0.61 mmol) remained as slightly brownish oil which was used without further purification. The crude amine, carboxylic acid **69**

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b (303 mg, 0.914 mmol) and HOBt (184 mg, 1.20 mmol) were dissolved in THF (5 mL) and EDC (176 mg, 0.918 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature within 3 h. After additional 2 h $EtN(iPr)_2$ (0.11 mL, 79 mg, 0.61 mmol) was added. The solution was stirred for an additional hour and then the solvent was removed in vacuo. The residue was dissolved in EtOAc (20 mL). After successive washings with 5% aqueous citric acid (5 mL), sat. aqueous $NaHCO_3$ (5 mL), and sat. aqueous NaCl (10 mL) the organic layer was dried with Na_2SO_4. Removal of the solvent in vacuo and CC (30 g, EtOAc) afforded amide **68** (325 mg, 75% based on **64**) as a white solid. M.p. 78–82 °C; $R_f = 0.24$ (EtOAc); $[\alpha]_D = -6.6$, $[\alpha]_{578} = -6.9$, $[\alpha]_{546} = -7.8$, $[\alpha]_{436} = -12.6$, $[\alpha]_{365} = -16.6$ ($c = 1.07$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3100$–3400 brs, 2980w (CH), 1725s (COOR), 1640s, 1530m, 1400s, 1365m, 1330m, 1255m, 1230m, 1155m, 1135m, 1090w, 1060w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.48, 1.49 (2s, 18H, 2*t*Bu), approx. 1.52–1.66 (m, 1H, 4′-H_A), 1.82–1.98 (m, 2H, 3′-H_A, 4′-H_B), 2.23–2.37 (m, 1H, 3′-H_B), 2.48 (t, $J = 6.7$ Hz, 2H, 2‴-H_2), 3.52–3.82 (m, 7H, 3-H_2, 3‴-H_2, OCH_3), 3.88 (m, 1H, 5′-H), 4.00–4.12 (m, 1H, 1″-H), 4.36 (t, $J = 7.2$ Hz, 1H, 2′-H), 4.48 (br dd, $J = 10.9$ and 7.2 Hz, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 5.93 (d, $J = 7.2$ Hz, 1H, NHZ), 6.34 (d, $J = 8.3$ Hz, 1H, N$^{1''}$H), 7.18 (m, 1H, N^{3}H), 7.30–7.38 (m, 5H, Ph), 8.72 (t, $J = 5.9$ Hz, 1H, N$^{1'''''}$H), 11.44 (s, 1H, NHBoc); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$ (C-2″), 28.0, 28.2 [2C(CH_3)$_3$], 28.4 (C-4′), 30.1 (C-3′), 36.2, 36.8 (C-2‴, C-3‴), 41.0 (C-3), 47.7 (C-1″), 52.8 (OCH_3), 54.2 (C-2), 67.1 (CH_2Ph), 78.4, 82.8 [2C(CH_3)$_3$], 79.3 (C-2′), 83.2 (C-5′), 128.0, 128.2, 128.5, 135.9 (Ph), 152.8 (C=N), 156.3 (Z-CO, Boc-CO), 163.4 (Boc-CO), 170.5 (2CONH), 173.9 (COO); ESI-MS: $[C_{33}H_{50}N_6O_{11}+H]^+$ calcd 707.36; found 707.35.

{3‴-Guanidino-propionyl}-{(2′*S*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino propionic acid} (61, as a trifluoroacetate): The preparation was done analogous to amide **14** starting from tripeptide **68** (95 mg, 0.13 mmol). After purification by preparative HPLC (3 runs, 21 mm ID, Rainin, RP 18, 21.6 mL min^{-1}, 20% to 40% B within 20 min A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) and lyophylization the trifluoracetate of **61** (59 mg, 72%) was obtained as a white solid. HPLC: $t_R = 9.2$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); IR (neat): $\tilde{\nu} = 2800$–3700s (NH, COOH), 1660 brs (C=O, C=N), 1535m, 1400m, 1205m, 1135m, 1070w, 720w, 700w; ^{1}H NMR (600 MHz, CD_3CN): $\delta = 1.08$ (d, $J = 7.5$ Hz, 3H, 2″-H_3), 1.51–1.60 (m, 1H, 4′-H_A), 1.78–1.88 (m, 2H, 3′-H_A, 4′-H_B), 2.16–2.23 (m, 1H, 3′-H_B), 2.38–2.48 (m, 2H, 2‴-H_2), 3.33–3.45 (m, 2H, 3‴-H_2), AB signal ($\delta_A = 3.51$, $\delta_B = 3.59$, $J_{AB} = 14.0$ Hz, additionally split by $J_A = 5.1$, 5.1 Hz, $J_B = 7.0$, 7.0 Hz, 2H, 3-H_2), 3.89–3.97 (m, 2H, 5′-H, 1″-H), 4.25 (dt, $J = 7.2$, 5.0 Hz, 1H, 2-H), 4.32 (dd, $J = 7.6$, 7.6 Hz, 1H, 2′-H), 5.07 (s, 2H, CH_2-Ph), 5.40 (brs, 2H*, NH/COOH), 6.65 (d, $J = 7.5$ Hz, 1H, NHZ), 7.03 (brs, 4H*, NH/COOH), 7.10 (d, $J = 8.0$ Hz, 1H, N$^{1''}$H), 7.30–7.38 (m, 5H, Ph), 7.51 (t, $J = 6.0$ Hz, 1H, N^{3}H), 7.68 (t, $J = 5.8$ Hz, 1H, N$^{1''''}$H); *these integrals sizes were slightly too large because the sample contained approx. 0.5 equiv water; ^{13}C NMR (75 MHz, CD_3CN): $\delta = 18.0$ (C-2″), 28.9 (C-4′), 31.1 (C-3′), 36.2 (C-2‴), 38.7 (C-3‴), 40.8 (C-3), 49.0 (C-1″), 55.6 (C-2), 67.2 (CH_2-Ph), 79.4 (C-2′), 83.7 (C-5′), 128.9, 129.1, 129.5, 138.0 (Ph), 157.3, 159.0 (Z-CO, C=N), 172.1, 173.3 (2CONH), 175.4 (COO); HRMS (FAB): $[C_{22}H_{33}N_6O_7]^+$ calcd 493.2411; found 493.2411.

{*N*-(*tert*-Butoxycarbonyl)-glycyl}-{(2′*R*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino methyl propionate} (71): The preparation was done as described for amide **53** using the following amounts of substrate and reagents: crude deprotected amine **66** (310 mg, approx. 0.788 mmol), Boc-glycine (160 mg, 0.913 mmol), HOBt (199 mg, 1.30 mmol), EDC (171 mg, 0.89 mmol), and $EtN(iPr)_2$ (0.14 mL, 0.11 g, 0.81 mmol). After CC (50 g, EtOAc followed by acetone/CH_2Cl_2 1:1) the amide **71** (350 mg, 81%) was obtained as a white solid. M.p. 63 °C; $R_f = 0.06$ (EtOAc); $[\alpha]_D = +71.3$, $[\alpha]_{578} = +75.2$, $[\alpha]_{546} = +85.6$, $[\alpha]_{436} = +151.5$, $[\alpha]_{365} = +253.4$ ($c = 1.08$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3315$ brs, 2980m (CH), 1720s (COOR), 1660s, 1530s, 1455w, 1395m, 1365m, 1250m, 1170m, 1075w, 740w, 700w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.44 (s, 9H, *t*Bu), superimposed by 1.40–1.60 (m, 1H, 4′-H_A), 1.87–2.02 (m, 1H, 4′-H_B), 2.13–2.33 (m, 2H, 3′-H_2), 3.54–4.06 (m, 9H, 3-H_2, 5′-H, 1″-H, 2‴-H_2, OCH_3), 4.32 (dd, $J = 7.9$, 3.8 Hz, 1H, 2′-H), 4.51 (m, 1H, 2-H), 5.13 (s, 2H, CH_2-Ph), 5.39 (brs, 1H, NHBoc), 6.51–6.68 (m, 1H, N$^{1''}$H), 7.01 (d, $J = 7.2$ Hz, 1H, NHZ), 7.28–7.40 (m, 5H, Ph), 8.33 (brs, 1H, N^{3}H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.2$ (C-2″), 28.2 [C(CH_3)$_3$], 28.6 (C-4′), 30.7 (C-3′), 40.6 (C-3), 44.6 (br C-2‴), 50.0 (C-1″), 52.4 (OCH_3), 54.7 (C-2), 66.8 (CH_2-Ph), 78.8 (C-2′), 85.1 (C-5′), 128.0, 128.4, 136.4 (Ph), 156.5 (Z-CO, Boc-CO), 171.0 (2CONH), 174.4 (COO); the signal for [C(CH_3)$_3$] was not detected.

{2‴-Guanidino-acetyl}-{(2′*R*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino propionic acid} (60, as a trifluoroacetate) via guanylation and deprotection: The guanylation was done as described for the guanidine derivatives **55**/**56** using the following amounts of substrate and reagents: Boc-protected amine **71** (321 mg, 0.583 mmol), TFA (2 mL); then isothiourea **54** (182 mg, 0.627 mmol), NEt_3 (0.25 mL, 0.18 g, 1.8 mmol), and $HgCl_2$ (188 mg, 0.692 mmol). CC (30 g, EtOAc) gave the corresponding guanidine derivative (350 mg, 87% based on **71**) as a colorless solid. M.p. 86–87 °C; $R_f = 0.34$ (EtOAc); $[\alpha]_D = +59.4$, $[\alpha]_{578} = +62.0$, $[\alpha]_{546} = +71.3$, $[\alpha]_{436} = +128.6$, $[\alpha]_{365} = +220.1$ ($c = 0.96$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3100$–3400m, 2980w (CH), 1725s (COOR), 1645s, 1550m, 1400s, 1370m, 1310m, 1230m, 1145s, 1095w, 1060w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.48, 1.50 (2s, 18H, 2*t*Bu), superimposed by 1.45–1.55 (m, 1H, 4′-H_A), 1.88–2.01 (m, 1H, 4′-H_B), 2.04–2.34 (m, 2H, 3′-H_2), 3.72 (s, 3H, OCH_3), 4.00 (d, $J = 5.5$ Hz, 2H, 2‴-H_2), superimposed by 3.62–4.07 (m, 4H, 3-H_2, 5′-H, 1″-H), 4.34 (dd, $J = 8.3$, 3.4 Hz, 1H, 2′-H), 4.49 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 6.93 (d, $J = 7.4$ Hz, 1H, NHZ), 7.25–7.38 (m, 5H, Ph), 7.65 (d, $J = 9.2$ Hz, 1H, N$^{1''}$H), 8.48 (br t, $J = 5.9$ Hz, 1H, N^{3}H), 8.82 (br t, $J = 5.4$ Hz, 1H, N$^{2'''}$H), 11.30 (s, 1H, NHBoc); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.1$ (C-2″), 28.0, 28.2 [2C(CH_3)$_3$], 28.6 (C-4′), 30.7 (C-3′), 40.6 (C-3), 45.3 (C-2‴), 50.1 (C-1″), 52.4 (OCH_3), 54.9 (C-2), 66.8 (CH_2-Ph), 78.9 (C-2′), 79.5, 83.6 [2C(CH_3)$_3$], 85.3 (C-5′), 127.9, 128.0, 128.4, 136.5 (Ph), 152.6 (C=N), 156.4, 156.5 (Z-CO, Boc-CO), 162.6 (Boc-CO), 169.9, 170.9 (2CONH), 174.7 (COO); $C_{32}H_{48}N_6O_{11}$ (692.76): calcd C 55.48, H 6.98, N 12.13; found C 55.26, H 7.14, N 12.15. The deprotection was done analogous to amide **14** starting from the corresponding guanidine derivative (210 mg, 0.303 mmol). After purification by preparative HPLC (5 runs, 21 mm ID, Rainin, RP 18, 21.6 mL min^{-1}, 20% to 40% B within 20 min A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) and lyophylization trifluoracetate of **60** (121 mg, 67%) was obtained as a white solid. HPLC: $t_R = 10.9$ min (Rainin, RP 18, 1 mL min^{-1}, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); IR (neat): $\tilde{\nu} = 2800$–3700s (NH; COOH), 1665 brs (C=O, C=N), 1550m, 1400m, 1345m, 1205s, 1135s, 1070m, 1030w, 720w, 700w; ^{1}H NMR (300 MHz, CD_3CN): $\delta = 1.07$ (d, $J = 6.4$ Hz, 3H, 2″-H_3), 1.39–1.51 (m, 1H, 4′-H_A), 1.82–1.97 (m, 1H, 4′-H_B), 1.99–2.25 (m, 2H, 3′-H_2), 3.49–4.11 (m, 6H, 3-H_2, 5′-H, 1″-H, 2‴-H_2), 4.20–4.37 (m, 1H, 2′-H), 4.38–4.52 (m, 1H, 2-H), 5.06 (s, 2H, CH_2-Ph), 6.83 (brs, 4H*, 4 exchangeable H's), 7.20–7.46 (m, 6H, Ph, N$^{1''''}$H), 7.58 (d, $J = 8.3$ Hz, 1H, N$^{1''}$H), 8.30 (brs, 1H, N^{3}H), 8.73 (brs, 2H*, 1 exchangeable H); *these integrals sizes were too large because the sample contained some water; ^{13}C NMR (75 MHz, CD_3CN): $\delta = 17.2$ (C-2″), 28.8 (C-4′), 31.3 (C- 3′), 41.1 (C-3), 45.1 (C-2‴), 50.9 (C-1″), 55.0 (C-2), 67.4 (CH_2-Ph), 79.2 (C-2′), 85.6 (C-5′), 128.5, 128.9, 129.1, 137.6 (Ph), 157.5, 158.3 (Z-CO, C=N), 169.3, 173.2 (2CONH), 176.3 (COO); ESI-MS: $[C_{22}H_{33}N_6O_7]^+$ calcd 479.23; found 479.19.

{3‴-[*N*$^{2''''}$,*N*$^{3''''}$-Bis-(*tert*-butoxycarbonyl)-guanidino]-propionyl}-{(2′*R*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino methyl propionate} (72): The Boc deprotection was done analogous to the deprotection of **64** using protected amine **66** (300 mg, 0.608 mmol) as starting material. The deprotected amine (230 mg, approx. 0.58 mmol) remained as slightly brownish oil which was used without further purification. The peptide coupling was performed according to the procedure described for the preparation of **53** without using Hünig's base: carboxylic acid **69b** (211 mg, 0.664 mmol), HOBt (133 mg, 0.869 mmol), and EDC (123 mg, 0.642 mmol). After CC [25 g, CH_2Cl_2/PE 1:1 (200 mL) followed by EtOAc] amide **72** (145 mg, 35% based on **66**) was obtained as a white solid. As a major severe side reaction, acid **69b** cyclized to a six-membered heterocycle **70** [60 mg, 29%; NMR, IR, MS, $R_f = 0.58$ (MTBE)]. Amide **72**: m.p. 91–93 °C; $R_f = 0.25$ (EtOAc); $[\alpha]_D = +44.8$, $[\alpha]_{578} = +47.1$, $[\alpha]_{546} = +53.6$, $[\alpha]_{436} = +95.9$, $[\alpha]_{365} = +161.8$ ($c = 1.16$, $CHCl_3$, $T = 20$ °C); IR (KBr): $\tilde{\nu} = 3100$–3400m, 2980w (CH), 1725 brs (COOR), 1640s, 1560m, 1400m, 1370m, 1330m, 1255w, 1230w, 1155m, 1060w; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (d, $J = 6.4$ Hz, 3H, 2″-H_3), 1.48, 1.49 (2s, 18H, 2*t*Bu), 1.45–1.55 (m, 1H, 4′-H_A), 1.85–1.99 (m, 1H, 4′-H_B), 2.09–2.38 (m, 2H, 3′-H_2), 2.49 (brs, 2H, 2‴-H_2), 3.55–3.81 (m, 7H, 3-H_A, 5′-H, 3‴-H_2, OCH_3), 3.86–4.08 (m, 2H, 3-H_B, 1″-H), 4.33 (br d,

$J = 8.3$ Hz, 1H, 2′-H), 4.47 (m, 1H, 2-H), 5.11 (s, 2H, CH_2-Ph), 6.97 (br d, $J = 9.0$ Hz, 1H, N$^{1''}$H), 7.17 (br d, $J = 7.5$ Hz, 1H, NHZ), 7.26 – 7.38 (m, 5H, Ph), 8.59 (br t, $J = 7.5$ Hz, 1H, N^{3}H), 8.66 (br t, $J = 7.7$ Hz, 1H, N$^{1''''}$H), 11.44 (s, 1H, NHBoc); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.0$ (C-2″), 28.0, 28.3 [2C(CH_3)$_3$], 28.6 (C-4′), 30.8 (C-3′), 36.6, 36.7 (C-2‴, C-3‴), 40.4 (C-3), 50.3 (C-1″), 52.3 (OCH_3), 55.0 (C-2), 66.7 (CH_2-Ph), 78.9 (C-2′), 79.5, 83.3 [2C(CH_3)$_3$], 85.3 (C-5′), 128.0, 128.1, 128.4, 136.5 (Ph), 152.8 (C=N), 156.5 (Z-CO, Boc-CO), 163.2 (Boc-CO), 171.0, 172.4 (2CONH), 174.7 (COO); ESI-MS: $[C_{33}H_{50}N_6O_{11}+H]^+$ calcd 707.36; found 707.35.

{3‴-Guanidino-propionyl}-{(2′*R*,5′*S*,1″*S*)-5′-(1″-aminoethyl)-tetrahydrofuran-2′-carbonyl}-{(2*S*)-3-amino-2-benzyloxycarbonylamino propionic acid} (62, as trifluoroacetate): The preparation was done analogous to amide **14** starting from tripeptide **72** (115 mg, 0.16 mmol). After purification by preparative HPLC (3 runs, 21 mm ID, Rainin, RP 18, 21.6 mL min^{-1}, 20% to 40% B within 20 min A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) and lyophylization trifluoracetate of **62** (78 mg, 79%) was obtained as a white solid. HPLC: $t_R = 9.6$ min (Rainin, RP 18, 1 mL min, 20% to 60% B within 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA); ^{1}H NMR (600 MHz, CD_3CN): $\delta = 1.02$ (d, $J = 6.8$ Hz, 3H, 2″-H_3), 1.40 (dddd, all $J \approx 10$ Hz, 1H, 4′-H_A), 1.90 – 1.95 (m, 1H, 4′-H_B), 2.08 – 2.20 (m, 2H, 3′-H_2), 2.38 – 2.54 (m, 2H, 2‴-H_2), 3.27 – 3.36 (m, 1H, 3‴-H_A), 3.38 – 3.44 (m, 1H, 3‴-H_B), 3.47 (ddd, $J = 14.0$, 3.9 and 3.9 Hz, 2H, 3-H_A), 3.70 (ddd, $J = 9.0$, 9.0, 5.9 Hz, 5′-H), 3.86 – 3.95 (m, 2H, 3-H_B, 1″-H), 4.27 (dd, $J = 8.5$, 2.4 Hz, 1H, 2′-H), 4.40 (m, 1H, 2-H), AB signal ($\delta_A = 5.05$, $\delta_B = 5.09$, $J_{AB} = 12.4$ Hz, 2H, CH_2-Ph), 5.67 (br s, 4H*, exchangeable H′s), 6.70 (br s, 4H*, exchangeable H′s), 7.12 – 7.38 (m, 8H, N$^{1''}$H, NHZ, N$^{3'''}$-H, Ph), 8.49 (br dd, $J = 7.3$, 4.2, 1H, N^{3}H); *these integrals sizes were too large because the sample contained approx. 1.5 equiv water; in addition a second conformer/rotamer (approx. 10 mol-%) was detected, but these signals were not reported above. ^{13}C NMR (75 MHz, CD_3CN): $\delta = 16.9$ (C-2″), 28.8 (C-4′), 31.3 (C-3′), 35.6 (C-2‴), 38.3 (C-3‴), 40.9 (C-3), 51.0 (C-1″), 55.2 (C-2), 67.2 (CH_2-Ph), 79.2 (C-2′), 86.1 (C-5′), 128.6, 128.8, 129.0, 137.6 (Ph), 157.3, 158.2 (Z-CO, C=N), 173.1, 173.6 (2CONH), 176.1 (COO); HRMS (FAB): $[C_{22}H_{33}N_6O_7]^+$ calcd 493.2411; found 493.2415.

Molecular modeling studies: All THF-RGD mimics were investigated by the following molecular modeling method:[40] One hundred stable conformers were generated for each compound by 500 ps molecular dynamics calculation at 900 K, subsequent annealing to 300 K, and energy minimization using the CFF91 forcefield of Discover (Molecular Simulation Inc., San Diego, CA). To avoid overestimation of the electrostatic effect, we adopted a distance dependent dielectric constant $4 \times R$ and assumed that the Asp and Arg surrogates were not charged. All molecular modeling was performed on a Silicon Graphics Octane computer using InsightII/Discover (Molecular Simulation Inc.). All calculated conformers with an enthalpy of less than 8 kcal mol^{-1} above the minimum conformer were used for the calculation of the individual conformer population according to a Boltzmann distribution ($T = 298$ K).

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[41] Experimental details for the binding assays are given in ref. [6c].

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