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Synthesis and Biological Evaluation of Dianhydrohexitol Integrin Antagonists

Frank Osterkamp,[a)] Hermut Wehlan,[a)] Ulrich Koert[a)]*,
Matthias Wiesner,[b)] Peter Raddatz,[b)] and Simon L. Goodman[b)]

Institut für Chemie der Humboldt-Universität zu Berlin[a]
Hessische Straße 1-2, D-10115 Berlin, Germany

Merck KGaA Preclinical Research[b]
Frankfurter Straße 250, D-64271 Darmstadt, Germany

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Abstract: The synthesis of a series of RGD mimetics is described. All compounds have a 1,4:3,6-dianhydrohexitol core, a variable linker to a guanidino group, and a serine ether to mimic the carboxylic acid. Two types of linkers were combined with 1,4:3,6-dianhydro-D-sorbitol (**1** - **4**) and with 1,4:3,6-dianhydro-L-iditol (**5**). The five compounds were tested as potential integrin antagonists in a receptor binding assay ($\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$ type). Receptor binding activities in the μmol range were observed.

Keywords: integrin antagonist, peptidomimetics, synthesis-design, 1,4:3,6-dianhydrohexitol.

Introduction

Integrins are a class of cell surface proteins who controll cell-cell and cell-matrix adhesion processes. [1] These cell surface receptors consist 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). Two classes of integrins have gained particular importance: the $\alpha_v\beta_3$ integrin and the $\alpha_{IIb}\beta_3$ integrin (also called GPIIb/IIIa). The $\alpha_v\beta_3$ integrin binds the natural ligands fibrinogen and vitronectin and is involved in angiogenesis, platelet aggregation and tumor growth. [2] $\alpha_v\beta_3$-Antagonists are promising drug candidates for different diseases such as cancer,

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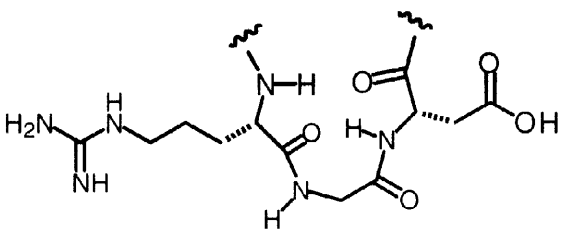
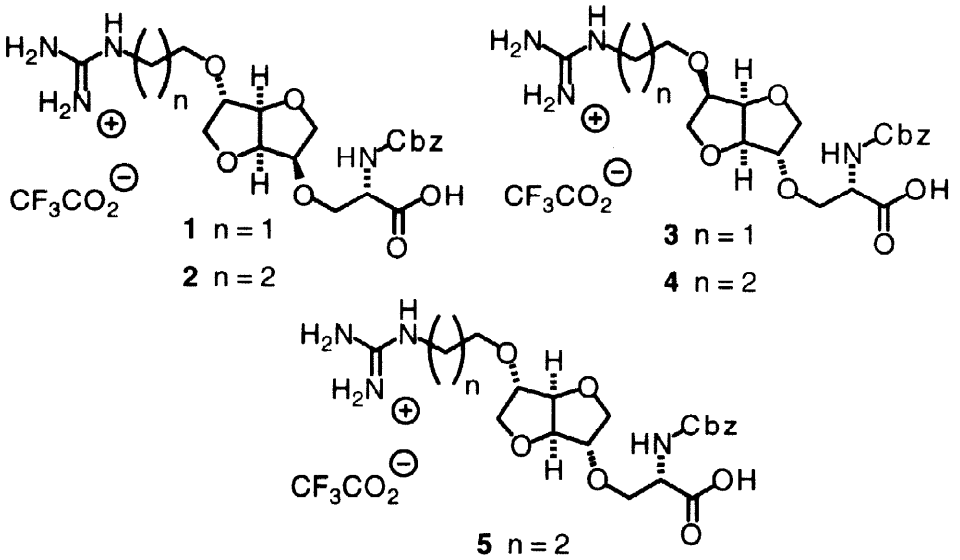
osteoporosis and diabetic retinopathy. The $\alpha_{IIb}\beta_3$ integrin is involved in blood platelet aggregation and its blocking has been investigated in the context of thrombosis therapy. [3] A common motif for the ligands found in the adhesive interactions with the $\alpha_{IIb}\beta_3$ and the $\alpha_v\beta_3$ type integrins is the RGD sequence.



R G D

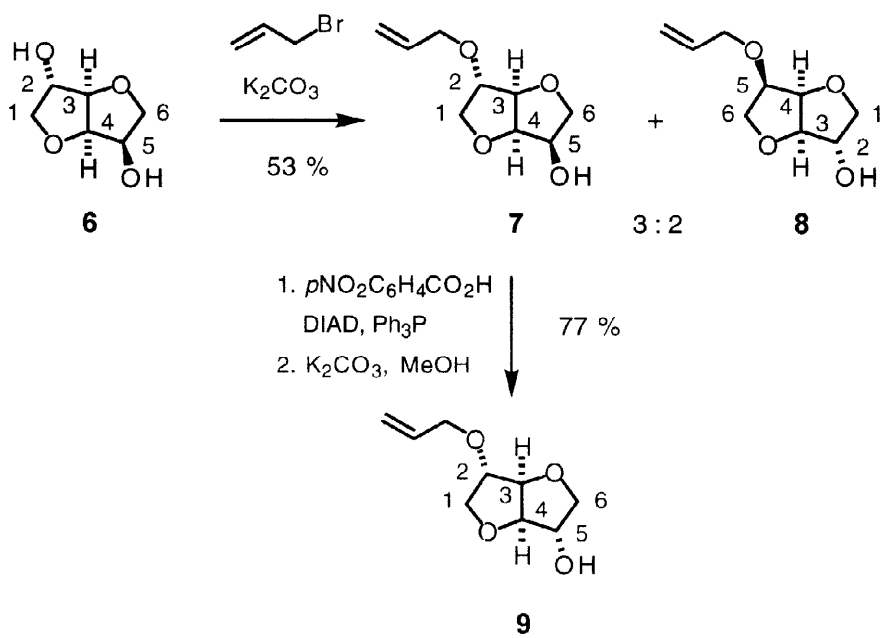
Intensive efforts have been made to discover selective $\alpha_{IIb}\beta_3$ and the $\alpha_v\beta_3$ type antagonists by structural variation of the RGD theme. [4,5] From the work with cyclic RGD peptides [6] it was found, that very potent $\alpha_v\beta_3$ type antagonists display a "glycine centered in a γ turn" conformation, while the most active $\alpha_{IIb}\beta_3$ inhibitors exhibit a "turn-extended-turn" conformation with a C^{α}_{Arg}-C^{α}_{Asp} distance of greater than 6.8 Å. [3] Highly potent non-peptide $\alpha_v\beta_3$ [7] antagonists and $\alpha_{IIb}\beta_3$ inhibitors [8] are presently in drug development.

In this paper we report the synthesis and biological evaluation of a series of RGD mimetics containing a 1,4:3,6-dianhydrohexitol as the central scaffold. The dianhydrohexitol unit is used as a template for organic nitrates in cardiovascular therapy. [9] In addition, its application as chiral template for asymmetric catalysis has been reported. [10] The good access to 1,4:3,6-dianhydrohexitols with different absolute and relative configuration led us to explore the scope of these compounds in RGD-mimetics. The 1,4:3,6-dianhydro derivatives of D-sorbitol and L-iditol were selected. The serine ether side chain had been shown to be a useful ligation of the carboxylic acid group of the RGD-motif. Therefore, we decided to work with this ligation. In attaching the guanidino function, it seemed reasonable to vary the length of the linker. With these premises five target structures resulted: compounds **1 - 4** from the D-sorbitol series and compound **5** from the L-iditol series.



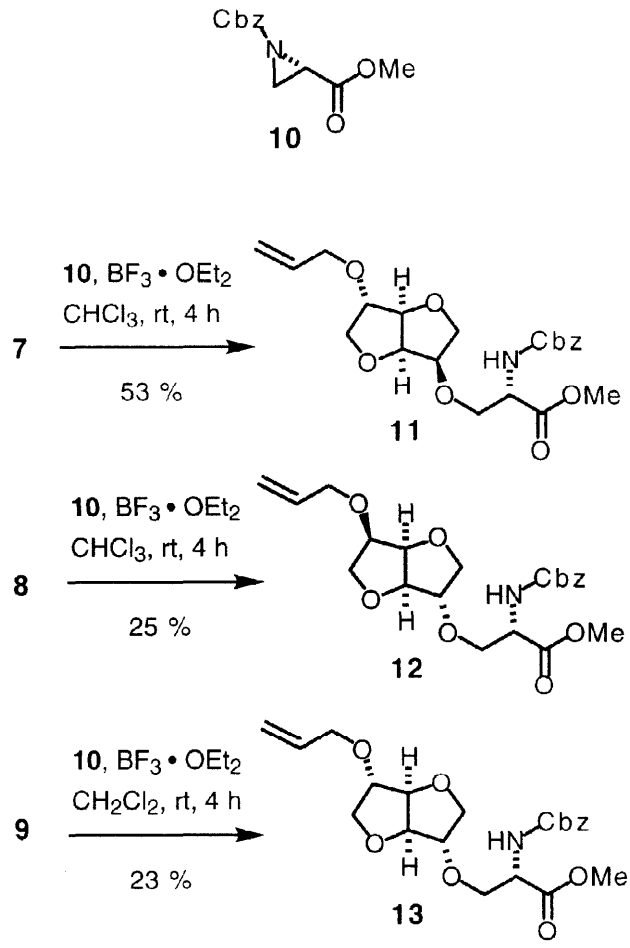
Results and Discussion

Synthesis: Starting point for the synthesis was isosorbit (1,4:3,6-dianhydro-D-sorbitol) **6**, which was converted into a 3:2 mixture of the two allyl ethers **7** and **8**. [11] The two allyl ethers could be separated by fractional distillation and were accessible in multigram scale. A Mitsunobu inversion of the secondary hydroxy group in **7** delivered compound **9** with the L-iditol configuration. [12]

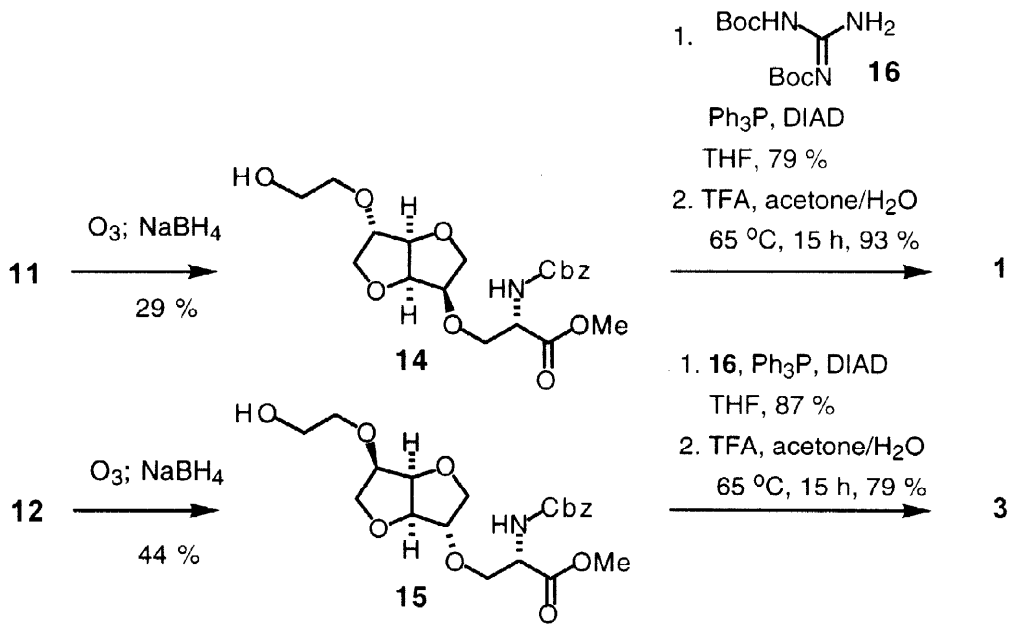


6 **7** **8** **9**

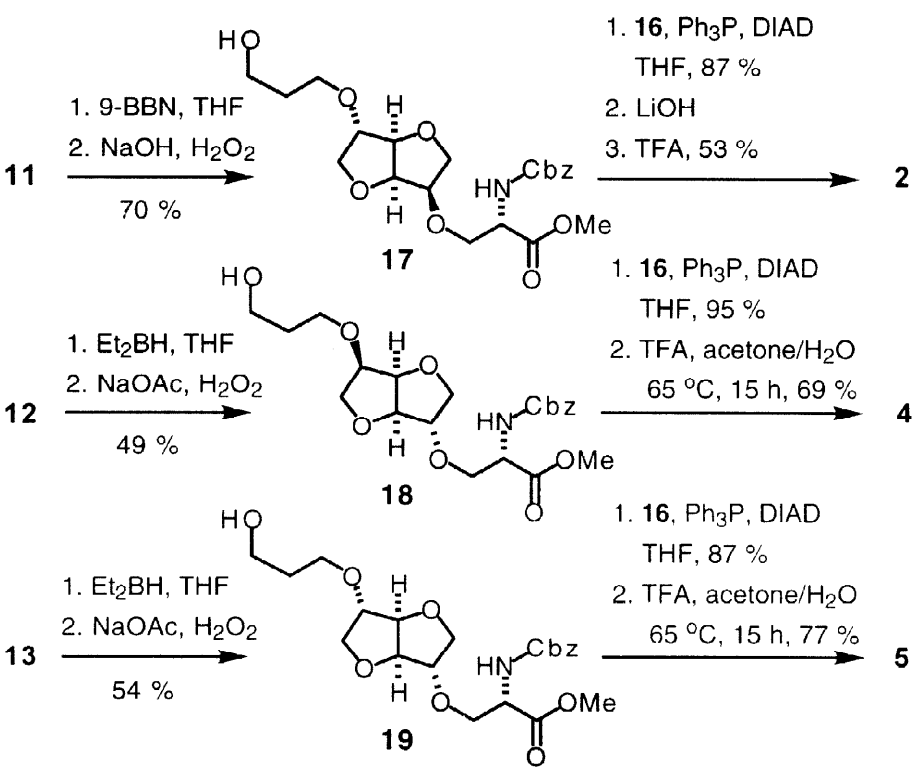
The serine-ether side chain was introduced by a Lewis-acid catalysed reaction of the aziridine **10** with the secondary alcohols **7**, **8** and **9**. [13] The N-Boc protected aziridine **10** was prepared from L-serine methyl ester according to literature procedures. [14] The regioselective opening of the aziridine gave rise to the products **11**, **12** and **13**. The yields of these reactions were only modest, even when an excess (5 equiv.) of alcohol was used. [15] One side reaction was the attack of the OH group on the Cbz group resulting in a benzyl ether formation.



Ozonolysis of the allyl ether in compounds **11** and **12** followed by reductive workup with sodium boron hydride gave the two primary alcohols **14** and **15**. The primary OH group was converted into a N-Boc-protected guanidino function with the guanidine reagent **16** under Mitsunobu conditions. [16] After acidic deprotection of the N-Boc groups and hydrolysis of the methyl esters the two dianhydrohexitol-RGD mimetics **1** and **3** which were obtained as TFA salts.



Hydroboration of **11**, **12** and **13** gave the three primary alcohols **17**, **18** and **19**. The three alcohols were transformed into the corresponding N-Boc-protected guanidine derivatives as described above. N-Boc-deprotection und hydrolysis of the methylesters resulted in the three dianhydrohexitol-RGD mimetics **2**, **4** and **5** which were obtained as TFA salts.



Biological evaluation:

The five RGD mimetics **1-5** were tested in a receptor binding assay for their biological activity. Activities in the micromolar range on $\alpha_{IIb}\beta_3$ or on $\alpha_v\beta_3$ (table 1) were observed for the sorbitol series (**1 - 4**).

Compound	$IC_{50}\ \alpha_{IIb}\beta_3$ (μmol)	$IC_{50}\ \alpha_v\beta_3$ (μmol)
1	8	>
2	2	7,5
3	7	>
4	3	4
5	>	>

Table 1. Effect of compounds (**1-5**) on ligand interaction with integrins. Biotinylated ligands vitronectin ($\alpha_v\beta_3$) or fibrinogen ($\alpha_{IIb}\beta_3$) were allowed to bind to immobilized integrins in the presence of the compounds **1-5**. The concentration necessary for half-maximal inhibition of ligand binding is shown. The sign > indicates that the IC_{50} had not been reached at the maximum concentration tested, (10 μM).

Conclusion

The work presented here introduces 1,4:3,6-dianhydrohexitols as core units for RGD mimetics. Synthetic routes to targets with different absolute and relative configuration were elaborated. (D-sorbitol: **1 - 4**, L-iditol: **5**). Compounds **1-4** showed receptor activities on $\alpha_{IIb}\beta_3$ and on $\alpha_v\beta_3$ in the μmol range without pronounced receptor selectivity.

Experimental Section

General: - All b.p.s and m.p.s are uncorrected values. - IR: Bruker IFS 88. – NMR: Bruker AC-300, DPX-300, AMX-500 and AMX-600. For ^{1}H NMR, $CDCl_3$ as solvent δ_H = 7.24, [D_6] DMSO as solvent δ_H = 2.50, [D_4] MeOH as solvent δ_H = 4.78; for ^{13}C NMR, $CDCl_3$ as solvent δ_C = 77.0, [D_6] DMSO as solvent δ_C = 39.5, [D_4] MeOH as solvent δ_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.

2-O-Allyl-1,4:3,6-dianhydro-D-sorbitol (7) and 5-O-Allyl-1,4:3,6-dianhydro-D-sorbitol (8): A suspension of isosorbit **6** (48.7 g, 300 mmol), K_2CO_3 (64.8 g, 470 mmol) and allylbromide (30.1 mL, 43.3 g, 358 mmol) in toluene (100 mL) was refluxed for 24 h. After cooling the precipitate was removed by filtration and the solvent was evaporated in vacuo. The remaining oil was diluted with water (250 mL) and extracted with MTBE (3 x 150 mL). The aqueous solution was saturated with NaCl and extracted with CH_2Cl_2 (4 x 100 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent in vacuo the remaing slightly yellow oil (29.4 g) was fractionally distilled in vacuo (2 x 10^{-2} mbar) using a 20-cm-Vigreux-column. **7** (18.4 g, 30%, bp. 58-61 °C/2 x 10^{-2} mbar) and **8** (8.50 g, 15%, Sdp. 78-80 °C/2 x 10^{-2} mbar) were obtained as colorless oils. Analytical data for **7**: - R_f = 0.51 (PE/EtOAc 1:1) . - $[\alpha]_D$ = + 54.4; $[\alpha]_{578}$ = + 56.7; $[\alpha]_{546}$ = + 63.5; $[\alpha]_{436}$ = + 100.3 ; $[\alpha]_{365}$ = + 142.7. (c = 1.10, $CHCl_3$, T = 20 °C). - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.73 (d, J = 7.0 Hz, 1H, OH), 3.55 (dd, J = 9.4 and 5.7 Hz, 1H, 6-H_A), 3.76 - 3.87 (m, 2H, 6-H_B, 1-H_A), 3.98 - 4.12 (m, 4H, 1-H_B, 1'-H_2, 2-H), 4.23 (ddd, J = 11.8, approx. 6.0 and approx. 6.0 Hz, 1H, 5-H), 4.43 (d, J = 4.4 Hz, 1H, 3-H), 4.58 (dd, J = 4.9 and 4.9 Hz, 1H, 4-H), 5.17 (dd, J = 10.3 and 1.6 Hz, 1H, 3'-H_E), 5.26 (dd, J = 17.2 and 1.6, 1H, 3'-H_Z), 5.88 (ddt, J = 15.8, J = 10.5, J = 5.3, 1H, 2'-H) . - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 70.5 (C-1'), 72.2 (C-5), 73.3 and 73.4 (C-1, C-6), 81.7 (C-

4), 83.4 (C-2), 85.9 (C-3), 117.6 (C-3′), 134.0 (C- 2′). Analytical data for **8**: R_f = 0.36 (PE/EtOAc 1:1). - $[\alpha]_D$ = + 110.0; $[\alpha]_{578}$ = + 114.5; $[\alpha]_{546}$ = + 128.8; $[\alpha]_{436}$ = + 208.0; $[\alpha]_{365}$ = + 305.3 (c = 1.03, $CHCl_3$, T = 20 °C). - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.37 (d, J = 4.1 Hz, 1H, OH), 3.89 - 4.32 (m, 8H, 1-H_2; 2-H, 5-H, 6-H_2, 1′-H_2), 4.41 (d, J = 3.7 Hz, 1H, 3-H), 4.67 (dd, J = 4.2 and 4.2 Hz, 1H, 4-H), 5.19 (dd, J = 9.8 and 1.1 Hz, 1H, 3′-H_E), 5.28 (dd, J = 16.4 and 1.1 Hz, 1H, 3′-H_Z), 5.86 - 5.99 (m, 1H, 2′-H). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 70.0, 71.6 and 75.8 (C-1, C-6, C-1′), 76.6, 79.4, 80.0 and 88.3 (C-2, C-3, C-4, C-5), 117.8 (C-3′), 134.4 (C-2′).

2-O-Allyl-1,4:3,6-dianhydro-L-iditol (9): To a suspension of *p*-nitrobenzoic acid (8.78 g, 52.6 mmol), PPh_3 (13.8 g, 52.6 mmol) and DIAD (12.0 mL, 12.4 g, 61.3 mmol) in toluene (110 mL) a solution of 2-O-allyl-isosorbit **7** (8.15 g, 43.8 mmol) in toluene (10 mL) was added dropwise. After 15 h at room temperature NaOH (41 mL of a 1.6 M aqueous solution, 65.7 mmol) was added and the reaction mixture was vigorously stirred for 2 h. Then it was cooled to 0 °C and the *pH* was adjusted to 5 – 6 by addition of conc. aqueous HCl solution. The obtained crystalline precipitate was removed by filtration from a pad of Celite and washed with little cold toluene. The filtrate was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with sat. aqueous NaCl solution (50 mL). After drying with Na_2SO_4 the solvents were removed in vacuo. The crude product was used without purification for ester hydrolysis. – R_f = 0.51 (PE/MTBE 1:1). A solution of the crude product in MeOH (150 mL) was treated with K_2CO_3 (13.8 g, 100 mmol). After stirring for 2 h the reaction mixture was concentrated to 75 mL and MTBE (100 mL) was added. After filtration the filtrate was concentrated in vacuo and purified by CC (200 g silica, CH_2Cl_2 → CH_2Cl_2/MTBE 1:1 → MTBE). The allyl ether **9** (6.29 g, 77%) was obtained as colorless oil. - R_f = 0.53 (MTBE). - $[\alpha]_D$ = + 13.2; $[\alpha]_{578}$ = + 14.1; $[\alpha]_{546}$ = + 15.3; $[\alpha]_{436}$ = + 19.7 (c = 0.34, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3415 s (OH), 3080 w (CH olef.), 2940/2870 s, 1465 w, 1425 w, 1335 w, 1275 w, 1080 m, 975 m, 915 m, 870 w, 840 w, 785 w, 735 w. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.13 (br. s, 1H, OH), 3.78 –3.92 (m, 4H, 1-H_2, 6-H_2), 3.98 – 4.11 (m, 3H, 1′-H_2, 2-H), 4.33 (br. s, 1H, 5-H), 4.54 (d, J = 4.0 Hz, 1H, 4-H), 4.68 (d, J = 4.0 Hz, 1H, 3-H), 5.21 (ddt, J = 10.3, 1.5 and 1.5 Hz, 1H, 3′-H_E), 5.30 (ddt, J = 17.3, 1.6 and 1.6 Hz, 1H, 3′-H_Z), 5.88 (ddt, J = 17.3, 10.4, and 5.6 Hz, 1H, 2'-H). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 70.6 (C-1′), 72.3 and 74.3(C-1, C-6), 75.9 (C-5), 82.8 (C-4), 85.2 and 87.6 (C-3, C-4), 117.6 (C-3′), 134.0 (C-2′). - HRMS [$C_9H_{14}O_4$] calcd.: 186.0892; found: 186.0893.

(2′S)-2-O-Allyl-5-O[2′(benzyloxycarbonylamino)- methyl-propionate-3′-yl]-1,4:3,6-dianhydro-D-sorbitol (11): To a solution of 2-O-allyl-isosorbit **7** (4.90 g, 26.3 mmol) and aziridine **10** (1.17 g, 5.00 mmol) in chloroform (7.5 mL) was added BF_3-etherate (0.75 mL of a 10% solution in chloroform) at 0 °C. After 20 min at this temperature the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat. aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (25 mL). The organic layer was dried with $MgSO_4$ and concentrated. Purification by CC (300 g silica, CH_2Cl_2/MTBE 8:1) afforded serine ether **11** (1.11 g, 53%) as a colorless viscous oil. Reisolation of the allyl compound **7** (3.15 g, 16.9 mmol) was done by elution with MTBE. - R_f = 0.57 (CH_2Cl_2/MTBE 2:1). - $[\alpha]_D$ = + 40.0; $[\alpha]_{578}$ = + 41.3; $[\alpha]_{546}$ = + 46.5; $[\alpha]_{436}$ = + 74.4; $[\alpha]_{365}$ = + 108.4 (c = 1.00, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3325 m (NH), 3065 w (CH olef.), 3030 w (ArH), 2950/2880 m (CH), 1725 s (CO), 1520 s, 1455 m, 1435 m, 1370 m, 1340 m, 1295 m, 1210 s, 1170 m, 1140 s, 1070 s, 1030 m, 925 w, 775 w, 740 w, 700 w. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.45 - 3.55 and 3.63 – 4.06 (m, 1H and m, 9H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2), 3.72 (s, 3H, OMe), 4.40 - 4.47 (m, 2H, 3-H, 2′-H), 4.63 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.07 (s, 2H, CH_2Ph), 5.12 (dd, J = 10.5 and 1.5 Hz, 1H, 3′′-H_E), 5.25 (dd, J = 17.3 and 1.5 Hz, 1H, 3′′-H_Z), 5.79 - 5.91 (m, 1H, 2′′-H), 6.12 (d, J = 8.3 Hz, 1H, NH), 7.30 - 7.34 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.5 (OMe), 54.4 (C-2′), 66.8 (CH_2Ph), 70.0, 70.2 and 70.4 (C-1, C-6, C-1′′), 73.1 (C-3′), 79.8, 80.4, 83.5 and 86.4 (C-2, C-3, C-4, C-5), 117.4 (C-3′′), 127.8, 128.0, 128.4 and 136.4 (Ph), 134.0 (C-2′′), 156.2 (Z-CO), 170.6 (COO). - $C_{21}H_{27}NO_8$ (421.45): calcd. C 59.85, H 6.46, N 3.32; found C 59.57, H 6.24, N 3.39.

(2′S)-5-O-Allyl-2-O-[2′-(benzyloxycarbonylamino)-methylpropionate-3′-yl]-1,4:3,6-dianhydro-D-sorbitol (12): A solution of 5-O-allyl-isosorbit **8** (6.84 g, 26.3 mmol) and aziridine **10** (1.68 g, 7.14 mmol) in chloroform (5 mL) was treated with BF_3-etherate (0.50 mL of a 10% solution in chloroform) at 0 °C. After 20 min the cooling was removed and the reaction mixture was diluted with EtOAc (100 mL) 4 h later. This solution was washed with sat. aqueous $NaHCO_3$ solution (25 mL) and sat. aqueous NaCl solution (25 mL) consecutively. The organic layer was dried with $MgSO_4$ and the solvents were removed under reduced pressure. Purification by CC (200 g silica, PE/MTBE 2:1 → 3:1) afforded serine ether **12** (750 mg, 25%) as a colorless oil. Excess 5-O-allyl-isosorbit **8** was eluted with EtOAc. Thus, allyl ether **8** (4.1 g, 22 mmol) was reisolated. - R_f = 0.55 (CH_2Cl_2/MTBE 2:1). - $[\alpha]_D$ = + 71.4; $[\alpha]_{578}$ = + 74.2; $[\alpha]_{546}$ =

+ 83.8; $[\alpha]_{436}$ = + 137.1; $[\alpha]_{365}$ = + 204.9 (c = 0.98, $CHCl_3$, *T* = 20 °C). - IR (neat): ν = 3325 s (NH), 3065 w (CH olef.), 3030 w (Ar-H), 2950/2875 s (CH aliph.), 1725 s (C=O), 1520 s, 1455 m, 1435 m, 1210 s, 1095 s, 1065 s, 740 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.55, 3.65 – 3.73 and 3.82 – 4.05 (dd, J = 8.3 and 8.3 Hz, 1H, m, 1H and m, 7H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_A, 1′′-H_2), 3.73 (s, 3H, OMe), 4.16 (dd, J = 12.4 and 5.7 Hz, 1H, 3′-H_B), 4.38 (d, J = 4.3 Hz, 1H, 3-H), 4.44 - 4.53 (m, 2H, 4-H, 2′-H), 5.10 (s, 2H, CH_2Ph), 5.18 (dd, J = 9.8 and 1.5 Hz, 1H, 3′′-H_E), 5.27 (dd, J = 17.3 and 1.5 Hz, 1H, 3′′-H_Z), 5.56 (d, J = 8.7 Hz, 1H, NH), 5.81 – 6.00 (m, 1H, 2′′-H), 7.30 - 7.34 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.6 (OMe), 54.2 (C-2′), 67.1 (CH_2Ph), 69.3, 69.9 and 71.6 (C-1, C-6, C-1′′), 73.0 (C-3′), 79.3, 80.2, 84.8 and 85.8 (C-2, C-3, C-4, C-5), 117.8 (C-3′′), 128.1, 128.2, 128.5 and 136.1 (Ph), 134.4 (C-2′′), 155.9 (Z-CO), 170.4 (COO). - $C_{21}H_{27}NO_8$ (421.45): calcd. C 59.85, H 6.46, N 3.32; found C 59.55, H 6.35, N 3.19.

(2′S)-2-O-Allyl-5-O-[2′-(benzyloxycarbonylamino)-methyl propionate-3′-yl]-1,4:3,6-dianhydro-L-iditol (13): A solution of 2-O-allyl-isoidit **9** (5.80 g, 31.1 mmol) and aziridine **10** (1.47 g, 6.23 mmol) in CH_2Cl_2 (10 mL) was treated at 0 °C with BF_3-etherate (3 drops). The ice bath was removed after 20 min. After stirring for 3 h the reaction mixture was diluted with EtOAc (100 mL) and washed with sat. aqueous $NaHCO_3$ solution (25 mL) and sat. aqueous NaCl solution (25 mL). The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuo. Purification by CC (200 g silica, CH_2Cl_2/MTBE 8:1) gave serine ether **13** (610 mg, 23%) as colorless oil. Excess of 2-O-allyl-isoidit **9** (4.30 g, 23.1 mmol) could be reisolated by elution with MTBE. - R_f = 0.27 (MTBE/PE 1:1). - $[\alpha]_D$ = + 31.1; $[\alpha]_{578}$ = + 32.6; $[\alpha]_{546}$ = + 36.7; $[\alpha]_{436}$ = + 58.4; $[\alpha]_{365}$ = + 85.3 (c = 0.87, $CHCl_3$, *T* = 20 °C). - IR (neat): ν = 3320 m (NH), 3065 w (CH olef.) 3030 w (Ar-H), 2950/2875 m (CH), 1725 s (CO)1520 s, 1455 m, 1440 m, 1340 m, 1290 m, 1210 s, 1175 w, 1085 s, 995 w, 920 w, 775 w, 740 w, 700 w. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.70 – 4.06 (m, 10 H, 1-H_2, 2-H, 5-H, 6- H_2, 3′-H_2, 1′′-H_2), 3.72 (s, 3H, OMe), 4.50 (s, 2H, 3-H,4-H), 4.53 (m_c, 1H, 2′-H), 5.13 (s, 2H, CH_2Ph), 5.20 (ddt, J = 10.5, 1.5 and 1.5 Hz, 1H, 3′′-H_E), 5.25 (ddt, J = 17.3, 1.6 and 1.6 Hz, 1H, 3′′-H_Z), 5.58 (d, J = 8.7 Hz, 1H, NH), 5.90 (ddt, J = 17.1, 10.5 and 5.5 Hz, 1H, 2′′-H), 7.30 - 7.38 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.7 (OMe), 54.3 (C-2′), 67.1 (CH_2Ph), 69.3, 70.5, 71.8 and 72.7 (C-1, C-6, C-3′, C-1′′), 82.7 83.9, 85.0 and 85.4 (C-2, C-3, C-4, C-5), 117.5 (C-3′′),

128.1, 128.2, 128.5 and 136.1 (Ph), 134.1 (C-2''), 170.4 (COO); the signal of Z-CO was not detected. - $C_{21}H_{27}NO_8$ (421.45): calcd. C 59.85, H 6.46, N 3.32; found C 59.59, H 6.47, N 3.24.

(2'S)-5-O-[2'-(Benzyloxycarbonylamino)-methyl propionate-3'-yl]-2-O-(2''-hydroxy-eth-1''-yl)-1,4:3,6-dianhydro-D-sorbitol (14): A solution of serine ether **11** (600 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was treated with a constant stream of ozone at - 78 °C until the characteristic blue color appeared. Excess ozone was driven out by passing argon through the reaction mixture for 5 min. Then a solution of $NaBH_4$ (160 mg, 4.26 mmol) in ethanol (15 mL) was added at - 78 °C and the reaction mixture was allowed to warm to 0 °C within 5 h. Excess $NaBH_4$ was destroyed by the addition of conc. acetic acid (0.2 mL). After removing the solvents in vacuo water (30 mL) was added to the residue. It was neutralized by careful addition of solid $NaHCO_3$ and extracted with EtOAc (4 x 75 mL). After drying with $MgSO_4$ the solvents were removed under reduced pressure. Purification of the residual oil by CC (50 g silica, EtOAc/PE 5:1 → EtOAc) gave alcohol **14** (170 mg, 29%) as a colorless oil. - R_f = 0.05 (MTBE). - $[\alpha]_D$ = + 34.0; $[\alpha]_{578}$ = + 35.7, $[\alpha]_{546}$ = + 39.9; $[\alpha]_{436}$ = + 63.7; $[\alpha]_{365}$ = + 91.9 (c = 0.96, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3435 br. s (OH, NH), 3035 w (Ar-H), 2950/2880 s (CH), 1715 s (CO), 1530 s, 1455 m, 1440 m, 1215 s, 1070 s, 735 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.11 (br. s, 1H, OH), 3.50 - 4.14 (m, 12H, 1-H_2, 2-H, 5-H, 6-H_2, 3'-H_2, 1''-H_2, 2''-H_2), 3.73 (s, 3H, OMe), 4.41 – 4.48 (m, 2H, 3-H, 2'-H), 4.61 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.11 (s, 2H, CH_2Ph), 6.12 (d, J = 8.0 Hz, 1H, NH), 7.30 - 7.34 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.5 (OMe), 54.5 (C-2'), 60.9 (C-2''), 66.8 (CH_2Ph), 70.1, 70.4 and 70.7 (C-1, C-6, C-1''), 73.1 (C-3'), 79.9, 80.4, 84.5 and 86.2 (C-2, C-3, C-4, C-5), 127.9, 128.0, 128.4 and 136.4 (Ph), 156.2 (Z-CO), 170.6 (COO). - HRMS [$C_{20}H_{27}NO_9$] calcd.: 425.1686; found: 425.1688.

(2'S)-2-O-[2'-(Benzyloxycarbonylamino)-methyl propionate-3'-yl]-5-O-(2''-hydroxy-eth-1''-yl)-1,4:3,6-dianhydro-D-sorbitol (15): A solution of serine ether **12** (700 mg, 1.66 mmol) in MeOH (10 mL) was treated with a constant stream of ozone at - 78 °C until the characteristic blue color appeared. Excess ozone was driven out by passing argon through the reaction mixture for 5 min. Then $NaBH_4$ (190 mg, 5.02 mmol) was added at - 78 °C and the reaction mixture was stirred for 15 h at - 25 °C. Excess $NaBH_4$ was destroyed by the addition of TFA (2 mL). After 1 h at - 25 °C toluene (10 mL) was added and the solvents were removed in vacuo at room temperature. The residue was codistilled with toluene (2 x 10 mL). The crude product was dissolved in EtOAc (150 mL) and washed with sat. aqueous $NaHCO_3$ solution (30 mL)

and sat. aqueous NaCl solution (30 mL). After drying with $MgSO_4$ the solvents were removed under reduced pressure. Purification of the residual oil by CC (65 g silica, EtOAc/PE 5:1 → 10:1 → EtOAc) gave (310 mg, 44%) of compound **15** as a colorless oil. - R_f = 0.07 (EtOAc/PE 5:1). - $[\alpha]_D$ = + 61.4; $[\alpha]_{578}$ = + 63.2; $[\alpha]_{546}$ = + 71.4; $[\alpha]_{436}$ = + 116.7; $[\alpha]_{365}$ = + 174.3 (c = 1.04, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3435 s (NH, OH), 3035 w (Ar-H), 2950/2875 s (CH), 1720 s (C=O), 1530 s, 1455 m, 1440 m, 1215 s, 1070 s, 740 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.75 (br. s, 1H, OH), 3.55, 3.67 – 3.77 and 3.86 – 4.07 (dd, J = 8.3 and 8.3 Hz, 1H, m, 5H and m, 6H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 2′′-H_2), 3.74 (s, 3H, OMe), 4.40 (d, J = 4.2 Hz, 1H, 3-H), 4.49 (m_c, 1H, 2′-H), 4.55 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.10 (s, 2H, CH_2Ph), 5.56 (d, J = 8.3 Hz, 1H, NH), 7.29 - 7.34 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 52.7 (OMe), 54.2 (C-2′), 61.8 (C-2′′), 67.1 (CH_2Ph), 69.3, 70.2 and 72.3 (C-1, C-6, C-1′′), 72.9 (C-3′), 80.2, 80.6, 84.7 and 85.9 (C-2, C-3, C-4, C-5), 128.1, 128.2, 128.5 and 136.1 (Ph), 155.9 (Z-CO), 170.4 (COO). - $C_{20}H_{27}NO_9$ (425.43): calcd. C 56.46, H 6.40, N 3.29; found C 56.71, H 6.70, N 2.99.

(2′S)-5-O-[2′-(Benzyloxycarbonylamino)-methyl propionate-3′-yl]-2-O-(3′′-hydroxy-prop-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol (17): A 0.5 M solution of 9-BBN (1.4 mL, 0.72 mmol) in THF was slowly added to a solution of serine ether **11** (100 mg, 0.237 mmol) in THF (2 mL) at - 10 °C. After stirring for 3 h at 0 °C sodium acetate (0.5 mL of a 5 M aqueous solution) and H_2O_2 (0.3 mL of a 30% aqueous solution) were added carefully and the reaction mixture was allowed to warm to room temperature. After 1 h at this temperature the reaction mixture was extracted with MTBE (4 x 10 mL). The combined organic layers were washed with sat. aqueous NaCl solution (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by CC (30 g silica, MTBE). The alcohol **17** (74 mg, 70%) was obtained as a viscous oil. - R_f = 0.06 (MTBE). - $[\alpha]_D$ = + 31.3; $[\alpha]_{578}$ = + 32.6; $[\alpha]_{546}$ = + 36.9; $[\alpha]_{436}$ = + 58.2; $[\alpha]_{365}$ = + 84.1 (c = 0.98, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3440 br. s (OH, NH), 3035 w (Ar-H), 2950/2880 s (CH), 1720 s (CO), 1530 s, 1455 m, 1435 m, 1215s, 1070 s, 740 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78 (tt, J = 5.8 and 5.8 Hz, 2H, 2′′-H), 2.07 (br. s, 1H, OH), 3.49 - 4.03 (m, 12H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3′′-H_2), 3.72 (s, 3H, OMe), 4.43 (m, 2H, 3-H, 2′-H), 4.59 (dd, J = 4.7 and 4.7 Hz, 1H, 4-H), 5.10 (s, 2H, CH_2Ph), 6.13 (d, J = 8.5 Hz, 1H, NH), 7.26 - 7.34 (m, 5H, Ph) . - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 32.1 (C-2′′), 52.5 (OMe), 54.4 (C-2′), 60.9 (C-3′′), 66.8 (CH_2Ph), 67.8, 70.1 and 70.3 (C-1, C-6, C-1′′), 73.1 (C-3′), 79.8, 80.4, 83.3 and 86.2 (C-2, C-3, C-4, C-5), 127.9, 128.0, 128.4 and

136.4 (Ph), 156.2 (Z-CO), 170.6 (COO). - $C_{21}H_{29}NO_9$ (425.43): calcd. C 57.39, H 6.65, N 3.19; found C 57.19, H 6.71, N 3.40.

(2′S)-2-O-[2′-(Benzyloxycarbonylamino)-methyl propionate-3′-yl]-5-O-(3′′-hydroxy-prop-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol (18): Borane-dimethylsulfide (474 µl, 5.00 mmol) was added at 0 °C to triethylborane (10 mL of a 1 M solution in THF, 10 mmol) in a Schlenk-tube and the mixture was stirred for 30 min. An aliquot of this diethyl borane solution (4.3 mL, 4.1 mmol) was added dropwise at - 10 °C to a solution of allyl ether **12** (575 mg, 1.36 mmol) in THF (10 mL). After 30 min the reaction mixture was allowed to warm to room temperature and stirred for further 5 h. The reaction was quenched at 0 °C by careful addition of water until the gas evolution stopped. Then sodium acetate (2.5 mL of a 5 M aqueous solution and H_2O_2 (1.5 mL of a 30% aqueous solution) were added carefully and the ice bath was removed. After 1 h at room temperature the mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with sat. aqueous NaCl solution (20 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by CC (50 g silica, EtOAc/PE 5:1 → 1:1 → EtOAc). The alcohol **18** (291 mg, 49%) was obtained as a colorless oil. - R_f = 0.22 (EtOAc). - $[\alpha]_D$ = + 71.1; $[\alpha]_{578}$ = + 74.4; $[\alpha]_{546}$ = + 83.9; $[\alpha]_{436}$ = + 137.1; $[\alpha]_{365}$ = + 204.8 (c = 1.05, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3435 s (NH, OH), 3030 w (Ar-H), 2950/2880 s (CH), 1720 s (C=O), 1530 s, 1455 m, 1440 m, 1215 s, 1125 m, 1070 s, 740 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.70 – 1.83 (m, 2H, 2′′-H_2), 2.74 (br. s, 1H, OH), 3.55 and 3.62 – 4.04 (dd, J = 8.1 and 8.1 Hz, 1H, and m, 11H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3′′-H_2), 3.72 (s, 3H, OMe), 4.40 (d, J = 4.2 Hz, 1H, 3-H), 4.47 (m_c, 1H, 2′-H), 4.58 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.10 (s, 2H, CH_2Ph), 5.55 (d, J = 8.3 Hz, 1H, NH), 7.29 - 7.34 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 31.8 (C-2′′), 52.6 (OMe), 54.2 (C-2′), 60.6 (C-3′′), 67.1 (CH_2Ph), 68.2, 69.3 and 70.2 (C-1, C-6, C-1′′), 72.9 (C-3′), 79.93, 79.95, 84.7 and 85.9 (C-2, C-3, C-4, C-5), 128.1, 128.2, 128.5 and 136.1 (Ph), 155.9 (Z-CO), 170.4 (COO). - $C_{21}H_{29}NO_9$ (439.47): calcd. C 57.39, H 6.65, N 3.19; found C 57.31, H 6.75, N 3.19.

(2′S)-5-O-[2′-(Benzyloxycarbonylamino)-methyl propionate-3′-yl]-2-O-(3′′-hydroxy-prop-1′′-yl)-1,4:3,6-dianhydro-L-iditol (19): Borane-dimethylsulfide (474 µl, 5.00 mmol) was added at 0 °C to triethylborane (10 mL of a 1 M solution in THF, 10 mmol) in a Schlenk-tube and the mixture was stirred for 2 h at 0 °C. An aliquot of this diethyl borane solution (2.2 mL, 2.1 mmol) was added dropwise at - 10°C

to a solution of allyl ether **13** (300 mg, 0.712 mmol) in THF (5 mL). After 30 min the reaction mixture was allowed to warm to room temperature and stirred for further 5 h. The reaction was quenched at 0 °C by careful addition of water until the gas evolution stopped. Then sodium acetate (1.2 mL of a 5 M aqueous solution) and H_2O_2 (0.8 mL of a 30% aqueous solution) were added carefully and the ice bath was removed. After 1 h at room temperature the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aqueous NaCl solution (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by CC (50 g silica, EtOAc/PE 5:1 → 1:1 → EtOAc). The alcohol **19** (170 mg, 54%) was obtained as a colorless oil. - R_f = 0.44 (EtOAc). - $[\alpha]_D$ = + 29.2; $[\alpha]_{578}$ = + 30.6; $[\alpha]_{546}$ = + 34.0; $[\alpha]_{436}$ = + 54.0; $[\alpha]_{365}$ = + 77.9 (c = 0.62, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3320 br. m (NH/OH), 3065 w (CH olef.), 3035 w (Ar-H), 2950/2875 s (CH), 1720 s (CO), 1530 s, 1455 m, 1440 m, 1400 w, 1340 s, 1215 s, 1175 m, 1080 s, 985 m, 915 m, 775 w, 740 w, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.82 (tt, J = 5.8 and 5.8 Hz, 2H, 2′′-H_2), 2.01 (br. s, 1H, OH), 3.60 – 4.01 (m, 12H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3′′-H_2), 3.77 (s, 3H, OMe), 4.46 – 4.55 (m, 3H, 3-H, 4-H, 2′-H), 5.13 (s, 2H, CH_2Ph), 5.60 (d, J = 9.0 Hz, 1H, NH), 7.30 - 7.42 (m, 5H, Ph). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 32.1 (C-2′′), 52.7 (OMe), 54.3 (C-2′), 60.9 (C-3′′), 67.1 (CH_2Ph), 67.9, 69.3, 71.8 and 72.1 (C-1, C-6, C-3′, C-1′′), 83.6, 83.8, 84.9 and 85.2 (C-2, C-3, C-4, C-5), 128.1, 128.2, 128.5 and 136.1 (Ph), 156.0 (Z-CO), 170.4 (COO). - HRMS [$C_{21}H_{29}NO_9$] calcd.: 439.1842; found: 439.1843.

(2′S)-5-O-[2′-(Benzyloxycarbonylamino)-propionic acid-3′-yl]-2-O-(2′′-guanidinium-eth-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol trifluoro acetate (1): Alcohol **14** (160 mg, 0.376 mmol), protected guanidine derivative **16** (202 mg, 0.779 mmol) and PPh_3 (153 mg, 584 mmol) were dissolved in THF (3 mL) and cooled down to 0 °C. DIAD (0.11 mL, 0.12 g, 0.58 mmol) was added dropwise. After 16 h at room temperature, water (3 drops) was added and the solvent was removed in vacuo. Purification by CC (30 g silica, PE/MTBE 1:1 → 3:1) gave 203 mg (79%) of the corresponding protected title compound as a colorless oil. - R_f = 0.18 (PE/MTBE 1:1). - $[\alpha]_D$ = + 18.4; $[\alpha]_{578}$ = + 20.0; $[\alpha]_{546}$ = + 21.4; $[\alpha]_{436}$ = + 33.5; $[\alpha]_{365}$ = + 47.7 (c = 0.96, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3385 s (NH), 2980/2880 s (CH), 1715 s (C=O), 1640 s, 1610 s, 1510 s, 1455 m, 1435 m, 1390 s, 1370 s, 1275 s, 1245 s, 1150 s, 1100 s, 980 m, 735 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.45 and 1.47 (2 s, 9H each, 2 x tBu), 3.73 (s, 3H, OMe), 3.46 - 4.18 (m, 12H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 2′′-H_2), 4.40 – 4.43 (m, 2H, 3-H, 2′-H), 4.56 (dd,

J = 4.7 and 4.7, 1H, 4-H), 5.11 (s, 2H, CH_2Ph), 6.08 (d, J = 8.7 Hz, 1H, NH), 7.28 - 7.34 (m, 5H, Ph), 9.24 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.9 and 28.3 (2 x C(CH_3)$_3$), 43.7 (C-2′′), 52.5 (OMe), 54.5 (C-2′), 66.8 (CH_2Ph), 67.1, 70.1 and 70.2 (C-1, C-6 and C-1′′), 73.4 (C-3′), 78.8 and 83.9 (2 x $C(CH_3)_3$), 79.8, 80.5, 83.9 and 86.3 (C-2, C-3, C-4, C-5), 127.9, 128.0, 128.4 and 136.4 (Ph), 154.9 (C=N), 156.2 (Z-CO), 160.4 and 163.7 (2 x Boc-CO), 170.6 (COO). A solution of this protected guanidine derivative (100 mg, 0.150 mmol) in acetone (1 mL) and water (1 mL) was treated with TFA (1 mL) at 70 °C (bath temperature). After 15 h at this temperature the solvents were removed in vacuo. Purification of the residual oil by preparative HPLC (41 mm ID, Rainin, RP 18, 40 mL/min, 25% B to 30% B in 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) afforded trifluoro acetate **1** (79 mg, 93%). - HPLC: R_t = 11.0 min (4 mm ID, Rainin, RP 18, 1 mL/min, 20% B to 60% B in 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA). - ^{1}H-NMR (300 MHz, CD_3CN): δ = 3.28 (m_c, 2H, 3′′-H_2), 3.47 (dd, J = 8.8 and 6.9 Hz, 1H, 1-H_A*), 3.59 (m_c, 2H, 1′′-H_2), 3.73 – 4.07 (m, 7H, 1-H_B*, 2-H, 5-H, 6-H_2*, 3′-H_2), 4.26 – 4.37 (m, 1H, 2′-H), 4.43 (d, J = 4.3 Hz, 1H, 3-H), 4.62 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), ca. 4.5 – 5.5 (very br. s, 3H, 3 exchangeable H′s), 5.11 (s, 2H, CH_2Ph), 6.39 (d, J = 7.7 Hz, 1H, NHZ), 6.79 (br. s, 3H, 3 exchangeable H′s), 7.30 – 7.44 (m, 5H, Ph), 7.61 (br. s, 1H, $N^{3''}H$); * assignment is possibly interchangeable. - ^{13}C-NMR (75 MHz, CD_3CN): δ = 42.7 (C-2′′), 55.5 (C-2′), 67.2 (CH_2Ph), 68.8 (C-1′′), 70.8, 71.0 and 73.7 (C-3′, C-1, C-6), 81.2, 81.3, 85.3 and 86.6 (C-2, C-3, C-4, C-5), 128.7, 128.9, 130.0 and 138.0 (Ph), 157.3 and 159.6 (Z-CO and C=N), 172.0 (COO). - HRMS: $C_{20}H_{29}N_4O_8$ calcd. 453.1985; found 453.1981.

(2′S)-5-O-[2′-(Benzyloxycarbonylamino)-propionic acid-3′-yl]-2-O-(3′′-guanidinium-prop-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol trifluoro acetate (2): The preparation and purification was done as described for the protected guanidine derivative corresponding to **1**. The following amounts of substrate and reagents were used: Alcohol **17** (400 mg, 0.910 mmol), protected guanidine **16** (474 mg, 1.82 mmol), PPh_3 (358 mg, 1.37 mmol) and DIAD (0.27 mL, 0.28 g, 1.4 mmol) to yield the corresponding protected title compound (540 mg, 87%) as a colorless oil. - R_f = 0.17 (PE/MTBE 1:1). - $[\alpha]_D$ = + 21.0; $[\alpha]_{578}$ = + 21.9; $[\alpha]_{546}$ = + 24.6; $[\alpha]_{436}$ = + 39.2; $[\alpha]_{365}$ = + 56.7 (c = 0.96, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3385 s (NH), 2975/2870 s (CH), 1715 s (C=O), 1640 s, 1610 s, 1510 s, 1455 m, 1440 m, 1390 m, 1370 s, 1280 s, 1225 s, 1150 s, 1100 s, 980 m, 735 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.46 and 1.49 (2 s, 9H

each, 2 x tBu), 1.82 (q, J = 5.7 Hz, 2H, 2′′-H_2), 3.73 (s, 3H, OMe), 3.44 - 4.05 (m, 12H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3′′-H_2), 4.39 – 4.46 (m, 2H, 3-H, 2′-H), 4.56 (dd, J = 4.7 and 4.7 Hz, 1H, 4-H), 5.11 (s, 2H, CH_2Ph), 6.08 (d, J = 8.3 Hz, 1H, NH), 7.30 - 7.34 (m, 5H, Ph), 9.27 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0 und 28.3 [2 x C(CH_3)$_3$], 29.1 (C-2′′), 42.2 (C-3′′), 52.5 (OMe), 54.5 (C-2′), 66.8 (CH_2Ph), 67.4, 70.0 and 70.1 (C-1, C-6, C-1′′), 73.2 (C-3′), 78.7 and 83.7 (2 x C(CH_3)$_3$), 79.7, 80.5, 84.3 and 86.3 (C-2, C-3, C-4, C-5), 127.9, 128.0, 128.4 and 136.4 (Ph), 154.9 (C=N), 156.2 (Z-CO), 160.7 and 163.8 (2 x Boc-CO), 170.6 (COO). - $C_{32}H_{48}N_4O_{12}$ (680.78): calcd. C 56.46, H 7.11, N 8.23; found C 56.57, H 7.07, N 8.13. A solution of this protected guanidine derivative (380 mg, 0.558 mmol) in THF (4 mL) was treated with LiOH (2.7 mL of a 0.3 M aqueous solution, 0.81 mmol) at room temperature. It was acidified with 5% aqueous citric acid solution to *pH* 3 after 20 min. The organic solvent was removed and the residue was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. aqueous NaCl solution (20 mL) and dried with $MgSO_4$. After removal of the solvents in vacuo the residue was dissolved in CH_2Cl_2 (4 mL) and TFA (1.5 mL) was added. After 2 h at room temperature the reaction mixture was azeotropically distilled with toluene (2 x 5 mL). The residual oil was purified by preparative HPLC (41 mm ID, 3 runs, Rainin, RP 18, 40 mL/min, 25% B to 30% B in 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) to yield trifluoro acetate **2** (172 mg, 53%). - HPLC: R_t = 12.1 min (4 mm ID, Rainin, RP 18, 1 mL/min, 20% B to 60% B in 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA). - ^{1}H-NMR (300 MHz, d_6-DMSO): δ = 1.68 (tt, J = 6.4 and 6.4 Hz, 2H, 2′′-H_2), 3.13 (dt, J = 6.3 and 6.3 Hz, 2H, 3′′-H_2), 3.32 – 4.32 (m, 13H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3 exchangeable H′s*), 4.39 (d, J = 4.5 Hz, 1H, 3-H), 4.56 (dd, J = 4.6 and 4.6 Hz, 1H, 4-H), 5.03 (s, 2H, CH_2Ph), 6.82 - 7.52 (m, 8H, Ph, 3 exchangeable H′s), 7.67 (t, J = 5.4 Hz, 1H, $N^{3''}$H); * this signal was superimposed by the signal of the residual water in the sample. - ^{13}C-NMR (75 MHz, d_6-DMSO): δ = 28.8 (C-2′′), 38.7 (C-3′′), 54.8 (C-2′), 65.7, 65.9, 69.3 and 69.7 (CH_2Ph, C-1, C-6, C-1′′), 72.8 (C-3′), 80.0, 80.2, 83.9 and 85.6 (C-2, C-3, C-4, C-5), 127.9, 128.1, 128.7 and 137.1 (Ph), 156.3 and 157.1 (Z-CO and C=N), 171.8 (COO). – FAB-MS: $C_{21}H_{31}N_4O_8$ calcd. 467.2; found 467.5.

(2′S)-2-O-[2′-(Benzyloxycarbonylamino)-propionic acid-3′-yl]-5-O-(2′′-guanidinium-eth-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol trifluoro acetate (3): The preparation was done as described for the protected guanidine derivative corresponding to **1**. The following amounts of substrate and reagents were

used: Alcohol **15** (270 mg, 0.635 mmol), protected guanidine **16** (330 mg, 1.26 mmol), PPh_3 (248 mg, 0.946 mmol) and DIAD (0.18 mL, 0.19 g, 0.94 mmol). Purification by CC (30 g silica, MTBE/PE 1:1 → 3:1) afforded the title compound (365 mg, 87%) as colorless, viscous oil. - R_f = 0.17 (PE/MTBE 1:1) . - $[\alpha]_D$ = + 50.8; $[\alpha]_{578}$ = + 52.8; $[\alpha]_{546}$ = + 59.6; $[\alpha]_{436}$ = + 98.2; $[\alpha]_{365}$ = + 149.3 (c = 1.06, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3385 s (NH), 2975/2875 s (CH), 1715 s (C=O), 1640 s, 1610 s, 1510 s, 1455 m, 1435 m, 1390 m, 1370 s, 1275 s, 1245 s, 1150 s, 1100 s, 985 m, 735 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.45 and 1.47 (2 s, 9H each, 2 x tBu), 3.73 (s, 3H, OMe), 3.51, 3.58 - 4.07 and 4.11 – 4.29 (t, J = 8.1 Hz, 1H, m, 9H and m, 2H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 2′′-H_2), 4.36 (d, J = 4.5 Hz, 1H, 3-H), 4.48 (m_c, 1H, 2′-H), 4.56 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.10 (s, 2H, CH_2Ph), 5.53 (d, J = 8.7 Hz, 1H, NH), 7.29 - 7.33 (m, 5H, Ph), 9.20 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0 and 28.3 (2 x $C(CH_3)_3$), 43.3 (C-2′′), 52.6 (OMe), 54.2 (C-2′), 67.1 (CH_2Ph), 68.0, 69.3 and 70.2 (C-1, C-6, C-1′′), 72.9 (C-3′), 78.6 and 84.0 (2 x $C(CH_3)_3$), 79.5, 80.4, 84.9 and 86.0 (C-2, C-3, C-4, C-5), 128.1, 128.2, 128.5 and 136.1 (Ph), 154.8 (C=N), 155.9 (Z-CO), 160.5 and 163.6 (2 x Boc-CO), 170.4 (COO). - $C_{31}H_{46}N_4O_{12}$ (666.73): calcd. C 55.85, H 6.95, N 8.40; found C 55.55, H 7.25, N 7.79. The preparation and purification was done as described for the trifluoro acetate **1**. The following amounts of substrate and reagents were used: Protected guanidine derivative corresponding to **3** (260 mg, 0.390 mmol), TFA (2 mL) to yield the title compound (174 mg, 79%) as a colorless oil. - HPLC: R_t = 12.0 min (4 mm ID, Rainin, RP 18, 1 mL/min, 20% B to 60% B in 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA). - ^{1}H-NMR (300 MHz, CD_3CN): δ = 3.30 (m_c, 2H, 2′′-H_2), 3.30, 3.56 – 3.97 and 4.05 (dd, J = 8.9 and 7.0 Hz, 1H, m, 8H and dt, J = 11.5 and 6.6 Hz, 1H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2), 4.37 (dt, J = 8.2 and 4.1 Hz, 1H, 2′-H), 4.41 (d, J = 4.3 Hz, 1H, 3-H), 4.51 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.08 (s, 2H, CH_2Ph), 6.10 (d, J = 8.1 Hz, 1H, NHZ), 6.59 (br. s, 3H, NH_2 and COOH), 7.10 (br. s, 1H, N^3 H), 7.23 - 7.40 (m, 5H, Ph), 7.58 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, CD_3CN): δ = 43.9 (C-2′′), 55.9 (C-2′), 68.0 (CH_2Ph), 70.4 and 70.9 (C-3′, C-1′′), 71.5 and 74.5 (C-1, C-6), 81.98, 82.04, 86.0 and 86.9 (C-2, C-3, C-4, C-5), 129.4, 129.6, 130.1 and 138.6 (Ph), 157.9 and 159.9 (Z-CO and C=N), 172.8 (COO). - HRMS: $C_{20}H_{29}N_4O_8$ calcd. 453.1985; found: 453.1962.

(2′S)-2-O-[2′(Benzyloxycarbonylamino)propionic acid-3′-yl]-5-O-(3′′-guanidino-prop-1′′-yl)-1,4:3,6-dianhydro-D-sorbitol trifluoro acetate (4): The preparation was done as described for the protected guanidine derivative corresponding to **1**. The following amounts of substrate and reagents were used: Alcohol **18** (260 mg, 0.592 mmol), protected guanidine **16** (307 mg, 1.18 mmol), PPh_3 (232 mg, 0.886 mmol) and DIAD (0.17 mL, 0.18 g, 0.90 mmol). Purification by CC (100 g silica, MTBE/PE 1:1 → 3:1) afforded the title compound (382 mg, 95%) as a colorless, viscous oil. - R_f = 0.19 (PE/MTBE 1:1). - $[\alpha]_D$ = + 42.8; $[\alpha]_{578}$ = + 44.6; $[\alpha]_{546}$ = + 50.3; $[\alpha]_{436}$ = + 81.8; $[\alpha]_{365}$ = + 122.1 (c = 0.98, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3385 s (NH), 2975/2875 s (CH), 1715 s (C=O), 1640 s, 1610 s, 1510 s, 1455 m, 1440 m, 1390 m, 1370 s, 1280 s, 1225 s, 1150 s, 1100 s, 980 m, 735 m, 700 m. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.46 and 1.49 (2 s, 9H each, 2 x tBu), 1.86 (tt, J = 6.4 and 6.4 Hz, 2H, 2′′-H_2), 3.73 (s, 3H, OMe), 3.43 – 3.55, 3.65 – 3.74 and 3.83 – 4.07 (m, 2H, m, 8H and m, 2H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2, 3′′-H_2), 4.37 (d, J = 4.1 Hz, 1H, 3-H), 4.47 - 4.53 (m, 2H, 4-H, 2′-H), 5.10 (s, 2H, CH_2Ph), 5.53 (d, J = 8.7 Hz, 1H, NH), 7.29 - 7.33 (m, 5H, Ph), 9.25 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0 and 28.3 (2 x $C(CH_3)_3$), 29.1 (C-2′′), 42.2 (C-3′′), 52.6 (OMe), 54.3 (C-2′), 67.1 (CH_2Ph), 68.3, 69.3 and 70.0 (C-1, C-6, C-1′′), 73.0 (C-3′), 78.7 and 83.7 (2 x $C(CH_3)_3$), 80.0, 80.2, 84.9 and 85.9 (C-2, C-3, C-4, C-5), 128.1, 128.2, 128.5 and 136.1 (Ph), 155.0 (C=N), 155.9 (*Z*-CO), 160.7 and 163.8 (2 x Boc-CO), 170.4 (COO). - $C_{32}H_{48}N_4O_{12}$ (680.78): calcd. C 56.46, H 7.11, N 8.23; found C 56.20, H 6.79, N 8.06. The preparation and purification was done as described for the trifluoro acetate **1**. The following amounts of substrate and reagents were used: Protected guanidine derivative corresponding to **4** (200 mg, 0.294 mmol), TFA (2 mL) to yield the trifluoro acetate **4** (118 mg, 69%) as a colorless oil. - HPLC: R_t = 12.7 min (4 mm ID, Rainin, RP 18, 1 mL/min, 20% B to 60% B in 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA). - ^{1}H-NMR (600 MHz, d_6-DMSO): δ = 1.69 (tt, J = 6.6 and 6.6 Hz, 2H, 2′′-H_2), 3.15 (dt, J = 7.0 and 5.5 Hz, 2H, 3′′-H_2), 3.39 (t, J = 8.1 Hz, 2H, 6-H_A), AB signal (δ_A = 3.43, δ_B = 3.58, J = 9.6 Hz, additionally split by J_A = 6.2 and 6.2 Hz, J_B = 6.2 and 6.2 Hz, 2H, 1′′-H_2), 3.66 – 3.71 (m, 2H, 3′-H_2), 3.71 – 3.82 (m, 3H, 1-H_2, 6-H_B), ca. 3.8 – 4.8 (very br.s , 3H, 3 exchangeable H′s), 3.92 (br. d, J = 3.7 Hz, 1H, 2-H), 3.94 (td, J = 7.0 and 4.8 Hz, 1H, 5-H), 4.18 (dt, J = 8.1 and 5.5 Hz, 1H, 2′-H), 4.40 (d, J = 4.4 Hz, 1H, 3-H), 4.50 (dd, J = 4.5 and 4.5 Hz, 1H, 4-H), 5.03 (s, 2H, CH_2Ph), 6.80 - 7.38 (m, 7H, Ph, 2 exchangeable H′s), 7.55 (d, J = 8.2 Hz, 1H, NHZ), 7.60 (t, J = 5.5 Hz, 1H, $N^{3''}H$). - ^{13}C-NMR (75 MHz, d_6-DMSO): δ = 28.8 (C-2′′), 38.0

(C-3′′), 54.3 (C-2′), 65.5 (CH_2Ph), 66.6 (C-1′′), 68.2 (C-3′), 69.4 (C-6), 72.6 (C-1), 79.6 and 79.7 (C-4, C-5), 84.1 (C-2), 85.2 (C-3), 127.7, 128.2, 128.9 and 137.0 (Ph), 156.1 and 156.9 (Z-CO and C=N), 171.5 (COO). – FAB-MS: $C_{21}H_{31}N_4O_8$ calcd. 467.2; found 467.5.

(2′S)-5-O-[2′-(Benzyloxycarbonylamino)-methyl propionate-3′-yl]-2-O-(3′′-guanidinium-prop-1′′-yl)- 1,4:3,6-dianhydro-L-iditol trifluoro acetate (5): The preparation was done as described for the protected guanidine derivative corresponding to **1**. The following amounts of substrate and reagents were used: Alcohol **19** (98 mg, 0.22 mmol), protected guanidine **16** (114 mg, 0.440 mmol), PPh_3 (87 mg, 0.33 mmol) and DIAD (0.066 mL, 69 mg, 0.34 mmol). After purification by CC (20 g silica, MTBE/PE 2:1) the title compound (130 mg, 87%) was obtained as a highly viscous colorless oil. - R_f = 0.16 (PE/MTBE 1:1). - $[\alpha]_D$ = + 22.9; $[\alpha]_{578}$ = + 24.4; $[\alpha]_{546}$ = + 26.9; $[\alpha]_{436}$ = + 42.3; $[\alpha]_{365}$ = + 60.2 (c = 0.63, $CHCl_3$, T = 20 °C). - IR (neat): ν = 3385 w (NH), 2975/2875 w (CH), 1715 s (CO), 1610 w, 1510 w, 1370 w, 1280 m, 1250 m, 1150 m, 1100 w, 885 w, 850 w, 810 w, 780 w, 745 w, 700 w. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.48 and 1.52 (2 s, 9H each, 2 x *t*Bu), 1.87 (m_c, 2H, 2′′-H_2), 3.51 (m_c, 2H, 3′′-H_2), 3.76 (s, 3H, OMe), 3.68 - 4.08 (m, 10H, 1-H_2, 2-H, 5-H, 6-H_2, 3′-H_2, 1′′-H_2), 4.46 (m_c, 2H, 3-H, 4-H), 4.50 (br. dt, J = 8.7 and 2.9 Hz, 1H, 2′-H), 5.12 (s, 2H, CH_2Ph), 5.65 (d, J = 8.7 Hz, 1H, NH), 7.27 - 7.42 (m, 5H, Ph), 9.25 (br. s, 2H, NH_2). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.9 and 28.2 (2 x $C(CH_3)_3$), 28.9 (C-2′′), 42.1 (C-3′′), 52.5 (OMe), 54.2 (C-2′), 67.0 (CH_2Ph), 67.4, 69.2, 71.6 and 72.1 (C-1, C-6, C-3′, C-1′′), 78.6 and 83.6 (2 x $C(CH_3)_3$), 83.3, 83.9, 84.9 and 85.2 (C-2, C-3, C-4, C-5), 128.0, 128.1, 128.4 and 136.0 (Ph), 154.8 and 155.9 (C=N and Z-CO), 160.6 and 163.7 (2 x Boc-CO), 170.3 (COO). - $C_{32}H_{48}N_4O_{12}$ (680.78): calcd. C 56.46, H 7.11, N 8.23; found C 56.34, H 7.13, N 7.96. To a solution of this protected guanidine derivative (53 mg, 0.078 mmol) in acetone (2 mL) and water (2 mL) 1 M aqueous HCl-solution (2 mL) was added and the reaction mixture was stirred at 65 °C (bath temperature). After 15 h at this temperature the solvents were removed in vacuo. The residual oil was purified by preparative HPLC (21 mm ID, 2 runs, Rainin, RP 18, 20 mL/min, 20% B to 30% B in 20 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA) to yield trifluoro acetate **5** (35 mg, 77%). - HPLC: R_t = 14.2 min (4 mm ID, Rainin, RP 18, 1 mL/min, 20% B to 60% B in 30 min, A: water + 0.2% TFA; B: acetonitrile + 0.2% TFA). ^{1}H-NMR (600 MHz, CD_3CN + 10% D_2O): δ = 1.75 (tt, J = 6.4 and 6.4 Hz, 2H, 2′′-H_2), 3.18 (t, J = 6.8 Hz, 2H, 3′′-H_2), AB signal (δ_A = 3.51, δ_B = 3.54, J_{AB} = 10.0 Hz, additionally split by J_A = 5.9 Hz, J_B = 6.0 Hz, 2H, 1′′-H_2), 3.68 – 3.75 and 3.77 –

3.80 (m, 3H and m, 2H, 1-H_2, 6-H_2, 3′-H_A), 3.87 – ca. 3.90 (m, 1H, 3′-H_B), 3.90 (dd, J = 3.0 and approx. 1.0 Hz, 1H, 2-H*), 3.93 (dd, J = 3.0 and approx. 1.0 Hz, 1H, 5-H*), 4.34 (dd, J = 4.1 and 4.1 Hz, 1H, 2′-H), 4.47 (m_c, almost s, 2H, 3-H, 4-H), 5.07 (m_c, almost s, 2H, CH_2Ph), 7.28 - 7.38 (m, 5H, Ph); * assignment was done according to a NOESY spectrum, 2-H displayed a strong NOE to 1′′-H_2 and a weak NOE to 2′′-H_2, in contrast 5-H showed a weak NOE to 2′-H. - ^{13}C-NMR (75 MHz, CD_3CN + 10% D_2O): δ = 29.3 (C-2′′), 39.4 (C-3′′), 55.2 (C-2′), 67.2 and 67.5 (CH_2Ph, C-1′′), 69.8 (C-3′), 72.6 (C-1, C-6), 84.3 (C-2), 84.6 (C-5), 85.6 and 85.8 (C-3, C-4), 128.7, 129.1 and 129.5 (Ph), 157.5 (Z-CO and C=N), 173.1 (COO). - FAB-HRMS [$C_{21}H_{31}N_4O_8$] calcd.: 467.2142; found: 467.2153.

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