Synthesis and Biological Evaluation of Protein:Geranylgeranyltransferase I Inhibitors Based on the CaaX Box: Incorporation of Sugar Amino Acids as Dipeptide Isosters

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Two orthogonally protected SAA building blocks were used in the synthesis of eight novel analogues of the CaaX motif present in the natural substrates of protein:geranylgeranyltransferase I (PGGT I), an enzyme involved in the post-translational modification of oncogenic proteins, *e.g.*, Ras K-4B. Remarkably, two compounds, which are stereochemically different at the C(1′) position of the SAA residue and at C(2) of the Cys residue, showed comparable activity in a PGGT-1 assay. Our results indicate that both (1,5-*cis*) and (1,5-*trans*) SAA building blocks can be used for the development of novel PGGT I inhibitors.

1. Introduction. – Protein isoprenylation, *i.e.*, the post-translational modification of proteins with isoprenoid lipids, is an important physiological event [1]. Prenylated proteins are key factors in various biological processes, *e.g.*, signal transduction and cell-cycle control. One of the most intensively studied prenylated proteins is Ras [2], a small GTP-binding protein that is an important switch in signal transduction pathways that mediate cell proliferation [3]. Isoprenylation of a specific cysteine residue in pre-Ras is the first and essential step in a series of post-translational modification events that leads to mature Ras. Blocking prenylation severely impairs the biological functioning of Ras [4].

The wide interest in Ras proteins is largely based on the existence of various Ras oncogens [1]. It is estimated that oncogenic Ras proteins are present in – and at least partially responsible for the proliferation of – *ca.* 40% of all human tumors [3]. The realization that inhibition of isoprenylation could also impair functioning of oncogenic Ras has inspired many academic and industrial groups to search for effective methodologies to block protein isoprenylation [4].

To date, three isoprenylating enzymes, namely protein:farnesyltransferase (PFT), protein:geranylgeranyltransferase I (PGGT I) and protein:geranylgeranyltransferase II (PGGT II) have been identified. Of the three isoprenyltransferases, PFT and PGGT I are thought to be responsible for the majority of protein isoprenylation events encountered in nature[1]). PFT and PGGT I are two closely related, heterodimeric metalloproteins [6], each with a Zn^{2+} ion present in the active site. PFT and PGGT I are composed of an α-subunit, which is identical in both enzymes, and a β-subunit, which

[1]) PGGT II isoprenylates exclusively Rab proteins [5].

shares *ca*. 30% homology. Both PFT and PGGT I catalyze the transfer of isoprenoid lipids from the corresponding pyrophosphate donors to Cys residues near the carboxylate terminus of the target proteins (*Fig. 1*). The target Cys residues are part of the so-called CaaX box, where C stands for Cys and aa for any aliphatic, hydrophobic dipeptide (containing, *e.g.*, Leu, Ile, and Val). Substrate specificities of PFT and PGGT I are determined by the nature of residue X: PFT modifies substrates where X is Met, Ser, Cys, Gln, or Ala whereas PGGT I normally modifies substrates where X is Leu or Phe. A further difference between the two enzymes is found in the isoprenoid lipid that is transferred. PFT catalyzes the transfer of farnesyl groups from farnesyl pyrophosphate, whereas PGGT I transfers the geranylgeranyl group from the corresponding geranylgeranyl pyrophosphate. Depending on the nature of the substrate proteins, further post-translational modifications may occur after isoprenylation [1][2].

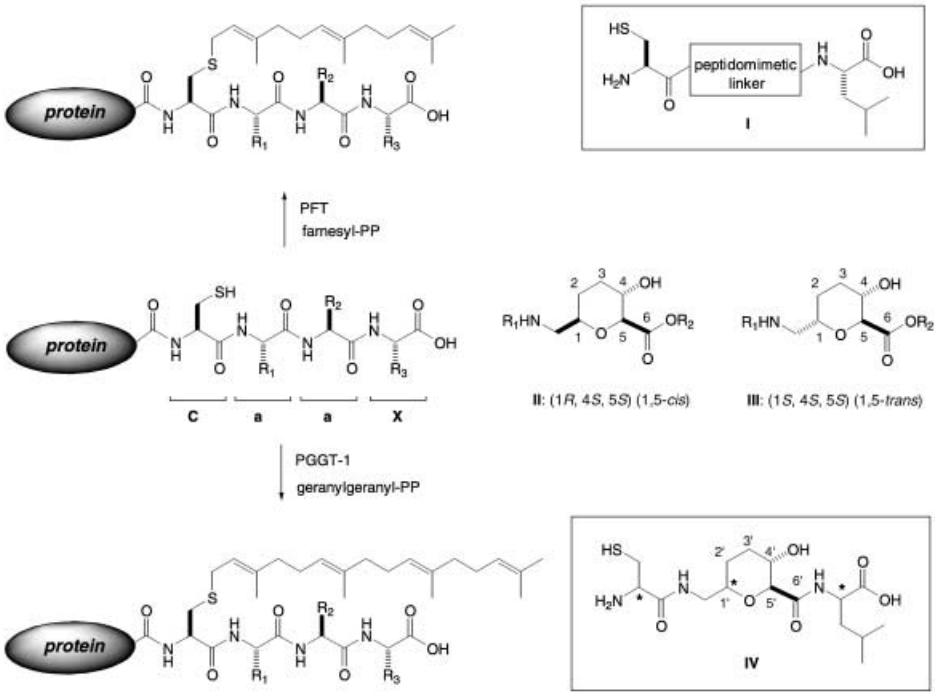

Fig. 1

Pre-Ras proteins are normally modified by PFT. It is, therefore, not surprising that the majority of research activities aimed at disabling protein isoprenylation is directed at the design of PFT inhibitors[2])[3]) [9]. It was recently demonstrated, however, that, upon blocking PFT, the most abundant human oncogenic Ras protein, Ras K-4B, is geranylgeranylated through the action of PGGT I [10][11]. Effective therapies based

[2]) For some recent work on protein:farnesyltransferase inhibitors, see [7].

[3]) For structural information on protein:farnesyltransferase, see [8].

on hindering Ras K-4B function, therefore, require the inhibition of both PFT and PGGT I [12a,b]. The recent finding that natural PGGT I substrates (*e.g.*, RhoA) may mediate oncogenesis and/or metastasis underlines the importance of PGGT I as a therapeutic target [13].

An attractive strategy for the generation of PGGT I inhibitors[4]) comprises the design of structural analogues of the CaaX motif present in natural PGGT I substrates [14][5]). In this approach, the important pharmacophoric groups, *i.e.*, the Cys and Leu side chains, are interconnected *via* predesigned peptidomimetic linkers of the general structure **I** (*Fig. 1*). Desirable properties in terms of biostability (*e.g.*, resistance to peptidases) and bioactivity (*e.g.*, inducement of the bioactive conformation [8]) can be introduced by variation of the peptidomimetic linker [10][15].

In this respect,we and others have demonstrated the potential of sugar amino acids (SAAs)[6]), modified carbohydrates featuring an amine and a carboxylate, as useful peptidomimetic building blocks [17]. For instance, we have shown the application of partially deoxygenated gluconic amino acids (**II**: (1,5-*cis*) and **III**: (1,5-*trans*), *Fig. 1*) as building blocks in the construction of novel PFT inhibitors [18]. Furthermore, we have demonstrated that SAA **II**, when incorporated in oligopeptidic sequences, is capable of adopting a β-turn in aqueous solution [19]. As an extension of these studies, we here report the use of SAAs **II** and **III** in the synthesis of eight novel tetrapeptide analogues of the general design **IV** (see *Fig. 1*) that resemble the CaaX domain in the natural substrates of PGGT I. We demonstrate that the nature of the SAA building block, in conjunction with the configuration (L or D) of the Cys and Leu pharmacophores, has a distinct influence on the ability of compounds **IV** to inhibit PGGT I.

2. Results and Discussion. – 2.1. *Synthesis of the SAA Building Blocks (1,5*-cis/trans*)* **3**, *(1,5*-trans*)* **7**, *and (1,5*-cis*)* **8**. To ensure rapid access to the targeted CaaX mimetics **IV** (*Fig. 1*), we set out to develop an efficient synthesis protocol for the preparation of orthogonally protected SAA building blocks. In our first approach (*Scheme 1*), glucal **1**, readily prepared [20] from methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate, was treated with Me_3SiCN and $BF_3 \cdot OEt_2$ [21], to give 4,5-dideoxyglucopyranosyl cyanides (1,5-*cis*/*trans*) **2** (86%, *cis*/*trans ca.* 3:5) as an inseparable mixture of diastereoisomers. Reduction of the olefin and CN functionalities in **2** [22] followed by protection of the resulting primary amine as the (*tert*-butoxy)carboxylate (Boc), and final saponification of the acetate gave SAAs **3** as an inseparable mixture of diastereoisomers in 30% yield over the four steps. Gratifyingly, the (1,5-*trans*/*cis*) cyanides **4** and **5** resulting from acidic hydrolysis of **2** [23] could be separated by silica-gel chromatography (*Scheme 1*). Moreover, *C*-glycosides **4** and **5** were also accessible from the known, partially deprotected methyl glucuronate-D-glucal **6** [24]. Thus, treatment of **6** with $Pd(OAc)_2$ and Me_3SiCN in MeCN at 80° gave cyanides (1,5-*trans*) **4** and (1,5-*cis*) **5** in a ratio of 1:1 in 76% yield [25]. The individual

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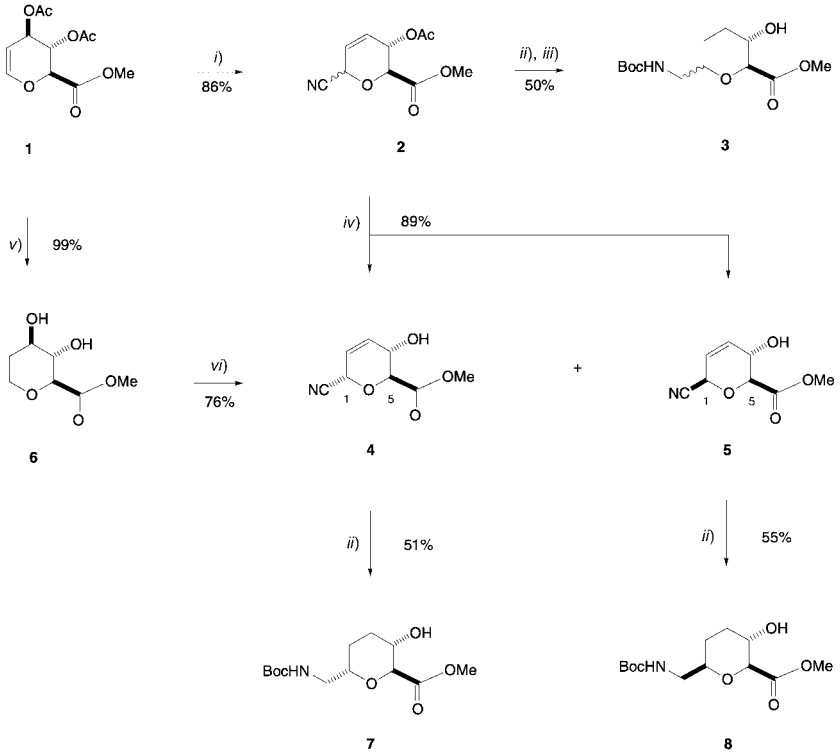
4) Tor some recent work on protein:geranylgeranyltransferase (inhibitors) see [12c–g].

5) The CaaX box has also been used as lead for the synthesis of PFT inhibitors [7j–q][18].

6) For some excellent reviews of sugar amino acids, see [16a–c]. For some examples of SAA as isosteric replacements in biologically active compounds, see [16d–g][17][18].

Scheme 1



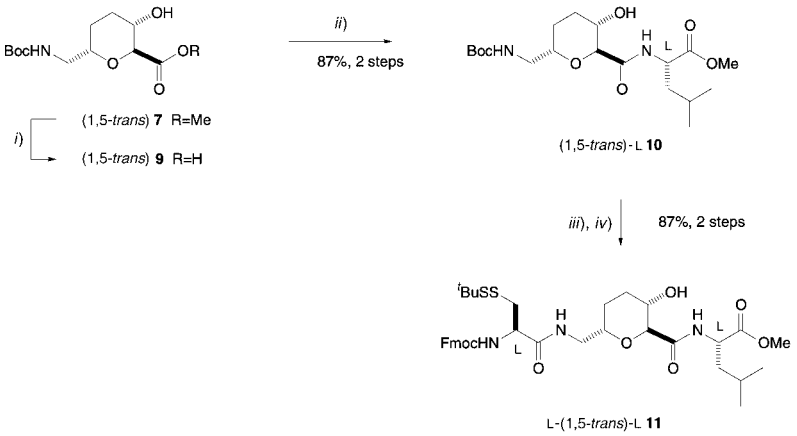
i) 1.1 Equiv. Me_3SiCN, 0.2 equiv. $BF_3 \cdot OEt_2$, CH_2Cl_2. *ii*) a) 10% Pd/C, MeOH/$CHCl_3$ 10:1, H_2 atm. (45 psi), 24 h; b) Boc_2O, Et_3N, CH_2Cl_2. *iii*) ^{t}BuOK, MeOH. *iv*) 0.05M HCl in MeOH, 60°, 5 h. *v*) MeONa, MeOH. *vi*) 5 mol-% $Pd(OAc)_2$, 5 equiv. Me_3SiCN, MeCN, 80°, 48 h.

diastereoisomers were then transformed (10% Pd/C, H_2; Et_3N, Boc_2O, CH_2Cl_2) into the corresponding orthogonally protected SAA building blocks (1,5-*trans*) **7** and (1,5-*cis*) **8**, in good overall yield.

2.2. *Synthesis of CaaX Mimetics* **16**–**18**, **20**, **22**, **24**, **26**, *and* **28**. The general route of synthesis of the fully protected CaaX mimetics is exemplified, as depicted in *Scheme 2*, in the preparation of compound L-(1,5-*trans*)-L **11**. Thus, saponification of the methyl ester in **7** and condensation of the resulting acid (1,5-*trans*) **9** [18] with Leu–OMe · HCl under the influence of PyBOP (= benzotriazol-1-yloxytripyridinophosphonium hexafluorophosphonate) and DiPEA (= *N*,*N*-diisopropylethylamine) in DMF afforded dimer (1,5-*trans*)-L **10** in 87% over the two steps. Removal of the Boc protective group in **10** and condensation of the resulting ammonium salt with Fmoc–L-Cys(S^{t}Bu)–OH (PyBOP, DiPEA, DMF) gave protected L-(1,5-*trans*)-L **11**. By the same synthetic procedure and with comparable efficiency, protected trimers **23** (from **7**) and **21** and **25** (starting from **8**; *Fig. 2*) were readily prepared.

In an alternative route to CaaX analogues **IV** (*Fig. 1*), the diastereoisomeric mixture of SAAs **3** is used in the initial peptide formation, followed by separation at a

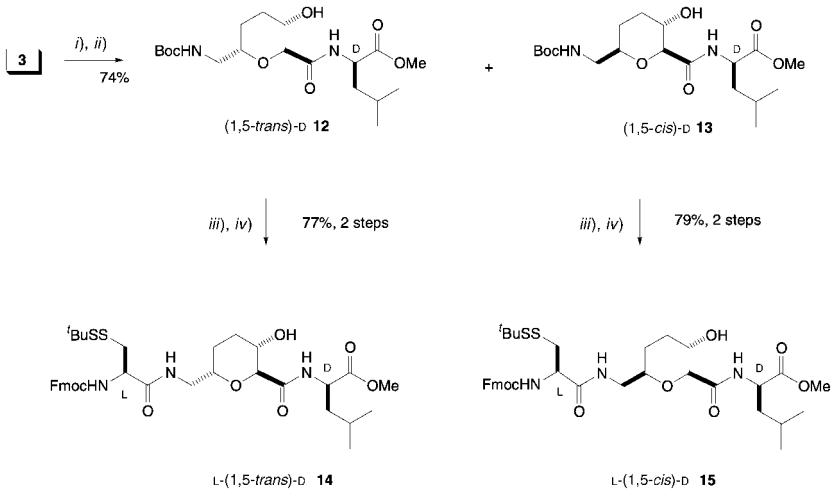
Scheme 2



i) 1.0 Equiv. LiOH (1.0M aq.), H_2O/dioxane 1:1, 0°. *ii*) 1.2 Equiv. L-Leu–OMe · HCl, 1.2 equiv. PyBOP, 4 equiv. DiPEA, DMF. *iii*) 50% TFA in CH_2Cl_2, 1.3 equiv. (i-Pr)$_3$SiH. *iv*) 1.2 Equiv. Fmoc–L-Cys(S^{t}Bu)–OH, 1.2 equiv. PyBOP, 4 equiv. DiPEA, DMF.

later stage (*Scheme 3*). Thus, saponification of SAAs (1,5-*cis*/*trans*) **3** followed by condensation with D-Leu–OMe · HCl (PyBOP, DiPEA, DMF) resulted in the formation of a mixture of diastereoisomeric dimers (1,5-*trans*)-D **12** and (1,5-*cis*)-D **13** (*cis*/*trans* 3:5), which could be readily separated by silica-gel chromatography. Elongation of the individual isomers with Fmoc–L-Cys(S^{t}Bu)–OH under the standard

Scheme 3



i) 1.0 Equiv. LiOH (1.0M aq.), H_2O/dioxane 1:1, 0°. *ii*) 1.2 Equiv. D-Leu–OMe · HCl, 1.2 equiv. PyBOP, 4 equiv. DiPEA, DMF. *iii*) 50% TFA in CH_2Cl_2, 1.3 equiv. (i-Pr)$_3$SiH. *iv*) 1.2 Equiv. Fmoc–L-Cys(S^{t}Bu)–OH, 1.2 equiv. PyBOP, 4 equiv. DiPEA, DMF.

conditions gave the respective fully protected trimers L-(1,5-*trans*)-D **14** and L-(1,5-*cis*)-D **15** in good yield. According to this protocol, D-(1,5-*trans*)-D **19** and D-(1,5-*cis*)-D **27** were prepared, completing the set of CaaX mimetics (*Fig. 2*).

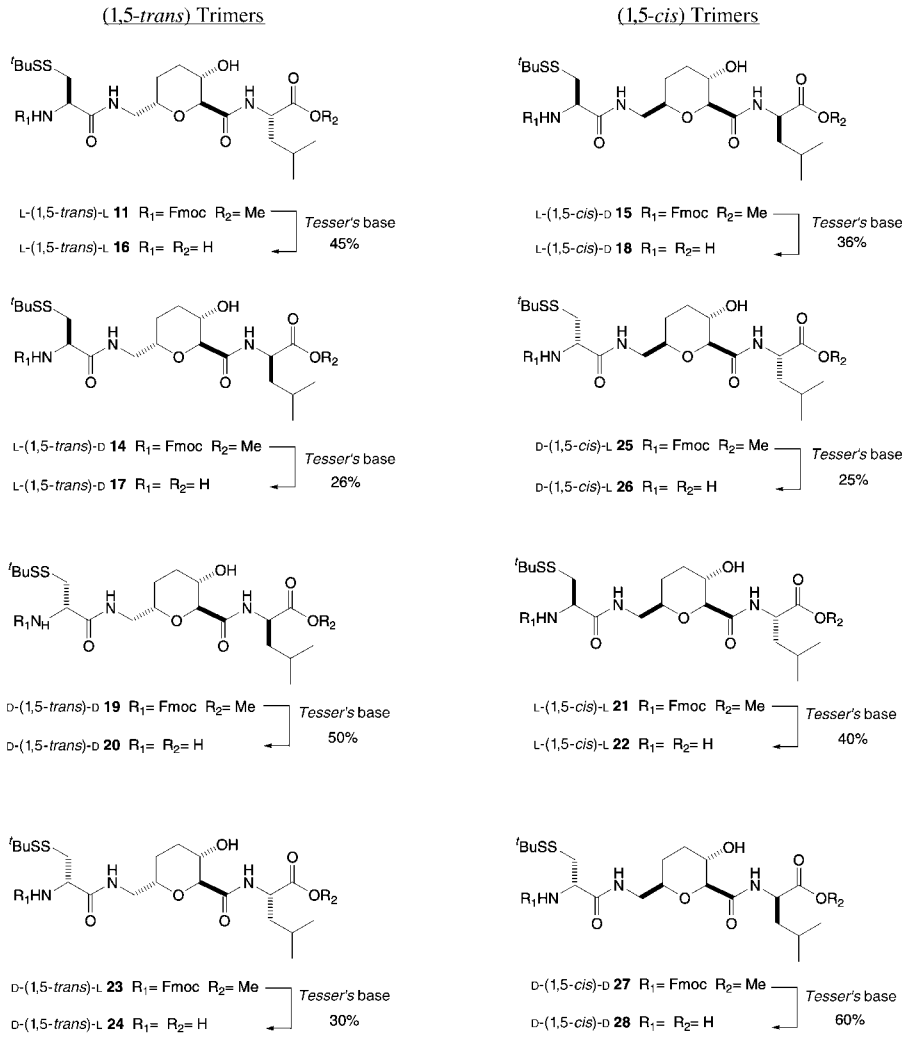


Fig. 2. *Structure of fully protected and deprotected trimers*

In a final deprotection step, concomitant removal of the Fmoc and methyl ester protecting groups in the eight CaaX mimetics proceeded smoothly with *Tesser*'s base (MeOH/dioxane/4M NaOH 15:4:1) to give the corresponding deprotected trimers **16**–**18**, **20**, **22**, **24**, **26**, and **28** (*Fig. 2*), which were purified by reverse-phase (RP) HPLC.

2.3. *NMR Analysis.* An important element in the design of our CaaX mimetics is the absolute configuration at C(5) relative to C(1) of the incorporated SAA building blocks. As epimerization may occur at various stages of the synthetic sequences

employed to prepare the trimeric CaaX analogues, we applied various NMR techniques to ensure that the individual configurational integrity of the SAA building blocks (**7** and **8**), as well as their synthetic precursors, is conserved in the final products. The initial *cis*/*trans* configuration was introduced onto the SAA scaffold in the course of the *Ferrier* rearrangement. To establish the absolute configurational outcome of the reaction, we applied NOESY experiments to the individual diastereoisomers of the SAA precursors (1,5-*trans*) **4** and (1,5-*cis*) **5**. Irradiation of H–C(5) (4.03 ppm, *Fig. 3*) in the more polar product (TLC analysis) of the 2,3-unsaturated glycopyranosyl cyanides showed enhancement of the signal of H–C(1) (5.17 ppm), which was in agreement with the (1,5-*cis*) configuration of **5**. As expected, irradiation of H–C(5) (5.18) and H–C(1) (4.25 ppm) in the less-polar product did not show a NOE, which is in agreement with the (1,5-*trans*)-configuration in **4**[7]).

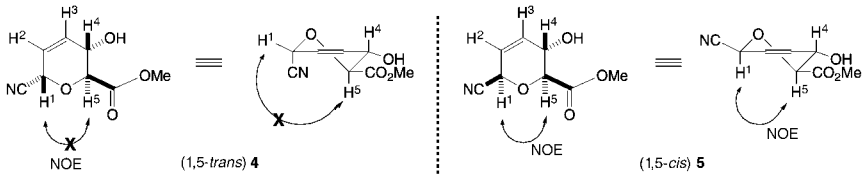


Fig. 3. *Structural assignment of (1,5-trans*) **4** *and (1,5-cis*) **5** *by NOE experiments*

To ensure that the initial configuration of the incorporated SAA building blocks is unchanged in the final products, we subjected trimer L-(1,5-*trans*)-L **11** to a NOESY correlation experiment (*Fig. 4*). The anticipated axial disposition of CH_2NH in L-(1,5-*trans*)-L **11** was confirmed by the observed NOE between H–C(5) (3.96 ppm) and the CH_2NH methylene protons (3.55 and 3.39 ppm, *Fig. 4*, boxed segments).

In addition to 2D-correlation ^{1}H-NMR, simple 1D ^{13}C-NMR provides rapid insight in the stereochemistry of *C*-glycosidic compounds. This is based on the general observation that the C(1) resonances for α-*C*-glycosides (1,5-*trans*) appear at higher field than those for the corresponding β-*C*-glycosides (1,5-*cis*) [26]. The chemical shifts of the hexopyranose C-atoms C(1–5) of the eight fully protected trimers, (*i.e.*, **11**, **14**, **15**, **19**, **21**, **23**, **25**, and **27**) are listed in *Table 1*. These results show that the chemical shift of C(1) of the (1,5-*trans*) compounds resonate at a higher field than those of the (1,5-*cis*) compounds. Interestingly, this characteristic difference in chemical shift is also observed for the resonances of C(2), C(3), C(4), and C(5). Analysis of the chemical shifts of the C-atoms of the SAA core of the unprotected L-(1,5-*trans*)-L **16** and L-(1,5-*cis*)-L **22** revealed a similar trend.

2.4. *Inhibition of PGGT I Activity by CaaX Mimetics* **16**–**18**, **20**, **22**, **24**, **26**, *and* **28**. The eight CaaX peptidomimetics were tested for their inhibitory activity against bovine PGGT I with purified enzyme in an *in-vitro* assay as published previously [27]. The thio *tert*-butyl protective group in the Cys residue is cleaved under the conditions of the assay (DTT(=dithiothreitol), pH 7.4) [28]. In *Table 2*, the IC_{50} values of the tested CaaX analogues are listed.

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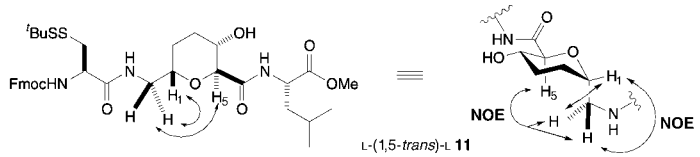
7) The negative $[\alpha]_D$ value for (1,5-*trans*) **4** ($[\alpha]_D^{25} = -134.4°$, $c = 1.0$, $CHCl_3$) and positive $[\alpha]_D$ value for (1,5-*cis*) **5** ($[\alpha]_D^{25} = +112.2°$, $c = 1.0$, $CHCl_3$), is consistent with data reported for optical rotations of 2,3-unsaturated *C*-glucopyranosides [26].



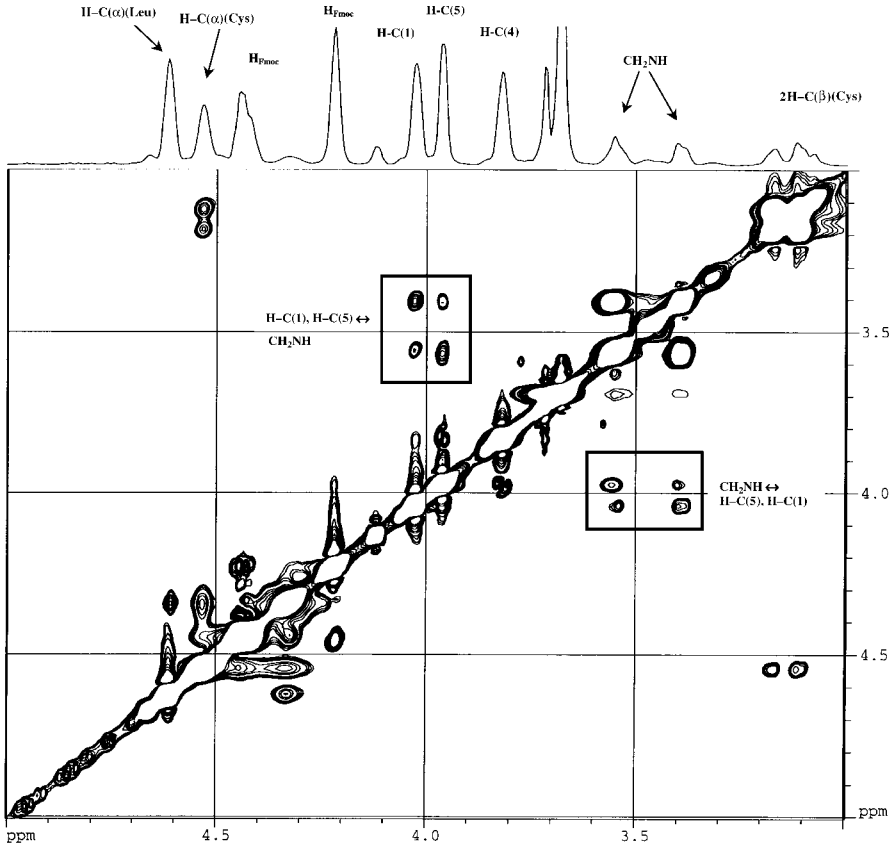


Fig. 4. *2D H,H-NOESY Spectrum of trimer* L-(1,5-*trans*)-L **11** ($CDCl_3$, 750 MHz)

As can be seen from *Table 2*, four of the eight CaaX mimetics (*i.e.*, **16**, **17**, **24**, and **26**) proved to be capable of inhibiting PGGT I in the μM range, whereas the remaining four (*i.e.*, **18**, **20**, **22**, and **28**) showed little or no inhibition at mM concentrations. Remarkably, the two most potent inhibitors of the series, **16** and **26**, contain (1,5-*trans*) and (1,5-*cis*) SAA residues, respectively. They further differ in the configuration of the Cys residue (L *vs.* D, resp.). On the other hand, incorporation of both D-amino acids in both examples leads to inactive compounds (*i.e.*, (1,5-*trans*) **20** and (1,5-*cis*) **28**).

Table 1. *^{13}C-NMR Chemical Shifts of C(1)–C(5) of Compounds* **11**, **14**, **19**, **23**, **15**, **21**, **25**, **27**, **16**, *and* **22**

		$\delta(^{13}C)$ [ppm]				
Protected trimer[a])		C(1)	C(2)	C(3)	C(4)	C(5)
L-(1,5-*trans*)-L	**11**	72.5	23.8	27.2	66.3	76.5
L-(1,5-*trans*)-D	**14**	72.3	23.3	26.4	65.4	76.1
D-(1,5-*trans*)-D	**19**	72.5	23.6	27.1	65.8	77.1
D-(1,5-*trans*)-L	**23**	72.1	23.6	26.3	66.1	75.0
L-(1,5-*cis*)-D	**15**	76.4	27.3	30.9	68.4	78.3
L-(1,5-*cis*)-L	**21**	77.2	27.5	31.4	68.9	78.9
D-(1,5-*cis*)-L	**25**	76.3	27.0	30.5	67.8	78.0
D-(1,5-*cis*)-D	**27**	76.6	27.2	30.6	68.1	78.1
Unprotected trimer[b])						
L-(1,5-*trans*)-L	**16**	70.9	22.3	26.2	63.3	77.5
L-(1,5-*cis*)-L	**22**	75.2	27.4	31.4	67.1	80.6

[a]) Measured in $CDCl_3$. [b]) Measured in (D_6)DMSO.

Table 2. *Inhibition (IC_{50}) of Bovine PGGT I by* **16**–**18**, **20**, **22**, **24**, **26**, *and* **28**

Compound		IC_{50}
L-(1,5-*trans*)-L	**16**	68 ± 16 μM
L-(1,5-*trans*)-D	**17**	241 ± 75 μM
D-(1,5-*trans*)-L	**24**	109 ± 30 μM
D-(1,5-*trans*)-D	**20**	> 1000 μM
L-(1,5-*cis*)-L	**22**	*ca.* 1000 μM
L-(1,5-*cis*)-D	**18**	> 1000 μM
D-(1,5-*cis*)-L	**26**	69 ± 20 μM
D-(1,5-*cis*)-D	**28**	*ca.* 1000 μM

3. Conclusions. – In summary, we have presented a useful strategy for the preparation of novel PGGT I inhibitors. Our approach is based on the incorporation of partially deoxygenated (1,5-*cis*/*trans*) SAA building blocks, which, in turn, were prepared from the common starting compound **1**. Variation of the SAA, in combination with the introduction of the Cys and Leu pharmacophores as the D- and L-amino acid derivatives, furnished eight novel peptidomimetics that resemble the CaaX motif present in PGGT I substrate proteins. Of these, four were found to be inhibitors of PGGT I in the μM range, whereas the other four showed no inhibition at mM concentrations.

The two most potent inhibitors of the series, L-(1,5-*trans*)-L **16** and D-(1,5-*cis*)-L **26**, differ both in the nature of the SAA building blocks and the stereochemistry of the Cys residues. This observation indicates that both (1,5-*trans*) **7** and (1,5-*cis*) **8** can be used for the development of novel PGGT I inhibitors. To develop the leads presented here into clinically relevant inhibitors, a detailed structure-activity study is required. We are pursuing our research activities along these lines, with focus on the preparation of other diastereoisomers, *e.g.*, by variation of the SAA core.

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Experimental Part

General. Solvents: MeCN, $CHCl_3$, 1,2-dichloroethane, CH_2Cl_2, DMF, dioxane, and toluene (p.a. *Baker*) were stored on molecular sieves (4 Å); MeOH (p.a. *Baker*) was stored on molecular sieves (3 Å). Petroleum ether (PE, 40–60 fraction) and AcOEt were of technical grade and were distilled before use. Et_3N (99%, Acros) was freshly distilled over CaH_2 before each use. DiPEA (peptide grade) and TFA were purchased from *Biosolve* and used without purification. L-Leu–OMe · HCl, Fmoc–L-Cys(S^{t}Bu)–OH, and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) were obtained from *Novabiochem* and used as received. D-Leu–OMe · HCl and Fmoc–D-Cys(S^{t}Bu)–OH were obtained from *Bachem* and were used as received. BF_3OEt_2, ^{i}Pr$_3$SiH, and 10% Pd/C were from *Aldrich*, and di-*tert*-butyl dicarbonate (Boc_2O), D-(+)-glucuronic acid-γ-lactone, trimethylsilyl cyanide (Me_3SiCN) and $Pd(OAc)_2$ were from *Fluka* and were used as received. Reversed-phase (RP) HPLC analysis and purification were performed on a *Jasco HPLC* system equipped with a *Merck Lichrosphere C18 100Å* column (4 × 250 mm). ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a *Bruker AC-200* (^{1}H-NMR 200 MHz, ^{13}C-NMR 50 MHz), *Bruker WM-300* (^{1}H-NMR 300 MHz; ^{13}C-NMR 75 MHz), *Bruker AV-400* (^{1}H-NMR 400 MHz, ^{13}C-NMR 100 MHz), *Bruker DMX-600* (^{1}H-NMR 600 MHz, ^{13}C-NMR 150 MHz), or a *Bruker DSX-750* (^{1}H-NMR 750 MHz, ^{13}C-NMR 188 MHz). Chemical shifts δ in ppm rel. to Me_4Si as internal standard; coupling constants J in Hz. ^{13}C-NMR: $CDCl_3$ soln.; middle resonance of $CDCl_3$ (77.0 ppm) as internal standard. MS: *Perkin-Elmer SCIEX API-165* quadrupole mass spectrometer; HR-MS: *API QSTAR™ Pulsar* (*Applied Biosystems*) *m/z*. Reactions were followed by TLC analysis on silica gel (*Schleicher & Schuell*, *F 1500 LS 254*) or *HPTLC* aluminium sheets (*Merck*, *silica gel 60*, *F254*), with detection by UV-absorption (254 nm) where applicable and charring at 150° with 20% H_2SO_4 in EtOH (25 g/l), ninhydrin (3 g/l) in EtOH/AcOH 100:3, $NH_4(Mo)_7O_{24} \cdot 4H_2O$ (25 g/l), and $NH_4Ce(SO_4)_4 \cdot 2H_2O$ (10 g/l) in 10% aq. H_2SO_4 or $KMnO_4$ (2%) in aq. K_2CO_3 (1%). Column chromatography (CC) was performed on silica gel (*Baker*; 0.063–0.200 mm).

General Procedures. General Procedure 1 (*GP 1*). *Hydrogenation and Boc Protection*. To a 0.25M soln. of the 2,3-unsaturated hexopyranosyl cyanide in MeOH/$CHCl_3$ 10:1 (20 ml) was added 10% Pd on activated carbon (25 mass %). The mixture was shaken overnight under H_2 (310 kPa). After TLC analysis (AcOEt) showed complete conversion of the starting material to a ninhydrin-positive product (base-line spot), the catalyst was filtered off over *Hyflo* and the solvent was removed under reduced pressure. The crude product was used without further purification for the next reaction. To a *ca*. 0.1M soln. of the crude amine in CH_2Cl_2, 1.2 equiv. of Boc_2O and 2.2 equiv. of Et_3N were added. After TLC analysis showed consumption of the starting material (PE/AcOEt 1:1), H_2O was added. The aq. layer was extracted with AcOEt (2×). The combined org. layers were washed with brine, dried ($MgSO_4$), and the solvent was removed *in vacuo*.

General Procedure 2 (*GP 2*). *Saponification of the Methyl Ester Sugar Amino Acid Building Block*. To a 0.1M soln. of the methyl ester in dioxane/H_2O 1:1 at 0° was added 1.1 equiv. LiOH (1.0M). After TLC analysis (AcOEt) showed consumption of the starting material, the reaction was neutralized (pH 7) by addn. of AcOH, and the solvents were removed *in vacuo*. The residue obtained was used without further purification for the amino acid coupling.

General Procedure 3 (*GP 3*). *Coupling of Sugar Amino Acid Building Block to Leu–OMe · HCl*. To a 0.1M soln. of the sugar amino acid in DMF was added Leu–OMe · HCl (1.2 equiv.), PyBOP (1.2 equiv.), and DiPEA (4 equiv.). After TLC analysis (PE/AcOEt 1:1) showed consumption of the starting material, DMF was removed *in vacuo*. The residue was dissolved in AcOEt and washed with H_2O (2×), sat. $NaHCO_3$ (2×), H_2O (2×), 5% $KHSO_4$ (2×), and brine. The org. phase was dried ($MgSO_4$), and the solvent was removed *in vacuo*.

General Procedure 4 (*GP 4*). *Boc Deprotection*. To a 0.05M soln. of the dimer in CH_2Cl_2 were added 1.3 equiv. of ^{i}Pr$_3$SiH and TFA (CH_2Cl_2/TFA 1:1). After TLC analysis (30 min, PE/AcOEt 1:1) showed consumption of the starting material, the mixture was co-evaporated with toluene (3×).

General Procedure 5 (*GP 5*). *Coupling of Dimer to Fmoc–Cys(S^{t}Bu)–OH*. To a 0.1M soln. of the deprotected dimer in DMF were added DiPEA (4 equiv.), Fmoc–Cys(S^{t}Bu)–OH (1.2 equiv.), and PyBOP (1.2 equiv.). After TLC analysis (PE/AcOEt 1:1) showed consumption of the starting material, the reaction was worked up as in GP 2.

General Procedure 6 (*GP 6*). *Deprotection of the Trimer with* Tesser's *Base.* A 0.01M soln. of the trimer in *Tesser*'s base (MeOH/dioxane/4M NaOH 15:4:1) was stirred at 0° and then was allowed to warm to r.t. After TLC analysis (PE/AcOEt 1:1) showed consumption of the starting material, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (3×). The aq. layer was collected and neutralized with AcOH. Evaporation gave the crude product, which was then subjected to purification by RP-HPLC.

Determination of IC_{50} *Values.* For the determination of the IC_{50} values of the CaaX analogues, the assay was repeated at least 3× in the presence of the various concentrations of the compounds (10 μM, 30 μM, 100 μM, 300 μM, and 1000 μM) and the concentration at 50% inhibition was determined by fitting a mathematical function to the concentration/inhibition curve. For an exhaustive description of the protocol, see [27].

Methyl 3,4-Di-O-*acetyl-1,2-dideoxy*-D-arabino-*hex-1-enopyranuronate* (**1**) was obtained from commercially available methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate as described in [20] as a white crystalline compound in 90% yield over 4 steps (250-mmol scale).

*Methyl (1*RS*)-4*-O-*Acetyl-1-cyano-1,2,3-trideoxy*-D-arabino-*hex-2-enopyranuronate* (**2**). To a soln. of **1** (5.01 g, 19.4 mmol; co-evaporated twice with 1,2-dichloroethane) in CH_2Cl_2 (50 ml) was added Me_3SiCN (2.91 ml, 23.3 mmol, 1.2 equiv.) and $BF_3 \cdot OEt_2$ (0.49 ml, 0.2 equiv.). The mixture was stirred for 1 h, after which TLC analysis (PE/acetone 4:1) showed complete conversion of the starting material. The reaction was quenched with sat. $NaHCO_3$ (50 ml) and diluted with AcOEt (50 ml). The aq. layer was extracted with AcOEt (2 × 50 ml). The combined org. phases were washed with sat. $NaHCO_3$ (50 ml) and brine (50 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo* and CC (PE/acetone 4:1) gave **2** as a yellow oil (3.76 g, 86%). ^{1}H-NMR (300 MHz, $CDCl_3$): mixture of diastereoisomers: 6.21 – 5.95 (*m*, H–C(2), H–C(3)); 5.55 (*m*, H–C(4)); 5.34, 5.22 (2 *dd*, *J* = 2.6, 7.1; *J* = 3.3, 4.0, H–C(1)); 4.47, 4.44 (2 *d*, *J* = 4.3, 6.3, H–C(5)); 3.81, 3.79 (2 *s*, MeO); 2.12, 2.09 (2 *s*, MeCO). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 169.4 (Me*C*O_2, *C*O_2Me); 126.7, 125.7 (C(2)); 124.8, 124.4 (C(3)); 115.1 (C≡N); 73.4, 72.4 (C(5)); 63.4, 62.8 (C(4)); 61.3, 60.9 (C(1)); 52.3, 52.2 (CO_2*Me*); 20.1 (*Me*CO). MS: 248.1 ($[M+Na]^+$).

*Methyl (1*S*)- and (1*R*)-1-Cyano-1,2,3-trideoxy*-D-arabino-*hex-2-enopyranuronate* (**4** and **5**, resp.). *Method 1:* To a soln. of **2** (2.00 g, 8.88 mmol; twice co-evaporated with 10 ml toluene) was added a 0.05M methanolic HCl soln. (50 ml). The mixture was stirred for 5 h at 60°, after which TLC analysis (AcOEt) showed complete conversion of the starting material. The reaction was quenched with sat. $NaHCO_3$ (50 ml) and diluted with AcOEt (50 ml). The aq. layer was extracted with AcOEt (50 ml). The combined org. phases were washed with sat. $NaHCO_3$ (25 ml) and brine (25 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo*, and CC (PE/AcOEt, 1:1) gave **4** and **5** as colorless oils (total yield 1.45 g, 89%). *Method 2:* To a soln. of *methyl 1,2-dideoxy*-D-arabino-*hex-1-enopyranuronate* (**6**) [23] (236 mg, 1.36 mmol; co-evaporated twice with 10 ml toluene) in Me_3CN (20 ml) was added 5 mol-% $Pd(OAc)_2$ (15 mg) and 5 equiv. Me_3SiCN (0.85 ml, 6.80 mmol). The mixture was stirred for 72 h at 80°, after which TLC analysis showed complete conversion of the starting material. The reaction was quenched with 0.1N HCl (25 ml), and the mixture was diluted with AcOEt (50 ml). The aq. layer was extracted with AcOEt (2 × 50 ml). The combined org. phases were washed with sat. $NaHCO_3$ (50 ml) and brine (50 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo* and CC (PE/AcOEt, 1:1) yielded **4** and **5** as colorless oils (total yield 189 mg, 76%).

Data of **4**: $[\alpha]_D^{25} = -134.4°$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.12 (*dt*, *J* = 2.2, H–C(2)); 5.83 (*ddd*, *J* = 2.0, 3.2, H–C(3)); 5.18 (*dd*, *J* = 2.3, 5.4, H–C(1)); 4.47 – 4.41 (*m*, H–C(4)); 4.25 (*d*, *J* = 8.1, H–C(5)); 3.87 (*s*, MeO). ^{13}C-NMR (APT, 75 MHz, $CDCl_3$): 169.7 (C=O); 131.8 (C(2)); 121.9 (C(3)); 115.4 (C≡N); 74.5 (C(1)); 63.7, (C(4), C(5)); 53.0 (CO_2*Me*). MS: 184.2 ($[M+H]^+$), 206.2 ($[M+Na]^+$). HR-MS: 184.0605 ($[C_8H_9NO_4+H^+]$; calc. 184.0609).

Data of **5**: $[\alpha]_D^{25} = +112.2°$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.13 (*dt*, *J* = 2.6, H–C(2)); 5.93 (*dt*, *J* = 1.9, H–C(3)); 5.17 (*dd*, *J* = 2.5, 4.7, H–C(1)); 4.54 – 4.49 (*m*, H–C(4)); 4.03 (*d*, *J* = 7.6, H–C(5)); 3.87 (*s*, MeO). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 169.5 (C=O); 131.3 (C(5)); 122.3 (C(3)); 115.5 (C≡N); 76.6 (C(1)); 63.2, 63.0 (C(4), C(5)); 52.9 (MeO). MS: 184.2 ($[M+H]^+$), 206.2 ($[M+Na]^+$). HR-MS: 184.0647 ($[C_8H_9NO_4+H]^+$; calc. 184.0609).

*Methyl (1*S*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy*-D-arabino-*hexopyranuronate* (**7**). Treatment of **4** (100 mg, 0.55 mmol) according to *GP 1* followed by CC (PE/AcOEt 1:1) yielded **7** as a colorless oil (87 mg, 51% over 2 steps). ^{13}C-NMR (600 MHz, $CDCl_3$): 5.08 (br. *s*, NH); 4.35 (br. *s*, H–C(1)); 4.14 (br. *s*, H–C(5)); 3.80 (*m*, H–C(4)); 3.74 (*s*, CO_2Me); 3.28, 3.12 (2 *m*, CH_2NH); 1.80, 1.70, 1.50 (3 *m*, 2 H–C(2), 2 H–C(3)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 170.7 (*C*O_2Me); 156.2 (*C*$O_2{}^t$Bu); 79.2 (Me_3C); 75.5 (C(1)); 72.3 (C(5)); 65.1 (C(4)); 52.1 (CO_2*Me*); 44.4 (CH_2NH); 28.5 (*Me*$_3$C); 26.6 (C(3)); 22.1 (C(2)). MS: 312.1 ($[M+Na]^+$).

*Methyl (1*R*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl-1,2,3-trideoxy-*D-arabino-*hexopyranuronate* (**8**). Treatment of **5** (362 mg, 1.98 mmol) according to *GP 1* followed by CC (PE/AcOEt 1:1) yielded **8** as a colorless oil (271 mg, 55%). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.07 (br. *s*, NH); 3.82 (*s*, CO_2Me); 3.80–3.6 (*m*, H–C(1), H–C(4), H–C(5)); 3.46–3.32 (*m*, CH_2NH); 2.20 (*m*, H–C(2)); 1.70, 1.59–1.48 (*m*, H–C(2), 2 H–C(3)); 1.45 (*s*, ^{t}Bu). ^{13}C-NMR (APT, 100 MHz, CD_3OD): 172.6 (CO_2Me); 158.3 ($CO_2{}^t$Bu); 82.8, 77.8, 68.6 (C(1), C(4), C(5)); 80.1 (Me_3C); 52.6 (CO_2Me); 45.5 (CH_2NH); 32.7 (C(3)); 28.7 (Me_3C); 28.6 (C(2)). MS: 312.1 ($[M+Na]^+$).

*Methyl (1*RS*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-*D-arabino-*hexopyranuronate* (**3**). Treatment of **2** (1.50 g, 6.67 mmol) according to *GP 1* followed by CC (PE/AcOEt 1:1) yielded *methyl (1*RS*)-3-*O*-Acetyl-1-({*N-*[(*tert-*butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-*D-arabino-*hexopyranuronate* as a colorless oil (1.26 g, 57% over two steps). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 169–168.8 (*C*OMe, *C*O_2Me); 155.7, 155.5 (*C*OO^tBu); 78.6, 78.5 (Me_3C); 77.9, 76.6, 74.9, 71.8, 68.1, 68.9 (C(1), C(4), C(5)); 51.8 (CO_2Me); 44.5, 44.9 (CH_2NH); 28.1, 26.5, 23.9, 22.0 (C(2), C(3)); 27.8 (Me_3C); 20.6, 20.3 (OCO*Me*). MS: 332.2 ($[M+H]^+$), 354.1 ($[M+Na]^+$).

The diastereoisomeric mixture (458 mg, 1.38 mmol) was dried by co-evaporation with dioxane (3 × 10 ml) and dissolved in MeOH (20 ml) followed by addn. of ^{t}BuOK (31 mg, 0.28 mmol). When the reaction was complete by TLC (PE/AcOEt 1:1), the mixture was neutralized (*Dowex*-H^+, pH 7), and the solvent was removed *in vacuo*. The product was washed with H_2O (25 ml) and brine (25 ml), extracted with AcOEt (2 × 25 ml), and the collected org. phases were dried ($MgSO_4$); CC (PE/AcOEt 1:1) afforded **3** as a colorless oil (346 mg, 87%). The NMR data were in full agreement with those of the individual diastereoisomers **7** and **8**.

*(1*S*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trihydroxy-*D-arabino-*hexopyranuronic Acid* (**9**). From **7** (25 mg, 86 μmol) and aq. LiOH (1.0M, 90 μl) according to *GP 2*. The crude product was used without purification for the amino acid coupling. ^{1}H-NMR (300 MHz, $CDCl_3/CD_3OD$): 4.32, 4.17, 3.95 (*m*, H–C(1), H–C(4), H–C(5)); 3.24–3.17 (*m*, CH_2NH); 1.89–1.72, 1.45 (*m*, 3 H, H–C(2), H–C(3)); 1.44 (br. *s*, ^{t}Bu). ^{13}C-NMR (APT, 50 MHz, $CDCl_3/CD_3OD$): 173.0 (COOH); 157.6 (*C*OO^tBu); 79.7 (Me_3C); 78.2 (C(1)); 72.5 (C(5)); 65.2 (C(4)); 45.1 (CH_2NH); 28.6 (Me_3C); 27.0 (C(3)); 22.4 (C(2)). MS: 298.2 ($[M+Na]^+$).

N-*[(1*S*)-1-({*N-*(tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl]-*L-*leucine Methyl Ester* (**10**). From **9** and L-Leu–OMe · HCl (19 mg, 0.1 mmol) according to *GP 3*, yield after CC (AcOEt) gave **10** as a colorless oil (30 mg, 87% over 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.00 (*d*, *J* = 8.3, Leu–NH); 4.80 (br. *s*, N*H*Boc); 4.62 (*m*, H–C(2)); 3.98 (*m*, H–C(1′)); 3.92 (*d*, *J* = 8.3, H–C(5′)); 3.74 (*s*, CO_2Me); 3.71 (*m*, H–C(4′)); 3.47, 3.26 (2 *m*, CH_2NH); 1.95, 1.90–1.56 (2 *m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.45 (*s*, ^{t}Bu); 0.96 (*dt*, *J* = 3.2, 3.3, 6.2, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 172.8, 171.8 (C(1), C(6′)); 155.9 (*C*OO^tBu); 79.6 (Me_3C); 73.5 (C(1′)); 72.7 (C(5′)); 67.6 (C(4′)); 52.3 (C(2)); 50.2 (CO_2Me); 41.4 (CH_2NH); 40.6 (C(3)); 28.3 (Me_3C); 28.1 (C(3′)); 26.4 (C(2′)); 24.9 (C(4)); 24.2 (C(2′)); 22.7, 21.9 (Me_2C(4)). MS: 403.5 ($[M+H]^+$), 425.3 ($[M+Na]^+$).

*(1*R*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trihydroxy-*D-arabino-*hexopyranuronic Acid.* From **8** (25 mg, 86 μmol) and aq. LiOH (1.0M, 90 μl) according to *GP 2*. The product was used without purification for the amino acid coupling. ^{13}C-NMR (APT, 50 MHz, CD_3OD): 173.9 (COOH); 158.0 (*C*OO^tBu); 81.5 (C(1)); 77.7 (C(5)); 68.3 (C(4)); 45.1 (CH_2NH); 32.4 (C(3)); 28.1 (C(2)); 28.7 (C(*Me*)$_3$); MS: 298.2 ($[M+Na]^+$).

N-*[(1*R*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-arabino-*hexapyranos-6-yl]-*L-*leucine Methyl Ester*. From **8** (25 mg, 86 μmol) and aq. LiOH (1.0M, 90 μl) according to *GP 2* and L–Leu–*O*Me · HCl (19 mg, 0.1 mmol) according to *GP 3*, and purification CC (AcOEt) gave the product as a colorless oil (32 mg, 92% over 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.02 (*d*, *J* = 7.2, Leu-NH); 4.85 (br. *s*, N*H*Boc); 4.59 (*m*, H–C(2)); 3.75 (*s*, CO_2Me); 3.64 (*d*, *J* = 9.5, H–C(5)); 3.54 (*m*, H–C(1′), H–C(4′)); 3.28 (*m*, CH_2NH); 2.20 (*m*, H–C(3′)); 1.80–1.40 (*m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.46 (*s*, ^{t}Bu); 0.96 (*t*, *J* = 5.8, 11.7, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 172.8, 172.2 (C(1), C(6′)); 156.0 (*C*OO^tBu); 79.5 (Me_3C); 78.2 (C(1′)); 77.5 (C(5′)); 68.3 (C(4′)); 52.4 (CO_2Me); 50.2 (C(2)); 44.7 (CH_2NH); 41.1 (C(3)); 30.6 (C(3′)); 28.4 (Me_3C); 27.1 (C(2′)); 24.9 (C(4)); 22.7, 21.9 (Me_2C(4)). MS: 403.5 ($[M+H]^+$), 425.3 ($[M+Na]^+$).

N-*[(1*RS*)-1-({*N-*[(*tert-*Butyl)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl]-*L-*leucine Methyl Ester*. From **3** (204 mg, 0.71 mmol) and aq. LiOH (1.0M, 0.75 ml) according to *GP 2*. The crude product was used without purification for coupling with L-Leu–OMe · HCl (154 mg, 0.85 mmol) according to *GP 3*. Purification by CC (PE/AcOEt 1:1) afforded the product as a colorless oil (241 mg, 84% over 2 steps). The NMR data of the product were in full agreement with those of the individual diastereoisomers.

N-*[(1*S*)-1-({*N-*[(*tert-*Butoxy)carbonyl]amino}methyl-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl]-*D-*leucine Methyl Ester* (**12**) *and* N-*[(1*R*)-1-({1-*[(*tert-*Butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-

arabino-*hexapyranos-6-yl*-D-*leucine Methyl Ester* (**13**). From **3** (75 mg, 0.26 mmol) and aq. LiOH (1.0M, 0.3 ml) according to *GP 2*. The crude product was used without purification for coupling with D-Leu–*O*Me · HCl (56 mg, 0.31 mmol) according to *GP 3*. Purification by CC (PE/AcOEt 1:1) afforded **12** and **13** as mixture of colorless oils (total yield 77 mg, 74% over 2 steps).

Data of **12**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.00 (*d*, *J* = 8.6, Leu-NH); 4.78 (br. *s*, N*H*Boc); 4.61 (*m*, H–C(2)); 3.95 (*m*, H–C(1′)); 3.90 (br. *s*, H–C(5′)); 3.82 (*m*, H–C(4′)); 3.75 (*s*, CO_2Me); 3.53, 3.18 (2*m*, CH_2NH); 1.94, 1.79–1.45 (2*m*, H–C(2′), H–C(3′), 2 H–C(3), H–C(4), ^{t}Bu); 0.96 (*d*, *J* = 5.4, *Me*$_2$C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.1, 171.7 (C(1), C(6′)); 155.9 (*C*OO^{t}Bu); 79.5 (Me$_3$*C*); 74.0 (C(1′)); 72.7 (C(5′)); 66.9 (C(4′)); 52.4 (C(2)); 50.1 (CO_2*Me*); 41.4 (CH_2NH); 41.1 (C(3)); 28.3 (*Me*$_3$C); 26.4 (C(3′)); 24.9 (C(4)); 23.9 (C(2′)); 22.7, 21.8 (*Me*$_2$C(4)). MS: 403.5 ([*M* + H]$^+$), 425.3 ([*M* + Na]$^+$).

Data of **13**: ^{1}H-NMR (300 MHz, $CDCl_3$): 7.05 (*d*, *J* = 6.9, Leu-NH); 4.84 (br. *s*, N*H*Boc); 4.61 (*m*, H–C(2)); 3.76 (*s*, CO_2Me); 3.71–3.51 (*m*, H–C(1′), H–C(4′), H–C(5′)); 3.36–3.17 (*m*, CH_2NH); 2.17, 1.76–1.36 (*m*, 2 H–C(2′), 2 H–C(3′), 2 H–C(3), H–C(4)); 1.46 (*s*, ^{t}Bu); 0.96 (*t*, *J* = 1.9, 3.9, *Me*$_2$C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 172.0, 172.4 (C(1), C(6′)); 155.2 (*C*OO^{t}Bu); 79.5 (Me$_3$*C*); 77.4 (C(1′)); 76.4 (C(5′)); 68.6 (C(4′)); 51.5 (C(2)); 49.3 (CO_2*Me*); 43.8 (CH_2NH); 40.2 (C(3)); 29.8 (C(3′)); 27.5 (*Me*$_3$C); 26.1 (C(2′)); 24.0 (C(4)); 21.9, 21.0 (*Me*$_2$C(4)). MS: 403.5 ([*M* + H]$^+$), 425.3 ([*M* + Na]$^+$).

N-*(1*S*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*L-*cysteinyl)*amino*]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*L-*leucine Methyl Ester* (**11**). From **10** (29 mg, 79 μmol) and Fmoc–L-Cys(S^{t}Bu)–OH (37 mg, 86 μmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **11** as a colorless oil (45 mg, 87% over 2 steps). ^{1}H-NMR (750 MHz, $CDCl_3$): 7.76 (*dd*, *J* = 2.3, 7.2, 2 arom. H); 7.58 (*dd*, *J* = 7.2, 16.3, 2 arom. H); 7.40 (*dd*, *J* = 4.8, 7.3, 2 arom. H); 7.30 (*t*, *J* = 7.2, 7.3, 2 arom. H); 7.12 (*d*, *J* = 7.4, Leu–NH); 6.79 (br. *s*, CONH); 6.07 (*d*, *J* = 5.3, Cys–NH); 4.61 (*m*, H–C(2)); 4.55 (*m*, H–C(2″)); 4.46–4.42 (*m*, CH_2O); 4.21 (*t*, H–C(9‴)); 4.02 (*m*, H–C(1′)); 3.96 (*d*, *J* = 7.7, H–C(5′)); 3.81 (*m*, H–C(4′)); 3.68 (*s*, CO_2Me); 3.55, 3.39 (2*m*, CH_2NH); 3.10 (*m*, 2 H–C(3″)); 1.93, 1.79 (2*m*, H–C(2′), H–C(3′)); 1.68–1.58 (*m*, H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.46 (*s*, ^{t}Bu); 0.92 (*dd*, *J* = 2.4, 5.7, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.3, 171.7, 170.7 (C(1), C(6′), C(1″)); 156.7 (Fmoc–CO); 144.7, 141.8 (2 arom. C); 128.3, 127.7, 125.9, 120.5 (arom. CH); 76.5 (C(5′)); 72.5 (C(1′)); 67.2 (C(10‴)); 66.3 (C(4′)); 55.5 (C(2″)); 52.2 (CO_2*Me*); 50.6 (C(2)); 48.1 (Me$_3$*C*S); 47.7 (C(9‴)); 43.3 (CH_2NH); 41.8, 40.9 (C(3), C(3″)); 29.8 (*Me*$_3$CS); 27.2 (C(3′)); 25.3 (C(4)); 23.8 (C(2′)); 23.0, 21.5 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*S*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*L-*cysteinyl)amino*]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*D-*leucine Methyl Ester* (**14**). From **12** (100 mg, 0.25 mmol) and Fmoc–L-Cys(S^{t}Bu)–OH (116 mg, 0.27 mmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **14** as a colorless oil (137 mg, 77% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.80 (*d*, *J* = 7.5, 2 arom. H); 7.60 (*d*, *J* = 7.5, 2 arom. H); 7.41 (*t*, *J* = 7.4, 7.5, 2 arom. H); 7.31 (*t*, *J* = 7.4, 2 arom. H); 7.10 (*d*, *J* = 8.8, Leu–NH); 6.74 (br. *s*, CONH); 5.78 (br. *s*, Cys–NH); 4.66 (*m*, H–C(2)); 4.45 (*dd*, *J* = 7.2, 10.5, CH_2O); 4.39 (*m*, H–C(2″)); 4.22 (*t*, *J* = 7.0, H–C(9‴)); 4.08 (*d*, *J* = 6.4, H–C(5′)); 3.98 (*m*, H–C(4′)); 3.89 (*m*, H–C(1′)); 3.71 (*s*, CO_2Me); 3.31, 3.11 (2 *m*, CH_2NH); 3.05 (*dd*, *J* = 6.9, 13.6, 2 H–C(3″)); 1.91 (*m*, H–C(3′)); 1.72–1.61 (*m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, ^{t}Bu); 0.93 (*t*, *J* = 4.2, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.4, 171.1, 170.1 (C(1), C(6′), C(1″)); 156.0 (Fmoc–CO); 143.6, 141.3 (2 arom. C); 127.8, 127.1, 125.0, 120.0 (arom. CH); 75.0 (C(5′)); 72.1 (C(1′)); 67.3 (C(10‴)); 66.1 (C(4′)); 54.8 (C(2″)); 52.5 (CO_2*Me*); 50.1 (C(2)); 48.6 (Me$_3$*C*S); 47.0 (C(9‴)); 42.1 (CH_2N_2); 41.1, 41.0 (C(3), C(3″)); 29.8 (*Me*$_3$CS); 26.3 (C(3′)); 24.8 (C(4)); 23.6 (C(2′)); 22.8, 21.7 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*R*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*L-*cysteinyl)amino*]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*D-*leucine Methyl Ester* (**15**). From **13** (53 mg, 132 μmol) and Fmoc–L-Cys(S^{t}Bu)–OH (68 mg, 158 μmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **15** as a colorless oil (75 mg, 79% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (*d*, *J* = 7.5, 2 arom. H); 7.58 (*d*, *J* = 7.4, arom. H); 7.39 (*t*, *J* = 7.4, 2 arom. H); 7.30 (*m*, 2 arom. H); 7.20 (*d*, *J* = 8.4, Leu–NH); 6.97 (br. *s*, CONH); 5.89 (br. *s*, Cys–NH); 4.60 (*m*, H–C(2)); 4.45–4.25 (*m*, H–C(2″), CH_2O); 4.21 (*t*, *J* = 6.9, 7.1, H–C(9‴)); 3.68 (*s*, CO_2Me); 3.68–3.53 (*m*, 4 H, H–C(1′), H–C(4′), H–C(5′), CH_2NH); 3.15 (*m*, 1 H, CH_2NH); 3.02 (*dd*, *J* = 7.4, 2 H–C(3″)); 2.15 (*m*, H–C(3′)); 1.70–1.35 (*m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, ^{t}Bu); 0.93 (*t*, *J* = 6.5, 6.6, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.0, 172.1, 170.3 (C(1), C(6′), C(1″)); 156.0 (Fmoc–CO); 143.5, 141.1 (arom. C); 127.6, 127.0, 125.0, 119.9 (arom. CH); 78.0 (C(5′)); 76.3 (C(1′)); 67.8 (C(4′)); 67.2 (C(10‴)); 54.7 (C(2″)); 52.3 (CO_2*Me*); 50.1 (C(1)); 48.3 (Me$_3$*C*S); 46.9 (C(9‴)); 43.4 (CH_2NH); 42.1, 41.0 (C(3), C(3″)); 30.5 (C(3′)); 26.7 (*Me*$_3$CS); 27.0 (C(2′)); 26.2 (C(4)); 21.7, 20.9 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*S*)-1{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*D-*cysteinyl)amino]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*D-*leucine Methyl Ester* (**19**). From **13** (26 mg, 65 μmol) and Fmoc–D-Cys(S*t*Bu)–OH (33 mg, 78 μmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **19** as a colorless oil (46 mg, 99% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.75 (*d*, *J* = 7.5, 2 arom. H); 7.57 (*d*, *J* = 7.4, 2 arom. H); 7.39 (*t*, *J* = 7.3, 7.5, 2 arom. H); 7.32–7.27 (*m*, 2 arom. H, Leu–NH); 7.03 (br. *s*, CONH); 5.97 (*d*, *J* = 7.3, Cys–NH); 4.70 (*m*, H–C(2)); 4.43–4.30 (*m*, H–C(2″), CH_2O); 4.20 (*t*, *J* = 7.1, H–C(9‴)); 4.15–4.05 (*m*, H–C(1′), H–C(4′), H–C(5′)); 3.81 (*m*, 1 H, C*H*$_2$NH), (*s*, CO_2*Me*); 3.22–3.09 (*m*, 1 H, C*H*$_2$NH, 2 H–C(3″)); 1.90, 1.73–1.50 (*m*, 2 H–C(2′), 2 H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, *t*Bu); 0.91, 0.85 (2*d*, *J* = 6.0, 3.9 Hz, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 174.1, 170.7, 170.6 (C(1), C(6′), C(1″)); 156.2 (Fmoc–CO); 143.6, 141.3 (2 arom. C); 127.8, 127.1, 125.1, 120.0 (arom. CH); 76.1 (C(5′)); 72.3 (C(1′)); 67.4 (C(10‴)); 65.4 (C(4′)); 55.0 (C(2″)); 52.5 (CO_2*Me*); 50.0 (C(2)); 48.4 (Me_3*C*S); 47.0 (C(9‴)); 41.8, 41.3 (CH_2NH, C(3), C(3″)); 29.8 (*Me*$_3$CS); 26.4 (C(3′)); 24.8 (C(4)); 23.3 (C(2′)); 22.8, 21.6 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*R*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*L-*cysteinyl)amino]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*L-*leucine Methyl Ester* (**21**). From N-*[(1*R*)-1-({*N-*[(*tert-*butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl]-*L-*leucine Methyl Ester* (42 mg, 104 μmol) and Fmoc–L-Cys(S*t*Bu)–OH (54 mg, 125 μmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **21** as a colorless oil (64 mg, 86% over 2 steps). ^{1}H-NMR (750 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.4, 2 arom. H); 7.57 (*d*, *J* = 7.4, 2 arom. H); 7.40 (*dd*, *J* = 7.4, 7.5, 2 arom. H); 7.30 (*t*, *J* = 3.7, 7.0, 2 arom. H); 7.25 (*d*, *J* = 7.4, Leu–NH); 6.82 (br. *s*, CONH); 6.24 (br. *s*, Cys–NH); 4.66 (*m*, H–C(2)); 4.48 (*m*, H–C(2″)); 4.41, 4.30, 4.20 (*m*, CH_2O, H–C(9‴)); 3.71 (*s*, CO_2Me); 3.54 (*m*, H–C(1′), H–C(4′), H–C(5′)); 3.47, 3.30 (2*m*, C*H*$_2$NH); 3.07 (*d*, *J* = 5.8, 2 H–C(3″)); 2.15 (*m*, H–C(3′)); 1.69–1.36 (*m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.33 (*s*, *t*Bu); 0.94 (*dd*, *J* = 5.9, 10.8, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.2, 171.1, 170.7 (C(1), C(6′), C(1″)); 156.6 (Fmoc–CO); 144.6, 141.7 (2 arom. C); 128.4, 127.6, 125.9, 120.5 (arom. CH); 78.9 (C(5′)); 77.2 (C(1′)); 68.9 (C(4′)); 67.2 (C(10‴)); 55.4 (C(2″)); 52.2 (CO_2*Me*); 50.6 (C(2)); 48.0 (Me_3*C*S); 47.6 (C(9‴)); 43.8 (CH_2NH); 43.0, 40.9 (C(3), C(3″)); 31.4 (C(3′)); 29.8 (*Me*$_3$CS); 27.5 (C(2′)); 25.2 (C(4)); 22.9, 21.6 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*S*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*D-*cysteinyl)amino]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexapyranos-6-yl)-*L-*leucine Methyl Ester* (**23**). From **10** (100 mg, 0.25 mmol) and Fmoc–D-Cys(S*t*Bu)–OH (116 mg, 0.27 mmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **23** as a colorless oil (129 mg, 72% over 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.77 (*d*, *J* = 7.5, 2 arom. H); 7.60 (*dd*, *J* = 2.2, 2.3, 2 arom. H); 7.41 (*t*, *J* = 7.4, 7.5, 2 arom. H); 7.30 (*m*, 2 arom. H); 7.00 (*d*, *J* = 8.8, Leu–NH); 6.70 (br. *s*, CONH); 6.20 (br. *d*, *J* = 5.8, Cys–NH); 4.64 (*m*, H–C(2)); 4.51 (*dd*, *J* = 6.7, 6.8, H–C(2″)); 4.25 (*m*, CH_2O, H–C(9‴)); 4.00 (*m*, H–C(1′), H–C(5′)); 3.87–3.72 (*m*, 2 H, C*H*$_2$NH, H–C(4)), (*s*, CO_2Me); 3.11 (*m*, 3 H, C*H*$_2$NH, 2 H–C(3″)); 1.97–1.50 (*m*, 2 H–C(2′), 2 H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, *t*Bu); 0.90 (*m*, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 172.6, 171.6, 170.1 (C(1), C(6′), C(1″)); 157.0 (Fmoc–CO); 144.7, 141.9 (2 arom. C); 128.3, 127.8, 126.0, 120.6 (arom. CH); 77.1 (C(5′)); 72.5 (C(1′)); 67.3 (C(10‴)); 65.8 (C(4′)); 55.6 (C(2″)); 52.2 (CO_2*Me*); 50.7 (C(2)); 48.1 (Me_3*C*S); 47.7 (C(9‴)); 42.7 (C(6′)); 42.3, 40.8 (C(3), C(3″)); 29.9 (*Me*$_3$CS); 27.1 (C(3′)); 25.4 (C(4)); 23.6 (C(2′)); 23.2, 21.4 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*R*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)-methoxy]carbonyl}-*D-*cysteinyl)amino]methyl}-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*L-*leucine Methyl Ester* (**25**). From N-*[(1*R*)-({*N-*[(*tert-*butoxy)carbonyl]amino}methyl)-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl]-*L-*leucine Methyl Ester* (195 mg, 0.48 mmol) and Fmoc–D-Cys(S*t*Bu)–OH (228 mg, 0.53 mmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **25** as a colorless oil (262 mg, 77% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.5, 2 arom. H); 7.59 (*d*, *J* = 7.5, 2 arom. H); 7.40 (*t*, *J* = 7.3, 7.6, 2 arom. H); 7.31 (*m*, 2 arom. H); 7.19 (*d*, *J* = 8.3, Leu–NH); 6.82 (br. *s*, CONH); 5.89 (br. *d*, *J* = 7.1, Cys–NH); 4.60 (*m*, H–C(2)); 4.45 (*m*, 3 H, H–C(2″), CH_2O, H–C(9‴)); 4.22 (*t*, *J* = 7.0, 7.1, 1 H, CH_2O); 3.69 (*s*, CO_2Me); 3.61–3.50 (*m*, H–C(1′), H–C(4′), H–C(5′)); 3.47, 3.35 (2*m*, C*H*$_2$NH); 3.10 (*m*, 2 H–C(3″)); 2.16 (*m*, H–C(3′)); 1.73–1.37 (2*m*, 2 H–C(2′), H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, *t*Bu); 0.95 (*t*, *J* = 6.2, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 173.1, 172.0, 170.4 (C(1), C(6′), C(1″)); 156.0 (Fmoc–CO); 143.6, 141.2 (2 arom. C); 127.7, 127.0, 125.0, 120.0 (4 arom. CH); 78.1 (C(5′)); 76.6 (C(1′)); 68.1 (C(4′)); 67.3 (C(10‴)); 54.6 (C(2″)); 52.4 (CO_2*Me*); 50.2 (C(2)); 48.5 (Me_3*C*S); 47.0 (C(9‴)); 43.7 (CH_2NH); 42.0, 41.1 (C(3), C(3″)); 30.6 (C(3′)); 29.8 (*Me*$_3$CS); 27.2 (C(2′)); 24.9 (C(4)); 22.7, 21.8 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

N-*((1*R*)-1-{[*N-*(*S-*[(*tert-*Butyl)sulfanyl]-*N-*{[(*9H-*fluoren-9-yl)methoxy]carbonyl}-*D-*cysteinyl)amino]-*methyl}-*1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl)-*D-*leucine Methyl Ester* (**27**). From **13** (39 mg, 97 μmol) and Fmoc–D-Cys(S*t*Bu)–OH (50 mg, 116 μmol) according to *GP 4* and *5*, purification by CC (AcOEt) afforded **27** as a colorless oil (63 mg, 91% over 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.6, 2 arom. H); 7.58 (*d*, *J* = 7.5, 2 arom. H); 7.40 (*t*, *J* = 7.2, 7.4, 2 arom. H); 7.30 (*m*, 2 arom. H, Leu–NH); 6.87 (br. *s*, CONH); 6.37 (br. *s*, Cys–NH); 4.62 (*m*, H–C(2)); 4.49–4.40 (*m*, H–C(2″), H–C(9‴)); 4.29–4.18 (*m*, CH_2O); 3.73 (*s*, CO_2Me); 3.67 (*m*, 1 H, C*H*$_2$NH); 3.63–3.50 (*m*, H–C(1′), H–C(5′)); 3.45 (*m*, H–C(4′)); 3.18–3.12 (*dt*, *J* = 5.3, 1 H, C*H*$_2$NH); 3.11 (*d*, *J* = 6.7, 2 H–C(3″)); 2.07 (*m*, H–C(3′)); 1.67–1.37 (2*m*, 2 H–C(2′), 2 H–C(3′), 2 H–C(3), H–C(4)); 1.34 (*s*, *t*Bu); 0.95 (*t*, *J* = 6.2, 7.3, Me_2C(4)). ^{13}C-NMR (APT, 50 MHz, $CDCl_3$): 174.5, 172.9, 171.5 (C(1), C(6′), C(1″)); 157.0 (Fmoc–CO); 144.2, 141.8 (2 arom. C); 128.4, 127.7, 125.7, 120.7 (4 arom. CH); 78.3 (C(5′)); 76.4 (C(1′)); 68.4 (C(4′)); 68.1 (C(10‴)); 55.1 (C(2″)); 53.1 (CO_2*Me*); 50.7 (C(2)); 49.0 (Me_3*C*S); 47.5 (C(9‴)); 43.7 (CH_2NH); 42.0, 41.7 (C(3), C(3″)); 30.9 (C(3′)); 30.4 (*Me*$_3$CS); 27.3 (C(2′)); 25.4 (C(4)); 23.4, 22.4 (*Me*$_2$C(4)). MS: 716.4 ([*M* + H]$^+$), 738.8 ([*M* + Na]$^+$).

The fully protected trimers were deprotected according to *GP 5* and subsequently purified by RP-HPLC (10–40% MeCN in 0.1% TFA/H_2O):

N-*{(1*S*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*L-*cysteinyl}amino)methyl]-*1,2,3-trideoxy-6-oxo-*D-*arabino-*hexopyranos-6-yl}-*L-*leucine* (**16**). From **11** (37 mg, 41 μmol) according to *GP 6*, purification by RP-HPLC afforded **16** as a foam (8.7 mg, 45%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.63 (*t*, *J* = 5.6, CONH); 7.95 (*d*, *J* = 8.0, Leu–NH); 4.76 (br. *s*, NH_2); 4.23 (*m*, H–C(2)); 4.08 (*d*, *J* = 3.1, H–C(5′)); 3.97 (*m*, H–C(4′)); 3.93 (*t*, *J* = 6.2, 6.4, H–C(2″)); 3.75 (*m*, H–C(1′)); 3.27 (*m*, C*H*$_2$NH); 3.08–3.17 (*m*, 2 H–C(3″)); 1.51–1.66 (*m*, H–C(2′), 2 H–C(3′), 2 H–C(3), H–C(4)); 1.40 (*m*, H–C(2′)); 1.31 (*s*, *t*Bu); 0.90, 0.85 (2*d*, *J* = 6.3, 6.4, Me_2C(4)). ^{13}C-NMR (APT, 100 MHz, (D_6)DMSO): 173.8, 169.9, 166.7 (C(1), C(6′), C(1″)); 77.5 (C(5′)); 70.9 (C(1′)); 63.3 (C(4′)); 51.8 (C(2)); 50.0 (C(2″)); 48.0 (Me_3*C*S); 42.6 (CH_2NH); 40.1, 39.9 (C(3), C(3″)); 29.4 (*Me*$_3$CS), 26.2 (C(3′)); 26.2 (C(4)); 22.3 (C(2′)); 22.8, 21.2 (*Me*$_2$C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2177 ([$C_{20}H_{37}N_3O_6S_2$ + H]$^+$; calc. 480.2202).

N-*{(1*R*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*L-*cysteinyl}amino)methyl]-*1,2,3-trideoxy-6-oxo-*D-*arabino-*hexopyranos-6-yl}-*L-*leucine* (**22**). From **21** (20 mg, 28 μmol) according to *GP 6*, purification by RP-HPLC afforded **22** as a foam (5.3 mg, 40%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.66 (*t*, *J* = 5.0, 5.6, CONH); 7.95 (*d*, *J* = 7.9, Leu–NH); 4.75 (br. *s*, NH_2); 4.28 (*m*, H–C(2)); 3.97 (*m*, H–C(2″)); 3.55 (*d*, *J* = 9.2, H–C(5′)); 3.44–3.19 (*m*, H–C(1′), H–C(4′), C*H*$_2$NH); 3.12 (*m*, 2 H–C(3″)); 1.97 (*m*, H–C(3′)); 1.51–1.75 (*m*, H–C(2′), 2 H–C(3), H–C(4)); 1.31 (*m*, *t*Bu, H–C(3′), H–C(2′)); 0.90, 0.87 (2*d*, *J* = 6.2, 6.0, Me_2C(4)). ^{13}C-NMR (APT, 100 MHz, (D_6)DMSO): 173.8, 170.1, 166.7 (C(1), C(6′), C(1″)); 80.6 (C(5′)); 75.2 (C(1′)); 67.1 (C(4′)); 51.7 (C(2)); 50.0 (C(2″)); 48.0 (Me_3*C*S); 43.2 (CH_2NH); 40.9, 40.0 (C(3), C(3″)); 31.4 (C(3′)); 29.4 (*Me*$_3$CS); 27.4 (C(2′)); 24.3 (C(4)); 22.7, 21.5 (*Me*$_2$C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2145 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*S*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*L-*cysteinyl}amino)methyl]-*1,2,3-trideoxy-6-oxo-*D-*arabino-*hexopyranos-6-yl}-*D-*leucine* (**17**). From **14** (9.0 mg, 13 μmol) according to *GP 6*, purification by RP-HPLC afforded **17** as a foam (1.6 mg, 26%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.70 (*d*, *J* = 4.4, CONH); 8.00 (*d*, *J* = 8.2, Leu–NH); 4.75 (br. *s*, NH_2); 4.20 (*m*, H–C(2)); 4.10 (*d*, *J* = 3.2, H–C(5′)); 3.95 (*m*, H–C(4′), H–C(2″)); 3.80 (*m*, H–C(6′)); 3.06–2.90 (*m*, C*H*$_2$NH, 2 H–C(3″)); 1.65–1.30 (2*m*, 2 H–C(3), H–C(4), 2 H–C(2′), 2 H–C(3′)); 1.27 (*s*, *t*Bu); 0.87 (2 *d*, *J* = 6.6, 6.5, Me_2C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2036 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*R*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*L-*cysteinyl}amino)methyl]-*1,2,3-trideoxy-6-oxo-*D-*arabino-*hexopyranos-6-yl}-*D-*leucine* (**18**). From **15** (43 mg, 60 μmol) according to *GP 6*, purification by RP-HPLC afforded **18** as a foam (10 mg, 36%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.77 (*t*, *J* = 5.9, CONH); 8.08 (*d*, *J* = 8.2, Leu–NH); 4.80 (br. *s*, NH_2); 4.32 (*m*, H–C(2)); 3.97 (*t*, *J* = 6.3, H–C(2″)); 3.53 (*d*, *J* = 9.3, H–C(5′)); 3.43–3.30 (*m*, 3 H, H–C(5′), H–C(4′)); C*H*$_2$NH); 3.11 (*m*, 3 H, C*H*$_2$NH, 2 H–C(3″)); 1.95 (*m*, H–C(3′)); 1.70–1.50 (*m*, 2 H–C(3), H–C(4), H–C(2′)); 1.35 (*m*, H–C(2′), H–C(3′)); 1.30 (*s*, *t*Bu)); 0.87 (2*d*, *J* = 6.6, 6.5, Me_2C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.1982 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*S*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*D-*cysteinyl}amino)methyl]-*1,2,3-trideoxy-6-oxo-*D-*arabino-*hexopyranos-6-yl}-*L-*leucine* (**24**). From **23** (10 mg, 14 μmol) according to *GP 6*, purification by RP-HPLC afforded **24** as a foam (2.0 mg, 30%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.62 (*dd*, *J* = 4.6, 4.6, CONH); 7.99 (*d*, *J* = 8.2, Leu–NH); 4.77 (br. *s*, NH_2); 4.26 (*m*, H–C(2)); 4.09 (*d*, *J* = 2.9, H–C(5′)); 4.00 (*m*, H–C(4′)); 3.95 (*m*, H–C(2″)); 3.78 (*m*, H–C(1′)); 3.36, 3.16–3.06 (2*m*, C*H*$_2$NH, 2 H–C(3″)); 1.70–1.55 (*m*, 2 H–C(3), H–C(4), H–C(2′), 2 H–C(3′)); 1.40 (*m*, H–C(2′)); 1.30 (*s*, *t*Bu); 0.87 (2 *d*, *J* = 6.6, 6.5, Me_2C(4)); MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2097 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*R*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*D-*cysteinyl}amino)methyl]-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl}-*L-*leucine* (**26**). From **25** (17 mg, 24 μmol) according to *GP 6*, purification by RP-HPLC afforded **26** as a foam (5.6 mg, 25%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.71 (*d*, *J* = 6.0, CONH); 8.08 (*d*, *J* = 8.2, Leu–NH); 4.80 (br. *s*, NH_2); 4.30 (*m*, H–C(2)); 3.97 (*t*, *J* = 6.3, H–C(2″)); 3.54 (*d*, *J* = 9.2, H–C(5′)); 3.44–3.35 (*m*, 3 H, H–C(1′), H–C(4′)), CH_2NH); 3.13 (*m*, 3 H, CH_2NH, 2 H–C(3″)); 1.95 (*m*, H–C(3′)); 1.70–1.50 (*m*, H–C(2′), 2 H–C(3), H–C(4)); 1.35 (*m*, H–C(2′), H–C(3′)); 1.30 (*s*, ^{t}Bu)); 0.87 (2*d*, *J* = 6.3, 6.4, Me_2C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2159 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*S*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*D-*cysteinyl}amino)methyl]-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl}-*D-*leucine* (**20**). From **19** (20 mg, 28 μmol) according to *GP 6*, purification by RP-HPLC afforded **20** as a foam (86.7 mg, 50%). ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.82 (*d*, *J* = 4.4, CONH); 8.00 (*d*, *J* = 8.2, Leu–NH); 4.60 (br. *s*, NH_2); 4.28 (*m*, H–C(2)); 4.08 (*d*, *J* = 3.2, H–C(5′)); 4.01 (*m*, H–C(2″)); 3.95 (*m*, H–C(4′)); 3.75 (*m*, H–C(1′)); 3.37–3.14 (*m*, CH_2NH, 2 H–C(3″)); 1.70–1.50 (*m*, 2 H–C(3), H–C(4), H–C(2′), 2 H–C(3′)); 1.39 (*m*, H–C(2′)); 1.30 (*s*, ^{t}Bu); 0.90, 0.86 (2*d*, *J* = 6.6, 6.5, Me_2C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2168 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

N-*{(1*R*)-1-[(*N-*{*S-*[(*tert-*Butyl)sulfanyl]-*D-*cysteinyl}amino)methyl]-1,2,3-trideoxy-6-oxo-*D-arabino-*hexopyranos-6-yl}-*D-*leucine* (**28**). From **27** (29 mg, 41 μmol) according to *GP 6*, purification by RP-HPLC afforded **28** (12 mg, 60%) as a foam. ^{1}H-NMR (750 MHz, (D_6)DMSO): 8.84 (*s*, CONH); 8.08 (*d*, *J* = 8.1, Leu–NH); 4.83 (br. *s*, NH_2); 4.27 (*m*, H–C(2)); 3.93 (*m*, H–C(2″)); 3.54 (*d*, *J* = 9.2, H–C(5′)); 3.44–3.15 (*m*, H–C(1′), H–C(4′), CH_2NH, 2 H–C(3″)); 1.95 (*m*, H–C(3′)); 1.75–1.50 (*m*, 2 H–C(3), H–C(4), H–C(2′)); 1.35–1.31 (*m*, ^{t}Bu, H–C(3′), H–C(2′)); 0.87 (2 *d*, *J* = 6.4, 6.5, Me_2C(4)). MS: 480.1 ([*M* + H]$^+$). HR-MS: 480.2199 ([$C_{20}H_{37}N_3O_6S_2$ – H]$^+$; calc. 480.2202).

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