

Efficient α -Mannosylation of Phenols: The Role of Carbamates as Scavengers for Activated Glycosyl Donors

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Received: 26.09.2012; Accepted after revision: 07.11.2012

Abstract: The boron trifluoride activation of trichloroacetimidate donors was found to be an efficient method for the α -mannosylation of tyrosine-containing acceptors. Most notably, these conditions are compatible with the commonly used carbamate protecting groups, whereas trichloroacetimidate activation with trimethylsilyl triflate or the use of glycosyl sulfoxides led to diminished yields in the presence of carbamates. In these cases, the competing reaction of the activated donors with the carbamate group was identified as a problematic side reaction. Taking advantage of this reactivity, various glycosyl carbamates were generated for the first time under non-acidic glycosylation conditions by reaction of different Boc-protected amino acids and dipeptides with glycosyl sulfoxides under different triflic anhydride activation.

Key words: glycosylation, natural products, phenols, sulfoxides, trichloroacetimidates

Introduction

The glycosylation of proteins and natural products is an efficient means for organisms to add an additional level of molecular complexity to the initial gene products.¹ In the case of ribosomally encoded proteins, N-linked glycosylation of asparagine residues and O-glycosylation of serine and threonine side chains are the most abundant structural motifs. Phenol glycosylation of tyrosine side chains, on the other hand, is far less common, and has mainly been identified in glycogenin, S-layer proteins,² and most recently in amyloid precursor proteins and β -peptides connected to Alzheimer's disease.³

In contrast, microorganisms produce a number of secondary metabolites that carry a carbohydrate moiety on the phenolic hydroxy group of tyrosine or hydroxyphenylglycine derivatives, respectively. The glycosylation pattern of these metabolites is structurally more diverse than on the protein level and features mono-, di-, and oligosaccharides composed of a variety of α - or β -linked L- and D-sugars attached to the phenolic side chain. Prominent examples with interesting biological activity are different glycopeptide antibiotics, e.g. vancomycin, teicoplanin,⁴ and ramoplanin,⁵ and the recently discovered group of anti-HIV cyclopeptides, the mirabamides.⁶

Our group is specifically interested in the chemical synthesis of the mannopeptimycins, a group of glycopeptide

antibiotics with excellent activity against resistant bacterial strains (methicillin resistant *Staphylococcus aureus*, MRSA, and vancomycin resistant enterococci, VRE).

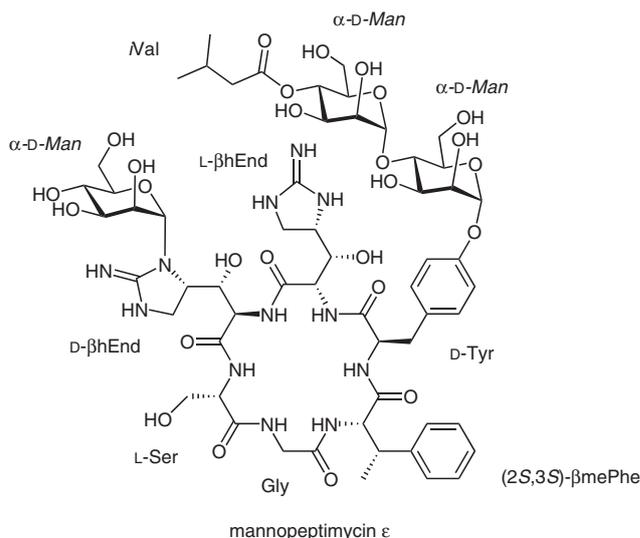


Figure 1 Structure of mannopeptimycin ϵ , the most active member of the naturally occurring mannopeptimycin antibiotics; β hEnd = β -hydroxyenduracididine; β mePhe = β -methylphenylalanine

The mannopeptimycins contain an α -(1 \rightarrow 4)-linked dimannoside that is attached to a D-tyrosine side chain (Figure 1).⁷ Like the 4'-O-isovaleroyl derivative mannopeptimycin ϵ , the most active member of the group, all naturally occurring mannopeptimycins with antibiotic activity contain a dimannoside that carries the small hydrophobic isovaleroyl group at the terminal mannose unit, whereas the unusual N-linked D-mannose unit attached to the cyclic guanidine of D- β -hydroxyenduracididine (D- β hEnd) is not essential for activity.⁸

While no total synthesis of the mannopeptimycins has been accomplished so far, efforts towards glycosylated fragments and structural analogues have been reported. A group at Wyeth described the synthesis of a mannopeptimycin derivative that contains a structurally simplified cyclopeptide portion.⁹ Because an unmodified dimannoside was the initial synthetic target, acyl groups (Ac and Bz) could be used as temporary protecting groups for the glycosyl donors that were required for the generation of an α -(1 \rightarrow 4)-dimannosyl tyrosine building block.¹⁰ As a consequence, this synthetic design is not generally applicable for esterified derivatives like mannopeptimycin ϵ

SYNTHESIS 2013, 45, 0027–0039

Advanced online publication: 07.12.2012

DOI: 10.1055/s-0032-1316820; Art ID: SS-2012-E0759-FA

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because of difficulties associated with the selective removal of such acyl groups in the presence of other lipid esters. Following a completely different approach, the O'Doherty group has used α -pyranone building blocks for the iterative construction of a mannopeptimycin ϵ derived glycosylated D-tyrosine unit as well as a small set of structural analogues.¹¹ Although efficient, this ingenious strategy will be limited in terms of introducing additional structural variations in the carbohydrate portion. Finally, the synthesis of a mannopeptimycin ϵ derived dimannosyl *N*-phenyl trifluoroacetimidate has been reported, but this donor was so far only used for the glycosylation of the side chain of a β -lactam acceptor.¹²

Because of the limitations described above, we were looking for an efficient and flexible methodology to reliably

attach different sugars to the tyrosine side chain via an α -linkage. Published synthetic studies on phenol and tyrosine glycosylation, however, have so far mostly been directed at the synthesis of β -glycosides of carbohydrates with an equatorial 2-OH group, e.g. glucose and galactose. Accordingly, in these cases glycosyl donors with 2-*O*-acyl groups were used, which ensured good β -selectivities by taking advantage of neighboring group participation.^{13–16} In principle, the same strategy can be used for the syntheses of α -linked mannosides, because, in this case, neighboring group participation of the now axially oriented 2-*O*-acyl blocks the β -side. As described above, however, the use of 2-*O*-acylated donors is problematic for the synthesis of mannopeptimycin-type dimannosides with a 4'-*O*-acyl group.

Biographical Sketches



Peter Schüler studied chemistry at the Philipps University Marburg and the University of Cambridge, UK. He obtained his Ph.D. in 2012 for his work towards the total synthesis of

the mannopeptimycins in the group of Dr. Markus Oberthür, where his main focus was the development of conditions for the efficient glycosylation of phenolic acceptors. Currently,

he is a member of the Pre-clinical Target Development Group of Dr. Aubry K. Miller at the German Cancer Research Center, Heidelberg.



Sebastian Fischer studied chemistry at the Philipps University Marburg, where he received his Diploma in 2010 after completing a thesis on the synthesis of

highly substituted *N*-hydroxyindoles. In April 2010, he started his Ph.D. research under the guidance of Dr. Markus Oberthür and Prof. Armin Geyer. His current

research is focused on the synthesis of nonproteinogenic amino acids and structurally complex peptides.



Michael Marsch worked for 21 years in the group of Prof. Gernot Boche after finishing his training as a chemistry laboratory technician at the Philipps University Marburg in 1979.

During this time, his main focus was on the X-ray structure determination of oxenoid, nitrenoid, and carbenoid compounds. He is now a member of the Department of Crystallography

at Marburg, working on the field measurement and X-ray crystal structure determination of small inorganic and organic molecules.



Markus Oberthür obtained his Ph.D. in 1999 for work on the synthesis of galacto-oligosaccharides in the group of Prof. Frieder W. Lichtenthaler at the TU Darmstadt. After postdoctoral studies from 2000–

2005 with Prof. Daniel Kahne, first at Princeton University and then at Harvard University and Harvard Medical School, he moved to Marburg as a Junior Group Leader, where he completed his habilita-

tion in 2012. His research interests include the chemistry and biology of cyclopeptides that act as antibiotics and antifungals as well as the bacterial iron transport mediated by siderophores.

The formation of α -glycosylated tyrosine derivatives by using donors that carry non-participating ether protecting groups at O2, on the other hand, has not been studied thoroughly, and only a few examples in which surprisingly low glycosylation yields were obtained, have been published.^{14a,17} Nevertheless, this second approach would not only avoid the tedious search for a compatible 2-*O*-acyl group but also simplify the synthesis of the required mannopeptimycin building blocks (*vide infra*). Accordingly, we surveyed a number of perbenzylated glycosyl donors regarding their performance in the α -mannosylation of different tyrosine acceptors. Here, we present the results of these studies that concluded in the identification of reliable glycosylation conditions for structurally complex donors and acceptors.

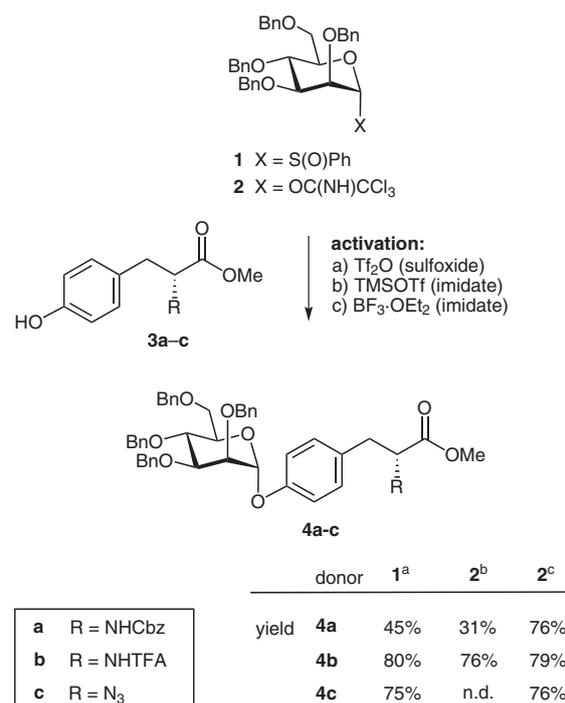
Results and Discussion

Model glycosylations: In our efforts towards the efficient and reliable synthesis of α -mannosylated tyrosine units, we evaluated various ‘classical’ mannosyl donors. These donors were uniformly protected with benzyl ethers, i.e. protecting groups that are orthogonal to the isovaleroyl ester present in the mannopeptimycin dimannosyl unit. Initially, the perbenzylated sulfoxide donor **1** was used, as glycosyl sulfoxides are known to be efficient donors for the glycosylation of phenols.¹⁸ Glycosylation of carbamate (Cbz) protected D-tyrosine methyl ester **3a** with sulfoxide **1** under triflic anhydride activation led to the α -mannosyl amino acid **4a**, albeit in only a moderate yield (45% at best). The corresponding Alloc derivative gave similar results, whereas Boc- and Teoc-protected derivatives performed even worse (yields <10%). Interestingly, the use of acceptors **3b** and **3c**¹⁹ in which the amines are protected as amide groups (trifluoroacetyl) or masked as an azido group, led to much higher yields of the mannosylation products **4b** and **4c** (80% and 75%, respectively).

The same dependence on the N-protecting group was observed when the corresponding trichloroacetimidate donor **2** was activated with trimethylsilyl triflate. Again, the carbamate-protected tyrosine **3a** could be mannosylated in only 31% yield, whereas trifluoroacetamide derivative **3b** led to mannoside **4b** in 76% yield. Similar results were obtained with other glycosyl donors, e.g. the corresponding glucosyl and galactosyl derivatives. We were also able to show that the low yield for carbamate-containing acceptors was directly related to the phenolic glycosylation site and not to the instability of the carbamate group under the glycosylation conditions, because sulfoxide **1** could be used for the efficient glycosylation of the primary alcohol of Cbz-L-Ser-OMe.

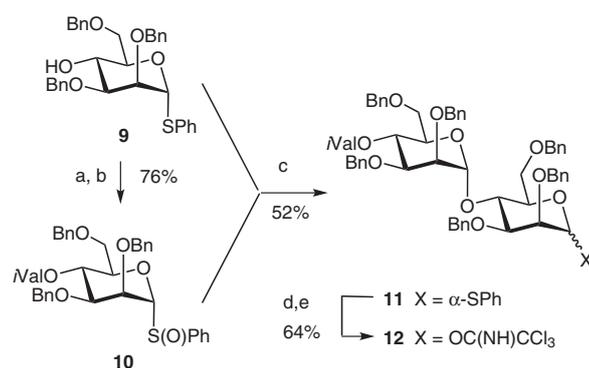
The incompatibility of carbamate protecting groups with standard glycosyl donors for the generation of α -glycosylated phenols would constitute a severe limitation for the synthesis of structurally complex carbohydrate-containing compounds because of the great utility of carbamates

as N-protecting group in general.²⁰ A solution to this problem was ultimately found after screening additional activation conditions for trichloroacetimidate **2**. The best results were obtained when donor **2** was activated with boron trifluoride–diethyl ether complex instead of trimethylsilyl triflate, which led to vastly improved yields for carbamate-containing acceptors. As exemplified for Cbz-protected tyrosine **3a**, the yield of mannoside **4a** increased from 31% to 76% when mannosyl trichloroacetimidate **2** was activated with 0.6 equivalents of boron trifluoride–diethyl ether complex (Scheme 1) at -30 °C. A similar increase was obtained for the mannosylation of the corresponding *N*-Alloc derivative. Not surprisingly, the activation method had no influence on the outcome of glycosylation reactions when acceptors without carbamate protecting groups were used, e.g. trifluoroacetamide **3b** or azide **3c**. In conclusion, our experiments showed that the glycosylation of phenolic acceptors with highly reactive glycosyl donors like sulfoxide **1** (activated by Tf_2O) or trichloroacetimidate **2** (in combination with TMSOTf) was only successful if no carbamate protecting groups were present in the molecule. The activation of trichloroacetimidates with boron trifluoride, on the other hand, proved to be compatible with carbamates and afforded the glycosylated tyrosine derivatives in good yields.



Scheme 1 Glycosylation of different D-tyrosine acceptors **3a–c** with mannosyl sulfoxide **1** and trichloroacetimidate donor **2**. *Reagents and conditions:* (a) Tf_2O (1 equiv), DTBP, CH_2Cl_2 , -60 °C to -45 °C; (b) TMSOTf (0.8 equiv), CH_2Cl_2 , -20 °C to 0 °C; (c) $\text{BF}_3 \cdot \text{OEt}_2$ (0.6 equiv), CH_2Cl_2 , -30 °C to 0 °C. DTBP = 2,6-di-*tert*-butylpyridine, TFA = trifluoroacetyl.

Efficient glycosylation of mannopeptimycin precursor peptides: The results of our model studies were confirmed during the glycosylation of different mannopeptimycin precursor peptides. Towards this end, we synthesized the dimannosyl trichloroacetimidate donor **12** (Scheme 2) starting from the known mannoside **9**.²¹ In addition to serving as the glycosyl acceptor, alcohol **9** can also be converted into an appropriate sulfoxide donor **10** by acylation (*i*ValCl, DMAP, Et₃N, CH₂Cl₂) to the 4-*O*-isovaleroyl derivative and subsequent oxidation with 3-chloroperoxybenzoic acid (MCPBA; 76% over 2 steps). Glycosylation of the thioglycoside acceptor **9** with sulfoxide **10** under triflic anhydride activation was rendered possible by the addition of 4-allyl-1,2-dimethoxybenzene to the reaction mixture,²² which afforded dimannoside **11** in acceptable yields.²³

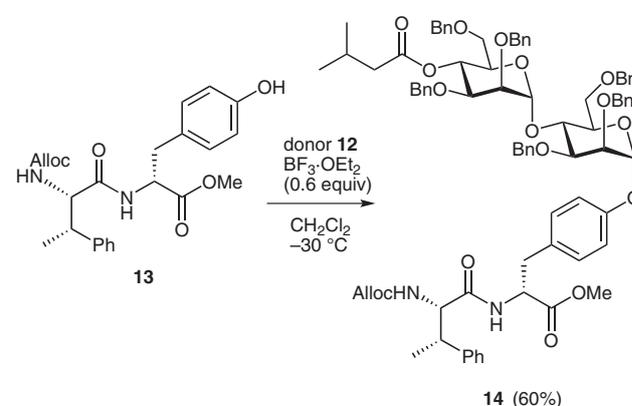


Scheme 2 Synthesis of dimannosyl building block **12**. *Reagents and conditions:* (a) *i*ValCl, DMAP, Et₃N, CH₂Cl₂, 0 °C; (b) MCPBA, CH₂Cl₂, -70 °C to -20 °C, 76% (2 steps); (c) Tf₂O, DTBP, 4-allyl-1,2-dimethoxybenzene, CH₂Cl₂, -70 °C to -25 °C, 52%; (d) NBS, acetone–H₂O, 0 °C, 81%; (e) Cl₃CCN, DBU, CH₂Cl₂, 0 °C, 79%.

Finally, thioglycoside **11** was transformed to the corresponding trichloroacetimidate donor **12** by hydrolysis of the thioglycoside (NBS, acetone–H₂O) and treatment of the resulting lactol with trichloroacetonitrile/DBU in

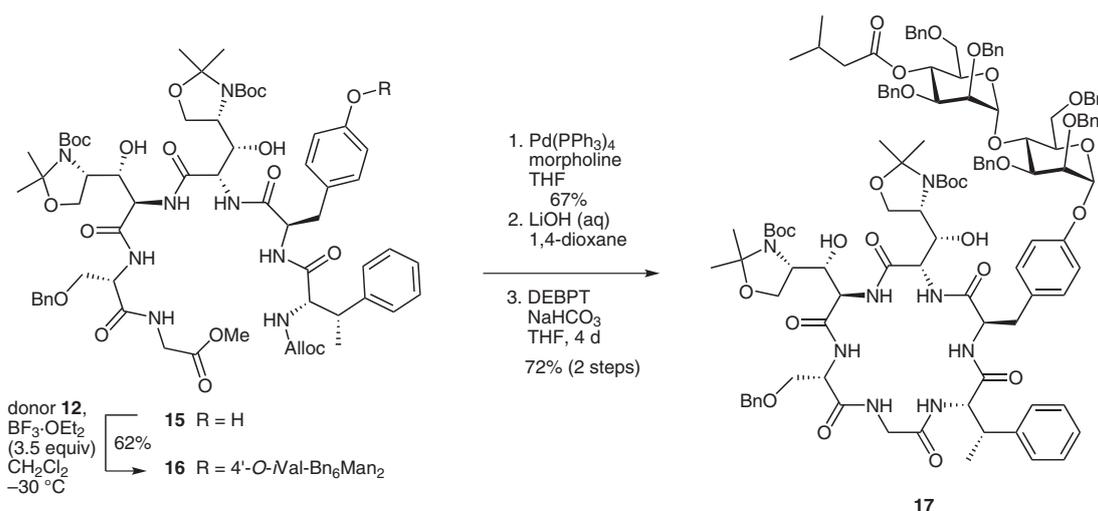
good overall yield (66%, 2 steps). Donor **12** was obtained as an anomeric mixture inseparable by flash chromatography and was used directly in the glycosylation reactions.

In parallel, we synthesized the Alloc-protected L-βmePhe-D-Tyr dipeptide **13**. The mannopeptimycin fragment **13** was assembled from a (2*S*,3*S*)-β-methylphenylalanine derivative that was obtained conveniently through a newly developed route that features a diastereoselective Strecker reaction (see Supporting Information). Dipeptide **13** was efficiently glycosylated with trichloroacetimidate **12** to afford dimannosyl dipeptide **14** (60%) when the donor was activated with boron trifluoride (0.6 equiv; Scheme 3). It should be noted that glycosylation of the carbamate containing **13** with trichloroacetimidates under trimethylsilyl triflate activation or sulfoxides under triflic anhydride activation led to a significant decrease in the yields of the glycosylated dipeptide, similar to the results of our model studies.



Scheme 3 Glycosylation of dipeptide **13** with dimannosyl donor **12**

In addition to this dipeptide fragment, we also synthesized hexapeptide **15** (see Supporting Information), a linear hexapeptide precursor to the mannopeptimycins (Scheme 4). This acceptor contains two β-hydroxyenduracididine

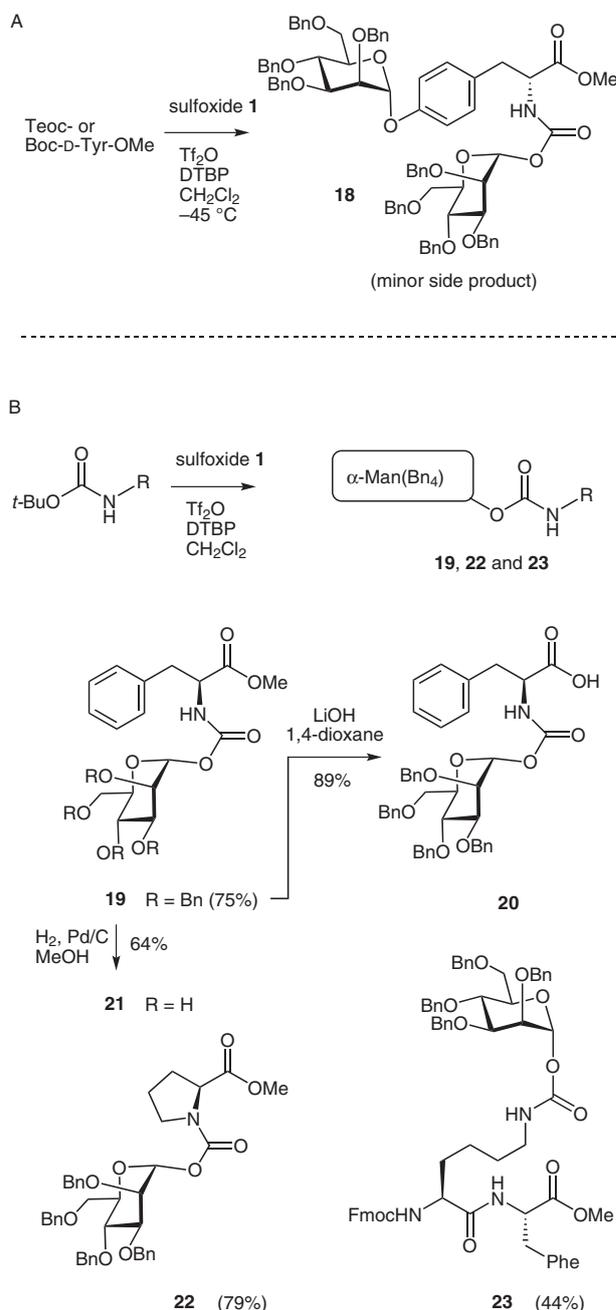


Scheme 4 Glycosylation of hexapeptide **15** and conversion into cyclopeptide **17**

analogues in which *N*-Boc-protected *N,O*-acetals serve as surrogates for the cyclic guanidine portion of these unusual amino acids.²⁴ Gratifyingly, the structurally complex peptide **15** could also be efficiently glycosylated to afford **16** in 62% yield (76% brsm) employing only a slight excess of trichloroacetimidate donor **12** (1.4 equiv). In comparison to previous reactions, it was imperative to raise the amount of boron trifluoride to 3.5 equivalents, presumably because of the larger number of carbonyl groups present in this acceptor, which might sequester some part of the Lewis acid through coordination. Following this successful glycosylation, the linear hexapeptide **16** could be deprotected at the C- and N-termini and cyclized to mannopeptimycin ϵ precursor cyclopeptide **17** by using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) for activation of the carboxylic acid.

Glycosyl carbamates: Even after the successful identification of generally applicable glycosylation conditions, the question remained why the trimethylsilyl triflate activation of trichloroacetimidates and sulfoxide activation with triflic anhydride, respectively, is incompatible with carbamate groups when very reactive perbenzylated donors are combined with less reactive phenolic acceptors. In our model studies, the glycosylation products of carbamate-protected acceptors were only isolated in yields below 50% for such combinations, and the only major additional reaction products following workup were the mannosyl lactol and the recovered acceptor. Other products of the glycosylation reaction remained elusive, e.g. β -anomers or C-glycosides²⁵ as possible alternate glycosylation products, glycals resulting from elimination within the activated donor,²⁶ or phenol triflates as a result of acceptor triflation. Therefore, the detection of an additional product that was formed in small amounts during the sulfoxide glycosylation of Boc- or Teoc-protected tyrosine methyl ester, the double glycosylation product **18** [Scheme 5 (A)], was extremely helpful for the interpretation of the observed reaction outcome. Obviously, in addition to the phenolic hydroxy group, the carbamate can also react with the activated glycosyl donor, which, after elimination of the *tert*-butyl or 2-(trimethylsilyl)ethyl group, respectively, led to the formation of a glycosyl carbamate.

To further investigate these findings, we submitted Boc-L-Phe-OMe to exactly the same glycosylation conditions [Scheme 5 (B)]. This carbamate-protected amino acid is missing a hydroxy group (alcohol or phenol) as a possible glycosylation site, and was converted in good yields into the carbamoyl-*O*-glycosylated product **19** [75% after optimization of the reaction conditions: donor **1** (1.8 equiv), $-25\text{ }^{\circ}\text{C}$, 18 h]. The presence of a glycosyl carbamate in **19** was unambiguously proven by a crystal structure (Figure 2),²⁷ which also confirmed the α -linkage of the mannose residue already assigned based on the $^3J_{1,2}$ and $^1J_{C,H}$ coupling constants²⁸ (1.5 Hz and 177 Hz, respectively) in the ^1H and HMBC spectra. Moreover, the fully protected **19** could be converted into the carboxylic acid **20** by treatment with aqueous lithium hydroxide solution in 1,4-di-



Scheme 5 Identification of glycosyl carbamates as reaction products. A: Side product **18** was identified by MS and ^1H NMR of crude product mixtures when Teoc-protected tyrosine acceptor was used and was isolated in 25% yield for the glycosylation of Boc-protected acceptor. B: Glycosyl carbamates **19**, **22**, and **23** were isolated as main products when Boc-containing compounds without any nucleophilic hydroxy groups were reacted with sulfoxide **1** under TiF_3 activation.

oxane, thereby furnishing a potential coupling partner for ligation to an amino group. We were also able to remove the benzyl protecting groups of **19** by hydrogenation, which led to carbamate **21** with an unprotected mannose moiety.

To explore the scope of the reaction conditions, we tested additional amino acid substrates. First, we could show that carbamate-protected secondary amines are also glycosyl-

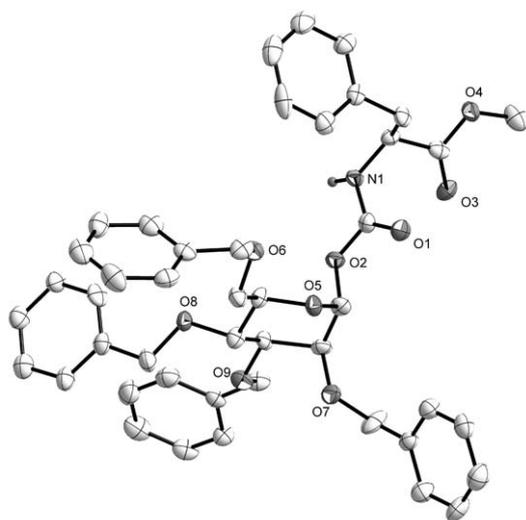


Figure 2 The single crystal X-ray structure of glyco-carbamate **19**²⁷ proves the α -configuration (O2) of the mannopyranose. The thermal ellipsoids correspond to 50% probability.

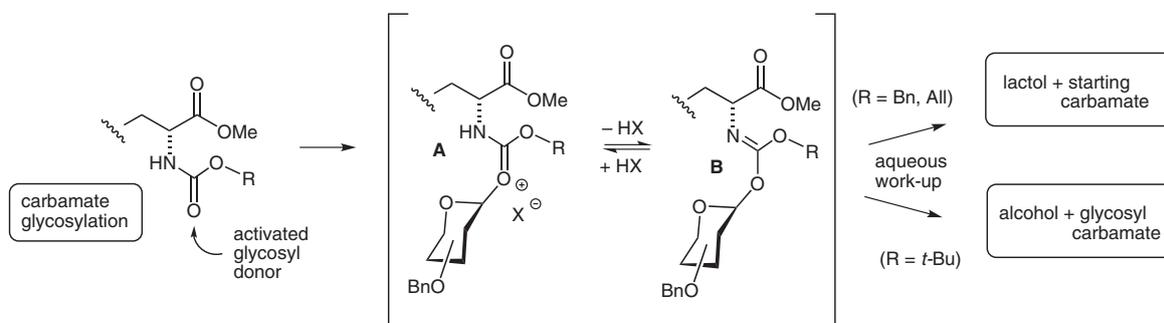
ated. In the event, mannosylation of Boc-protected L-proline methyl ester with sulfoxide **1** led to glycosyl carbamate **22** with similar efficiency (79%).²⁹

Next, a chemoselective carbamate glycosylation was explored. In our model glycosylation reactions, glycosyl carbamates could only be detected when Boc and Teoc derivatives were used as acceptors. Because both groups contain reasonably good cationic leaving groups [the *tert*-butyl and 2-(trimethylsilyl)ethyl cation, respectively], we reasoned that other carbamates, e.g. Fmoc, that contain less-stabilized groups, could very well be tolerated. Indeed, we found that a Fmoc- and Boc-containing dipeptide [Fmoc-L-Lys(NHBoc)-L-Phe-OMe] could be converted into the monomannosyl carbamate **23**, i.e. glycosylation was only observed in the lysine side chain, whereas the Fmoc group remained intact.³⁰

Glycosyl carbamates have previously been prepared by different methods, most notably by the reaction of lactols with isocyanates,³¹ the reaction of amines with activated sugar carbamates³² or carbonates,³³ and by the acid-catalyzed glycosylation of carbamate-protected amines with either glycosyl trichloroacetimidates³⁴ or glycosyl or-

thoesters.³⁵ In the latter cases, the formation of glycosyl carbamates was also observed serendipitously as a by-product of an attempted O-glycosylation of a Boc-protected amino acid acceptor. This outcome was proposed to evolve through the intermediacy of a carbamic acid generated via acid-catalyzed removal of the *tert*-butyl group, which subsequently serves as a glycosyl acceptor.³⁵ Here, we observed this alternate reaction pathway for the first time under basic glycosylation conditions (sulfoxide activation with triflic anhydride in the presence of a pyridine base), which should exclude the formation of carbamic acids as reaction intermediates. Instead, the direct attack of the activated donor at the carbamate carbonyl group is most probably involved, which is then followed by elimination of the *tert*-butyl group. This reaction pathway is similar to the conversion of Boc-carbamates into trialkylsilyl carbamates when treated with trialkylsilyl triflates.³⁶

Following this reasoning, such an attack of the activated glycosyl donor could also account for the three reaction outcomes that were observed when tyrosine acceptors are used. Firstly, in amide-protected derivatives, e.g. **3b**, the carbonyl oxygen of the amide group is much less nucleophilic than the phenolic group, whereas in azide **3c**, a possible second glycosylation site is missing completely. Accordingly, such acceptors are efficiently glycosylated at the phenolic hydroxy group with a variety of highly reactive glycosyl donors, e.g. **1** and **2**, under different activation conditions. Secondly, in carbamate protected acceptors, e.g. **3a**, the carbonyl oxygen of the carbamate group is only slightly less nucleophilic than the phenolic hydroxy group. As a result, a significant part of such acceptors is glycosylated at the carbamate group instead of the phenol when sulfoxide donors (Tf₂O activation) and trichloroacetimidate donors (TMSOTf activation) are used, i.e. under conditions that generate glycosyl triflates. In addition to the desired phenol glycoside **4a**, this would lead to intermediates of type **A** or their neutral elimination products **B** (Scheme 6). These intermediates, which effectively sequester the activated donor and prevent it from further glycosylating the phenolic group, are then hydrolyzed during the aqueous workup, either to the original carbamate (R = Cbz or Alloc) or towards glycosyl carbamates (R = *t*-Bu or Teoc), i.e. depending on the stability of the cationic leaving groups liberated from the different carbamate groups. This interpretation would explain the



Scheme 6 Glycosylated carbamates of type **A** and their elimination products **B** could sequester the activated glycosyl donor. Upon hydrolysis, the observed reaction mixtures are formed depending on the relative stability of the two possible leaving groups (R vs. sugar).

low yields for the tyrosine glycosylation irrespective of the type of carbamate group employed, as well as for formation of the minor side product **18** only in cases where reasonably good cationic leaving groups are present. So far, we have never observed glycosyl carbamates in the reaction mixture prior to aqueous workup, which also supports this view. Thirdly, and most importantly from a synthetic point of view, the activation of trichloroacetimidates with boron trifluoride is able to revert the reaction outcome towards predominant phenol glycosylation, irrespective of the N-protecting group. The activated donor that is formed in the presence of boron trifluoride preferentially reacts at the phenolic hydroxy group, possibly because this species is less reactive than the corresponding anomeric triflate generated by trimethylsilyl triflate activation. Further studies to provide additional experimental data concerning this mechanistic proposal are currently under way.

Conclusion

The glycosylation of phenolic hydroxy groups is widespread among natural products with interesting biological activity. The chemical glycosylation of such rather unreactive acceptors is still a challenge, because subtle changes of reaction conditions can have a profound impact on the efficiency of these transformations.

During our synthetic studies, we found that carbamate groups within the acceptor molecule have a negative impact on the glycosylation yield when two of the most common glycosyl donors are used, namely glycosyl trichloroacetimidates and sulfoxides. The diminished yields were traced back to a sequestration of the activated donor by the carbamate group, which in some cases led to glycosyl carbamates as side products. We were able to determine conditions that circumvent this problem, specifically the use of trichloroacetimidate donors that are activated by boron trifluoride. This methodology allows the efficient glycosylation of structurally complex peptides that contain multiple carbamate groups with mono- and disaccharide donors, thus highlighting the reliability of the presented approach.^{37,38} These results are of importance for the glycosylation of phenolic acceptors in general and should be helpful for the proper choice of coupling partners and protecting group patterns used in future total synthesis efforts aimed at the generation of compounds containing glycosylated phenols.

In addition, the efficient and chemoselective generation of glycosyl carbamates under basic conditions using glycosyl sulfoxides and Boc-protected amino acids developed here nicely complements the known acid-mediated protocols for the formation of these glycoconjugates.

All reactions were carried out under an argon atmosphere. All chemicals were of reagent grade and were used as purchased. Solvents were dried according to established procedures. TLC was performed on silica gel 60 F₂₅₄ plates (Merck KGaA). Detection was

carried out by fluorescence quenching under UV light ($\lambda = 254$ nm) or by staining with 20% H₂SO₄ or ninhydrin soln followed by heating to ca. 300 °C. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm) from Merck KGaA. The petroleum ether (PE) used was of the fraction boiling in the 40–60 °C range. NMR spectra were recorded on Bruker AV 300, Bruker DRX 400, AV 500, DRX 500, and DRX 600 spectrometers at the NMR facilities, Philipps-Universität Marburg referenced to the solvent residual signal. All coupling constants are $J_{H,H}$ couplings unless indicated otherwise. All signals are described as they appear in the 1D ¹H NMR spectra, i.e. the actual multiplicity and not the expected one is given and the coupling constants of each signal are actual values for each signal and not averaged ones. Signals were assigned with the aid of COSY, HMBC and HMQC spectra. Diastereotopic protons are labeled according to their chemical shifts: $\delta_a < \delta_b$. In the NMR data listings, the β -hydroxyenduracididine precursor amino acids are abbreviated L- and D-Hep, respectively. HRMS (ESI) were acquired with a LTQ-FT mass spectrometer (Thermo Fischer Scientific); the resolution was set to 100,000. The optical rotation was measured on a Perkin-Elmer 241 polarimeter.

Model glycosylations were performed according to General Procedure A or B. The acceptor phenols were prepared according to established procedures. For the synthesis of tyrosine derivatives **3a** and **3b**, D-Tyr-OMe was acylated with benzyl chloroformate or trifluoroacetic anhydride, respectively. Azido-D-Tyr-OMe (**3c**) was prepared from D-Tyr-OMe using imidazole-1-sulfonyl azide.¹⁹ The perbenzylated sulfoxide **1** was prepared by MCPBA oxidation³⁹ of the corresponding phenyl thioglycoside.⁴⁰ The known trichloroacetimidate donor **2** was synthesized from the corresponding lactol (DBU, Cl₃CCN), which in turn was obtained from the phenyl thioglycoside by treatment with NBS/H₂O.⁴⁰ Mannoside **9** was prepared according to known procedures.²¹

Experimental details for the synthesis of (2*S*,3*S*)- β -methylphenylalanine, dipeptide **13**, and hexapeptide **15** and copies of NMR spectra are given in the Supporting Information. Details of the synthesis of tetrapeptide **S8** (see Supporting Information for the structure) will be described in a separate account.

Mannosylation of Phenolic Acceptors with Sulfoxides; General Procedure A

Sulfoxide **1**^{39,40} (1.5 equiv) and DTBP (3.0 equiv) were coevaporated with toluene (2 \times) and dissolved in CH₂Cl₂ (5 mL/mmol sulfoxide) under argon. After the addition of molecular sieves (4 Å), the soln was stirred at r.t. (30 min). The soln was cooled to –70 °C and Tf₂O (1.5 equiv) was added. The mixture was stirred for 5 min at –60 °C, a soln of the acceptor **3** (1 equiv) [previously coevaporated with toluene (2 \times)] in CH₂Cl₂ (5 mL/mmol) was added, and the mixture was stirred at –60 °C to –45 °C for 1 h. The reaction was stopped by the addition of MeOH, diluted with CH₂Cl₂, and poured into sat. aq NaHCO₃-brine (1:1). The aqueous phase was extracted with CH₂Cl₂ (3 \times) and the combined organic phases were dried (MgSO₄), filtered, and evaporated. Purification of the residue by flash chromatography (PE–EtOAc, 2:1) gave the mannosylated phenol **4**.

Mannosylation of Phenolic Acceptors with Trichloroacetimidates; General Procedure B

To a soln of 2,3,4,6-tetra-*O*-benzyl-mannose⁴⁰ (1 equiv) and trichloroacetonitrile (4.5 equiv) in CH₂Cl₂ (20 mL/mmol lactol) at 0 °C was added DBU (0.3 equiv). After 30 min at this temperature, the mixture was evaporated and purified directly by flash chromatography (PE–EtOAc, 6:1 to 2:1), which gave trichloroacetimidate **2** as a colorless oil (85–90%). To a soln of trichloroacetimidate **2** (1.5 equiv) and the acceptor **3** (1 equiv) in CH₂Cl₂ was added either TMSOTf (0.8 equiv based on donor **2**) at –20 °C or BF₃·OEt₂ (0.6 equiv based on donor **2**) at –30 °C. The mixture was warmed to 0 °C over 1 h and the reaction was stopped by the addition of Et₃N. Evaporation of the mixture and purification of the residue by flash chromatography (PE–EtOAc, 2:1) gave the mannosylated phenol **4**.

Benzoyloxycarbonyl-D-Tyr-O-(2,3,4,6-tetra-O-benzyl- α -D-mannopyranosyl)-OMe (4a)

Mannoside **4a** was prepared according to General Procedure A and B and was obtained as a colorless oil; yields: see Scheme 1; R_f = 0.55 (PE–EtOAc, 2:1).

^1H NMR (300 MHz, DMSO- d_6): δ = 2.80 (dd, 2J = 13.6, $^3J_{\alpha,\beta\text{a}}$ = 10.0 Hz, 1 H, β -H $_{\text{a}}^{\text{Tyr}}$), 2.97 (dd, 2J = 13.6, $^3J_{\alpha,\beta\text{b}}$ = 5.0 Hz, 1 H, β -H $_{\text{b}}^{\text{Tyr}}$), 3.52–3.75 (m, 3 H, H5, 2 H6), 3.61 (s, 3 H, OCH $_3$), 3.87 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.2 Hz, 1 H, H4), 3.98 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3,4}$ = 9.3 Hz, 1 H, H3), 4.09 (dd, $^3J_{1,2}$ = 2.1, $^3J_{2,3}$ = 3.0 Hz, 1 H, H2), 4.19 (ddd, $^3J_{\alpha,\beta\text{t}}$ = 5.2, $^3J_{\alpha,\text{NH}}$ = 7.9, $^3J_{\alpha,\beta\text{h}}$ = 10.2 Hz, 1 H, α -H $^{\text{Tyr}}$), 4.35–4.81 (m, 8 H, 4 CH $_2^{\text{Bn}}$), 4.95 and 5.00 (2 d, 2J = 12.6 Hz, each 1 H, CH $_2^{\text{Cbz}}$), 5.69 (d, $^3J_{1,2}$ = 1.9 Hz, 1 H, H1), 6.93–7.04 (m, 2 H, o -H $_{\text{arom}}^{\text{Tyr}}$), 7.11–7.47 (m, 27 H, H $_{\text{arom}}$), 7.82 (d, $^3J_{\alpha,\text{NH}}$ = 8.2 Hz, 1 H, NH).

^{13}C NMR (75 MHz, CDCl $_3$): δ = 37.4 (C- β^{Tyr}), 52.3 (OCH $_3$), 55.6 (C- α^{Tyr}), 65.4 (CH $_2^{\text{Czb}}$), 68.8 (C6), 70.8, 71.9 (CH $_2^{\text{Bn}}$), 72.0 (C5), 72.2, 74.1 (3 CH $_2^{\text{Bn}}$), 74.2 (C2), 74.3 (C4), 79.4 (C3), 96.5 (C1), 116.7, 121.1, 127.4, 127.6, 127.6, 127.7, 127.8, 127.9, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.7, 130.3 (CH $_{\text{arom}}$), 138.2, 138.3, 138.5, 139.5 (C $_{\text{arom}}$), 150.4, 155.0 (C $_{\text{arom}}^{\text{Tyr}}$, C=O $^{\text{Czb}}$), 169.6 (COOMe).

HRMS (ESI): m/z [M + Na] $^+$ calcd for C $_{52}$ H $_{53}$ NNaO $_{10}$: 874.3567; found: 874.3579.

Trifluoroacetyl-D-Tyr-O-(2,3,4,6-tetra-O-benzyl- α -D-mannopyranosyl)-OMe (4b)

Mannoside **4b** was prepared according to General Procedure A and B and was obtained as a colorless oil; yields: see Scheme 1; R_f = 0.50 (PE–EtOAc, 2:1).

^1H NMR (300 MHz, DMSO- d_6): δ = 2.96 (dd, 2J = 13.8, $^3J_{\alpha,\beta\text{a}}$ = 10.6 Hz, 1 H, β -H $_{\text{a}}^{\text{Tyr}}$), 3.14 (dd, 2J = 13.9, $^3J_{\alpha,\beta\text{b}}$ = 4.9 Hz, 1 H, β -H $_{\text{b}}^{\text{Tyr}}$), 3.48–3.57 (m, 1 H, H6 $_{\text{a}}$), 3.60–3.71 (m, 5 H, H5, H6 $_{\text{b}}$, OCH $_3$), 3.87 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.2 Hz, 1 H, H4), 3.98 (dd, $^3J_{2,3}$ = 3.0, $^3J_{3,4}$ = 9.2 Hz, 1 H, H3), 4.08–4.13 (m, 1 H, H2), 4.31–4.84 (m, 9 H, 4 CH $_2^{\text{Bn}}$, α -H $^{\text{Tyr}}$), 5.72 (d, $^3J_{1,2}$ = 1.6 Hz, 1 H, H1), 7.01–7.44 (m, 24 H, H $_{\text{arom}}$), 9.92 (d, $^3J_{\alpha,\text{NH}}$ = 8.0 Hz, 1 H, NH).

^{13}C NMR (75 MHz, DMSO- d_6): δ = 34.8 (C- β^{Tyr}), 52.4 (OCH $_3$), 54.1 (C- α^{Tyr}), 68.7 (C6), 70.8, 71.9 (2 CH $_2^{\text{Bn}}$), 72.0 (C5), 72.2, 74.1 (2 CH $_2^{\text{Bn}}$), 74.1 (C2), 74.2 (C4), 78.9 (C3), 95.6 (C1), 116.7, 127.3, 127.4, 127.5, 127.5, 127.6, 127.7, 127.7, 128.1, 128.2, 128.2, 130.1 (CH $_{\text{arom}}$), 130.5, 138.2, 138.4, 138.5 (C $_{\text{arom}}$), 154.5 (OC $_{\text{arom}}$), 156.3 (q, $^3J_{\text{C,F}}$ = 36.8 Hz, C=O $^{\text{TFA}}$), 170.4 (COOMe).

HRMS (ESI): m/z [M + Na] $^+$ calcd for C $_{46}$ H $_{46}$ F $_3$ NNaO $_9$: 836.3022; found: 836.3020.

Azido-D-Tyr-O-(2,3,4,6-tetra-O-benzyl- α -D-mannopyranosyl)-OMe (4c)

Mannoside **4c** was prepared according to General Procedure A and B and was obtained as a colorless oil; yields: see Scheme 1; R_f = 0.45 (PE–EtOAc, 4:1).

^1H NMR (300 MHz, acetone- d_6): δ = 2.96 (dd, 2J = 14.1, $^3J_{\alpha,\beta\text{a}}$ = 8.5 Hz, 1 H, β -H $_{\text{a}}^{\text{Tyr}}$), 3.12 (dd, 2J = 14.1, $^3J_{\alpha,\beta\text{b}}$ = 5.4 Hz, 1 H, β -H $_{\text{b}}^{\text{Tyr}}$), 3.62–3.88 (m, 3 H, H5, 2 H6), 3.74 (s, 3 H, OCH $_3$), 4.09 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.2 Hz, 1 H, H4), 4.09 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3,4}$ = 9.3 Hz, 1 H, H3), 4.17 (dd, $^3J_{1,2}$ = 2.1, $^3J_{2,3}$ = 3.0 Hz, 1 H, H2), 4.29 (dd, $^3J_{\alpha,\beta\text{t}}$ = 5.4, $^3J_{\alpha,\beta\text{a}}$ = 8.5 Hz, 1 H, α -H $^{\text{Tyr}}$), 4.46–4.98 (m, 8 H, 4 CH $_2^{\text{Bn}}$), 5.69 (d, $^3J_{1,2}$ = 1.9 Hz, 1 H, H1), 7.04–7.11 (m, 2 H, CH $_{\text{arom}}$), 7.16–7.39 (m, 22 H, CH $_{\text{arom}}$).

^{13}C NMR (75 MHz, CDCl $_3$): δ = 37.2 (C- β^{Tyr}), 52.8 (OCH $_3$), 63.8 (C- α^{Tyr}), 70.3 (C6), 72.5, 73.5, 73.7 (3 CH $_2^{\text{Bn}}$), 73.7 (C5), 75.4 (CH $_2^{\text{Bn}}$), 75.7 (C4), 76.1 (C2), 80.8 (C3), 97.7 (C1), 116.7 (o -CH $_{\text{arom}}^{\text{Tyr}}$), 127.3, 127.4, 127.5, 127.5, 127.6, 127.7, 127.7, 128.1, 128.2, 128.2, 130.1 (CH $_{\text{arom}}$), 130.5, 138.2, 138.4, 138.5 (C $_{\text{arom}}$), 154.5 (OC $_{\text{arom}}$), 170.4 (COOMe).

HRMS (ESI): m/z [M + Na] $^+$ calcd for C $_{44}$ H $_{45}$ N $_3$ NaO $_8$: 766.3104; found: 766.3115.

Phenyl 2,3,6-Tri-O-benzyl-4-O-isovaleroyl-1-thio- α -D-mannopyranoside S-Oxide (10)

Thioglycoside **9** 21 (2.16 g, 3.98 mmol) and Et $_3$ N (2.49 mL, 17.8 mmol) were dissolved in CH $_2$ Cl $_2$ (50 mL). Isovaleroyl chloride (1.41 mL, 11.9 mmol) and DMAP (30 mg, cat.) were added at 0 $^\circ\text{C}$ and the mixture was stirred for 6 h at 0 $^\circ\text{C}$. The reaction was quenched by the addition of MeOH (3 mL) and diluted with CH $_2$ Cl $_2$ (100 mL). The mixture was washed with 2 M HCl (50 mL) and sat. aq NaHCO $_3$ (50 mL), and dried (MgSO $_4$); the solvent was evaporated to afford the crude 4-O-isovaleroyl derivative (2.3 g).

The crude 4-O-isovaleroyl derivative was dissolved in CH $_2$ Cl $_2$ (250 mL) and was subsequently treated dropwise with a soln of MCPBA (70–75%, 1.03 g, 4.2–4.5 mmol) in CH $_2$ Cl $_2$ (100 mL) at –70 $^\circ\text{C}$. The mixture was slowly warmed to –20 $^\circ\text{C}$ over a period of 6 h, and then sat. aq NaHCO $_3$ (100 mL) was added. After the addition of brine (300 mL), the phases were separated, the aqueous phase was extracted with CH $_2$ Cl $_2$ (2 \times 200 mL), and the combined organic phases were dried (MgSO $_4$) and evaporated. Purification of the residue by flash chromatography (PE–EtOAc, 4:1) afforded the sulfoxide **10** (3.08 g, 76% over 2 steps) as a colorless amorphous powder; R_f = 0.35 (PE–EtOAc, 4:1).

^1H NMR (300 MHz, CDCl $_3$): δ = 0.89 and 0.90 (2 d, 3J = 6.3 Hz, each 3 H, 2 CH $_3^{\text{iVal}}$), 1.98–2.12 (m, 3 H, CH $_2^{\text{iVal}}$, CH $^{\text{iVal}}$), 3.48–3.62 (m, 2 H, 2 H6), 4.22 (dd, $^3J_{2,3}$ = 3.0, $^3J_{3,4}$ = 9.5 Hz, 1 H, H3), 4.23–4.32 (m, 1 H, H5), 4.33–4.36 (m, 1 H, H2), 4.42–4.56 (m, 6 H, 3 CH $_2^{\text{Bn}}$), 4.58 (d, $^3J_{1,2}$ = 2.1 Hz, 1 H, H1), 5.39 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.5 Hz, 1 H, H4), 7.12–7.24 (m, 5 H, CH $_{\text{arom}}$), 7.27–7.50 (m, 13 H, CH $_{\text{arom}}$), 7.54–7.59 (m, 2 H, CH $_{\text{arom}}$).

^{13}C NMR (75 MHz, CDCl $_3$): δ = 22.4 (2 CH $_3^{\text{iVal}}$), 25.5 (CH $^{\text{iVal}}$), 43.3 (CH $_2^{\text{iVal}}$), 67.6 (C4), 70.0 (C6), 71.0 (C2), 72.6, 72.6, 73.5 (3 CH $_2^{\text{Bn}}$), 76.5 (C5), 76.6 (C3), 95.8 (C1), 124.3, 127.7, 127.8, 128.0, 128.3, 128.3, 129.2, 131.2 (CH $_{\text{arom}}$), 137.4, 137.8, 137.9, 141.6 (C $_{\text{arom}}$), 171.9 (C=O).

HRMS (ESI): m/z [M + Na] $^+$ calcd for C $_{38}$ H $_{42}$ NaO $_7$ S: 665.2543; found: 665.2561.

Phenyl 2,3,6-Tri-O-benzyl-4-O-(2',3',6'-tri-O-benzyl-4'-O-isovaleroyl- α -D-mannopyranosyl)-1-thio- α -D-mannopyranoside (11)

Acceptor **9** (422 mg, 0.78 mmol, 1.0 equiv), DTBP (0.52 mL, 2.33 mmol, 3.0 equiv), and 4-allyl-1,2-dimethoxybenzene (0.32 mL, 1.87 mmol, 2.4 equiv) were coevaporated with toluene (2 \times 10 mL). The residue was dissolved in CH $_2$ Cl $_2$ (10 mL), molecular sieves (4 \AA) were added, and the resulting mixture was stirred at r.t. for 30 min under argon. The mixture was cooled to –70 $^\circ\text{C}$ and then Tf $_2$ O (0.16 mL, 0.93 mmol, 1.2 equiv) was added dropwise, followed by a soln of sulfoxide **10** (600 mg, 0.93 mmol, 1.2 equiv) in CH $_2$ Cl $_2$ (4 mL). The mixture was slowly warmed to –25 $^\circ\text{C}$ over 1 h, quenched with Et $_3$ NH (0.4 mL), diluted with CH $_2$ Cl $_2$ (100 mL), and poured into sat. aq NaHCO $_3$ –brine–H $_2$ O (1:1:2, 100 mL). The aqueous phase was extracted with CH $_2$ Cl $_2$ (2 \times 50 mL) and the combined organic phases were dried (MgSO $_4$) and evaporated. Purification of the residue by flash chromatography (PE–EtOAc, 10:1, 8:1, 6:1) afforded disaccharide **11** (427 mg, 52%) as a colorless syrup; R_f = 0.45 (PE–EtOAc, 4:1).

^1H NMR (500 MHz, CDCl $_3$): δ = 0.87 and 0.88 (2d, 3J = 6.6 Hz, each 3 H, 2 CH $_3^{\text{iVal}}$), 1.97–2.10 (m, 3 H, CH $^{\text{iVal}}$, CH $_2^{\text{iVal}}$), 3.47 (dd, 2J = 10.6, $^3J_{5',6\text{a}'}$ = 2.8 Hz, 1 H, H6' $_{\text{a}}$), 3.53 (dd, 2J = 10.6, $^3J_{5',6\text{b}'}$ = 6.2 Hz, 1 H, H6' $_{\text{b}}$), 3.72 (dd, $^3J_{1',2'}$ = 2.5, $^3J_{2',3'}$ = 2.8 Hz, 1 H, H2'), 3.73 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3,4}$ = 9.2 Hz, 1 H, H3), 3.83 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3',4'}$ = 9.6 Hz, 1 H, H3'), 3.83 (dd, 2J = 10.8, $^3J_{5,6\text{a}}$ = 6.9 Hz, 1 H, H6 $_{\text{a}}$), 3.93 (ddd, $^3J_{5',6\text{a}'}$ = 2.7, $^3J_{5',6\text{b}'}$ = 6.2, $^3J_{4',5'}$ = 9.7 Hz, 1 H, H5'), 3.96 (dd, 2J = 11.1, $^3J_{5,6\text{b}}$ = 1.9 Hz, 1 H, H6 $_{\text{b}}$), 4.00 (dd, $^3J_{1,2}$ = 2.0, $^3J_{2,3}$ = 3.1 Hz, 1 H, H2), 4.12 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.3 Hz, 1 H, H4), 4.28–4.36 (m, 5 H, H5, 2 CH $_2^{\text{Bn}}$), 4.45–4.70 (m, 8 H, 4 CH $_2^{\text{Bn}}$), 5.31 (d, $^3J_{1,2}$ = 2.2 Hz, 1 H, H1'), 5.37 (dd, $^3J_{3',4'}$ = 9.7, $^3J_{4',5'}$ = 9.8 Hz, 1 H, H4'), 5.61 (d, $^3J_{1,2}$ = 1.9 Hz, 1 H, H1), 7.15–7.56 (m, 35 H, CH $_{\text{arom}}$).

^{13}C NMR (126 MHz, CDCl_3): δ = 22.6 (2 $\text{CH}_3^{\text{iVal}}$), 25.6 (CH^{iVal}), 43.6 ($\text{CH}_2^{\text{iVal}}$), 68.7 ($\text{C}4'$), 70.3 ($\text{C}6'$), 70.5 ($\text{C}5'$, $\text{C}6$), 71.2 (CH_2^{Bn}), 71.8 ($\text{C}3'$), 71.9, 72.3 (2 CH_2^{Bn}), 72.5 ($\text{C}5$), 73.1, 73.2, 73.7 (3 CH_2^{Bn}), 75.4, 75.4, 75.5 ($\text{C}2$, $\text{C}4$, $\text{C}2'$), 77.0 ($\text{C}3'$), 80.1 ($\text{C}3$), 85.6 ($\text{C}1$), 100.4 ($\text{C}1'$), 127.3, 127.5, 127.5, 127.6, 127.6, 127.6, 127.8, 127.9, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.7, 129.2, 132.2 (CH_{arom}), 134.2, 137.9, 137.9, 138.4, 138.6, 138.6, 138.9 (C_{arom}), 172.0 ($\text{C}=\text{O}^{\text{iVal}}$).

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{65}\text{H}_{70}\text{NaO}_{11}\text{S}$: 1081.4537; found: 1081.4556.

(2,3,6-Tri-*O*-benzyl-4-*O*-chloroacetyl- α -D-mannopyranosyl)-(1 \rightarrow 4)-2,3,6-tri-*O*-benzyl- α -D-mannopyranosyl Trichloroacetimidate (12)

Thioglycoside **11** (620 mg, 0.58 mmol) was dissolved in acetone– H_2O (19:1, 12 mL) and cooled to 0 °C. After the addition of NBS (313 mg, 1.76 mmol, 3 equiv), the mixture was stirred for 30 min at 0 °C. The reaction was stopped by the addition of 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ soln (1 mL), diluted with EtOAc (150 mL), and washed with sat. aq NaHCO_3 soln–brine (1:1, 50 mL). The organic phase was dried (MgSO_4), evaporated, and the residue was purified by flash chromatography (PE–EtOAc, 3:1, 2:1) to afford the corresponding lactol (460 mg, 81%) as a colorless solid; R_f = 0.45 (PE–EtOAc, 4:1).

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 0.81 and 0.82 (2 d, 3J = 6.6 Hz, each 3 H, 2 $\text{CH}_3^{\text{iVal}}$), 1.88 (septet, 3J = 6.7 Hz, 1 H, CH^{iVal}), 2.06 (d, 3J = 6.9 Hz, 2 H, $\text{CH}_2^{\text{iVal}}$), 3.28 (dd, 2J = 10.9, $^3J_{5,6a}$ = 2.8 Hz, 1 H, $\text{H}6'_a$), 3.30–3.33 (m, 1 H, $\text{H}6'_b$), 3.62 (dd, 2J = 10.8, $^3J_{5,6a}$ = 5.0 Hz, 1 H, $\text{H}6_a$), 3.67 (dd, 2J = 10.7, $^3J_{5,6b}$ = 1.8 Hz, 1 H, $\text{H}6_b$), 3.72 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3,4}$ = 9.8 Hz, 1 H, $\text{H}3'$), 3.75 (ddd, $^3J_{5,6a}$ = 3.1, $^3J_{5,6b}$ = 4.6, $^3J_{4,5}$ = 10.0 Hz, 1 H, $\text{H}5'$), 3.84 (dd, $^3J_{1,2}$ = 2.2, $^3J_{2,3}$ = 2.9 Hz, 1 H, $\text{H}2'$), 3.85–3.90 (m, 3 H, $\text{H}5$, $\text{H}2$, $\text{H}3$), 3.93 (dd, $^3J_{3,4}$ = 9.2, $^3J_{4,5}$ = 9.5 Hz, 1 H, $\text{H}4$), 4.18–4.65 (m, 12 H, 6 CH_2^{Bn}), 5.17 (dd, $^3J_{1,2}$ = 2.2, $^3J_{\text{OH}}$ = 4.1 Hz, 1 H, $\text{H}1$), 5.19 (dd, $^3J_{3,4}$ = 9.9, $^3J_{4,5}$ = 10.0 Hz, 1 H, $\text{H}4'$), 5.30 (d, $^3J_{1,2}$ = 1.9 Hz, 1 H, $\text{H}1'$), 6.73 (d, $^3J_{1,\text{OH}}$ = 4.3 Hz, 1 H, 1-OH), 7.08–7.38 (m, 30 H, CH_{arom}).

^{13}C NMR (126 MHz, 300 K, $\text{DMSO}-d_6$): δ = 22.0, 22.0 (2 $\text{CH}_3^{\text{iVal}}$), 24.9 (CH^{iVal}), 42.6 ($\text{CH}_2^{\text{iVal}}$), 67.4 ($\text{C}4'$), 68.9 ($\text{C}6'$), 69.9 ($\text{C}6$), 70.0 (CH_2^{Bn}), 70.0 ($\text{C}5$), 70.5 ($\text{C}5'$), 70.5, 71.5, 71.6, 72.2, 72.4 (5 CH_2^{Bn}), 73.6 ($\text{C}4$), 74.6 ($\text{C}2'$), 74.8 ($\text{C}2'$), 76.4 ($\text{C}3'$), 79.4 ($\text{C}3$), 90.9 ($\text{C}1$), 98.7 ($\text{C}1'$), 127.0, 127.2, 127.3, 127.3, 127.3, 127.3, 127.4, 127.4, 127.4, 127.5, 127.5, 128.0, 128.1, 128.1, 128.1, 128.1, 128.2 (CH_{arom}), 138.1, 138.2, 138.3, 138.3, 138.4, 138.7 (C_{arom}), 171.1 ($\text{C}=\text{O}^{\text{iVal}}$).

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{59}\text{H}_{66}\text{NaO}_{12}$: 989.4452; found: 989.4431.

The lactol (110 mg, 114 μmol) and trichloroacetonitrile (51 μL , 512 μmol , 4.5 equiv) were dissolved in CH_2Cl_2 (2 mL) under an atmosphere of argon. At 0 °C, DBU (5 μL , 34 μmol , 0.3 equiv) was added. After stirring for 30 min, the solvent was evaporated and the crude product was purified by flash chromatography (PE–EtOAc, 6:1, 4:1) to afford trichloroacetimidate **12** (100 mg, 79%) as a colorless oil, which was used directly in the glycosylation reactions; R_f = 0.48 (PE–EtOAc, 4:1).

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{61}\text{H}_{66}\text{Cl}_3\text{NNaO}_{12}$: 1132.3543; found: 1132.3522 (correct isotope pattern).

Alloc-L-(3S)- β mePhe-D-Tyr-{*O*-[2,3,6-tri-*O*-benzyl-4-*O*-(2',3',6'-tri-*O*-benzyl-4'-*O*-isovaleroyl- α -D-mannopyranosyl)- α -D-mannopyranosyl]-OMe (14)

Trichloroacetimidate **12** (100 mg, 90 μmol , 1.3 equiv) and dipeptide **13** (30 mg, 68 μmol , 1 equiv) were dissolved in CH_2Cl_2 (2 mL). The mixture was cooled to –30 °C and $\text{BF}_3\cdot\text{OEt}_2$ (7 μL , 54 μmol , 0.6 equiv based on donor **12**) was added. After 1 h at this temperature, the reaction was quenched by the addition of Et_3N (0.2 mL) and purified directly by flash chromatography (PE–EtOAc, 2:1) to afford the dimannosyl dipeptide **14** (57 mg, 60%) as a colorless amorphous solid; R_f = 0.20 (PE–EtOAc, 2:1).

^1H NMR (500 MHz, acetone- d_6): δ = 0.86, 0.88 (2 d, 3J = 6.7 Hz, each 3 H, 2 $\text{CH}_3^{\text{iVal}}$), 1.14 (d, $^3J_{\beta,\text{Me}}$ = 7.1 Hz, 3 H, $\text{CH}_3^{\text{mePhe}}$), 1.98 (septet, 3J = 6.7 Hz, 1 H, CH^{iVal}), 2.08–2.12 (m, 2 H, $\text{CH}_2^{\text{iVal}}$), 2.97 (dd, 2J = 14.0, $^3J_{\alpha,\beta a}$ = 9.2 Hz, 1 H, $\beta\text{-H}_a^{\text{Tyr}}$), 3.09–3.17 (m, 1 H, $\beta\text{-H}^{\text{mePhe}}$), 3.16 (dd, 2J = 14.2, $^3J_{\alpha,\beta b}$ = 5.2 Hz, 1 H, $\beta\text{-H}_b^{\text{Tyr}}$), 3.41–3.48 (m, 2 H, $\text{H}6'$), 3.62–3.71 (m, 2 H, $\text{H}6$), 3.66 (s, 3 H, OCH_3), 3.79 (m, 1 H, $\text{H}5$), 3.87 (dd, $^3J_{2,3}$ = 2.9, $^3J_{3,4}$ = 9.8 Hz, 1 H, $\text{H}3'$), 3.90 (m, 1 H, $\text{H}5'$), 3.94 (dd, $^3J_{1,2}$ = 2.1, $^3J_{2,3}$ = 3.1 Hz, 1 H, $\text{H}2'$), 4.10 (dd, $^3J_{2,3}$ = 3.1, $^3J_{3,4}$ = 9.2 Hz, 1 H, $\text{H}3$), 4.19 (dd, $^3J_{1,2}$ = 2.4, $^3J_{2,3}$ = 3.1 Hz, 1 H, $\text{H}2$), 4.25 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.4 Hz, 1 H, $\text{H}4$), 4.30–4.80 (m, 14 H, 6 \times CH_2^{Bn} , CH_2^{All}), 4.32–4.38 (m, 1 H, $\alpha\text{-H}^{\text{mePhe}}$), 4.64–4.75 (m, 1 H, $\alpha\text{-H}^{\text{Tyr}}$), 5.05–5.11, 5.13–5.20 (2 m, each 1 H, $=\text{CH}_2^{\text{All}}$), 5.38 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.9 Hz, 1 H, $\text{H}4'$), 5.40 (d, $^3J_{1,2}$ = 1.7 Hz, 1 H, $\text{H}1'$), 5.69 (d, $^3J_{1,2}$ = 1.7 Hz, 1 H, $\text{H}1$), 5.77–5.86 (m, 1 H, $=\text{CH}^{\text{All}}$), 5.92 (br d, $^3J_{\alpha,\text{NH}}$ = 8.9 Hz, 1 H, NH^{mePhe}), 6.96–7.51 (m, 39 H, H_{arom}), 7.66 (br d, $^3J_{\alpha,\text{NH}}$ = 8.4 Hz, 1 H, NH^{Tyr}).

^{13}C NMR (126 MHz, acetone- d_6): δ = 19.1 ($\text{CH}_3^{\text{mePhe}}$), 22.7 (2 $\text{CH}_3^{\text{iVal}}$), 26.1 (CH^{iVal}), 37.6 ($\text{C}-\beta^{\text{Tyr}}$), 42.9 ($\text{C}-\beta^{\text{mePhe}}$), 43.9 ($\text{CH}_2^{\text{iVal}}$), 52.3 (OCH_3), 54.8 ($\text{C}-\alpha^{\text{Tyr}}$), 60.7 ($\text{C}-\alpha^{\text{mePhe}}$), 65.7 ($\text{OCH}_2^{\text{All}}$), 69.1 ($\text{C}4'$), 70.6 ($\text{C}6$), 70.9 ($\text{C}6'$), 71.7, 72.1 (2 \times CH_2^{Bn}), 72.2 ($\text{C}5'$), 73.0 (CH_2^{Bn}), 73.1 ($\text{C}5$), 73.3, 73.5, 73.9 (4 \times CH_2^{Bn}), 75.0 ($\text{C}4$), 75.0 ($\text{C}2$), 76.4 ($\text{C}2'$), 78.0 ($\text{C}3'$), 80.7 ($\text{C}3$), 97.3 ($\text{C}1'$), 100.7 ($\text{C}1$), 117.1 ($=\text{CH}_2^{\text{All}}$), 117.8 (2 $m\text{-CH}_{\text{arom}}^{\text{Tyr}}$), 127.4, 128.0, 128.1, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 128.8, 128.9, 128.9, 129.0, 129.0, 129.1, 129.1, 129.2, 129.3, 131.3, 131.3 (CH_{arom}), 131.3 ($o\text{-CH}_{\text{arom}}^{\text{Tyr}}$), 131.9 ($i\text{-C}_{\text{arom}}^{\text{Tyr}}$), 134.3 ($=\text{CH}^{\text{All}}$), 139.4, 139.6, 139.6, 139.6, 139.8, 139.9, 143.4 ($i\text{-C}_{\text{arom}}$), 156.5 ($p\text{-C}_{\text{arom}}^{\text{Tyr}}$, $\text{C}=\text{O}^{\text{carbamate}}$), 171.7 ($\text{C}=\text{O}^{\text{amide}}$), 172.1 ($\text{C}=\text{O}^{\text{iVal}}$), 172.5 (COOMe).

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{83}\text{H}_{93}\text{N}_2\text{O}_{17}$: 1389.6474; found: 1389.6472.

Dimannosylated Linear Hexapeptide 16

Trichloroacetimidate **12** (160 mg, 144 μmol , 1.4 equiv) and linear hexapeptide **15** (126 mg, 101 μmol , 1 equiv) were dissolved in CH_2Cl_2 (1.5 mL) and cooled to –30 °C. $\text{BF}_3\cdot\text{OEt}_2$ (62 μL , 504 μmol , 3.5 equiv based on donor **12**) was added dropwise, and the reaction was stirred at this temperature for 40 min. The reaction was stopped by the addition of Et_3N (0.2 mL), and the mixture was diluted with CH_2Cl_2 (30 mL) and washed with sat. aq $\text{NH}_4\text{Cl}-\text{H}_2\text{O}$ (1:1, 15 mL) and sat. aq NaHCO_3 (15 mL). The organic phase was dried (MgSO_4) and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2 –MeOH, 60:1, 40:1, 20:1). This afforded unreacted acceptor **15** (23 mg, 18%) and the glycosylated hexapeptide **16** (137 mg, 62%) as a colorless solid; R_f = 0.50 (CH_2Cl_2 –MeOH, 20:1).

$[\alpha]_D^{22} +33.1$ (c 1.0, CHCl_3).

^1H NMR (500 MHz, 350 K, $\text{DMSO}-d_6$): δ = 0.84, 0.85 (2 d, 3J = 6.6 Hz, each 3 H, 2 $\text{CH}_3^{\text{iVal}}$), 0.92 (d, $^3J_{\beta,\text{Me}}$ = 7.1 Hz, 3 H, $\text{CH}_3^{\text{mePhe}}$), 1.38 (br s, 3 H, $\text{CH}_3^{\text{i-Pr}}$), 1.42 (br s, 9 H, CH_3^{Boc}), 1.44 (br s, 12 H, $\text{CH}_3^{\text{i-Pr}}$, CH_3^{Boc}), 1.49 (br s, 3 H, $\text{CH}_3^{\text{i-Pr}}$), 1.51 (br s, 3 H, $\text{CH}_3^{\text{i-Pr}}$), 1.91 (septet, 3J = 6.6 Hz, 1 H, CH^{iVal}), 2.07 (d, 3J = 6.8 Hz, 2 H, $\text{CH}_2^{\text{iVal}}$), 2.79 (dd, 2J = 14.0, $^3J_{\alpha,\beta a}$ = 9.7 Hz, 1 H, $\beta\text{-H}_a^{\text{Tyr}}$), 2.90 (dq, $^3J_{\beta,\text{Me}}$ = 6.8, $^3J_{\alpha,\beta}$ = 7.5 Hz, 1 H, $\beta\text{-H}^{\text{mePhe}}$), 3.11 (dd, 2J = 14.1, $^3J_{\alpha,\beta b}$ = 4.3 Hz, 1 H, $\beta\text{-H}_b^{\text{Tyr}}$), 3.28–3.44 (m, 2 H, $\text{H}6_a$, $\text{H}6'_a$), 3.51–3.60 (m, 2 H, $\text{H}6_b$, $\text{H}6'_b$), 3.61 (s, 3 H, OCH_3), 3.67–3.72 (m, 2 H, $\beta\text{-H}_2^{\text{Ser}}$), 3.71–3.75 (m, 1 H, $\text{H}5$), 3.75–3.80 (m, 3 H, $\text{H}3'$, $\text{H}5'$, $\delta\text{-H}_a^{\text{L-Hep}}$), 3.82–3.87 (m, 2 H, $\text{H}2'$, $\delta\text{-H}_a^{\text{D-Hep}}$), 3.87–3.94 (m, 4 H, $\gamma\text{-H}_a^{\text{D-Hep}}$, $\gamma\text{-H}_a^{\text{L-Hep}}$, CH_2^{Gly}), 3.97–4.03 (m, 2 H, $\text{H}3$, $\beta\text{-H}^{\text{L-Hep}}$), 4.08 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.4 Hz, 1 H, $\text{H}4$), 4.10 (dd, $^3J_{1,2}$ = 2.4, $^3J_{2,3}$ = 3.0 Hz, 1 H, $\text{H}2$), 4.09–4.13 (m, 2 H, $\delta\text{-H}_b^{\text{D-Hep}}$, $\delta\text{-H}_b^{\text{L-Hep}}$), 4.22 (t, 3J = 9.0 Hz, 1 H, $\alpha\text{-H}^{\text{mePhe}}$), 4.25–4.30 (m, 1 H, $\beta\text{-H}^{\text{D-Hep}}$), 4.26–4.52 (m, 13 H, $\text{OCH}_2^{\text{All}}$, 5.5 OCH_2^{Bn}), 4.33–4.37 (m, 1 H, $\alpha\text{-H}^{\text{D-Hep}}$), 4.45–4.48 (m, 1 H, $\alpha\text{-H}^{\text{L-Hep}}$), 4.59 (ddd, $^3J_{\alpha,\beta a}$ = 5.7, $^3J_{\alpha,\text{NH}}$ = 7.5, $^3J_{\alpha,\beta b}$ = 8.0 Hz, 1 H, $\alpha\text{-H}_{\text{Ser}}$), 4.63–4.75 (m, 4 H, 1.5 OCH_2^{Bn} , $\alpha\text{-H}^{\text{Tyr}}$), 4.89 (br d, 3J = 5.7 Hz, 1 H, $\text{OH}^{\text{L-Hep}}$), 4.91 (br s, 1 H, $\text{OH}^{\text{D-Hep}}$), 5.04–5.16 (m, 2 H, $=\text{CH}_2^{\text{All}}$), 5.21 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.8 Hz, 1 H, $\text{H}4'$), 5.29 (d, $^3J_{1,2}$ = 2.2 Hz, 1 H, $\text{H}1'$), 5.60 (d, $^3J_{1,2}$ = 2.2 Hz, 1 H, $\text{H}1$), 5.73–5.79 (m, 1

H, =CH^{All}), 6.42 (br s, 1 H, NH^{mePhe}), 6.97–7.40 (m, 44 H, H_{arom}), 7.98 (br s, 1 H, NH^{Ser}), 7.99 (br d, $^3J_{\alpha, \text{NH}} = 7.2$ Hz, 1 H, NH^{L-Hep}), 8.13 (br t, $^3J_{\text{CH}_2\alpha, \text{NH}} = 6.4$ Hz, 1 H, NH^{Gly}), 8.16 (br s, 1 H, NH^{D-Hep}), 8.19 (br d, $^3J = 6.7$ Hz, 1 H, NH^{Tyr}).

¹³C NMR: (126 MHz, 350 K, DMSO-*d*₆): $\delta = 18.3$ (CH₃^{mePhe}), 21.6 (2 CH₃^{iVal}), 24.1 (2 CH₃^{iPr}), 24.5 (CH^{iVal}), 26.1 (2 CH₃^{iPr}), 27.7 (CH₃^{Boc}), 27.8 (CH₃^{Boc}), 36.6 (C- β ^{Tyr}), 40.5 (CH₂^{Gly}), 41.2 (C- β ^{mePhe}), 42.4 (CH₂^{iVal}), 51.1 (OCH₃), 52.6 (C- α ^{Ser}), 54.0 (C- α ^{Tyr}), 54.9 (C- α ^{L-Hep}), 56.6 (C- α ^{D-Hep}), 58.1, 58.4 (C- γ ^{D-Hep}, C- γ ^{L-Hep}), 59.6 (C- α ^{mePhe}), 62.4 (C- δ ^{D-Hep}), 62.5 (C- δ ^{L-Hep}), 64.1 (OCH₂^{Allyl}), 67.5 (C4'), 69.0 (2 C, C6, C6'), 69.4 (C- β ^{Ser}), 69.4 (C- β ^{D-Hep}), 70.2 (CH₂Ph, C- β ^{L-Hep}), 70.4 (CH₂Ph), 70.5 (C5), 71.4, 71.4, 71.6, 71.9 (CH₂Ph), 72.5 (C4), 73.6 (C2), 74.9 (C2'), 76.2 (C5', C3'), 78.7 (C3), 79.0, 79.1 (C_q^{Boc}), 92.7, 92.9 (C_q^{iPr}), 95.9 (C1'), 98.6 (C1), 116.4 (=CH₂^{All}), 116.4, 125.7, 126.7, 126.7, 126.8, 126.8, 126.9, 126.9, 127.0, 127.1, 127.1, 127.2, 127.2, 127.4, 127.6, 127.6, 127.7, 127.7, 129.7, 127.8, 131.4 (CH_{arom}, C_{arom}), 132.9 (=CH^{All}), 137.8, 137.9, 137.9, 137.9, 138.0, 138.1, 142.6 (C_{arom}), 151.3, 151.4 (C=O^{Boc}), 154.2 (C=O^{Alloc}), 154.4 (*p*-C_{arom}^{Tyr}), 169.3 (COOMe), 169.4, 170.3, 170.4 (C=O^{amide}), 170.6 (C=O^{iVal}).

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₂₁H₁₅₀N₈NaO₃₀: 2219.0389; found: 2219.0402.

Dimannosyl Cyclopeptide 17

To a soln of linear hexapeptide **16** (81 mg, 37 μ mol, 1 equiv) in THF (degassed, 0.5 mL) was added morpholine (16 μ L, 184 μ mol, 5 equiv) and Pd(PPh₃)₄ (9 mg, 8 μ mol, 0.2 equiv), and the mixture was stirred for 30 min at r.t. After evaporation of the solvent, the residue was directly purified by flash chromatography (CH₂Cl₂–MeOH, 40:1, 20:1, 10:1), which afforded the corresponding terminal amine (52 mg, 67%) as an amorphous solid; *R*_f = 0.30 (CH₂Cl₂–MeOH, 20:1).

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₁₇H₁₄₇N₈O₂₈: 2113.0358; found: 2113.0375.

The amine (52 mg, 25 μ mol) was dissolved in 1,4-dioxane (0.5 mL) and treated with aq 1 M LiOH (50 μ L, 50 μ mol, 2 equiv) at 8 °C. After stirring for 90 min, the reaction was stopped by the addition of 2 M HCl (38 μ L, 75 μ mol, 3 equiv), and the solvents were removed under reduced pressure to afford the N- and C-terminally deprotected hexapeptide.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₁₆H₁₄₅N₈O₂₈: 2099.0202; found: 2099.0232.

The crude residue was dissolved in THF (25 mL) and cooled with an ice-water bath. Following the addition of solid NaHCO₃ (8 mg, 100 μ mol, 4 equiv) and DEPBT (22 mg, 75 μ mol, 3 equiv), the mixture was stirred at r.t. for 4 d. After evaporation of the solvent, the residue was partitioned between EtOAc (30 mL) and sat. aq NaHCO₃ (20 mL). The organic phase was washed with sat. aq NaHCO₃ (20 mL) and brine (20 mL), dried (MgSO₄), and evaporated. Purification of the residue by flash chromatography (CH₂Cl₂–MeOH, 60:1, 40:1, 20:1) afforded cyclopeptide **17** (37 mg, 72%) as a colorless, amorphous solid; *R*_f = 0.40 (CH₂Cl₂–MeOH, 20:1).

[α]_D²² +37.7 (*c* 1.0, CHCl₃).

¹H NMR (500 MHz, 350 K, DMSO-*d*₆): $\delta = 0.72$ (br s, 3 H, CH₃^{mePhe}), 0.84, 0.85 (2 d, $^3J = 6.7$ Hz, each 3 H, 2 CH₃^{iVal}), 1.30 (br s, 3 H, CH₃^{iPr}), 1.41 (br s, 9 H, CH₃^{Boc}), 1.42 (br s, 3 H, CH₃^{iPr}), 1.48 (br s, 9 H, CH₃^{Boc}), 1.49 (br s, 3 H, CH₃^{iPr}), 1.56 (br s, 3 H, CH₃^{iPr}), 1.91 (septet, $^3J = 6.7$ Hz, 1 H, CH^{iVal}), 2.04–2.08 (m, 2 H, CH₂^{iVal}), 2.76 (dd, $^2J = 14.0$, $^3J_{\alpha, \beta\text{a}} = 10.2$ Hz, 1 H, β -H_a^{Tyr}), 2.90 (dq, $^3J_{\beta, \text{Me}} = 6.7$, $^3J_{\alpha, \beta} = 7.1$ Hz, 1 H, β -H^{mePhe}), 3.22 (br d, $^2J = 13.8$ Hz, 1 H, β -H_b^{Tyr}), 3.34 (dd, $^2J = 11.0$, $^3J_{5,6} = 3.0$ Hz, 1 H, H6'_a), 3.37 (d, $^2J = 11.0$, $^3J_{5,6} = 4.6$ Hz, 1 H, H6'_b), 3.42 (br d, $^2J = 11.0$ Hz, 1 H, CH_a^{Gly}), 3.57–3.63 (m, 2 H, 6H), 3.65 (dd, $^2J = 9.5$, $^3J = 8.0$ Hz, 1 H, β -CH_a^{Ser}), 3.73–3.80 (m, 5 H, CH_b^{Gly}, β -H_b^{Ser}, H5, H3', H5'), 3.80–3.87 (m, 5 H, δ -H_a^{D-Hep}, δ -H_a^{L-Hep}, γ -H_a^{D-Hep}, γ -H_a^{L-Hep}, H2'), 3.89 (br s, 1 H, β -H^{L-Hep}), 3.97 (br s, 1 H, α -H^{D-Hep}), 4.00 (dd, $^3J_{2,3} = 3.1$,

$^3J_{3,4} = 9.0$ Hz, 1 H, H3), 4.07–4.14 (m, 4 H, δ -H_b^{D-Hep}, δ -H_b^{L-Hep}, H2, H4), 4.25 (br t, $^3J = 6.6$ Hz, 1 H, β -H^{D-Hep}), 4.28, 4.34 (2 d, each 1 H, OCH₂^{Bn}), 4.34–4.41 (m, 1 H, α -H^{mePhe}), 4.26–4.49 (m, 7 H, 3.5 OCH₂^{Bn}), 4.49–4.59 (m, 2 H, α -H^{L-Hep}, α -H^{Ser}), 4.51, 4.54, 4.69, 4.70 (3 d and 1 s, 5 H, 2.5 OCH₂^{Bn}), 4.65–4.78 (m, 3 H, α -H^{Tyr}, OH^{D-Hep}, OH^{L-Hep}), 5.20 (t, $^3J_{3',4'} = ^3J_{4',5'} = 9.6$ Hz, 1 H, H4'), 5.29 (d, $^3J_{1',2'} = 2.0$ Hz, 1 H, H1'), 5.56 (d, $^3J_{1,2} = 2.1$ Hz, 1 H, H1), 7.00–7.40 (m, 45 H, H_{arom}, NH^{L-Hep}), 7.76 (br s, 1 H, NH^{mePhe}), 7.83 (br s, 1 H, NH^{Gly}), 8.26 (br s, 1 H, NH^{Ser}), 8.42 (br d, $^3J = 8.4$ Hz, 1 H, NH^{Tyr}), 8.58 (br s, 1 H, NH^{D-Hep}).

¹³C NMR: (126 MHz, 350 K, DMSO-*d*₆): $\delta = 18.0$ (CH₃^{mePhe}), 21.3 (2 CH₃^{iVal}), 23.5, 23.7 (2 CH₃^{iPr}), 23.9 (CH^{iVal}), 25.3, 25.6 (2 CH₃^{iPr}), 27.4 (CH₃^{Boc}), 27.5 (CH₃^{Boc}), 34.6 (C- β ^{Tyr}), 39.7 (C- β ^{mePhe}), 40.8 (CH₂^{Gly}), 42.0 (CH₂^{iVal}), 51.2 (C- α ^{Ser}), 53.1 (C- α ^{Tyr}), 54.1 (C- α ^{L-Hep}), 56.7 (C- α ^{mePhe}), 57.4 (C- α ^{D-Hep}), 57.8 (C- γ ^{D-Hep}, C- γ ^{L-Hep}), 62.0 (C- δ ^{D-Hep}), 62.5 (C- δ ^{L-Hep}), 67.2 (C4'), 68.0 (C- β ^{L-Hep}), 68.5 (C- β ^{Ser}), 68.6 (C6, C6'), 69.8, 70.1 (CH₂Ph), 70.3 (C- β ^{D-Hep}), 70.4 (C5), 71.2 (C5'), 71.3, 71.4, 71.6, 71.8, 71.9 (CH₂Ph), 72.8 (C4), 73.1 (C2), 74.3 (C2'), 75.8 (C3'), 78.5 (C3), 78.2, 79.2 (C_q^{Boc}), 92.4, 92.7 (C_q^{iPr}), 95.7 (C1'), 98.3 (C1), 116.1, 125.5–142.7 (C_{arom}), 154.3 (*p*-C_{arom}^{Tyr}), 170.5 (C=O^{iVal}).

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₁₆H₁₄₃N₈O₂₇: 2081.0096; found: 2081.0107.

Methyl N-(2,3,4,6-Tetra-O-benzyl- α -D-mannopyranosyloxycarbonyl)-L-phenylalaninate (19)

Sulfoxide **1** (259 mg, 0.4 mmol, 1.8 equiv) and DTBP (0.15 mL, 0.69 mmol, 3.1 equiv) were coevaporated with toluene (2 \times 5 mL). The residue was dissolved in CH₂Cl₂ (2 mL), molecular sieves (4 Å) were added, and the resulting mixture was stirred at r.t. for 30 min under argon. After cooling the mixture to –70 °C, Tf₂O (52 μ L, 0.31 mmol, 1.4 equiv) was added dropwise, followed by a soln of Boc-L-Phe-OMe (56 mg, 0.22 mmol, 1 equiv) in CH₂Cl₂ (1 mL). After stirring for 18 h at –25 °C, the reaction was quenched by the addition of MeOH (0.1 mL), diluted with CH₂Cl₂ (30 mL), and poured into a mixture of sat. aq NaHCO₃–brine (1:1, 30 mL). The aqueous phase was extracted with CH₂Cl₂ (3 \times 20 mL) and the combined organic phases were dried (MgSO₄) and evaporated. Purification of the residue by flash chromatography (PE–EtOAc, 4:1) afforded glycocarbamate **19** (124 mg, 75%) as a colorless solid. Crystallization of an analytical sample (PE–THF–Et₂O) gave crystals suitable for X-ray analysis.²⁷ *R*_f = 0.20 (PE–EtOAc, 4:1).

¹H NMR (400 MHz, acetone-*d*₆): $\delta = 3.00$ (dd, $^2J = 13.8$, $^3J_{\alpha, \beta\text{a}} = 9.1$ Hz, 1 H, β -H_a^{Phe}), 3.17 (dd, $J = 13.8$, $^3J_{\alpha, \beta\text{b}} = 5.3$ Hz, 1 H, β -H_b^{Phe}), 3.65 (s, 3 H, OCH₃), 3.66–3.73 (m, 1 H, H6_a), 3.75–3.83 (m, 2 H, H6_b, H5), 3.86–3.94 (m, 2 H, H2, H3), 4.03 (t, $^3J = 9.3$ Hz, 1 H, H4), 4.43–4.55 (m, 1 H, α -H^{Phe}), 4.51–4.90 (m, 8 H, 4 OCH₂^{Bn}), 6.04 (d, $^3J_{1,2} = 1.5$ Hz, 1 H, H1), 6.94 (d, $^3J_{\text{NH}, \alpha} = 8.8$ Hz, 1 H, NH), 7.16–7.46 (m, 25 H, H_{arom}).

¹³C NMR (100 MHz, acetone-*d*₆): $\delta = 38.2$ (C- β ^{Phe}), 52.4 (OCH₃), 56.4 (C- α ^{Phe}), 70.1 (C6), 72.4, 73.3, 73.8 (3 \times CH₂Ph), 74.8 (C5), 75.3 (C2, C4), 75.5 (CH₂Ph), 80.7 (C3), 93.1 (C1), 127.6, 128.1, 128.2, 128.3, 128.5, 128.6, 128.6, 128.7, 129.0, 129.0, 129.1, 129.1, 129.2, 130.1 (CH_{arom}), 138.1, 139.7, 139.8, 139.8, 139.9 (C_{arom}), 154.8 (C=O^{carbamate}), 172.6 (COOMe).

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₄₅H₄₇NNaO₉: 745.3251; found: 745.3257.

N-(2,3,4,6-Tetra-O-benzyl- α -D-mannopyranosyloxycarbonyl)-L-phenylalanine (20)

To a soln of ester **19** (24 mg, 32 μ mol) in 1,4-dioxane (0.4 mL) was added at 8 °C aq 1 M LiOH soln (64 μ L, 64 μ mol, 2 equiv). The mixture was stirred for 3 h at this temperature and then it was diluted with EtOAc (20 mL), washed with sat. aq NH₄Cl–H₂O (1:1), and dried (MgSO₄). Evaporation of the solvent gave acid **20** (21 mg, 89%) as a colorless solid; *R*_f = 0.50 (CH₂Cl₂–MeOH, 9:1).

^1H NMR (400 MHz, acetone- d_6): δ = 2.96 (dd, 2J = 14.0, $^3J_{\alpha,\beta\text{a}}$ = 8.4 Hz, 1 H, $\beta\text{-H}_\text{a}^{\text{Phe}}$), 3.19 (dd, 2J = 14.0, $^3J_{\alpha,\beta\text{b}}$ = 4.9 Hz, 1 H, $\beta\text{-H}_\text{b}^{\text{Phe}}$), 3.64 (dd, 2J = 11.0, $^3J_{5,6\text{a}}$ = 1.7 Hz, 1 H, H_{6a}), 3.70–3.76 (m, 2 H, H₅, H_{6b}), 3.74 (dd, $^3J_{1,2}$ = 2.1, $^3J_{2,3}$ = 3.2 Hz, 1 H, H₂), 3.80 (dd, $^3J_{2,3}$ = 3.1, $^3J_{3,4}$ = 9.5 Hz, 1 H, H₃), 4.02 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.7 Hz, 1 H, H₄), 4.44 (dd, $^3J_{\alpha,\beta\text{a}}$ = 9.0, $^3J_{\alpha,\beta\text{b}}$ = 5.4 Hz, 1 H, $\alpha\text{-H}^{\text{Phe}}$), 4.44–4.84 (m, 8 H, 4 CH₂^{Bn}), 6.03 (d, $^3J_{1,2}$ = 2.0 Hz, 1 H, H₁), 7.10–7.39 (m, 25 H, H_{arom}).

^{13}C NMR (100 MHz, acetone- d_6): δ = 38.2 (C- β^{Phe}), 55.9 (C- α^{Phe}), 67.7 (C₆), 69.3, 72.7, 73.1 (3 CH₂^{Bn}), 74.1 (C₅), 74.5 (C₂), 74.9 (C₄), 75.8 (CH₂^{Bn}), 80.0 (C₃), 92.9 (C₁), 127.4, 128.2, 128.3, 128.4, 128.7, 128.7, 128.9, 129.0 (CH_{arom}), 129.9 (*o*-CH_{arom}^{Phe}), 137.6, 138.5, 138.8 (C_{arom}), 155.1 (C=O_{carbamate}), 174.4 (COOH).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₄₄H₄₅NNaO₉: 754.2987; found: 754.2975.

Methyl *N*-(α -D-Mannopyranosyloxycarbonyl)-L-phenylalaninate (21)

Glycocarbamate **19** (24 mg, 32 μmol) was dissolved in MeOH (0.5 mL), and 10% Pd/C was added (5 mg). The mixture was stirred at r.t. under an atmosphere of H₂ (1 bar) for 12 h, diluted with CH₂Cl₂ (2 mL), and purified directly by flash chromatography (CH₂Cl₂–MeOH, 6:1), which afforded the tetraol **21** (8 mg, 64%) as a colorless solid; R_f = 0.25 (CH₂Cl₂–MeOH, 9:1).

^1H NMR (400 MHz, CD₃OD): δ = 2.95 (dd, J = 13.8, $^3J_{\alpha,\beta\text{a}}$ = 9.3 Hz, 1 H, $\beta\text{-H}_\text{a}^{\text{Phe}}$), 3.16 (dd, J = 13.8, $^3J_{\alpha,\beta\text{b}}$ = 5.2 Hz, 1 H, $\beta\text{-H}_\text{b}^{\text{Phe}}$), 3.59–3.64 (m, 1 H, H₅), 3.66–3.74 (m, 3 H, H₄, H₃, H_{6a}), 3.70 (s, 3 H, OCH₃), 3.74 (dd, $^3J_{1,2}$ = 1.7, $^3J_{2,3}$ = 3.2 Hz, 1 H, H₂), 3.79 (dd, 2J = 12.1, $^3J_{5,6\text{b}}$ = 2.2 Hz, 1 H, H_{6b}), 4.41 (dd, $^3J_{\alpha,\beta\text{a}}$ = 9.3, $^3J_{\alpha,\beta\text{b}}$ = 5.3 Hz, 1 H, $\alpha\text{-H}^{\text{Phe}}$), 5.80 (d, $^3J_{1,2}$ = 1.9 Hz, 1 H, H₁), 7.18–7.25 (m, 5 H, CH_{arom}).

^{13}C NMR (100 MHz, CD₃OD): δ = 38.5 (C- β^{Phe}), 52.7 (OCH₃), 57.0 (C- α^{Phe}), 62.7 (C₆), 68.0 (C₄), 71.2 (C₂), 72.2 (C₃), 76.6 (C₅), 96.1 (C₁), 127.9, 129.5, 130.3, 138.3 (C_{arom}), 156.4 (C=O_{carbamate}), 173.6 (COOMe).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₇H₂₃NNaO₉: 408.1265; found: 408.1259.

Methyl *N*-(2,3,4,6-Tetra-*O*-benzyl- α -D-mannopyranosyloxycarbonyl)-L-prolinate (22)

Boc-L-Pro-OMe (27 mg, 118 μmol , 1 equiv) and DTBP (98 μL , 425 μmol , 3.6 equiv) were coevaporated with toluene (2 \times 5 mL). The residue was dissolved in CH₂Cl₂ (2 mL), molecular sieves (4 \AA) were added, and the resulting mixture was stirred at r.t. for 30 min under argon. After cooling the mixture to -70 $^\circ\text{C}$, Tf₂O (35 μL , 212 μmol , 1.8 equiv) was added dropwise, followed by a soln of sulfoxide **1** (138 mg, 212 μmol , 1.8 equiv) in CH₂Cl₂ (1 mL), and the mixture was slowly warmed to r.t. over 5 h. The reaction was quenched by the addition of MeOH (0.1 mL), diluted with CH₂Cl₂ (30 mL), and poured into a mixture of sat. aq NaHCO₃–brine (1:1, 30 mL). The aqueous phase was extracted with CH₂Cl₂ (3 \times 20 mL) and the combined organic phases were dried (MgSO₄) and evaporated. Purification of the residue by flash chromatography (PE–EtOAc, 4:1, 3:1) afforded glycocarbamate **22** (65 mg, 79%) as a colorless oil; R_f = 0.40 (PE–EtOAc, 2:1).

^1H NMR (400 MHz, DMSO- d_6 , mixture of *cis*- and *trans*-isomers, ratio 3:2): δ = 1.77–1.96 (m, 3 H, *cis*- + *trans*- β^{Pro} -H_a, 2 γ^{Pro} -H), 2.13–2.30 (m, 1 H, *cis*- + *trans*- β^{Pro} -H_b), 3.28–3.35 (m, 1.2 H, *cis*- δ^{Pro} -CH₂), 3.41 (t, $^3J_{\gamma,\delta}$ = 7.0 Hz, 0.8 H, *trans*- δ^{Pro} -CH₂), 3.58 (s, 1.2 H, *trans*-OCH₃), 3.60–3.64 (m, 1 H, *cis*- + *trans*-H_{6a}), 3.61 (s, 1.8 H, *cis*-OCH₃), 3.65–3.74 (m, 2.4 H, *trans*-H₃, *cis*- + *trans*-H₄, *cis*- + *trans*-H_{6b}), 3.79–3.84 (m, 1 H, *trans*-H₂, *cis*-H₃), 3.84–3.93 (m, 1.6 H, *cis*-H₂, *cis*- + *trans*-H₅), 4.24 (dd, $^3J_{\alpha,\beta}$ = 3.9, $^3J_{\alpha,\beta}$ = 9.0 Hz, 0.6 H, *cis*- α^{Pro} -CH), 4.35 (dd, $^3J_{\alpha,\beta}$ = 4.1, $^3J_{\alpha,\beta}$ = 8.5 Hz, 0.4 H, *trans*- α^{Pro} -CH), 4.43–4.81 (m, 8 H, 4 CH₂Ph), 5.95 (d, $^3J_{1,2}$ = 1.8 Hz, 0.6 H, *cis*-H₁), 5.97 (d, $^3J_{1,2}$ = 1.8 Hz, 0.4 H, *trans*-H₁), 7.16–7.23, 7.24–7.39 (2 m, 2 H and 18 H, *cis*- + *trans*- $\beta\text{H}_{\text{arom}}$).

^{13}C NMR (100 MHz, DMSO- d_6): δ = 23.1 (*trans*-C- γ^{Pro}), 23.7 (*cis*-C- γ^{Pro}), 29.4 (*cis*-C- β^{Pro}), 30.1 (*trans*-C- β^{Pro}), 46.2 (*cis*-C- δ^{Pro}), 46.7 (*trans*-C- δ^{Pro}), 51.9 (*cis*-OCH₃), 52.0 (*trans*-OCH₃), 58.5 (*trans*-C- α^{Pro}), 58.7 (*cis*-C- α^{Pro}), 68.7 (C₆), 70.7 (CH₂Ph), 71.0 (C₅), 71.9, 71.9, 72.3, 72.3, 73.3 (C₄), 73.4 (C₂), 73.6 (CH₂Ph), 73.7, 73.8, 73.9, 74.2, 78.2 (*cis*-C₃), 79.6 (*trans*-C₃), 91.9 (C₁), 127.3, 127.4, 127.4, 127.4, 127.5, 127.5, 127.5, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 128.1, 128.2, 128.2, 128.2, 139.8, 139.8, 139.9 (C_{arom}), 151.2 (*trans*-C=O_{carbamate}), 151.8 (*cis*-C=O_{carbamate}), 172.3 (*cis*-COOMe), 172.8 (*trans*-COOMe).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₄₁H₄₅NNaO₉: 718.2992; found: 718.2975.

N^u-Fmoc-L-Lys-*N*^e-(2,3,4,6-tetra-*O*-benzyl- α -D-mannopyranosyloxycarbonyl)-L-Phe-OMe (23)

Perbenzylated sulfoxide **1** (129 mg, 0.2 mmol, 1.5 equiv) and DTBP (91 μL , 0.41 mmol, 3.1 equiv) were coevaporated with toluene (2 \times 5 mL). The residue was dissolved in CH₂Cl₂ (4 mL), and molecular sieves (4 \AA) were added. The resulting mixture was stirred for 30 min under an argon atmosphere. The mixture was cooled -70 $^\circ\text{C}$ and Tf₂O (30 μL , 0.2 mmol, 1.5 equiv) was added dropwise followed by a soln of Fmoc-L-Lys-*N*^e-Boc-L-Phe-OMe (83 mg, 131 μmol) in CH₂Cl₂ (5 mL). The mixture was stirred at -25 $^\circ\text{C}$ for 18 h, and the reaction was stopped by the addition of MeOH (0.3 mL), diluted with CH₂Cl₂ (30 mL) and poured into sat. aq NaHCO₃–brine–H₂O (1:1:2, 30 mL). The aqueous phase was extracted with CH₂Cl₂ (3 \times 20 mL), and the combined organic phases were dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (CH₂Cl₂–MeOH, 100:1, then 80:1), which afforded mannosyl carbamate **23** (43 mg, 39 μmol , 44%) as a colorless solid; R_f = 0.30 (CH₂Cl₂–MeOH, 40:1).

^1H NMR (500 MHz, acetone- d_6): δ = 1.32–1.46 (m, 2 H, 2 $\gamma\text{-H}^{\text{Lys}}$), 1.47–1.57 (m, 2 H, 2 $\delta\text{-H}^{\text{Lys}}$), 1.59–1.70 (m, 1 H, $\beta\text{-H}_\text{a}^{\text{Lys}}$), 1.74–1.85 (m, 1 H, $\beta\text{-H}_\text{b}^{\text{Lys}}$), 3.02 (dd, J = 13.8, $^3J_{\alpha,\beta\text{a}}$ = 7.8 Hz, 1 H, $\beta\text{-H}_\text{a}^{\text{Phe}}$), 3.09–3.18 (m, 3 H, $\beta\text{-H}_\text{b}^{\text{Phe}}$, 2 $\epsilon\text{-H}^{\text{Lys}}$), 3.64 (s, 3 H, OCH₃), 3.69 (d, 2J = 10.7 Hz, 1 H, H_{6a}), 3.77 (dd, 2J = 11.2, $^3J_{5,6\text{b}}$ = 4.7 Hz, 1 H, H_{6b}), 3.79–3.84 (m, 1 H, H₅), 3.91 (dd, $^3J_{2,3}$ = 3.0, $^3J_{3,4}$ = 9.5 Hz, 1 H, H₃), 3.98 (dd, $^3J_{1,2}$ = 1.7, $^3J_{2,3}$ = 3.0 Hz, 1 H, H₂), 4.04 (t, $^3J_{3,4}$ = $^3J_{4,5}$ = 9.3 Hz, 1 H, H₄), 4.15–4.21 (m, 1 H, $\alpha\text{-H}^{\text{Lys}}$), 4.22 (br t, 3J = 7.3 Hz, 1 H, CH^{Fmoc}), 4.26–4.39 (m, 2 H, CH₂^{Fmoc}), 4.51–4.68 (m, 5 H, 2 CH₂^{Bn}, CH_a^{Bn}), 4.69–4.75 (m, 1 H, $\alpha\text{-H}^{\text{Phe}}$), 4.76 (br s, 2 H, CH₂^{Bn}), 4.89 (d, 2J = 11.0 Hz, 1 H, CH_b^{Bn}), 6.14 (d, $^3J_{1,2}$ = 1.7 Hz, 1 H, H₁), 6.52–6.63 (m, 2 H, $\alpha\text{-NH}^{\text{Lys}}$, $\epsilon\text{-NH}^{\text{Lys}}$), 7.12–7.46 (m, 29 H, H_{arom}), 7.48 (d, $^3J_{\text{NH},\alpha}$ = 7.8 Hz, 1 H, NH^{Phe}), 7.65–7.73 (m, 2 H, H_{arom}^{Fmoc}), 7.82–7.88 (m, 2 H, H_{arom}^{Fmoc}).

^{13}C NMR (125 MHz, acetone- d_6): δ = 23.5 ($\gamma\text{-C}^{\text{Lys}}$), 30.3 ($\delta\text{-C}^{\text{Lys}}$), 32.6 ($\beta\text{-C}^{\text{Lys}}$), 38.4 ($\beta\text{-C}^{\text{Phe}}$), 41.4 ($\epsilon\text{-C}^{\text{Lys}}$), 48.1 (C^{Fmoc}), 52.4 (OCH₃), 54.2 ($\alpha\text{-C}^{\text{Phe}}$), 56.2 ($\alpha\text{-C}^{\text{Lys}}$), 67.3 (CH₂^{Fmoc}), 70.1 (C₆), 72.3, 73.3, 73.8, 75.4 (4 CH₂Ph), 74.7 (C₅), 75.6 (C₄), 75.7 (C₂), 80.8 (C₃), 92.6 (C₁), 120.8 (CH_{arom}^{Fmoc}), 126.2, 127.6, 128.1, 128.2, 128.3, 128.5, 128.6, 128.6, 129.0, 129.0, 129.1, 129.1, 129.2 (CH_{arom}), 130.1 (*o*-CH_{arom}^{Phe}), 136.8, 138.1, 139.7, 139.8, 139.8, 139.9 (C_{arom}), 142.1 (CH_{arom}^{Fmoc}), 145.0, 145.1 (C_{arom}^{Fmoc}), 155.1 (C=O_{carbamate}^{Man}), 157.0 (C=O_{carbamate}^{Fmoc}), 172.5 (COOMe).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₆₆H₆₉N₃NaO₁₂: 1118.4779; found: 1118.4799.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft DFG (Ob-332/1-1 and 1-2). P.S. thanks the Schering Foundation for a predoctoral fellowship.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

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