Galactosylated 5-Hydroxylysine Mimetics for Glycopeptide Synthesis

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The design and synthesis of four galactosylated 5-hydroxylysine mimetic building blocks (**2**–**5**), conveniently protected for solid-phase glycopeptide synthesis, is described. Our approach features: *i*) a short and divergent route to the corresponding protected amino acid aglycons **6**–**9** that involves selective ring-opening of enantiopure 5-hydroxylated 6-oxo-1,2-piperidinedicarboxylate **10** and **11** with sodium borohydride in ethanol with formation of the corresponding 1,2-diol; *ii*) a common δ-lactam precursor **12**, readily accessible from Boc-Asp-O*t*Bu (3 steps, 74% yield), that can be hydroxylated with a high level of asymmetric induction; *iii*) the use of tetrapivaloylated galactosyl bromide as galactosyl donor to avoid or limit orthoester formation. The four galactosylated hydroxylysine analogues **2**–**5** are suitable building blocks for incorporation into immunodominant peptides derived from type II collagen (CII) and for future investigations aimed at determining the fine specificity of arthritogenic T-cells in collagen-induced arthritis (CIA), a mouse model for rheumatoid arthritis (RA).

Introduction

In type II collagen (CII), lysine residues can undergo hydroxylation followed by glycosylation with either a β-D-galactopyranosyl or an α-D-glucopyranosyl-(1→2)-β-D-galactopyranosyl moiety.[1] Recent results suggest that a T-cell response towards glycosylated peptide fragments of CII could play an important role in the development of rheumatoid arthritis.[2] In particular, the CII-derived peptide **1** encompassing residues 256−270 and containing a galactosylated (2*S*,5*R*)-5-hydroxylysyl (Gal-5-Hyl) residue at position 264 (Figure 1), has been identified as an immunodominant T-cell epitope in CIA, a mouse model for RA.[2b]

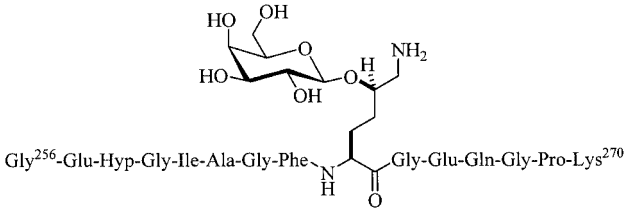

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Figure 1. CII-derived glycopeptide **1**: immunodominant T-cell epitope in CIA

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The groups of Kihlberg and Holmdahl have shown that more than two-thirds of helper T-cell hybridomas obtained from mice immunized with heterologous CII responded to glycopeptide **1** and that the glycosylated hydroxylysine side-chain at position 264 could serve as a primary T-cell receptor (TCR) contact.[2,3] Structure-activity relationship studies aimed at probing the fine specificity of arthritogenic T-cells using CII glycopeptide analogues modified at position 264 are thus particularly relevant in the context of CIA and RA.

Using a series of CII glycopeptides modified at the carbohydrate moiety (substitution of glucosyl, deoxy sugars and 4-fluoro or 4-methoxy sugar for the galactosyl), Kihlberg, Holmdahl and co-workers have delineated the effect of each individual hydroxyl group of the sugar moiety on the T-cell recognition pattern and demonstrated the importance of the hydroxyl group at C-4 in generating a full T-cell response.[4] This set of glycopeptides was obtained by solid-phase synthesis using glycosylated hydroxylysine building blocks; the *N*-Fmoc-protected hydroxylysine aglycon being prepared in a three-step procedure from commercially available (2*S*,5*R*)-5-hydroxylysine.[5] Additionally, removing the ε-amine function (galactosylated hydroxynorvaline at position 264) was found to be detrimental for the recognition by arthritogenic T-cells.[2b]

As both the galactose and the ε-primary amine are involved in the interaction with the TCR functional groups, we reasoned that glycopeptides incorporating unnatural 5-hydroxylysine derivatives modified at the ε-amino group and/or at C-5 could be useful to further define the specificity of arthritogenic T-cells as well as to generate Altered

Peptide Ligands (APLs)[6] potentially useful for induction of tolerance in the CIA model.

Herein, we report on the design and synthesis of four galactosylated 5-hydroxylysine mimetics **2**−**5** suitably protected for solid-phase synthesis of CII(256−270)-derived glycopeptides using Fmoc chemistry (Figure 2). The modifications include the replacement of the ε-amino function by a hydroxyl group (dihydroxynorleucine derivative **2**), the inversion of stereochemistry at C-5 [(2*S*,5*S*)-5-hydroxylysine derivative **3**], the permutation of the ε-amino and galactosyl moieties [(2*S*,5*S*)-5-azido-6-hydroxynorleucine derivative **4**] and the introduction of a methyl substituent at C-5 [(2*S*,5*R*)-5-hydroxy-5-methyllysine derivative **5**]. We recently described a short and stereoselective route to (2*S*,5*R*)-5-hydroxylysine based on a stereocontrolled hydroxylation of enolates generated from *N*-protected-6-substituted piperidin-2-ones (e.g. **12**) followed by direct ring opening of the resulting α-hydroxylated lactams under reductive conditions to generate the corresponding 1,2-diols.[7] This approach is versatile and has now been extended to the synthesis of the four orthogonally protected aglycons **6**−**9** required for the preparation of the galactosylated building blocks **2**−**5** (Figure 2).

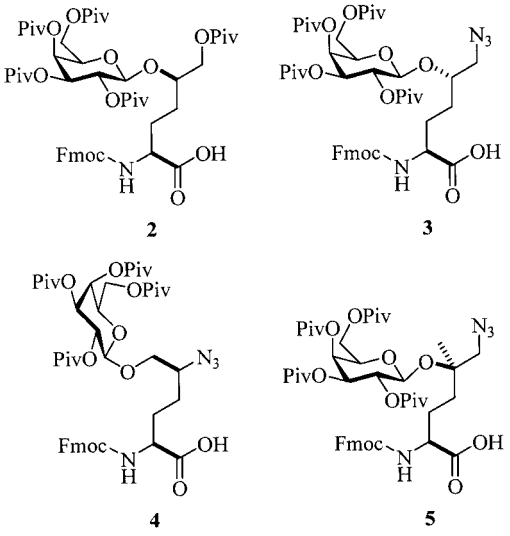


Figure 2. Galactosylated building blocks **2**−**5**

Results and Discussion

Our retrosynthetic analysis of the four orthogonally protected hydroxylysine aglycons **6**−**9** is shown in Figure 3. The synthesis of the three amino acids **6**−**8** utilizes α-hydroxylated δ-lactam **10** as a common precursor. Lactam **10** is a highly versatile chiral synthon which has been used previously in the synthesis of (2*S*,5*R*)-5-hydroxylysine as well as in the synthesis of two intermediates required in the total synthesis of bone collagen cross-link (+)-pyridinoline.[7,8] Alternatively, 5-methylated-5-hydroxylysine derivative **9** should be obtained from the α-alkylated- α-hydroxylated lactam **11**. Both hydroxylated lactams **10** and **11** derive from (2*S*)-6-oxo-1,2-piperidinedicarboxylate **12** which is readily accessible in 74% yield (three steps) from Boc-Asp-O*t*Bu.

The general protecting group scheme developed for our aglycons is the following. The N^{α}-amino functionality was protected with an Fmoc group for convenient solid-phase peptide synthesis. We chose to protect the acid function with a *tert*-butyl ester. This protection is sensitive to acidic conditions, and thus to Lewis acids, but should allow quantitative orthogonal cleavage after the glycosylation step. Besides these common protecting groups, the azide function (compounds **7**−**9**) was considered as a temporary protecting group for the N^{ε}-amine (the reduction of the azide function can be performed safely on a solid support at the end of the elongation of the peptide chain[9]) and the pivaloyl (Piv) protecting group (compound **6**) was used to protect

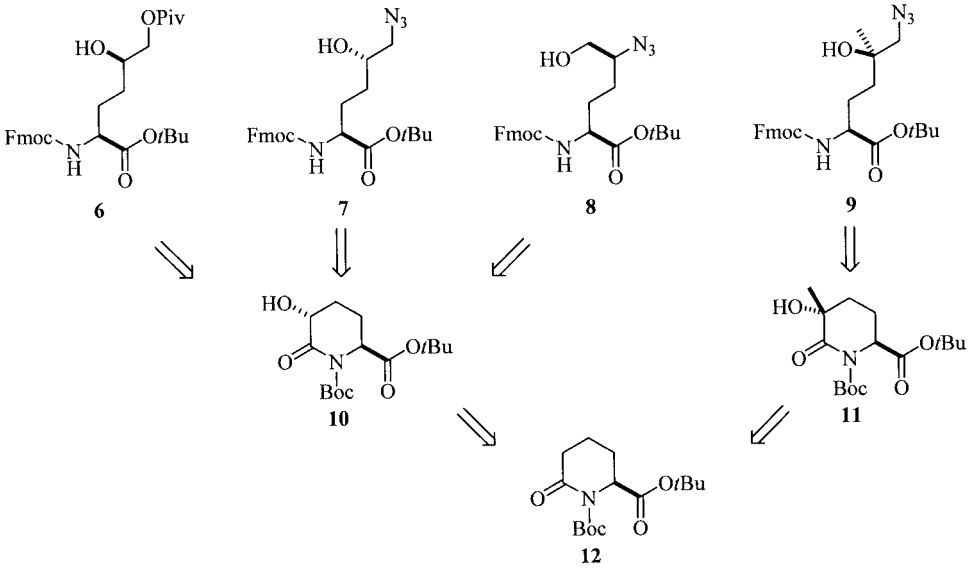
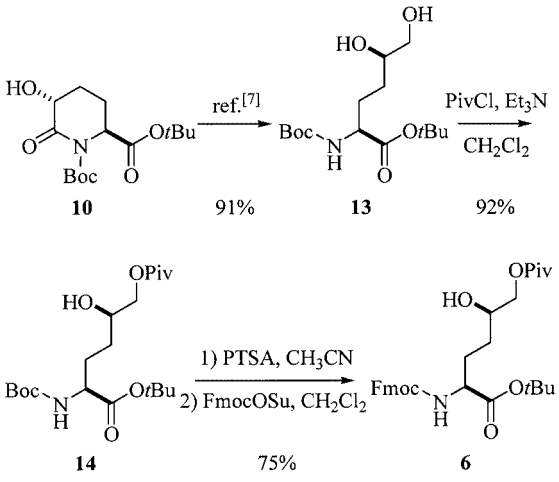


Figure 3. Retrosynthesis of hydroxylysine aglycons **6**−**9** starting from a common precursor **12**

the primary alcohol of the 1,2-diol (removal of this group will be concomitant with the deprotection of the carbohydrate moiety following cleavage of the peptide from the resin).

(2S,5R)-5,6-Dihydroxynorleucine Derivative 6

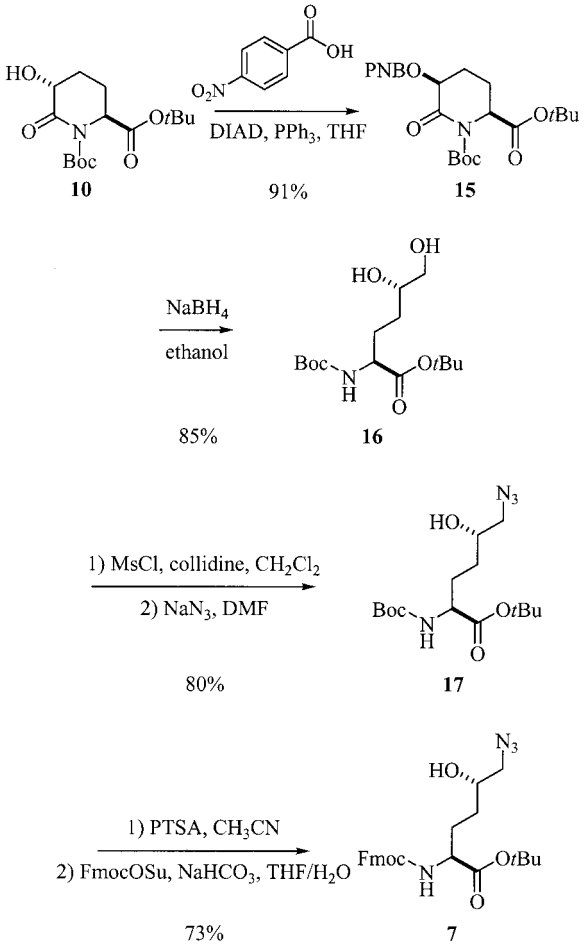
Enantiopure hydroxylated piperidinone **10** was transformed into the corresponding 1,2-diol **13** by treatment with $NaBH_4$ in ethanol as described previously.[7] The primary alcohol group of **13** was protected with a pivaloyl functional group. This reaction was highly regioselective and the protected 1,2-diol **14** was obtained in 92% yield. Selective removal of the *N*-Boc protecting group with *p*-toluenesulfonic acid (PTSA) in acetonitrile, followed immediately by neutralization with a 1 N NH_4OH solution, gave the free amine, which was quantitatively reprotected by reaction with FmocOSu in the absence of base to give aglycon **6** in 63% overall yield from **10** (4 steps; Scheme 1).



Scheme 1. Synthesis of the (2*S*,5*R*)-5,6-dihydroxynorleucine derivative **6**

(2S,5S)-5-Hydroxylysine Derivative 7

The inversion of stereochemistry at C-5 was cleanly performed by treatment of α-hydroxylated lactam **10** with *p*-nitrobenzoic acid under Mitsunobu conditions (Scheme 2).[10] Lactam **15** was isolated in 91% yield after flash chromatography. The diastereomeric purity of **15** was confirmed by comparison of its ^1H NMR spectrum with that of a pure sample of (5*R*)-**15** prepared by reaction of **10** with *p*-nitrobenzoyl chloride. The signal of the H-(C-2) proton in **15** is shifted upfield by ca. 0.2 ppm compared to the same proton in (5*R*)-**15**. The reductive ring-opening of **15** by $NaBH_4$ in ethanol was accompanied by the removal of the *p*-nitrobenzoate protecting group (PNB) to afford the 1,2-diol **16** in 85% yield. Selective mesylation of the primary alcohol and quantitative conversion of the crude mesylate by nucleophilic substitution with NaN_3 gave the 1,2-azido alcohol **17**. Selective deprotection of the N^{α}-Boc protecting group and reaction of the crude primary amine with FmocOSu under basic aqueous conditions gave (2*S*,5*S*)-5-hydroxylysine derivative **7** (45% overall yield from **10**) ready for glycosylation (Scheme 2).

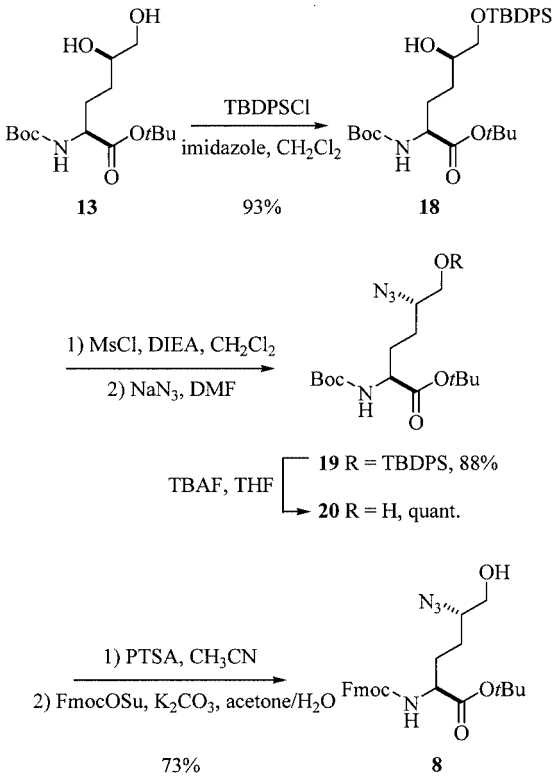


Scheme 2. Synthesis of the (2*S*,5*S*)-5-hydroxylysine derivative **7**

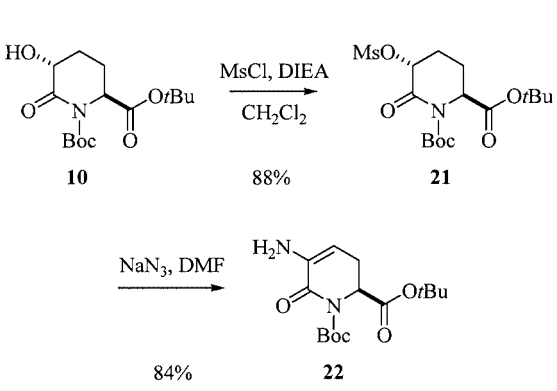
(2S,5S)-5-Azido-6-hydroxynorleucine Derivative 8

Two routes were investigated. The first one started with 1,2-diol **13**, which was selectively protected on the primary alcohol with a *tert*-butyldiphenylsilyl (TBDPS) functional group (Scheme 3). Silyl ether **18** was obtained in 93% yield and subjected to methanesulfonylation, followed by nucleophilic substitution with NaN_3, to give **19** in 88% yield. Removal of the TBDPS protection in the presence of fluoride ions (TBAF) quantitatively yielded **20**. Finally, the previously described deprotection/reprotection sequence gave (2*S*,5*S*)-5-azido-6-hydroxynorleucine derivative **8** in 73% yield.

Alternatively, α-hydroxylated lactam **10** was mesylated to **21** in 88% yield (Scheme 4). Upon nucleophilic substitution with NaN_3, the formed α-azido lactam decomposed spontaneously to the corresponding α-amino α,β-unsaturated lactam **22**, which was isolated in 84% yield. α-Azido carbonyl compounds with α-hydrogens are highly base sensitive and well-known to rearrange to the corresponding α-imino carbonyl or α-amino α,β-unsaturated carbonyl compounds (enol form if β-hydrogens are present).[11]

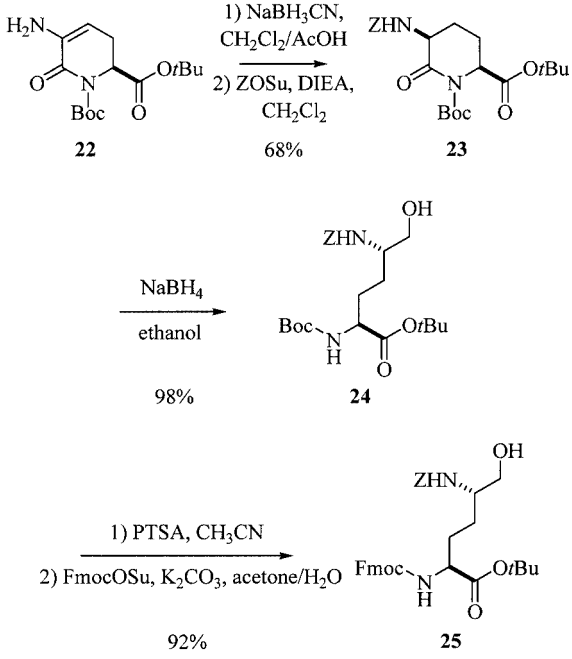


Scheme 3. Synthesis of the (2*S*,5*S*)-5-azido-6-hydroxynorleucine derivative **8**

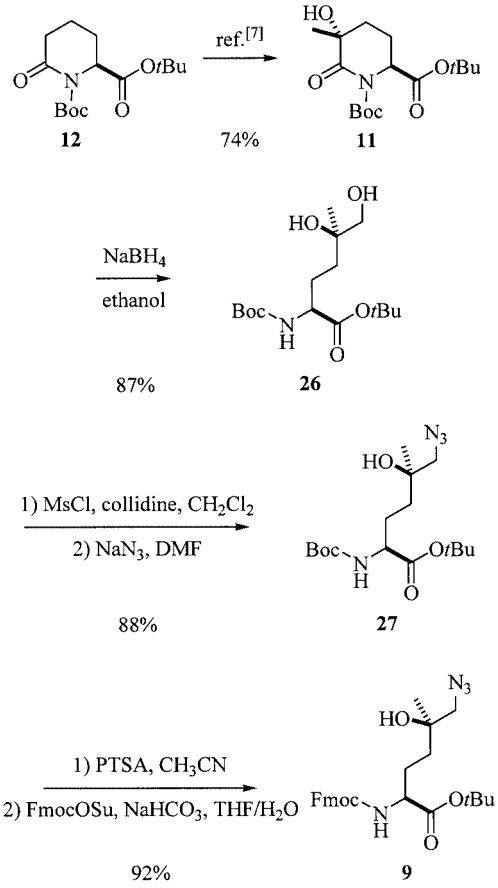


Scheme 4. Synthesis of the ene-amine **22**

Reduction of **22** with sodium cyanoborohydride proceeded with a high diastereoselectivity (*dr* > 95:5)[12] and gave the *N*-protected α-amino lactam **23** in 68% yield after protection of the primary amine with a Z group (Scheme 5). The stereochemistry at C-5 in **23** was deduced from the ^{1}H NMR spectrum of the crude product by comparison with that of the *cis*-lactam **15**. In this case again, the H-(C-2) proton is shielded by about 0.2 ppm compared to the minor isomer. Reductive opening of the lactam ring by $NaBH_4$ afforded the *N*-protected aglycon **24**, which was converted into the *N*-Fmoc-protected aglycon **25** by the previously described deprotection/reprotection sequence. Compared to **8**, the side chain of **25** also bears a combination of δ-amino and ε-hydroxyl groups, but the azide function has been replaced by a urethane protected amino group.



Scheme 5. Synthesis of the aglycon **25**



Scheme 6. Synthesis of the (2*S*,5*R*)-5-hydroxy-5-methyllysine derivative **9**

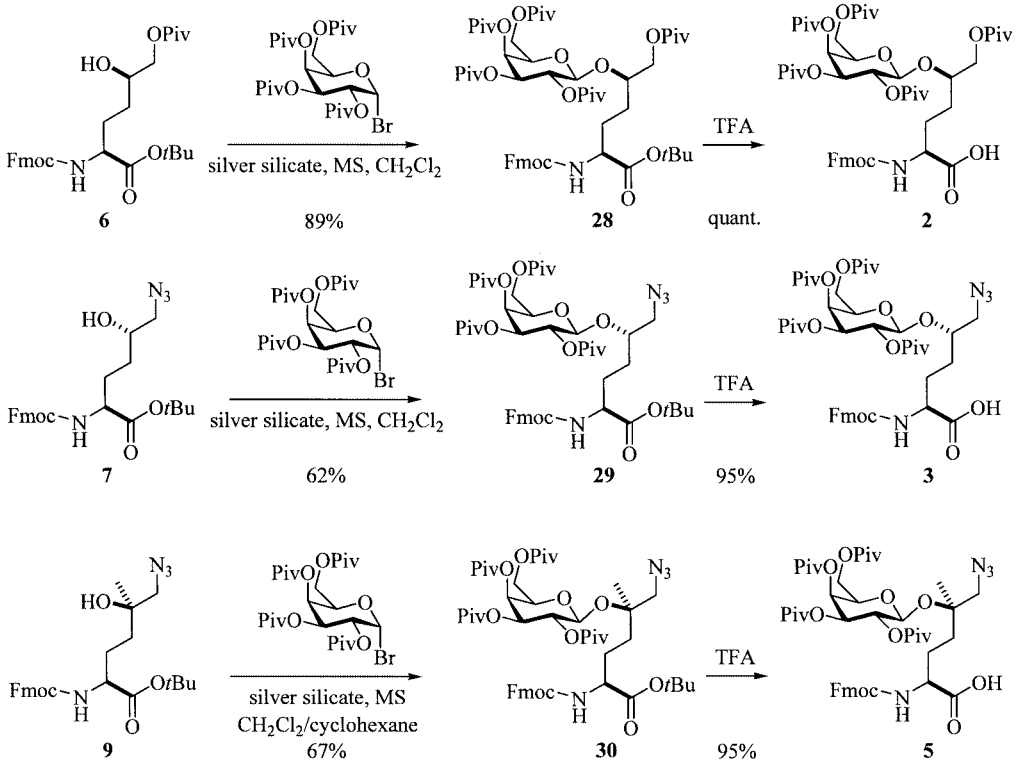
(2S,5R)-5-Hydroxy-5-methyllysine Derivative 9

The 5-hydroxylysine derivative methylated at the 5-position was prepared in a manner analogous to (2*S*,5*R*)-5-hydroxylysine, but starting from the previously described α-methylated α-hydroxylated lactam **11**.[7] Briefly, lactam **11** was obtained as the sole diastereomer (*dr* 98:2, 74% yield) in a two-step procedure involving methylation of the Li-enolate derived from **12** and stereoselective hydroxylation of the Li-enolate of the resulting α-methylated lactam. Ring opening of lactam **11** using $NaBH_4$ afforded the expected 1,2-diol **26** in high yield (Scheme 6). Selective mesylation of the primary alcohol directly followed by nucleophilic substitution with NaN_3 gave the corresponding 1,2-azido alcohol **27** in 88% yield. The N^{α}-Fmoc-protected (2*S*,5*R*)-5-hydroxy-5-methyllysine derivative **9** was obtained in 92% yield using the two-step procedure described for the preparation of **7**.

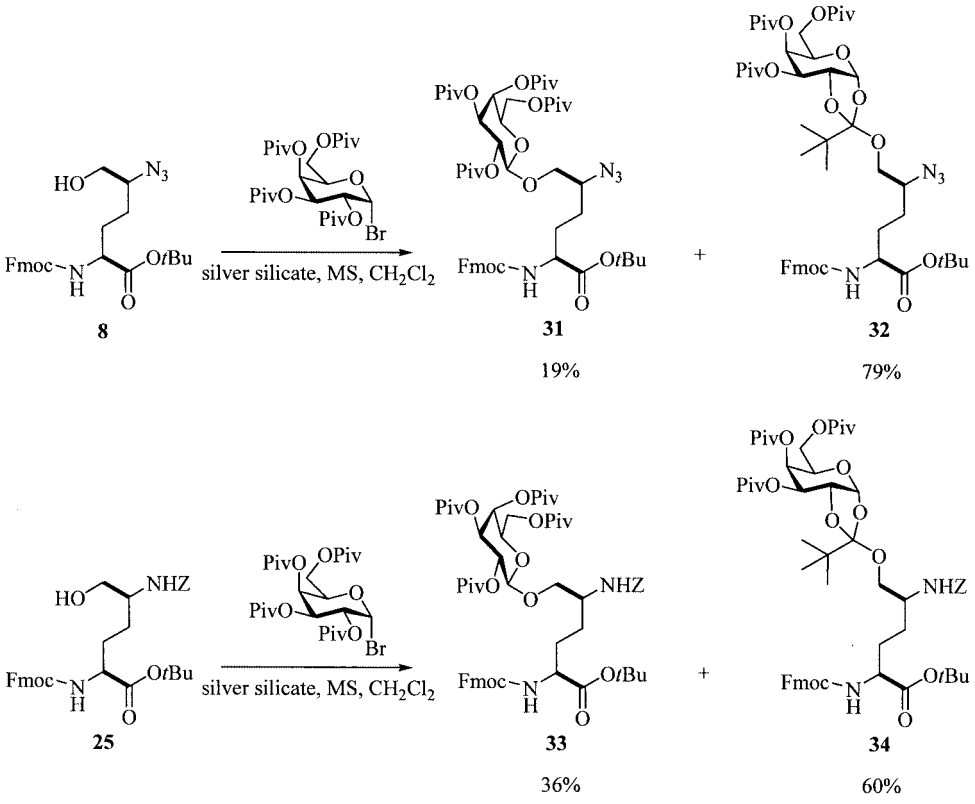
Galactosylation of Hydroxylysine Mimetics 6−9

Several syntheses of β-galactosylated (2*S*,5*R*)-5-hydroxylysine building blocks have been reported in the literature in recent years.[13] Koenigs−Knorr[14] and Schmidt's trichloroacetimidate[15] methodologies, both of which are very effective for the synthesis of mono- and disaccharides, have been employed in these studies. In all cases stereocontrol was imparted by the use of an acetyl as participating group in the 2-position, i.e. peracetylated galactosyl donors. The outcome of the galactosylation, however, was found to be strongly influenced by the nature of the protecting groups on the 5-Hyl aglycon. The best results were obtained by Kihlberg and co-workers with Fmoc-5-Hyl(*Z*)-OAll which was galactosylated in 82% yield using peracetylated galactosyl bromide in the presence of silver silicate.[13b]

In contrast, the galactosylation of 5-hydroxylysine mimetics **6**−**9** was performed with tetra-pivaloylated galactosyl bromide. The choice of a pivaloylated galactosyl donor stemmed from difficulties experienced during the galactosylation of (5*R*)-**7** en route to the synthesis of the naturally occurring CII glycopeptide incorporating a Gal-5-Hyl residue.[16] All our attempts to use peracetylated galactosyl donors (e.g. bromide or trichloroacetimidates) with (5*R*)-**7** aglycon resulted in poor yields of the desired Gal-5-Hyl derivative and led almost exclusively to the formation of the corresponding orthoester and/or the C-5 acetylated hydroxylysine derivatives (manuscript in preparation). The course of the reaction was dramatically improved and the formation of orthoester suppressed upon replacement of acetyl groups by the bulkier pivaloyl groups on the galactosyl donor.[16−18] Our optimal procedure for glycosylation was the following: tetra-pivaloylated galactosyl bromide (1.5 equiv.)/silver silicate/CH_2Cl_2/room temp./8 h. Under these conditions, galactosylated 5-hydroxylysine mimetics **2**, **3** and **5** (Scheme 7) were obtained in good to excellent yield (62−89%). The low reactivity of the tertiary alcohol in acceptor **9** necessitated a slight adjustment of this general procedure. In this case, the galactosyl bromide (1.5 equiv.) was divided into six equal portions added every 12 h and cyclohexane was used as a co-solvent to reduce the rate of degra-



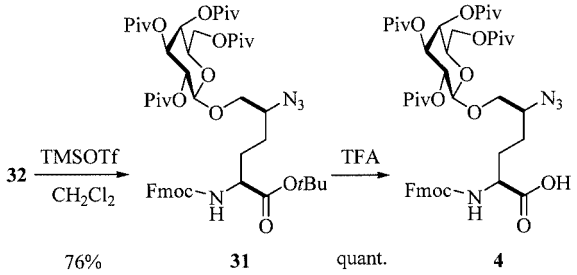
Scheme 7. Synthesis of the galactosylated building blocks ready for use in solid-phase glycopeptide synthesis



Scheme 8. Galactosylation of the aglycons **8** and **25**

dation of the galactosyl donor. C_{18} RP-HPLC monitoring of the galactosylation indicated completion of the reaction after three days.

Galactosylation of **8** under our optimized procedure resulted in the formation of the corresponding orthoester **32**, which was recovered in 79% yield and gave only a low yield of the desired galactosylated building block **31** (19% yield; Scheme 8). In an attempt to evaluate the influence of the azido group on the glycosylation reaction, aglycon **25** was also subjected to galactosylation under our optimized procedure. Although the yield of the galactosylated product increased to 36%, the corresponding orthoester **34** was still the major product. The structures of **32** and **34** were unambiguously assigned by examination of the ^{1}H NMR spectra. The downfield chemical shift of the anomeric proton (δ = 5.8 ppm) and its coupling constant with H−C(2) of the galactosyl (J = 4.7 Hz) are characteristic of orthoester formation.



Scheme 9. Synthesis of the galactosylated building block **4**

Subsequently, we found that the orthoester **32** could be rearranged to the expected galactosylated derivative **31** in 76% yield by treatment with a catalytic amount of TMSOTf (Scheme 9). Under the same conditions, rearrangement of orthoester **34** gave **33** in low yield together with a major byproduct. Additionally, these two compounds were inseparable by chromatography and the galactosylated derivative **33** was not isolated from the crude product.

The expected β-glycosidic linkage in **28**−**31** and **33** was confirmed by the large coupling constants between the anomeric proton and H−C(2) of the galactosyl (δ = 4.4−4.8 ppm, $J \approx 8$ Hz). In all cases cleavage of the *tert*-butyl ester group by treatment with TFA afforded galactosylated (2*S*,5*R*)-5-hydroxylysine mimetics **2**−**5** in quantitative, yield.

Conclusion

We have recently proposed a divergent strategy for the synthesis of 5- and 4-hydroxylysine derivatives based on the use of enantiopure α- and β-monohydroxylated δ-lactams as key intermediates, respectively.[7,19] This approach has now been extended to the design and synthesis of four novel non-natural *N*-Fmoc-protected hydroxylysine analogues **6**−**9** incorporating modifications either at the ε-amino function or at C-5. These amino acid aglycons have been glycosylated in good yield using tetra-pivaloylated galactosyl bromide in the presence of silver silicate. The use of

cyclohexane as a co-solvent was found to be critical to achieve galactosylation of the tertiary alcohol of aglycon **9** in good yield. In addition, galactosylated derivative **4** was recovered in good yield only after rearrangement of the corresponding orthoester which was formed as the major product during the glycosylation reaction.

The resulting galactosylated building blocks **2**−**5** are suitably protected for use in solid-phase synthesis and their incorporation at position 264 of the immunodominant peptide epitope CII(256−270) will be reported in a forthcoming study. The resulting CII(256−270) glycopeptide analogues should prove useful to further define the specificity of CII-specific T cells in CIA.

Experimental Section

Materials: Tetra-pivaloylated galactosyl bromide was prepared by a two-step procedure starting from commercial D-galactose.[20] Filtration through a plug of silica gave pure galactosyl bromide as a white solid which could be stored at 4 °C for several weeks without degradation. Silver silicate was prepared according to the reported procedure[21] and dried at 110 °C under high-vacuum for 6 h before use.

General Methods: THF was distilled from Na/benzophenone. CH_2Cl_2 and cyclohexane were distilled from CaH_2. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck) with detection by UV light and charring with 1% w/w ninhydrin in ethanol followed by heating. Flash column chromatography was carried out on silica gel (0.063−0.200 nm). HPLC analysis was performed on a Nucleosil C_{18} column (5 μm, 3.9 × 150 mm) by using a linear gradient of A (0.1% TFA in H_2O) and B (0.08% TFA in CH_3CN) at a flow rate of 1.2 mL/min with UV detection at 214 nm. Optical rotations were recorded with a Perkin−Elmer polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 300 apparatus.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-6-[(2,2-dimethylpropanoyl)oxy]-5-hydroxyhexanoate (14):** Pivaloyl chloride (188 mg, 1.56 mmol) dissolved in 1.0 mL of CH_2Cl_2 was added to a solution of 1,2-diol **13** (250 mg, 0.78 mmol)[7] in a mixture of 2.5 mL of CH_2Cl_2 and 2.5 mL of pyridine at 0 °C. After being stirred for 2 h at 0 °C, the solution was quenched by addition of water. The solvent was evaporated and replaced by EtOAc. The solution was washed with 1 N $KHSO_4$, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography to yield pure **14** (290 mg, yield: 92%) as a colourless oil. HPLC: t_R = 11.19 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = −8.9 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.21 (br. d, J = 8.0 Hz, 1 H), 4.23−4.14 (m, 1 H), 4.04 (dd, J = 11.3, 4.0 Hz, 1 H), 3.96 (dd, J = 11.3, 6.2 Hz, 1 H), 3.86−3.78 (m, 1 H), 2.01−1.90 (m, 1 H), 1.72−1.62 (m, 1 H), 1.56−1.48 (m, 2 H), 1.42 (s, 9 H), 1.40 (s, 9 H), 1.17 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.6 (C), 171.7 (C), 155.6 (C), 82.0 (C), 79.8 (C), 69.6 (CH), 68.3 (CH_2), 53.6 (CH), 38.8 (C), 29.5 (CH_2), 29.0 (CH_2), 28.3 (3 CH_3), 27.9 (3 CH_3), 27.0 (3 CH_3) ppm. $C_{20}H_{37}NO_7$: calcd. C 59.53, H 9.24, N 3.47; found C 59.29, H 9.57, N 3.50.

***tert*-Butyl (2*S*,5*R*)-6-[(2,2-Dimethylpropanoyl)oxy]-2-{[(9*H*-fluoren-9-ylmethoxy)carbony]amino}-5-hydroxyhexanoate (6):** The monoprotected 1,2-diol **14** (100 mg, 0.248 mmol) was dissolved in 2.0 mL of CH_3CN cooled to 0 °C. PTSA (94 mg, 0.496 mmol) was added and the resulting mixture was stirred at 0 °C for 2 h. The mixture was then allowed to reach room temperature, stirred for an additional 2 h, and checked by TLC (EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). The reaction was quenched by the addition of 30.0 mL of aqueous 1 N NH_4OH. The solution was extracted with 30.0 mL (2 × 15.0 mL) of CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 2.0 mL of CH_2Cl_2 and FmocOSu (100 mg, 0.297 mmol) was added. The solution was stirred at room temperature and checked by TLC (EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). After complete consumption of the starting amine, CH_2Cl_2 was evaporated off and replaced by EtOAc. The solution was washed with 1 N $KHSO_4$ and water, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 98:2) to yield pure **6** (97 mg, yield: 75% for 2 steps) as a colourless oil. HPLC: t_R = 14.30 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +4.9 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H), 7.60 (d, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.3 Hz, 2 H), 7.31 (t, J = 7.3 Hz, 2 H), 5.57 (br. d, J = 8.0 Hz, 1 H), 4.39 (d, J = 7.0 Hz, 2 H), 4.37−4.29 (m, 1 H), 4.22 (t, J = 7.0 Hz, 1 H), 4.10 (dd, J = 11.3, 3.8 Hz, 1 H), 4.00 (dd, J = 11.2, 6.4 Hz, 1 H), 3.90−3.82 (m, 1 H), 2.70 (br. s, 1 H), 2.11−1.98 (m, 1 H), 1.81−1.67 (m, 1 H), 1.61−1.52 (m, 2 H), 1.47 (s, 9 H), 1.21 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.7 (C), 171.5 (C), 156.1 (C), 143.9 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 82.3 (C), 69.7 (CH), 68.4 (CH_2), 67.0 (CH_2), 54.0 (CH), 47.2 (CH), 38.8 (C), 29.4 (CH_2), 28.9 (CH_2), 28.0 (3 CH_3), 27.2 (3 CH_3) ppm. $C_{30}H_{39}NO_7$: calcd. C 68.55, H 7.48, N 2.66; found C 68.83, H 7.88, N 2.31.

Di(*tert*-butyl) (2*S*,5*S*)-5-[(4-Nitrobenzoyl)oxy]-6-oxo-1,2-piperidinedicarboxylate (15): *p*-Nitrobenzoic acid (436 mg, 2.61 mmol) and PPh_3 (685 mg, 2.61 mmol) were added to a solution of **10** (550 mg, 1.74 mmol)[7] in 30.0 mL of THF at ambient temperature. The solution was cooled to 0 °C and DIAD (528 mg, 2.61 mmol) dissolved in 8.0 mL of THF was introduced with a hypodermic syringe. The mixture was allowed to reach room temperature and stirred overnight. Evaporation of the solvent gave an oil, which was dissolved in EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:7) to yield pure **15** (738 mg, yield: 91%) as a white solid. HPLC: t_R = 13.87 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = −12.1 (c = 1.0, $CHCl_3$). M.p. 48−49 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32−8.24 (m, 4 H), 5.59 (dd, J = 12.1, 6.4 Hz, 1 H), 4.59−4.56 (m, 1 H), 2.38−2.22 (m, 3 H), 2.15−2.03 (m, 1 H), 1.51 (s, 9 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 170.1 (C), 167.2 (C), 163.8 (C), 152.5 (C), 150.6 (C), 135.0 (C), 131.1 (2 CH), 123.4 (2 CH), 83.9 (C), 82.7 (C), 71.0 (CH), 59.1 (CH), 27.9 (3 CH_3), 27.8 (3 CH_3), 25.1 (CH_2), 23.9 (CH_2) ppm. $C_{22}H_{28}N_2O_9$: calcd. C 56.89, H 6.08, N 6.03; found C 56.59, H 6.21, N 5.89.

***tert*-Butyl (2*S*,5*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5,6-dihydroxyhexanoate (16):** Sodium borohydride (155 mg, 4.09 mmol) was added to a solution of **15** (380 mg, 0.82 mmol) in 4.0 mL of absolute ethanol at 0 °C. The mixture was allowed to reach room temperature and stirred for 4 h. After being quenched with water, the mixture was stirred for a further 10 min. The solvent was evaporated and the residue dissolved in EtOAc. The resulting solution was washed with a saturated $NaHCO_3$ solution and water. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc) to give pure **16** (222 mg, yield: 85%) as a colourless oil. HPLC: t_R =

5.85 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +3.5 (*c* = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.34 (br. d, *J* = 7.9 Hz, 1 H), 4.12−4.01 (m, 1 H), 3.68−3.59 (m, 1 H), 3.54 (dd, *J* = 11.2, 3.1 Hz, 1 H), 3.37 (dd, *J* = 11.2, 7.5 Hz, 1 H), 1.80−1.69 (m, 2 H), 1.41−1.33 (m, 2 H), 1.40 (s, 9 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 172.1 (C), 155.7 (C), 81.9 (C), 79.7 (C), 71.5 (CH), 66.5 (CH_2), 53.9 (CH), 28.8 (CH_2), 28.7 (CH_2), 28.3 (3 CH_3), 27.9 (3 CH_3) ppm. $C_{15}H_{29}NO_6$: calcd. C 56.41, H 9.15, N 4.39; found C 56.35, H 9.28, N 4.60.

***tert*-Butyl (2*S*,5*S*)-6-Azido-2-[(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (17):** Collidine (534 μL, 4.01 mmol) was added to a solution of the 1,2-diol **16** (128 mg, 0.40 mmol) in 8.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and MsCl (50 mg, 0.44 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added. After being stirred for 20 h at 0 °C, the reaction was quenched by addition of water (3.0 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 N $KHSO_4$, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 5.0 mL of DMF. NaN_3 (52 mg, 0.80 mmol) was added to the solution, which was heated to 80 °C for 16 h. After being cooled to room temperature, water was added to the solution, which was extracted twice with EtOAc. The combined organic layers were washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:7) to yield pure **17** (110 mg, yield: 80% for 2 steps) as a colourless oil. HPLC: t_R = 9.55 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +5.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.17 (br. d, *J* = 7.3 Hz, 1 H), 4.21−4.12 (m, 1 H), 3.80−3.72 (m, 1 H), 3.32 (dd, *J* = 12.4, 3.8 Hz, 1 H), 3.23 (dd, *J* = 12.4, 7.1 Hz, 1 H), 1.89−1.69 (m, 2 H), 1.56−1.43 (m, 2 H), 1.44 (s, 9 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.7 (C), 155.5 (C), 82.1 (C), 79.8 (C), 70.1 (CH), 56.9 (CH_2), 53.6 (CH), 29.8 (CH_2), 29.0 (CH_2), 28.3 (3 CH_3), 27.9 (3 CH_3) ppm. $C_{15}H_{28}N_4O_5$: calcd. C 52.31, H 8.19, N 16.27; found C 52.42, H 8.45, N 16.11.

***tert*-Butyl (2*S*,5*S*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino}-5-hydroxyhexanoate (7):** *p*-Toluenesulfonic acid (88 mg, 0.463 mmol) was added to a solution of **17** (80 mg, 0.232 mmol) in 2.0 mL of CH_3CN at 0 °C. The mixture was stirred at 0 °C for 4 h and consistently checked by TLC (EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). The mixture was then allowed to reach room temperature and stirred for an additional 4 h (until **17** disappeared). The reaction was quenched by addition of 30.0 mL of 1 N NH_4OH. The solution was extracted with 30.0 mL (2 × 15.0 mL) of CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 2.0 mL of THF and the same volume of water was added to the solution. Solid $NaHCO_3$ (39 mg, 0.464 mmol) and a solution of FmocOSu (94 mg, 0.279 mmol) in 0.5 mL of THF were added to the solution, which was stirred at room temperature for 3 h. The THF was then evaporated off and replaced by EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, brine, 1 N $KHSO_4$, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 98:2) to yield pure **7** (79 mg, yield: 73% for 2 steps) as a colourless oil. HPLC: t_R = 13.22 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +3.5 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.60 (d, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 5.59 (br. d, *J* = 7.9 Hz, 1 H), 4.40 (d, *J* = 7.0 Hz, 2 H), 4.32−4.25 (m, 1 H), 4.21 (t, *J* = 6.9 Hz, 1 H), 4.82−4.73 (m, 1 H), 3.34−3.30 (m, 1 H), 3.27−3.19 (m, 1 H), 2.80 (br. s, 1 H), 1.89−1.77 (m, 2 H), 1.60−1.43 (m, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.5 (C), 156.1 (C), 143.9 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 82.4 (C), 70.1 (CH), 67.0 (CH_2), 57.0 (CH_2), 54.0 (CH), 47.2 (CH), 29.6 (CH_2), 28.9 (CH_2), 28.0 (3 CH_3) ppm. $C_{25}H_{30}N_4O_5$: calcd. C 64.36, H 6.48, N 12.01; found C 64.59, H 6.57, N 11.94.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-6-{[*tert*-butyl(diphenyl)silyl]oxy}-5-hydroxyhexanoate (18):** Imidazole (85 mg, 1.25 mmol) and TBDPSCl (327 mg, 1.19 mmol) dissolved in 1.0 mL of CH_2Cl_2 were added to a solution of **13** (190 mg, 0.595 mmol)[7] in 5.0 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 30 min and immediately quenched by the addition of water. After evaporation of CH_2Cl_2, the residue was dissolved in EtOAc, washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexane, 2:8) yielded pure **18** (308 mg, yield: 93%) as a colourless oil. HPLC: t_R = 16.03 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = +8.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67−7.64 (m, 4 H), 7.41−7.34 (m, 6 H), 5.22 (br. d, *J* = 8.0 Hz, 1 H), 4.21−4.15 (m, 1 H), 3.75−3.68 (m, 1 H), 3.62 (dd, *J* = 10.1, 4.0 Hz, 1 H), 3.51 (dd, *J* = 10.1, 7.0 Hz, 1 H), 2.78 (br. s, 1 H), 2.00−1.90 (m, 1 H), 1.70−1.58 (m, 1 H), 1.53−1.48 (m, 2 H), 1.43 (s, 9 H), 1.42 (s, 9 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.9 (C), 155.5 (C), 135.5 (4 CH), 133.1 (2 C), 129.8 (2 CH), 127.8 (4 CH), 81.6 (C), 79.5 (C), 71.6 (CH), 67.9 (CH_2), 53.9 (CH), 29.3 (CH_2), 28.7 (CH_2), 28.3 (3 CH_3), 27.8 (3 CH_3), 26.8 (3 CH_3), 19.2 (C) ppm. $C_{31}H_{47}NO_6Si$: calcd. C 66.75, H 8.49, N 2.51; found C 66.52, H 8.47, N 2.76.

***tert*-Butyl (2*S*,5*S*)-5-Azido-2-[(*tert*-butoxycarbonyl)amino]-6-{[*tert*-butyl(diphenyl)silyl]oxy}hexanoate (19):** *N*,*N*-Diisopropylethylamine (56 mg, 0.433 mmol) was added to a solution of **18** (120 mg, 0.215 mmol) in 3.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and MsCl (62 mg, 0.429 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added. After removing the ice bath, the reaction was stirred at room temperature until total consumption of **18** (checked by TLC). CH_2Cl_2 was evaporated and replaced by EtOAc. The organic phase was washed with 1 N $KHSO_4$, brine, and a saturated $NaHCO_3$ solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 3.0 mL of DMF. NaN_3 (42 mg, 0.646 mmol) was added to the solution, which was heated to 80 °C for 16 h. After being cooled to room temperature, water was added to the solution, which was extracted twice with EtOAc. The combined organic layers were washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:9) to yield pure **19** (110 mg, yield: 88% for 2 steps) as a colourless oil. HPLC: t_R = 18.77 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = −1.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75−7.67 (m, 4 H), 7.46−7.26 (m, 6 H), 5.07 (br. d, *J* = 8.0 Hz, 1 H), 4.24−4.18 (m, 1 H), 3.73 (dd, *J* = 10.6, 3.8 Hz, 1 H), 3.63 (dd, *J* = 10.6, 6.6 Hz, 1 H), 3.45−3.35 (m, 1 H), 1.83−1.71 (m, 3 H), 1.54−1.35 (m, 1 H), 1.47 (s, 9 H), 1.43 (s, 9 H), 1.08 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.5 (C), 155.4 (C), 135.6 (4 CH), 132.9 (2 C), 129.8 (2 CH), 127.8 (4 CH), 82.1 (C), 79.7 (C), 67.1 (CH_2), 63.3 (CH), 53.4 (CH), 29.6 (CH_2), 28.3 (3 CH_3), 27.8 (3 CH_3), 26.7 (3 CH_3), 25.9 (CH_2), 19.1 (C) ppm. $C_{31}H_{46}N_4O_5Si$: calcd. C 63.89, H 7.96, N 9.61; found C 63.51, H 7.86, N 9.28.

***tert*-Butyl (2*S*,5*S*)-5-Azido-2-[(*tert*-butoxycarbonyl)amino]-6-hydroxyhexanoate (20):** Tetrabutylammonium fluoride supported on silica (750 mg, 1.0−1.5 mmol/g) was added to a solution of **19**

(250 mg, 0.429 mmol) in 5.0 mL of anhydrous THF. The suspension was gently stirred for 2 h and checked by TLC (EtOAc/hexane, 3:7). Supported-TBAF was filtered and washed with EtOAc. The filtrate was evaporated and crude **20** was purified through a short pad of silica gel (EtOAc/hexane, 3:7) to afford pure **20** (148 mg, yield: 100%) as a colourless oil. HPLC: t_R = 10.22 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +15.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12 (br. d, J = 7.0 Hz, 1 H), 4.23−4.16 (m, 1 H), 3.70 (dd, J = 11.2, 4.2 Hz, 1 H), 3.59 (dd, J = 11.3, 6.8 Hz, 1 H), 3.53−3.46 (m, 1 H), 2.06 (br. s, 1 H), 1.97−1.85 (m, 1 H), 1.81−1.72 (m, 1 H), 1.69−1.57 (m, 2 H), 1.47 (s, 9 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C), 155.5 (C), 82.3 (C), 79.9 (C), 65.1 (CH_2), 63.4 (CH), 53.2 (CH), 29.6 (CH_2), 28.3 (3 CH_3), 27.9 (3 CH_3), 26.2 (CH_2) ppm. $C_{15}H_{28}N_4O_5$: calcd. C 52.31, H 8.19, N 16.27; found C 52.36, H 8.46, N 16.07.

***tert*-Butyl (2*S*,5*S*)-5-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino}-6-hydroxyhexanoate (8):** *p*-Toluenesulfonic acid (132 mg, 0.694 mmol) was added to a solution of **20** (120 mg, 0.348 mmol) in 2.0 mL of CH_3CN at 0 °C. The mixture was stirred until **20** totally disappeared (checked by TLC, EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). The reaction was quenched by the addition of 30.0 mL of aqueous 1 N NH_4OH. The solution was extracted with 30.0 mL (2 × 15.0 mL) of CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 2.0 mL of acetone and the same volume of water was added to the solution. Solid K_2CO_3 (144 mg, 1.04 mmol) and a solution of FmocOSu (176 mg, 0.522 mmol) in 1.0 mL of acetone were added to the solution, which was stirred at room temperature for 3 h. Acetone was evaporated and replaced by EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, brine and 1 N $KHSO_4$, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH, 98:2) to yield pure **8** (118 mg, yield: 73% for 2 steps) as a colourless oil. HPLC: t_R = 13.69 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +9.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.3 Hz, 2 H), 7.31 (m, 2 H), 5.49 (br. d, J = 7.9 Hz, 1 H), 4.40 (d, J = 7.1 Hz, 2 H), 4.33−4.26 (m, 1 H), 4.21 (t, J = 7.0 Hz, 1 H), 3.72−3.69 (m, 1 H), 3.61−3.55 (m, 1 H), 3.51−3.44 (m, 1 H), 2.23 (br. s, 1 H), 2.00−1.76 (m, 2 H), 1.70−1.58 (m, 1 H), 1.52−1.40 (m, 1 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C), 156.0 (C), 143.8 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 82.6 (C), 67.0 (CH_2), 65.2 (CH_2), 63.5 (CH), 53.8 (CH), 47.1 (CH), 29.4 (CH_2), 28.0 (3 CH_3), 26.1 (CH_2) ppm. $C_{25}H_{30}N_4O_5$: calcd. C 64.36, H 6.48, N 12.01; found C 64.05, H 6.54, N 11.88.

Di(*tert*-butyl) (2*S*,5*R*)-5-[(Methylsulfonyl)oxy]-6-oxo-1,2-piperidinedicarboxylate (21): *N*,*N*-Diisopropylethylamine (164 mg, 1.27 mmol) was added to a solution of **10** (200 mg, 0.215 mmol)[7] in 2.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and MsCl (145 mg, 1.26 mmol) dissolved in 0.5 mL of CH_2Cl_2 was added. After removing the ice bath, the reaction was stirred at room temperature for 16 h. CH_2Cl_2 was evaporated off and replaced by EtOAc. The organic phase was washed with 1 N $KHSO_4$, brine, and a saturated $NaHCO_3$ solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography (EtOAc/hexane, 3:7) gave pure **21** (220 mg, yield: 88%) as a white solid. HPLC: t_R = 11.30 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +19.7 (c = 1.0, $CHCl_3$). M.p. 121−123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (m, 1 H), 4.60 (m, 1 H), 3.20 (s, 3 H), 2.31−2.17 (m, 2 H), 2.15−2.03 (m, 2 H), 1.48 (s, 9 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 169.6 (C), 166.0 (C), 151.1 (C), 84.5 (C), 83.0 (C), 76.6 (CH_3), 58.4 (CH), 39.1 (CH), 27.8 (3 CH_3), 27.7 (3 CH_3), 26.1 (CH_2), 21.7 (CH_2) ppm.

Di(*tert*-butyl) (2*S*)-5-Amino-6-oxo-3,6-dihydro-1,2(2*H*)-pyridinedicarboxylate (22): Compound **21** (500 mg, 1.27 mmol) was dissolved in 6.0 mL of DMF. NaN_3 (413 mg, 6.35 mmol) was added to the solution, which was heated to 45 °C for 16 h. After being cooled to room temperature, water was added to the solution, which was extracted twice with EtOAc. The combined organic layers were washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 1:1) to yield pure **22** (334 mg, yield: 84%) as a yellowish oil. The ene-amine **22** was found to decompose within several hours and was therefore used immediately in the next reaction step. HPLC: t_R = 6.00 (linear gradient, 30−100% B, 20 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35−5.31 (m, 1 H), 4.76−4.72 (m, 1 H), 3.67 (br. s, 2 H), 2.68−2.62 (m, 2 H), 1.49 (s, 9 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 170.0 (C), 161.9 (C), 152.2 (C), 135.9 (C), 103.6 (CH), 83.3 (C), 82.3 (C), 57.2 (CH), 27.9 (3 CH_3), 27.8 (3 CH_3), 25.1 (CH_2) ppm.

Di(*tert*-butyl) (2*S*,5*S*)-5-{[(Benzyloxy)carbonyl]amino}-6-oxo-1,2-piperidinedicarboxylate (23): The ene-amine **22** (75 mg, 0.240 mmol) was dissolved in 2.0 mL of CH_2Cl_2. Glacial acetic acid (0.2 mL, 10% v/v) was then introduced with a hypodermic syringe and the mixture was cooled to 0 °C. $NaBH_3CN$ (45 mg, 0.716 mmol) was added to the solution and the mixture was allowed to reach room temperature. The reaction was stirred for 3 h at room temperature and quenched by addition of water. The organic phase was washed with a saturated $NaHCO_3$ solution, dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in 2.0 mL of CH_2Cl_2 and DIEA (82 μL, 0.482 mmol) was added. The solution was cooled to 0 °C prior to the addition of ZOSu (120 mg, 0.481 mmol). The mixture was allowed to reach room temperature and stirred overnight. CH_2Cl_2 was evaporated, replaced by EtOAc and the organic layer was washed with 1 N $KHSO_4$, brine and a saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/pentane, 1:1) to give pure **23** (73 mg, yield: 68% for 2 steps) as a colourless oil. HPLC: t_R = 14.13 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = −5.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.28 (m, 5 H), 5.75 (m, 1 H), 5.09 (s, 2 H), 4.48 (m, 1 H), 4.25−4.17 (m, 1 H), 2.49−2.42 (m, 1 H), 2.21−2.16 (m, 2 H), 1.70−1.56 (m, 1 H), 1.48 (s, 9 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 170.7 (C), 170.4 (C), 156.1 (C), 152.7 (C), 136.3 (C), 128.5 (2 CH), 128.1 (CH), 128.0 (2 CH), 83.7 (C), 82.5 (C), 66.9 (CH_2), 59.7 (CH), 54.3 (CH), 27.9 (6 CH_3), 26.9 (CH_2), 24.5 (CH_2) ppm. $C_{23}H_{32}N_2O_7$: calcd. C 61.59, H 7.19, N 6.25; found C 61.49, H 7.43, N 6.15.

***tert*-Butyl (2*S*,5*S*)-5-{[(Benzyloxy)carbonyl]amino}-2-[(*tert*-butoxycarbonyl)amino]-6-hydroxyhexanoate (24):** Sodium borohydride (42 mg, 1.11 mmol) was added to a solution of **23** (100 mg, 0.222 mmol) in 4.0 mL of EtOH at 0 °C. The mixture was allowed to reach room temperature and stirred for 3 h. After being quenched by addition of water, the mixture was stirred for a further 10 min. Evaporation of the solvent gave an oil which was dissolved in EtOAc. The solution was washed with 1 N $KHSO_4$, brine and a saturated $NaHCO_3$ solution, and dried with Na_2SO_4. Evaporation of the filtrate afforded an oil which was filtered through a silica pad (EtOAc/hexane, 6:4). Pure **24** was recovered (99 mg, yield: 98%) as a colourless oil. HPLC: t_R = 11.70 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +6.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 7.37−7.29 (m, 5 H), 5.30 (br. d, J = 8.4 Hz, 1 H), 5.16 (m, 1 H), 5.07 (s, 2 H), 4.20−4.08 (m, 1 H), 3.73−3.51 (m, 3 H), 2.6 (br. s, 1 H), 1.90−1.77 (m, 1 H), 1.72−1.54 (m, 3 H), 1.43 (s, 9 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.7 (C), 156.6 (C), 155.6 (C), 136.4 (C), 128.5 (2 CH), 128.1 (CH), 128.0 (2 CH), 82.1 (C), 79.9 (C), 66.8 (CH_2), 64.8 (CH_2), 53.7 (CH), 52.8 (CH), 30.1 (CH_2), 28.3 (3 CH_3), 28.0 (3 CH_3), 26.9 (CH_2) ppm. $C_{23}H_{36}N_2O_7$: calcd. C 61.04, H 8.02, N 6.19; found C 61.18, 8.21; 5.98.

***tert*-Butyl (2*S*,5*S*)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-6-hydroxyhexanoate (25):** *p*-Toluenesulfonic acid (116 mg, 0.610 mmol) was added to a solution of (138 mg, 0.305 mmol) of **24** in 3.0 mL of CH_3CN at 0 °C. The mixture was stirred until **24** had totally disappeared (checked by TLC, EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). The reaction was quenched by the addition of 30.0 mL of aqueous 1 N NH_4OH. The solution was extracted with 30.0 mL (2 × 15.0 mL) of CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 3.0 mL of acetone and the same volume of water was added to the solution. Solid K_2CO_3 (126 mg, 0.912 mmol) and a solution of FmocOSu (154 mg, 0.457 mmol) in 1.0 mL of acetone were added to the solution, which was stirred at room temperature for 3 h. Acetone was evaporated and replaced by EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, brine and 1 N $KHSO_4$, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 4:6) to yield pure **25** (160 mg, yield: 92% for 2 steps) as a colourless oil. HPLC: t_R = 14.45 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +3.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.4 Hz, 2 H), 7.58 (d, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.1 Hz, 2 H), 7.32−7.26 (m, 7 H), 5.62 (br. d, J = 7.6 Hz, 1 H), 5.29 (br. d, J = 7.9 Hz, 1 H), 5.07 (s, 2 H), 4.37 (d, J = 7.1 Hz, 2 H), 4.26−4.16 (m, 2 H), 3.72−3.54 (m, 3 H), 2.87 (br. s, 1 H), 1.72−1.56 (m, 4 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.5 (C), 156.7 (C), 156.1 (C), 143.9 (C), 143.8 (C), 141.3 (2 C), 136.4 (C), 128.5 (2 CH), 128.1 (3 CH), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 82.3 (C), 66.9 (CH_2), 66.8 (CH_2), 64.8 (CH_2), 54.2 (CH), 52.7 (CH), 47.2 (CH), 29.4 (CH_2), 28.0 (3 CH_3), 27.2 (CH_2) ppm. $C_{33}H_{38}N_2O_7$: calcd. C 68.97, H 6.67, N 4.87; found C 68.32, H7.06, N 4.37.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-5,6-dihydroxy-5-methylhexanoate (26):** Sodium borohydride (575 mg, 15.20 mmol) was added to a solution of **11** (1.00 g, 3.03 mmol)[7] in 12.0 mL of absolute ethanol at 0 °C. The mixture was allowed to reach room temperature and stirred overnight. After being quenched by addition of water, the mixture was stirred for a further 10 min. The solvent was evaporated and the residue dissolved in EtOAc and washed with a saturated $NaHCO_3$ solution and water. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc) to give pure **26** (882 mg, yield: 87%) as a colourless oil. HPLC: t_R = 6.63 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +9.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (br. d, J = 7.9 Hz, 1 H), 4.01−3.93 (m, 1 H), 3.75 (br. s, 1 H), 3.44 (br. s, 1 H), 3.26 (s, 2 H), 1.79−1.67 (m, 1 H), 1.59−1.46 (m, 1 H), 1.43−1.26 (m, 2 H), 1.31 (s, 9 H), 1.28 (s, 9 H), 0.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 172.0 (C), 155.7 (C), 81.6 (C), 79.5 (C), 72.3 (C), 69.3 (CH_2), 54.2 (CH), 33.5 (CH_2), 28.2 (3 CH_3), 27.8 (3 CH_3), 22.9 (CH_2), 20.8 (CH_3) ppm. $C_{16}H_{31}NO_6$: calcd. C 57.64, H 9.37, N 4.20; found C 57.44, H 9.58, N 4.19.

***tert*-Butyl (2*S*,5*R*)-6-Azido-2-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-5-methylhexanoate (27):** Collidine (2.28 mL, 17.12 mmol) was added to a solution of **26** (570 mg, 1.71 mmol) in 36.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and MsCl (206 mg, 1.80 mmol) dissolved in 2.0 mL of CH_2Cl_2 was added. After being stirred for 20 h at 4 °C, the reaction was quenched with water (13.0 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 N $KHSO_4$, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 7.0 mL of DMF. NaN_3 (333 mg, 5.12 mmol) was added to the solution, which was heated to 80 °C for 16 h. After being cooled to room temperature, water was added to the solution, which was extracted twice with EtOAc. The combined organic layers were washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/hexane, 3:7) to yield **27** (540 mg, yield: 88% for 2 steps) as a colourless oil. HPLC: t_R = 11.09 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +9.0 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (br. d, J = 7.7 Hz, 1 H), 4.30−4.23 (m, 1 H), 3.23 (s, 2 H), 2.58 (br. s, 1 H), 1.97−1.89 (m, 1 H), 1.69−1.57 (m, 3 H), 1.46 (s, 9 H), 1.44 (s, 9 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.6 (C), 151.5 (C), 82.1 (C), 79.9 (C), 72.4 (C), 61.3 (CH_2), 53.6 (CH), 33.9 (CH_2), 28.3 (3 CH_3), 28.0 (3 CH_3), 27.5 (CH_2), 21.0 (CH_3) ppm. $C_{16}H_{30}N_4O_5$: calcd. C 53.61, H 8.44, N 15.63; found C 54.04, H 8.30, N 15.39.

***tert*-Butyl (2*S*,5*R*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino}-5-hydroxy-5-methylhexanoate (9):** *p*-Toluenesulfonic acid (531 mg, 2.79 mmol) was added to a solution of **27** (500 mg, 1.39 mmol) in 10.0 mL of CH_3CN at 0 °C. The mixture was stirred for 9 h and consistently checked by TLC (EtOAc/pyridine/acetic acid/water, 8:2:0.5:1). The reaction was quenched by the addition of 100 mL of aqueous 1 N NH_4OH. The solution was extracted with 100 mL (2 × 50.0 mL) of CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 8.0 mL of THF and the same volume of water was added to the solution. Solid $NaHCO_3$ (233 mg, 2.78 mmol) and FmocOSu (518 g, 1.54 mmol), dissolved in 2.0 mL of THF, were added to the mixture stirred at ambient temperature. After 3 h the THF was evaporated and replaced by EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, brine, 1 N $KHSO_4$, dried with Na_2SO_4 and concentrated in vacuo. Purification of the crude product by flash column chromatography (CH_2Cl_2/MeOH, 98:2) gave pure **9** (618 mg, yield: 92% for 2 steps) as a colourless oil. HPLC: t_R = 14.50 (linear gradient, 30−100% B, 20 min). $[\alpha]_D$ = +5.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H), 7.61 (d, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.4 Hz, 2 H), 7.31 (t, J = 7.4 Hz, 2 H), 5.71 (br. d, J = 8.0 Hz, 1 H), 4.40 (d, J = 7.1 Hz, 2 H), 4.40−4.31 (m, 1 H), 4.22 (t, J = 7.1 Hz, 1 H), 3.22 (s, 2 H), 2.72 (br. s, 1 H), 2.04−1.94 (m, 1 H), 1.80−1.59 (m, 3 H), 1.49 (s, 9 H), 1.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 171.5 (C), 156.2 (C), 143.9 (C), 143.8 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 82.4 (C), 72.3 (CH_2), 67.0 (C), 60.9 (CH_2), 54.2 (CH), 47.1 (CH), 34.2 (CH_2), 28.0 (3 CH_3), 27.1 (CH_2), 24.3 (CH_3) ppm. $C_{26}H_{32}N_4O_5$: calcd. C 64.98, H 6.71, N 11.66; found C 65.16, H 6.96, N 11.34.

General Procedures for Galactosylation. Procedure A: One equivalent of the desired aglycon and tetra-pivaloylated galactosyl bromide (1.5 equiv.) were placed in an argon-filled, round-bottomed flask and dissolved in dry CH_2Cl_2 to give a ca. 0.1 M solution of acceptor. Powdered 4-Å molecular sieves was added and the sus-

pension was stirred for 30 min. The mixture was protected from light, and silver silicate (5.0 equiv.) was added. The reaction was stirred for 8 h at room temperature. C_{18} RP-HPLC analysis showed completion of the reaction, and the dark-brown suspension was filtered through a plug of Celite®. The solvent was evaporated to give a brownish residue which was purified by flash column chromatography (Et_2O/pentane, 3:7).

Procedure B: One equivalent of the desired aglycon and tetra-pivaloylated galactosyl bromide (0.5 equiv.) were placed in an argon-filled, round-bottomed flask and dissolved in dry CH_2Cl_2 to give a ca. 0.4 M solution of acceptor. The solution was diluted by addition of distilled cyclohexane with a hypodermic syringe to give a ca. 0.1 M solution of galactosyl acceptor. Powdered 4-Å molecular sieves was added and the suspension was stirred for 30 min. The mixture was protected from light, and silver silicate (5.0 equiv.) was added. The reaction was stirred for 24 h at room temperature. The conversion rate was checked by C_{18} RP-HPLC, bromide (0.5 equiv.) was added for a second time and the reaction was stirred again for 24 h. This operation was repeated four more times (overall addition of galactosyl donor: 3.0 equiv.). After 6 days, C_{18} RP-HPLC showed completion of the reaction and the dark-brown suspension was filtered through a plug of Celite®. The solvent was evaporated to give a brownish residue which was purified by flash column chromatography (Et_2O/pentane, 3:7).

General Procedure for Removal of *tert*-Butyl Ester Group. Procedure C: The required galactosylated derivative was dissolved in TFA to give a ca. 0.1 M solution. The resulting solution was stirred for 2 h at ambient temperature. Following addition of a large volume of hexane, the solvents were evaporated to afford the corresponding galactosylated building block ready for use in solid phase peptide synthesis (SPPS).

General Procedure for Orthoester Rearrangement. Procedure D: Powdered 4-Å molecular sieves were added to a ca. 0.1 M solution of orthoester in CH_2Cl_2 cooled to 0 °C. A 0.1 M solution of TMSOTf (0.1 equiv.) in CH_2Cl_2 was introduced with a hypodermic syringe. The solution was placed in a cold room and stirred at 4 °C overnight. The reaction was quenched by addition of a large volume of water and CH_2Cl_2 was evaporated and replaced by EtOAc. The solution was washed with a saturated $NaHCO_3$ solution, brine and 1 N $KHSO_4$, dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (Et_2O/pentane, 3:7).

***tert*-Butyl (2*S*,5*R*)-6-[(2,2-Dimethylpropanoyl)oxy]-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)Dhn(5-OPiv)-O*t*Bu (28):** Galactosylated building block **28** was prepared from **6** according to procedure A. Purification of the crude product gave **28** (382 mg, yield: 89%) as a white foam. HPLC: t_R = 19.30 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = −1.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.5 Hz, 2 H), 7.60 (br. d, J = 7.3 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.31 (dt, J = 7.5, 1.3 Hz, 2 H), 5.39 (br. d, J = 2.5 Hz, 1 H), 5.32 (br. d, J = 8.0 Hz, 1 H), 5.19 (dd, J = 10.4, 7.5 Hz, 1 H), 5.09 (dd, J = 10.4, 3.3 Hz, 1 H), 4.66 (d, J = 7.7 Hz, 1 H), 4.43 (dd, J = 10.6, 7.3 Hz, 1 H), 4.35−4.29 (m, 1 H), 4.24−4.19 (m, 1 H), 4.14−4.08 (m, 4 H), 4.04−3.95 (m, 2 H), 3.87 (m, 1 H), 1.97−1.83 (m, 1 H), 1.70−1.54 (m, 3 H), 1.47 (s, 9 H), 1.25 (s, 9 H), 1.20 (s, 9 H), 1.16 (s, 9 H), 1.13 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.1 (C), 177.8 (C), 177.3 (C), 176.8 (C), 176.4 (C), 171.1 (C), 155.9 (C), 143.8 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.0 (2 CH), 120.0 (2 CH), 100.0 (CH), 82.5 (C), 76.2 (CH), 71.1 (CH), 70.9 (CH), 69.0 (CH), 67.1 (CH_2), 66.7 (CH), 65.2 (CH_2), 61.2 (CH_2), 54.0 (CH), 47.1 (CH), 39.0 (2 C), 38.7 (3 C), 28.5 (CH_2), 28.0 (3 CH_3), 27.4 (CH_2), 27.1 (9 CH_3), 27.0 (3 CH_3), 26.9 (3 CH_3) ppm. $C_{56}H_{81}NO_{16}$: calcd. C 65.67, H 7.97, N 1.37; found C 65.48, H 8.06, N 1.26.

(2*S*,5*R*)-6-[(2,2-Dimethylpropanoyl)oxy]-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)Dhn(5-OPiv)-OH (2): The *N*-Fmoc-protected derivative **2** was obtained from **28** according to procedure C (322 mg, yield: 100%) as a colourless oil. HPLC: t_R = 17.84 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = +5.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.3 Hz, 2 H), 7.61−7.57 (m, 2 H), 7.39 (t, J = 7.3 Hz, 2 H), 7.30 (dt, J = 7.5, 1.1 Hz, 2 H), 5.45 (br. d, J = 8.0 Hz, 1 H), 5.38 (d, J = 3.1 Hz, 1 H), 5.19 (dd, J = 10.4, 7.5 Hz, 1 H), 5.10 (dd, J = 10.4, 3.1 Hz, 1 H), 4.65 (d, J = 7.5 Hz, 1 H), 4.46−4.34 (m, 3 H), 4.22−3.94 (m, 6 H), 3.91−3.84 (m, 1 H), 2.10−1.96 (m, 1 H), 1.81−1.54 (m, 3 H), 1.25 (s, 9 H), 1.21 (s, 9 H), 1.19 (s, 9 H), 1.12 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.3 (C), 177.9 (C), 177.4 (C), 176.9 (C), 176.7 (C), 175.8 (C), 156.1 (C), 143.7 (C), 143.6 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.0 (2 CH), 120.0 (2 CH), 100.2 (CH), 76.2 (CH), 71.1 (CH), 70.9 (CH), 69.0 (CH), 67.2 (CH_2), 66.7 (CH), 65.0 (CH_2), 61.2 (CH_2), 53.5 (CH), 47.1 (CH), 39.0 (C), 38.7 (2 C), 38.7 (2 C), 27.9 (CH_2), 27.4 (CH_2), 27.1 (15 CH_3) ppm. $C_{52}H_{73}NO_{16}$: calcd. C 64.51, H 7.60, N 1.45; found C 64.04, H 7.80, N 1.42.

***tert*-Butyl (2*S*,5*S*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)(5*S*)Hyl-O*t*Bu (29):** Galactosylated building block **29** was prepared from **7** according to procedure A. Purification of the crude product gave **29** (295 mg, yield: 62%) as a white foam. HPLC: t_R = 19.19 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = +1.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 5.45 (br. d, J = 8.0 Hz, 1 H), 5.39 (dd, J = 3.3, 0.9 Hz, 1 H), 5.20 (dd, J = 10.4, 7.7 Hz, 1 H), 5.10 (dd, J = 10.4, 3.3 Hz, 1 H), 4.71 (d, J = 7.7 Hz, 1 H), 4.38−4.35 (m, 2 H), 4.33−4.26 (m, 1 H), 4.21 (t, J = 7.0 Hz, 1 H), 4.14 (dd, J = 10.8, 6.6 Hz, 1 H), 4.06−4.00 (m, 1 H), 3.95 (t, J = 6.8 Hz, 1 H), 3.82−3.73 (m, 1 H), 3.31 (br. d, J = 5.7 Hz, 2 H), 1.95−1.77 (m, 3 H), 1.68−1.54 (m, 1 H), 1.47 (s, 9 H), 1.25 (s, 9 H), 1.17 (s, 9 H), 1.16 (s, 9 H), 1.11 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.7 (C), 177.3 (C), 176.8 (C), 176.6 (C), 171.4 (C), 155.9 (C), 143.9 (C), 143.8 (C), 141.3 (2 C), 127.7 (2 CH), 127.0 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 99.8 (CH), 82.3 (C), 75.6 (CH), 71.1 (CH), 71.0 (CH), 68.8 (CH), 67.0 (CH_2), 66.7 (CH), 61.1 (CH_2), 54.7 (CH_2), 53.8 (CH), 47.1 (CH), 39.0 (C), 38.8 (C), 38.7 (2 C), 28.3 (CH_2), 28.2 (CH_2), 27.9 (3 CH_3), 27.1 (12 CH_3) ppm. $C_{51}H_{72}N_4O_{14}$: calcd. C 63.47, H 7.52, N 5.81; found C 63.03, H 7.60, N 5.53.

(2*S*,5*S*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)(5*S*)Hyl-OH (3): The *N*-Fmoc-protected derivative **3** was obtained from **29** according to procedure C (198 mg, yield: 95%) as a white foam. HPLC: t_R = 17.04 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = +2.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (br. s, 1 H), 7.76 (d, J = 7.5 Hz, 2 H), 7.61−7.58 (m, 2 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.30 (dt, J = 7.5, 1.1 Hz, 2 H), 5.50 (d, J = 8.1 Hz, 1 H), 5.39 (d, J = 3.1 Hz, 1 H), 5.22 (dd, J = 10.4, 7.7 Hz, 1 H), 5.11 (dd, J = 10.4, 3.1 Hz, 1 H), 4.74 (d, J = 7.9 Hz, 1 H), 4.44−4.33 (m, 3 H), 4.24−4.13 (m, 2 H), 4.05−3.94 (m, 2 H), 3.87 (m, 1 H), 3.36−3.26 (m, 2 H), 1.84−1.72 (m, 1 H), 1.67−1.52 (m, 3 H), 1.25 (s, 9 H), 1.18 (s, 9 H), 1.16 (s, 9 H), 1.11

(s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.9 (C), 177.4 (C), 177.0 (C), 176.9 (C), 175.8 (C), 156.2 (C), 143.8 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 99.9 (CH), 75.1 (CH), 71.0 (2 CH), 69.0 (CH), 67.1 (CH_2), 66.7 (CH), 61.2 (CH_2), 54.8 (CH_2), 52.9 (CH), 47.1 (CH), 39.0 (2 C), 38.8 (C), 38.7 (C), 28.1 (CH_2), 27.9 (CH_2), 27.0 (12 CH_3) ppm. $C_{47}H_{64}N_4O_{14}$: calcd. C 62.10, H 7.10, N 6.16; found C 62.49, H 7.14, N 6.00.

***tert*-Butyl (2*S*,5*R*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-5-methylhexanoate, Fmoc-(GalPiv$_4$)Hyl(5-Me)-O*t*Bu (30):** Galactosylated building block **30** was prepared from **9** according to procedure B. Purification of the crude product gave **30** (683 mg, yield: 67%) as a white foam. HPLC: t_R = 18.64 (linear gradient, 60−100% B, 20 min). $[\alpha]_D$ = +0.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.5 Hz, 2 H), 7.59 (d, J = 7.3 Hz, 2 H), 7.39 (t, J = 7.3 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 5.42−5.35 (m, 2 H), 5.22 (dd, J = 10.4, 7.7 Hz, 1 H), 5.09 (dd, J = 10.4, 3.3 Hz, 1 H), 4.79 (d, J = 7.7 Hz, 1 H), 4.45−4.33 (m, 2 H), 4.27−4.16 (m, 2 H), 4.12−4.02 (m, 2 H), 3.96−3.92 (m, 1 H), 3.55 (d, J = 13.0 Hz, 1 H), 3.06 (d, J = 13.0 Hz, 1 H), 1.89−1.78 (m, 1 H), 1.72−1.60 (m, 3 H), 1.48 (s, 9 H), 1.25 (s, 9 H), 1.23 (s, 3 H), 1.18 (s, 9 H), 1.14 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.8 (C), 177.3 (C), 177.0 (C), 176.2 (C), 171.1 (C), 155.8 (C), 143.9 (C), 143.8 (C), 141.3 (2 C), 127.7 (2 CH), 127.0 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 95.8 (CH), 82.4 (C), 79.3 (C), 71.1 (CH), 71.0 (CH), 68.8 (CH), 67.1 (CH_2), 66.9 (CH), 61.9 (CH_2), 57.9 (CH_2), 54.2 (CH), 47.1 (CH), 39.0 (C), 38.8 (C), 38.7 (2 C), 33.6 (CH_2), 28.0 (3 CH_3), 27.2 (3 CH_3), 27.1 (9 CH_3), 26.8 (CH_2), 20.6 (CH_3) ppm. $C_{52}H_{74}N_4O_{14}$: calcd. C 63.78, H 7.62, N 5.72; found C 63.62, H 7.64, N 5.41.

(2*S*,5*R*)-6-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-5-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-5-methylhexanoate, Fmoc-(GalPiv$_4$)Hyl(5-Me)-OH (5): The *N*-Fmoc-protected derivative **5** was obtained from **30** according to procedure C (125 mg, yield: 95%) as a white foam. HPLC: t_R = 13.79 (linear gradient, 60−100% B, 20 min). $[\alpha]_D$ = +4.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (br. s, 1 H), 7.74 (d, J = 7.3 Hz, 2 H), 7.59 (d, J = 7.3 Hz, 2 H), 7.38 (t, J = 7.3 Hz, 2 H), 7.28 (dt, J = 7.4, 0.9 Hz, 2 H), 5.55 (br. d, J = 7.5 Hz, 1 H), 5.39 (d, J = 3.3 Hz, 1 H), 5.22 (dd, J = 10.2, 7.5 Hz, 1 H), 5.10 (dd, J = 10.2, 3.3 Hz, 1 H), 4.77 (d, J = 7.5 Hz, 1 H), 4.42−4.30 (m, 3 H), 4.19 (t, J = 7.0 Hz, 1 H), 4.13−4.02 (m, 2 H), 3.97−3.92 (m, 1 H), 3.54 (d, J = 12.8 Hz, 1 H), 3.07 (d, J = 12.8 Hz, 1 H), 1.96−1.87 (m, 1 H), 1.73−1.58 (m, 3 H), 1.25 (s, 9 H), 1.22 (s, 3 H), 1.18 (s, 9 H), 1.13 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.0 (C), 177.4 (C), 177.1 (C), 176.6 (C), 176.5 (C), 156.3 (C), 143.8 (C), 143.7 (C), 141.2 (2 C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 95.9 (CH), 79.3 (C), 71.1 (2 CH), 68.9 (CH), 67.2 (CH_2), 66.8 (CH), 61.8 (CH_2), 57.8 (CH_2), 53.9 (CH), 47.0 (CH), 39.0 (C), 38.7 (C), 38.6 (2 C), 34.0 (CH_2), 27.2 (6 CH_3), 27.1 (6 CH_3), 26.2 (CH_2), 20.7 (CH_3) ppm. $C_{48}H_{66}N_4O_{14}$: calcd. C 62.46, H 7.21, N 6.07; found C 62.58, H 7.12, N 5.93.

***tert*-Butyl (2*S*,5*S*)-5-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-6-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-hexanoate, Fmoc-(GalPiv$_4$)Hnl(5-N$_3$)-O*t*Bu (31). Starting from 8:** Galactosylated building block **31** was prepared according to procedure A. Purification of the crude product gave **31** (65 mg, yield: 19%) as a colourless oil.

Starting from 32: The galactosylated derivative **31** (272 mg, yield: 76%) was obtained by rearrangement of the corresponding orthoester **32** (procedure D). HPLC: t_R = 19.35 (linear gradient, 50−100% B, 20 min). TLC R_f = 0.33 (Et_2O/pentane, 3:7). $[\alpha]_D$ = +4.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.40 (d, J = 2.6 Hz, 1 H), 5.37 (br. d, J = 8.0 Hz, 1 H), 5.24 (dd, J = 10.4, 7.9 Hz, 1 H), 5.09 (dd, J = 10.4, 3.3 Hz, 1 H), 4.56 (d, J = 7.9 Hz, 1 H), 4.39−4.37 (m, 2 H), 4.27−4.14 (m, 3 H), 4.06−3.94 (m, 2 H), 3.86−3.83 (m, 1 H), 3.56−3.43 (m, 2 H), 1.93−1.78 (m, 3 H), 1.58−1.40 (m, 1 H), 1.48 (s, 9 H), 1.26 (s, 9 H), 1.18 (s, 18 H), 1.11 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.8 (C), 177.3 (C), 176.9 (C), 176.5 (C), 171.1 (C), 155.9 (C), 143.9 (C), 143.7 (C), 141.3 (2 C), 127.7 (2 CH), 127.0 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 101.3 (CH), 82.6 (C), 71.9 (CH_2), 71.1 (CH), 70.9 (CH), 68.5 (CH), 67.0 (CH_2), 66.6 (CH), 61.4 (CH), 61.1 (CH_2), 53.8 (CH), 47.1 (CH), 39.0 (C), 38.8 (C), 38.7 (2 C), 29.4 (CH_2), 28.0 (3 CH_3), 27.1 (3 CH_3), 27.0 (9 CH_3), 26.6 (CH_2) ppm. $C_{51}H_{72}N_4O_{14}$: calcd. C 63.47, H 7.52, N 5.81; found C 63.35, H 7.63, N 5.54.

Orthoester 32: Compound **32** was prepared from **8** according to procedure A. Purification of the crude product gave **32** (280 mg, yield: 79%) as a colourless oil. TLC R_f = 0.60 (Et_2O/pentane, 3:7). $[\alpha]_D$ = +33.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.4 Hz, 2 H), 7.58 (d, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.4 Hz, 2 H), 7.30 (t, J = 7.4 Hz, 2 H), 5.80 (d, J = 4.7 Hz, 1 H), 5.57−5.55 (m, 1 H), 5.41−5.38 (m, 1 H), 5.39 (br. d, J = 8.0 Hz, 1 H), 5.04 (dd, J = 6.2, 2.4 Hz, 1 H), 4.41−4.33 (m, 3 H), 4.28−4.18 (m, 2 H), 3.96 (m, 2 H), 3.59−3.52 (m, 1 H), 3.50−3.41 (m, 2 H), 1.97−1.81 (m, 3 H), 1.64−1.53 (m, 1 H), 1.48 (s, 9 H), 1.25 (s, 9 H), 1.19 (s, 9 H), 1.17 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.9 (C), 177.3 (C), 176.3 (C), 171.1 (C), 155.9 (C), 143.9 (C), 143.7 (C), 141.3 (2 C), 127.9 (C), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 96.9 (CH), 82.6 (C), 78.7 (CH), 72.5 (CH), 70.8 (CH), 67.0 (CH_2), 66.0 (CH), 64.9 (CH_2), 61.1 (CH), 60.2 (CH_2), 53.8 (CH), 47.1 (CH), 39.0 (2 C), 38.7 (2 C), 29.6 (CH_2), 28.0 (3 CH_3), 27.2 (3 CH_3), 27.1 (6 CH_3), 26.6 (CH_2), 25.2 (3 CH_3) ppm.

***tert*-Butyl (2*S*,5*S*)-5-{[(Benzyloxy)carbonyl]amino}-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-6-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)Hnl(5-NHZ)-O*t*Bu (33). Starting from 25:** Galactosylated building block **33** was prepared according to procedure A. Purification of the crude product gave **33** (96 mg, yield: 36%) as a colourless oil. HPLC: t_R = 18.22 (linear gradient, 50−100% B, 20 min). TLC R_f = 0.27 (Et_2O/pentane, 1:1). $[\alpha]_D$ = −8.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H), 7.61 (m, 2 H), 7.41−7.28 (m, 9 H), 5.44 (br. d, J = 8.2 Hz, 1 H), 5.38 (d, J = 2.4 Hz, 1 H), 5.19−5.14 (m, 1 H), 5.18 (dd, J = 10.4, 7.7 Hz, 1 H), 5.10−5.01 (m, 3 H), 4.45 (d, J = 7.9 Hz, 1 H), 4.41−4.34 (m, 2 H), 4.32−4.19 (m, 2 H), 4.15−4.09 (m, 1 H), 4.08−4.00 (m, 1 H), 3.91 (t, J = 6.9 Hz, 1 H), 3.84−3.73 (m, 2 H), 3.64−3.60 (m, 1 H), 1.92−1.50 (m, 4 H), 1.46 (s, 9 H), 1.28 (s, 9 H), 1.17 (s, 9 H), 1.14 (s, 9 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.8 (C), 177.3 (C), 176.8 (C), 176.6 (C), 171.4 (C), 156.0 (2 C), 143.9 (2 C), 141.3 (2 C), 136.4 (C), 128.5 (2 CH), 128.2 (3 CH), 127.7 (2 CH), 127.1 (2 CH), 125.2 (2 CH), 120.0 (2 CH), 101.5 (CH), 82.3 (C), 71.7 (CH_2), 71.0 (CH), 70.9 (CH), 68.6 (CH), 67.0 (CH_2), 66.8 (CH_2), 66.6 (CH), 60.9 (CH_2), 54.0 (CH), 50.5 (CH), 47.2 (CH), 39.0 (C), 38.8 (2 C), 38.7 (C), 29.3 (CH_2), 28.0 (3 CH_3), 27.9 (CH_2), 27.2 (3 CH_3), 27.1 (9 CH_3) ppm. $C_{59}H_{80}N_2O_{16}$: calcd. C 66.03, H 7.51, N 2.61; found C 66.08, H 7.65, N 2.65.

Orthoester 34: Compound **34** was prepared from **25** according to procedure A. Purification of the crude product gave **34** (161 mg, yield: 60%) as a colourless oil. TLC R_f = 0.66 (Et_2O/pentane, 1:1).

$[\alpha]_D$ = +32.8 (*c* = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.4 Hz, 2 H), 7.61−7.59 (m, 2 H), 7.41−7.28 (m, 9 H), 5.80 (d, *J* = 4.7 Hz, 1 H), 5.57−5.55 (m, 1 H), 5.41−5.38 (m, 1 H), 5.39 (br. d, *J* = 8.0 Hz, 1 H), 5.04 (dd, *J* = 6.2, 2.4 Hz, 1 H), 4.41−4.33 (m, 3 H), 4.28−4.18 (m, 2 H), 3.96 (dd, *J* = 11.0, 7.7 Hz, 1 H), 3.59−3.52 (m, 1 H), 3.50−3.41 (m, 2 H), 1.64−1.53 (m, 4 H), 1.48 (s, 9 H), 1.25 (s, 9 H), 1.19 (s, 9 H), 1.17 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 177.9 (C), 177.3 (C), 176.3 (C), 171.1 (C), 155.9 (2 C), 143.9 (C), 143.7 (C), 141.3 (2 C), 136.4 (C), 127.9 (C), 128.5 (2 CH), 128.3 (3 CH), 127.7 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 96.9 (CH), 82.6 (C), 78.7 (CH), 72.5 (CH), 70.8 (CH), 67.0 (CH_2), 66.0 (CH), 64.9 (CH_2), 61.1 (CH), 60.2 (CH_2), 53.8 (CH), 47.1 (CH), 39.0 (2 C), 38.7 (2 C), 29.6 (CH_2), 28.0 (3 CH_3), 27.2 (3 CH_3), 27.1 (6 CH_3), 26.6 (CH_2), 25.2 (3 CH_3) ppm.

(2*S*,5*S*)-5-Azido-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}-6-*O*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)hexanoate, Fmoc-(GalPiv$_4$)Hnl(5-N$_3$)-OH (4): The *N*-Fmoc-protected derivative **4** was obtained from **31** according to procedure C (223 mg, yield: 100%) as a white foam. HPLC: t_R = 16.66 (linear gradient, 50−100% B, 20 min). $[\alpha]_D$ = +1.7 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.93 (br. s, 1 H), 7.75 (d, *J* = 7.5 Hz, 2 H), 7.59−7.57 (m, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 5.43 (br. d, *J* = 8.0 Hz, 1 H), 5.39 (d, *J* = 3.3 Hz, 1 H), 5.24 (dd, *J* = 10.2, 7.9 Hz, 1 H), 5.10 (dd, *J* = 10.4, 3.3 Hz, 1 H), 4.55 (d, *J* = 7.9 Hz, 1 H), 4.43−4.39 (m, 2 H), 4.23−4.08 (m, 3 H), 4.05−3.93 (m, 2 H), 3.86−3.83 (m, 1 H), 3.58−3.39 (m, 2 H), 2.03−1.80 (m, 2 H), 1.61−1.38 (m, 2 H), 1.25 (s, 9 H), 1.17 (s, 18 H), 1.11 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 178.0 (C), 177.4 (C), 176.9 (C), 176.7 (C), 176.1 (C), 156.1 (C), 143.8 (C), 143.6 (C), 141.3 (2 C), 127.8 (2 CH), 127.1 (2 CH), 125.1 (2 CH), 120.0 (2 CH), 101.2 (CH), 71.7 (CH_2), 71.1 (CH), 70.9 (CH), 68.5 (CH), 67.2 (CH_2), 66.6 (CH), 61.3 (CH), 61.1 (CH_2), 53.3 (CH), 47.1 (CH), 39.1 (C), 38.8 (C), 38.7 (2 C), 28.9 (CH_2), 27.1 (3 CH_3), 27.0 (9 CH_3), 26.8 (CH_2) ppm. MS (MALDI-TOF): *m*/*z* = 947.65 $[M + K]^+$, 930.52 $[M + Na]^+$.

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