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Synthesis of a C-Glycoside Analogue of β-D-Galactosyl Hydroxylysine and Incorporation in a Glycopeptide from Type II Collagen

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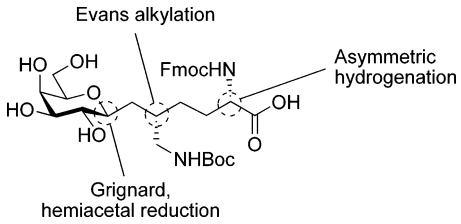

A stereoselective synthesis of the C-glycoside analogue of β-D-galactosyl-(5*R*,2*S*)-hydroxylysine (**1**) has been achieved starting from tetra-*O*-benzyl-D-galactopyranosyl lactone. The synthesis involved establishment of three stereogenic centers in an unambiguous manner. A facially selective Grignard reaction followed by a silane reduction was used for the anomeric position of the C-galactose residue. An Evans allylation established the configuration of the δ-aminomethylene group of the hydroxylysine moiety, whereas an asymmetric hydrogenation utilizing Burk's catalyst was used for the α-amino acid moiety itself. The synthesis was completed in 17 steps with an overall yield of 18%, resulting in the most complex and functionalized C-glycoside analogue of a naturally occurring glycosylated amino acid prepared to date. In addition, amino acid **1** was incorporated in a glycopeptide from type II collagen known to be crucial for the response of autoimmune T cells obtained in models of rheumatoid arthritis. A preliminary immunological study revealed that four out of five members in a panel of T cell hybridomas were able to recognize this C-linked glycopeptide when presented by A^q class II MHC molecules.

Introduction

Recognition of foreign antigens is essential for the immune system to operate properly. To achieve this, antigen presenting cells (APCs, e.g., macrophages, dendritic cells, or B cells), which are key components of the immune system, take up and degrade both foreign and endogenous proteins to shorter peptides. These peptides are then presented at the cell surface of the APC bound to class II major histocompatibility complex molecules (MHCII).[1−3] The MHCII−peptide complex interacts with receptors on $CD4^+$ T cells, an interaction which activates the T cell and results in mobilization of the immune system toward the foreign antigen from which the presented peptide originates. However, T cells occasionally recognize self-peptides presented by MHCII molecules, thereby generating reactions to endogenous antigens which may lead to development of autoimmune disease.

In rheumatoid arthritis (RA), which is regarded as an autoimmune disease, native collagen is attacked and degraded by the immune system, eventually resulting in bone erosion in peripheral joints.[4] In collagen-induced arthritis (CIA), which is a widely used model for RA, immunization of mice with type II collagen (CII) from rat leads to symptoms similar to RA (e.g., erythema and swelling of peripheral joints).[5,6] Although the details of the processes leading to RA and CIA are not fully

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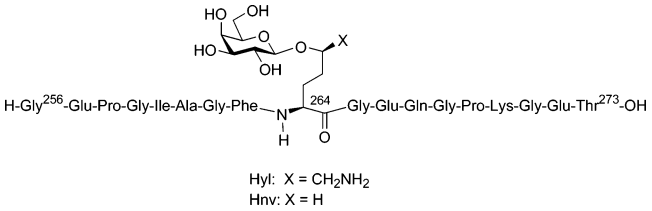

FIGURE 1. Type II collagen peptide epitope 256−273 from rat with galactose on hydroxylysine (Hyl) or hydroxynorvaline (Hnv) in position 264.

known, it is clear that both diseases are associated with certain class II MHC molecules. In humans, DR4 and DR1 class II MHC molecules are associated with RA,[7,8] and in mice, A^q class II MHC molecules are connected with CIA.[9] In CIA, the type II collagen epitope that is presented by A^q was first identified to be CII256-270,[10] and later, the minimal core peptide epitope required for stimulating T cells was found to be CII260-267.[11] Mice that are transgenic for the human DR4 present a sequence from collagen located between residues 259 and 273, but in this case the core epitope is shifted three amino acids toward the C-terminus and begins with residue 263. Most $CD4^+$ T cells obtained in A^q and DR4 mice recognize either of these peptide epitopes with a galactosylated hydroxylysine in position 264 (Hyl,[264] cf. Figure 1).[12−14] Studies with glycopeptides modified at position 264, e.g.. analogues with deoxygenated galactose moieties linked to hydroxylysine,[15,16] a derivative having the galactose moiety O-linked to hydroxynorvaline (Hnv^{264}),[14,17] or a C-galactoside analogue of hydroxynorvaline,[18] have shown that the fine structural details of position 264 are important for the recognition by the T cell receptor.

Due to the inherent lability of the anomeric bond of glycosides, N- or O-glycosylated amino acids can be rapidly enzymatically degraded under physiological conditions.[19,20] In contrast, C-glycosylated amino acids are completely stable under physiological conditions. C-Glycosides were initially proposed to adopt conformations very similar to those of O-glycosides,[21−23] but more recent studies have shown that they populate conformations around the exo anomeric bond not found for O-glycosides.[24,25] The major differences between O- and C-glycosides can be found for the dipole moment, the anomeric effect, as well as the ability to form hydrogen bonds. During recent years, a growing number of publications in the areas of biological evaluation[26−29] of C-glycosides and the synthesis of C-glycosylated amino acids[18,30−38] have appeared.

In our ongoing studies of altered glycopeptides based on the sequence from the type II collagen epitope CII259-273, a C-glycoside of galactosylated hydroxylysine constitutes an important analogue in efforts to study and manipulate the response of T cells obtained in models for RA. Previous studies of a few T cell hybridomas with a glycopeptide having a C-galactosylated hydroxynorvaline at position 264 of CII256-270 gave promising results.[18] In view of these initial results, we now present the synthesis of a C-glycosidic analogue of β-D-galactosyl hydroxylysine. The C-glycoside was further incorporated in the CII259-273 epitope and evaluated for recognition by T cells when presented by A^q MHCII molecules on the surface of APCs.

Results and Discussion

Retrosynthetic Analysis and Initial Synthetic Attempts. From the outset, the synthetic strategy focused on the need to control three stereogenic centers in the C-glycosidic analogue of β-D-galactosylated hydroxylysine (**1**, cf. Figure 2). These centers were (i) the anomeric position of the C-galactosyl residue, (ii) the δ-aminomethylene group in the amino acid moiety, and (iii) the α-amino acid moiety itself. Three retrosynthetic routes (Figure 2A−C) were devised for the construction of **1**. The starting point for these routes was the same, i.e., use of galactosyl lactone **2** in a stereoselective Grignard reaction which was followed by a silane mediated reduction to give the β-C-glycoside. Route A, which was investigated first, then relied on an Evans alkylation of **I** with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) to establish the stereogenic center in the δ-position. The stereogenic center in the α-position was to be

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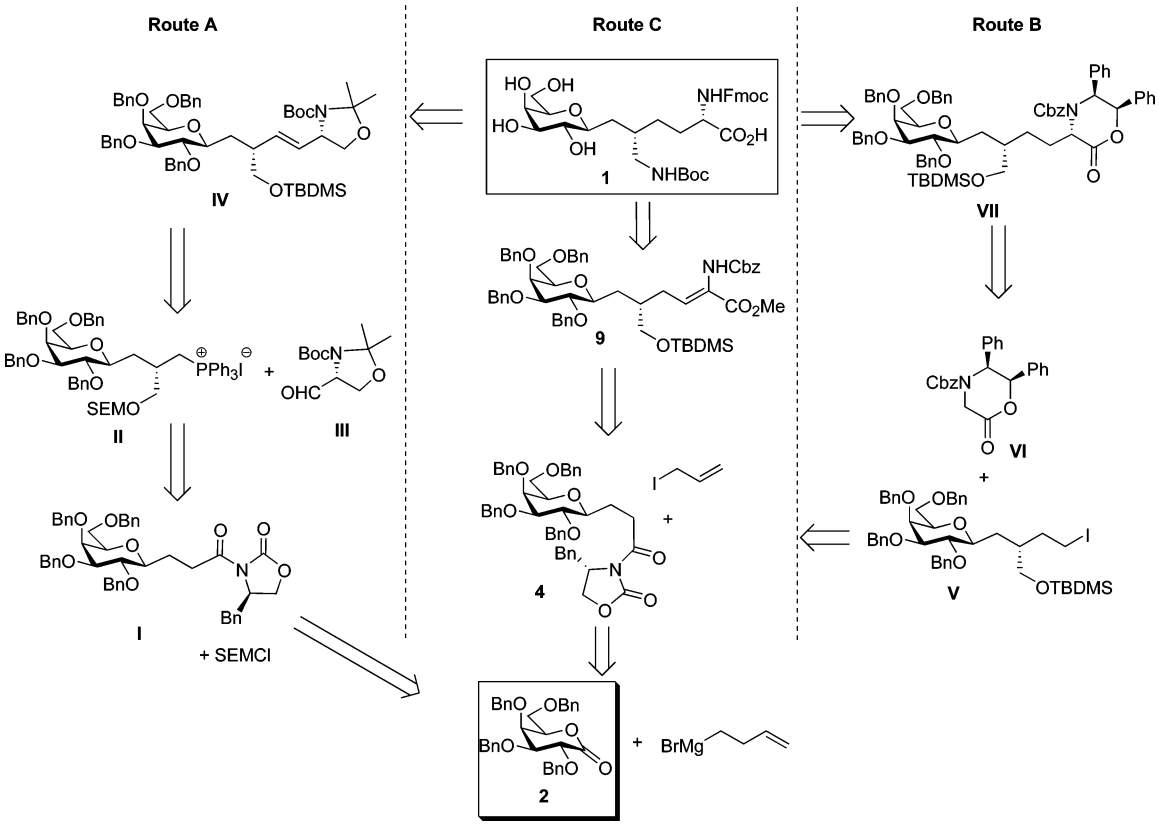

FIGURE 2. Retrosynthetic analysis of C-galactosylated hydroxylysine **1**.

incorporated from Garner's aldehyde (**III**) via a Wittig reaction.[18] For route A, the synthesis proceeded smoothly to the Wittig reaction, where formation of phosphonium salt **II** was slow and the attempted coupling of **II** with Garner's aldehyde (**III**) did not give any reaction at all. In view of these difficulties, route B was attempted instead. For route B the stereogenic center in the δ-position was introduced via an Evans alkylation of **4** with allyl iodide as described in more detail for route C (cf. below). The stereogenic center of the α-amino acid moiety was then to be established via an alkylation of Williams chiral morpholinone **VI** with iodide **V**.[39] Synthesis according to this route proceeded smoothly up to the Williams alkylation, which was very sluggish and provided product **VII** only in low yields. Moreover, the subsequent hydrogenation−reprotection steps yielded complex mixtures of products, and consequently, this route was also abandoned. For route C, control of the three stereogenic centers was envisioned to be achieved using (i) the Grignard reaction-silane reduction sequence starting from **2** to establish the anomeric center as outlined for route A, (ii) an Evans alkylation of **4** for the δ-position, and (iii) an asymmetric hydrogenation of **9** for the α-amino acid moiety.[40,41] The Grignard reaction−silane reduction and the Evans alkylation have already been investigated for similar substrates by us.[18,32] For the asymmetric hydrogenation several catalysts are available, but Burk's catalyst ([(COD)Rh−(*S*,*S*)-Et-DuPHOS]OTf) was envisioned as the most promising candidate due to its selectivity, commercial availability and because it tolerates a high degree of functionalization in the substrate.[42,43]

Synthesis of a C-Galactosyl Analogue of Hydroxylysine via Route C. Starting from galactopyranosyl lactone **2**,[44] a four-step sequence consisting of addition of homoallylmagnesium bromide to the lactone, reduction of the resulting hemiacetal with triethylsilane, ozonolytic cleavage of the terminal alkene,[32] and a Jones oxidation was carried out (Scheme 1). This gave carboxylic acid **3** in which the first of the three stereogenic centers of **1** had been established. Evans chiral (*S*)-4-benzyloxazolidinone[40] was coupled to **3**[31] via a mixed pivaloyl anhydride to give **4** in 88% yield. Alkylation of **4** with sodium hexamethyldisilazane and allyl iodide produced **5** as a single stereoisomer as determined by ^{1}H NMR spectroscopy (88% yield), thereby incorporating the second stereogenic center. According to the synthetic strategy, the exocyclic carbonyl carbon in **5** corresponds to the ϵ-carbon in the hydroxylysine moiety of **1**. Consequently Evans chiral auxiliary was reductively removed by treatment of **5** with lithium aluminumhydride to give alcohol **6**.[45] It was found that TBDMS-protection of alcohol **6**, directly after workup, to give **7** was beneficial as it facilitated purification and improved the total yield (82% from **5**).

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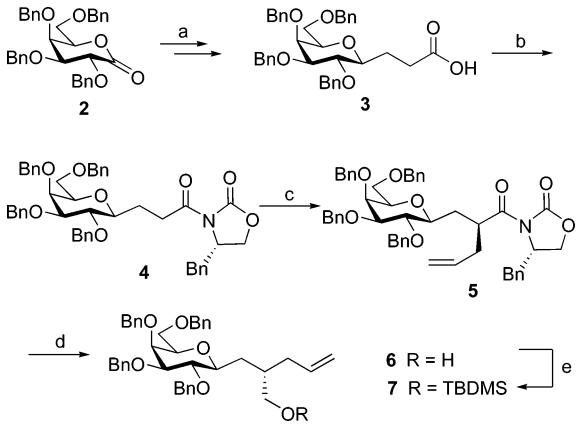
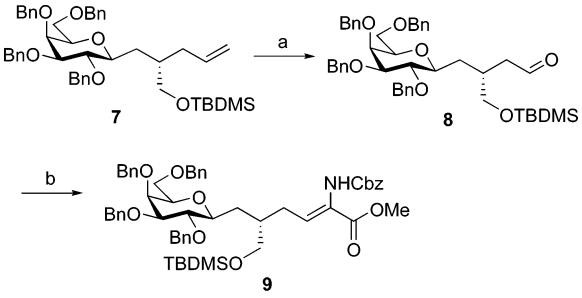
(45) It is interesting to note the ease of this reduction, as compared to reduction of the allylated product obtained from the diastereomeric (*R*)-benzyloxazolidinone analogue of **4**. This analogue was much more resistant to reduction and required treatment with $LiEt_3BH$ to avoid aldehyde formation (cf. ref 32).

SCHEME 1[a]



[a] Reagents and conditions: (a) four steps, see ref 32 (87%); (b) (i) Et_3N, Me_3CCOCl, THF, −78 °C, (ii) (*S*)-4-benzyloxazolidin-2-one, BuLi, THF, −78 °C (88%); (c) NaHMDS, allyl iodide, THF, −78 °C (70%); (d) $LiAlH_4$, Et_2O, rt; (e) TBDMSOTf, collidine, CH_2Cl_2, rt (82% from **5**).

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) O_3, CH_2Cl_2, −78 °C, (ii) PS−PPh_3, CH_2Cl_2, −78 °C to rt (96%); (b) $(MeO)_2P(O)CH(NHCbz)CO_2Me$, DBU, CH_2Cl_2, rt (92%).

With TBDMS ether **7** in hand, the alkene functionality was converted to aldehyde **8** by cleavage with ozone followed by treatment with polymer-bound triphenylphosphine, which removed the excess of ozone (Scheme 2). Next, formation of the protected enamine **9**, required for the asymmetric hydrogenation, was found to proceed smoothly via a Horner−Emmons olefination[46] of **8** with commercially available glycine phosphite. The two stereoisomers of **9** (*Z*/*E* 98:2) that resulted from the olefination reaction could be separated by chromatography on silica gel. However, they were used without separation in the following asymmetric hydrogenation with Burk's catalyst as it has been shown that use of *Z*/*E* mixtures is not detrimental for the stereoselectivity.[42]

After reaching key enamide **9**, chiral induction to form the α-amino acid moiety was addressed. Since Burk's catalyst is known to tolerate a wide array of functional groups, the hydrogenation could potentially be performed at a number of different stages in the synthetic route. For instance, hydrogenation could be performed directly on **9** having the TBDMS ether intact, after removal of the TBDMS ether to give the corresponding alcohol **10**, or after conversion of the alcohol to an azide or a Boc-protected amine. Thus, should the reaction fail or give poor selectivity for one substrate other options could be explored. Toward this goal, removal of the TBDMS ether in **9** with tetrabutylammonium fluoride was first attempted (Scheme 3). Unfortunately, this reaction was plagued by the formation of significant amounts (approximately 15%) of the two stereoisomeric byproducts **11**, resulting from a 1,4-conjugated nucleophilic attack of the intermediate alkoxide on the conjugated alkene. This side-reaction could, however, be avoided by carrying out the deprotection of the TBDMS group under acidic conditions giving **10** in 76% yield. Conversion of alcohol **10** to the corresponding azide was then attempted via a Mitsunobu reaction.[47,48] Unfortunately, intramolecular cyclization[49] of the Cbz-protected amine and the alcohol moiety turned out to be more favored than substitution with azide. 2,3-Dehydropiperidine **12** was thus the only product that was isolated from the Mitsunobu reaction.

Due to the side reactions discussed above, investigation of the asymmetric hydrogenation was only carried out with TBDMS ether **9**, alcohol **10**, and two derivatives of **10** in which the hydroxyl group had been protected with triisopropylsilyl and pivaloyl groups, respectively (Table 1). First, TBDMS ether **9** was submitted to the standard hydrogenation conditions used with Burk's catalyst (degassed methanol as solvent, H_2 at 75 psi, 2 mol % catalyst).[42] Agitation for 72 h produced the desired amino acid, albeit as an unsatisfactory 4:1 mixture of the two epimers (cf. Table 1, entry 1). At atmospheric pressure, no discernible conversion took place. In an attempt to improve the selectivity, the free alcohol **10** was treated under the same conditions (75 psi) as first used for TBDMS ether **9**. Again, the selectivity was disappointing giving a 7:4 diastereomeric mixture of **13** (entry 2). It is well-known that significant steric hindrance from the substrate can compete with the ligands of the catalyst and influence the selectivity.[42] For this reason, the steric bulk of **10** was increased by attaching either a TIPS or a pivaloyl group to the hydroxyl group, but this had only a minor influence on the selectivity (entries 3 and 4). We therefore hypothesized that the steric hindrance from the benzylated galactose moiety played a key role for the outcome of the reaction. This hypothesis was based both on the unusually poor selectivity and on the low rate of reaction. Hydrogenations with Burk's catalyst generally proceed with excellent ee/de (>95%)[42,43,46] and are usually completed in 24 h or less, even at atmospheric pressure. Consequently, it was decided to explore different reaction conditions with **9** as substrate.

According to the mechanistic theory for hydrogenation with Burk's catalyst, the selectivity is expected to increase with higher temperature and lower H_2 pressure.[50] Therefore, the hydrogenation was attempted in a sealed tube at atmospheric H_2 pressure and with heating. For the convenience of controlling the temperature and pressure, a microwave oven was used. Gratifyingly, after 10 min at 100 °C, roughly 50% of TBDMS protected enamide **9** had been converted to the desired amine. Complete conversion was achieved after a total of 40 min and the selectivity was increased to >99:1 (entry 5). To our dismay, when the reaction was carried out under identical conditions but with a different batch of catalyst, no reaction could be observed. Different batches of the catalyst appeared to have

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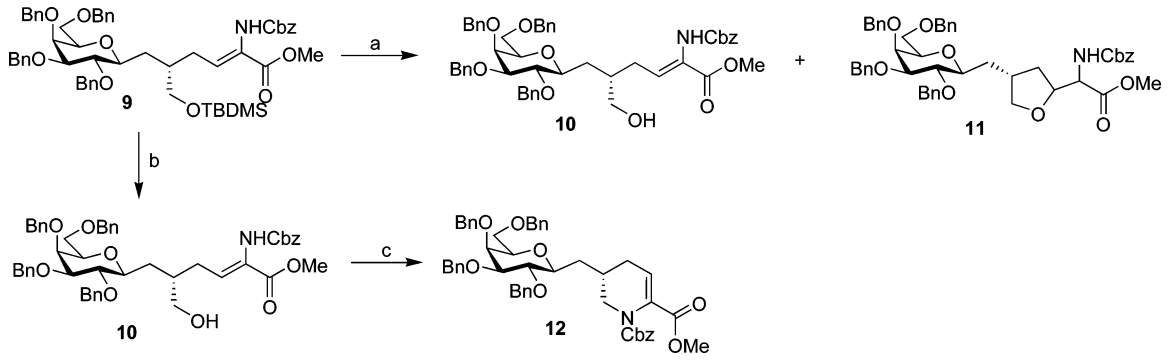
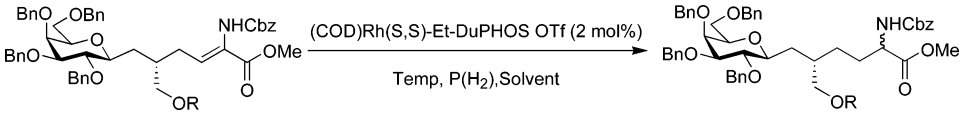
SCHEME 3[a]



[a] Reagents and conditions: (a) TBAF, THF, rt (**10**: 70%, **11**: appr. 15%); (b) TFA/H_2O 9:1, rt (76%); (c) PPh_3, DEAD, DPPA (diphenylphosphoryl azide), THF, rt (90%).

TABLE 1. Asymmetric Hydrogenation Using Burk's Catalyst[a]



					selectivity	
entry	R	solvent	*P* (psi)	*T* (°C)	(2*S*)	(2*R*)
1	TBDMS	MeOH	75	rt	4	1
2	H	MeOH	75	rt	7	4
3	TIPS	MeOH	75	rt	4	1
4	Piv	MeOH	75	rt	5	2
5	TBDMS	MeOH	15	100	>99	1
6	TBDMS	MeOH	15	70	11	1
7	TBDMS	*i*-PrOH	15	80	36	1
8	TBDMS	*i*-PrOH	15	75	75	1
9	TBDMS	*i*-PrOH	15	70	>99	1

[a] For all reactions, 2 mol % of Rh-DuPHOS was used. For further details, see the Experimental Section.

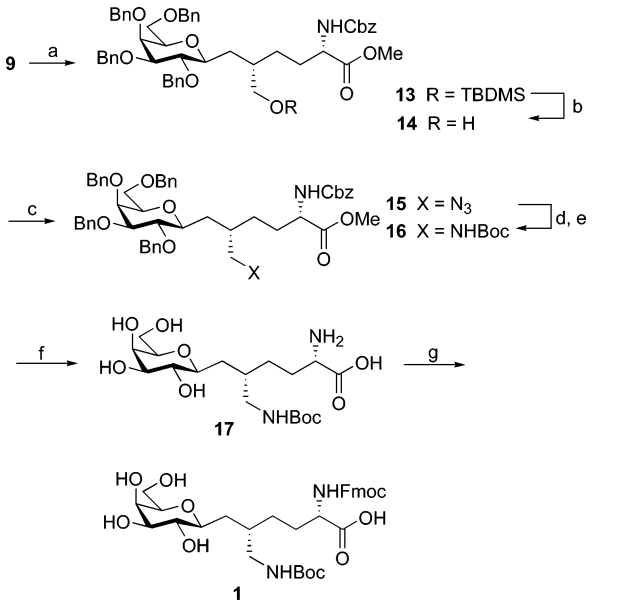
different thermal stability, and the results from the first batch could never be reproduced. By lowering the temperature (70 °C, entry 6) a product of lower diastereomeric purity (11:1) was obtained. Moreover, the stereoselectivity was improved when 2-propanol was used as solvent instead of methanol. At 80 °C the reaction still proceeded well and gave a 36:1 mixture of isomers (entry 7). By lowering the temperature to 75 °C, the selectivity was improved to 75:1 and at 70 °C it became >99:1 (entries 8 and 9).[51] This result is in contrast with our previous observations using methanol as solvent, where the temperature-selectivity trend was the opposite as discussed above. Nonetheless, these conditions gave reproducible results with excellent selectivity (>99% de) and yields using different batches of catalyst. The stereochemical outcome of the asymmetric hydrogenation using Burk's catalyst is regarded as very predictable, Rh-(*S*,*S*)-Et-DuPHOS provides the *S*-isomer, and Rh-(*R*,*R*)-Et-DuPHOS provides the *R*-isomer. Therefore, with a selectivity as high as >99:1 the major isomer was assumed to be the expected 2*S*-form. The stereochemical assignment was further supported by the fact that T cell hybridomas specific for the galactosylated glycopeptide CII259−273 (cf. Figure 1) were able to recognize the analogous C-linked glycopeptide **18** (cf. below).

Due to the poor solubility of **9** in 2-propanol, the reaction was difficult to scale-up in the microwave oven. Instead repeated reactions had to be performed on a rather small scale (appr. 0.25 mmol) and protected amino acid **13** could be isolated in 95% yield after removal of the catalyst on silica gel (Scheme 4). Compound **13** was then deprotected with tetrabutylammonium fluoride to afford alcohol **14** (94%). Considering the failure for the azide substitution on the corresponding unsaturated alcohol **10**, the subsequent Mitsunobu reaction caused some concern. However, when applied to alcohol **14** azide **15** was successfully obtained in an excellent 93% yield. The azide was then reduced using Staudinger conditions, either at 130 °C for 15 min, or at rt for 16 h. It was found that it was important that the THF used as solvent contained sufficient amounts of water (approximately 3−5% H_2O) to allow the phosphine-amine complex to be hydrolyzed; a process that requires high temperature or long reaction times. The resulting amine was directly protected with a Boc-group without workup to give **16** in 97% yield. Hydrolysis of the methyl ester, followed by hydrogenation over palladium on charcoal in acetic acid removed the Cbz-group and the benzyl ethers, and gave **17**. The α-amino group of **17** was directly protected with an Fmoc group to afford the desired C-glycosidic building block **1**, suitably protected for peptide synthesis (56% yield over the three steps from **16**).

C-Glycopeptide Synthesis. The C-glycosylated building block **1** was incorporated in glycopeptide **18**, which corresponds to residues 259−273 from rat type II collagen (CII259-273, Figure 3). This sequence is known to bind well both to the murine class II MHC molecule A^q and also to human DR4. Residues Ile^{260} and Phe^{263} serve as anchor points for binding of CII259−273 to A^q, whereas the epitope is shifted three amino

(51) 99.8% de according to ^1H NMR spectroscopy. This compares very well with HPLC analysis that shows a selectivity of 99.7% de.

SCHEME 4[a]



[a] Reagents and conditions: (a) ([(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf), H_2 (1 atm), *i*-PrOH, 70 °C (95%); (b) TBAF, THF, rt (94%); (c) PPh_3, DEAD, DPPA (diphenylphosphoryl azide), THF, rt (93%); (d) PPh_3, THF/H_2O, 130 °C; (e) Boc_2O, TEA, THF/H_2O, rt (97% from **15**); (f) (i) LiOH, THF/H_2O, rt, (ii) Pd−C, H_2 (75 psi), AcOH, rt; (g) FmocOSu, Na_2CO_3, MeCN, rt (56% from **16**).

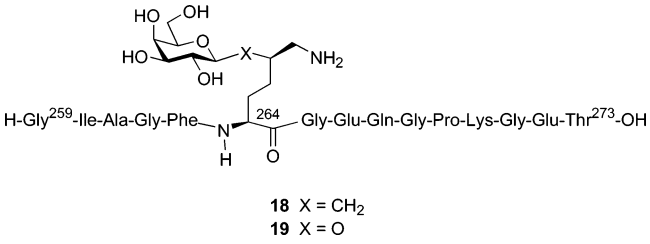


FIGURE 3. Structure of glycopeptides **18** and **19**.

acids toward the C-terminus for binding to DR4 with Phe^{263} as sole anchor residue. Hence, glycopeptide **18** would allow for studies of both A^q and DR4 restricted T cell hybridomas.

The synthesis of glycopeptide **18** was performed on the solid phase using standard conditions according to the Fmoc protocol.[17,52,53] A polystyrene resin grafted with poly(ethylene glycol) spacers (Tentagel) that were functionalized with a 4-alkoxybenzyl alcohol linker was used in the synthesis. First, residues 265−273 were sequentially coupled to the peptide-resin after activation of the amino acids with HBTU in the presence of diisopropylethylamine. Then C-glycosylated amino acid **1** was coupled with HBTU in the presence of 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine,[54] and finally, residues 259−263 were coupled sequentially as their pentafluorophenyl esters in order to avoid esterification of the unprotected hydroxyl groups of the galactose moiety.[55,56] Cleavage of the Fmoc protective groups was achieved by treatment with piperidine. After completion of the solid-phase synthesis, acid-catalyzed cleavage from the resin, and deprotection of the protective groups found on the amino acid residues, was accomplished with TFA and a standard scavenger cocktail. This gave glycopeptide **18** in 7% yield overall yield based on the capacity of the resin, following purification by reversed phase HPLC.[57]

A Preliminary Immunological Study. A preliminary investigation of the immune response to C-linked glycopeptide **18** was performed using a panel of T cell hybridomas obtained previously from mice having CIA.[10,13,14,58] The hybridomas were chosen as representative members from one of five groups of hybridomas that had been found to have different fine specificity for the galactose moiety on hydroxylysine 264 in CII259-273, as established earlier using deoxygenated galactose analogues.[15] Each hybridoma was incubated with antigen-presenting spleen cells which express A^q class II MHC molecules and C-linked glycopeptide **18** or the corresponding O-linked glycopeptide **19** (cf. Figure 3). Recognition of either of the MHC-glycopeptide complexes by a T cell hybridoma resulted in activation of the hybridoma and subsequent secretion of the cytokine interleukin 2 (IL-2) into the medium. The secreted IL-2 was then quantified using an antibody/streptavidin-Eu^{3+} based assay. For three of the five hybridomas, an approximately 10-fold higher concentration of C-linked glycopeptide **18** was required to give a stimulation equivalent to the reference **19**. For one hybridoma T cell stimulation was found to be of the same magnitude with **18** as for **19**, whereas **18** did not elicit any response from the remaining hybridoma. More comprehensive studies with **18** will be published separately.

Conclusions. Synthesis of C-glycosylated hydroxylysine **1** was completed in 17 steps from galactosyl lactone **2** in a total yield of 18%. This constitutes the most complex C-glycosidic analogue of a naturally occurring glycosylated amino acid synthesized to date. Furthermore, building block **1** was incorporated in a peptide, corresponding to residues 259−273 from type II collagen to give glycopeptide analogue **18**. In a preliminary evaluation **18** was found to retain the ability of the corresponding, native O-linked glycopeptide **19** to stimulate T cell hybridomas obtained in CIA, a model for rheumatoid arthritis.

Experimental Section

(4*S*)-4-Benzyl-3-[3-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)propionyl]oxazolidin-2-one (4). Triethylamine (3.0 mL, 21.6 mmol) was added to a solution of carboxylic acid **3** (11.8 g, 19.7 mmol) in THF (200 mL) cooled to −78 °C. The solution was stirred for 5 min, and pivaloyl chloride (2.67 mL, 21.6 mmol) was added. After 15 min, a mixture of (*S*)-4-benzyloxazolidin-2-one (3.48 g, 19.7 mmol) and butyllithium (10.1 mL, 1.95 M in hexanes, 19.7 mmol) in THF (60 mL) was transferred to this solution via cannula. The mixture was stirred for 30 min at −78 °C, and then the reaction was quenched by addition of NH_4Cl (aq, satd). The phases were separated and the organic phase was washed twice with NaCl (aq, satd). The combined water phases were extracted three times with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chroma-

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(57) The poor yield can be explained by problems with a contaminated column during the HPLC-purification, which resulted in that the purification had to be repeated several times. Some material was also consumed at two stages during the solid-phase synthesis when small amounts of peptide was cleaved from the resin and analyzed with mass spectroscopy.

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tography (*n*-heptane/EtOAc 5:2) gave oxazolidinone **4** (13.1 g, 88%) as a white amorphous solid: $[\alpha]_D = 11.0$ (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.17 (m, 25H, Ph), 4.99 and 4.71 (2d, 2H, *J* = 11.2 Hz, PhC*H*$_2$O), 4.96 and 4.63 (2d, 2H, *J* = 12.4 Hz, PhC*H*$_2$O), 4.76 and 4.68 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.66−4.59 (m, 1H, NCH), 4.45 and 4.41 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.10 (2d, 2H, *J* = 5.2 Hz, $COOCH_2$), 4.02 (d, 1H, *J* = 2.7 Hz, H-4), 3.72 (t, 1H, *J* = 9.3 Hz, H-2), 3.62 (dd, 1H, *J* = 2.7, 9.3 Hz, H-3), 3.58−3.52 (m, 3H, H-5 and H-6), 3.33 (dt, 1H, *J* = 2.4, 9.3 Hz, H-1), 3.28 (dd, 1H, *J* = 13.4, 3.2 Hz, PhC*H*$_2$), 3.19−2.99 (m, 1H, $COCH_2$), 2.71 (dd, 1H, *J* = 13.4, 9.7 Hz, PhC*H*$_2$), 2.39−2.29 (m, 1H, $COCH_2CH_2$), 1.94−1.83 (m, 1H, $COCH_2CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1 (*C*OCH_2), 153.5 (NCOO), 84.9 (C-3), 79.1 (C-2), 78.6 (C-1), 77.0 (C-5), 75.5 (Ph*C*H_2O), 74.6 (Ph*C*H_2O), 73.6 (Ph*C*H_2O), 72.3 (Ph*C*H_2O), 73.7 (C-4), 68.8 (C-6), 66.2 ($COOCH_2$), 55.2 (NCH), 38.0 (Ph*C*H_2), 32.0 ($COCH_2$), 26.6 ($COCH_2CH_2$); HR-MS (FAB) calcd for $C_{47}H_{49}NNaO_8$ 778.3356 $[M + Na]^+$, found 778.3358.

(4*S*)-4-Benzyl-3-[(2*S*)-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosylmethyl)pent-4-enoyl]oxazolidin-2-one (5). A solution of oxazolidinone **4** (12.9 g, 17.1 mmol) in THF (200 mL) was cooled to −78 °C and treated with NaHMDS (3.50 g, 18.2 mmol). After 30 min, allyl iodide (5.48 mL, 59.7 mmol) was added dropwise. After being stirred for 2 h, the reaction mixture was allowed to reach room temperature and was then stirred an additional 30 min. The solution was poured onto NH_4Cl (aq, satd), the phases were separated and the organic phase was washed twice with NaCl (aq, satd). The combined water phases were extracted twice with CH_2Cl_2, and the combined organic phases were then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (*n*-heptane/EtOAc 7:1 → 4:1) to provide **5** (9.53 g, 70%) as a colorless oil: $[\alpha]_D = 20.0$ (*c* 3.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.15 (m, 25H, Ph), 5.85−5.72 (m, 1H, CH_2CHN), 5.08 (d, 1H, *J* = 17.1 Hz, CH_2CHN), 5.03 (d, 1H, *J* = 10.4 Hz, CH_2CHN), 4.95 and 4.67 (2d, 2H, *J* = 10.8 Hz, PhC*H*$_2$O), 4.94 and 4.59 (2d, 2H, *J* = 11.6 Hz, PhC*H*$_2$O), 4.74 and 4.67 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.49−4.41 (m, 1H, NCH), 4.42 and 4.31 (2d, 2H, *J* = 12.0 Hz, PhC*H*$_2$O), 4.16−4.07 (m, 1H, COCH), 3.95 (d, 1H, *J* = 2.1 Hz, H-4), 3.85 (dd, 1H, *J* = 3.0, 9.1 Hz, $COOCH_2$), 3.63 (t, 1H, *J* = 9.2 Hz, H-2), 3.59−3.53 (m, 2H, H-3, $COOCH_2$), 3.46 (t, 1H, *J* = 7.4 Hz, H-6), 3.44 (t, 1H, *J* = 7.4 Hz, H-5), 3.39−3.31 (m, 2H, H-1, H-6), 3.27 (dd, 1H, *J* = 13.4, 2.9 Hz, PhC*H*$_2$), 2.54 (dd, 1H, *J* = 13.4, 10.2 Hz, PhC*H*$_2$), 2.48−2.39 (m, 1H, CH_2CHCH_2), 2.35−2.26 (m, 1H, CH_2CHCH_2), 2.14 (dq, 1H, *J* = 14.2, 2.7 Hz, $COCHCH_2$), 2.00−1.90 (m, 1H, $COCHCH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3 (*C*OCH), 153.5 (*C*$OOCH_2$), 117.5 (*C*H_2CHN), 84.8 (C-3), 79.1 (C-2), 78.6 (C-1), 76.6 (C-5), 75.5 (Ph*C*H_2O), 74.7 (Ph*C*H_2O), 74.0 (C-4), 73.4 (Ph*C*H_2O), 72.4 (Ph*C*H_2O), 68.7 (C-6), 65.6 ($COOCH_2$), 55.6 (N*C*H), 39.5 (CO*C*H), 38.3 (Ph*C*H_2), 37.8 (CH_2CHCH_2), 34.1 ($COCHCH_2$); HR-MS (FAB) calcd for $C_{50}H_{53}NNaO_8$ 818.3669 $[M + Na]^+$, found 818.3665.

2(*S*)-(*tert*-Butyldimethylsilanyloxymethyl)-1-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)pent-4-ene (7). $LiAlH_4$ (147 mg, 3.88 mmol) was added to oxazolidinone **5** (3.09 g, 3.88 mmol) in Et_2O (100 mL) at room temperature. After being stirred for 15 min, the reaction was quenched by addition of NaOH (5 M, ca. 0.5 mL) followed by filtration through a pad of Celite and concentration affording crude alcohol **6** as a colorless oil. The alcohol was dissolved in CH_2Cl_2 (10 mL) without further purification, after which 2,3,5-collidine (1.03 mL, 7.76 mmol) and TBDMSOTf (1.34 mL, 5.82 mmol) were added. $NaHCO_3$ (0.5 mL, aq, satd) was added after stirring for 20 min. The reaction mixture was dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (*n*-heptane/EtOAc 9:1) gave **7** (2.33 g, 82%) as a white amorphous solid: $[\alpha]_D = 3.4$ (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.24 (m, 20H, Ph), 5.84−5.72 (m, 1H, CH_2CH), 5.02 (d, 1H, *J* = 17.8 Hz, CH_2CH), 4.98 (d, 1H, *J* = 9.5 Hz, CH_2CH), 4.96 and 4.66 (2d, 2H, *J* = 11.9 Hz, PhC*H*$_2$O), 4.93 and 4.65 (2d, 2H, *J* = 10.7 Hz, PhC*H*$_2$O), 4.76 and 4.69 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.48 and 4.43 (2d, 2H, *J* = 11.8 Hz, PhC*H*$_2$O), 4.00 (d, 1H, *J* = 2.1 Hz, H-4), 3.67−3.59 (m, 3H, H-2, H-3, $SiOCH_2$), 3.59−3.54 (m, 2H, H-5, H-6), 3.51 (t, 1H, *J* = 6.3 Hz, H-6), 3.41 (dd, 1H, *J* = 10.2, 5.8 Hz, $SiOCH_2$), 3.33 (t, 1H, *J* = 8.9 Hz, H-1), 2.25−2.16 (m, 1H, CH_2CHCH_2), 2.14−2.06 (m, 1H, CH_2CHCH_2), 1.95−1.84 (m, 2H, $SiOCH_2CH$, $SiOCH_2CHCH_2$), 1.46 (t, 1H, *J* = 9.6 Hz, $SiOCH_2CHCH_2$), 0.89 (s, 9H, $SiCCH_3$), 0.02 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 116.0 (*C*H_2-CH), 85.1 (C-3), 79.9 (C-2), 78.3 (C-1), 77.1 (C-4), 75.7 (Ph*C*H_2O), 74.5 (Ph*C*H_2O), 73.6 (Ph*C*H_2O), 72.4 (Ph*C*H_2O), 73.9 (C-5), 69.2 (C-6), 65.9 ($SiOCH_2$), 37.3 ($SiOCH_2CH$), 34.6 (CH_2CHCH_2), 33.3 ($SiOCH_2CHCH_2$), 26.1 ($SiCCH_3$), 18.4 ($SiCCH_3$), −5.3 ($SiCH_3$); HR-MS (FAB) calcd for $C_{46}H_{60}NaO_6Si$ 759.4057 $[M + Na]^+$, found 759.4055.

(3*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)-4-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)butyraldehyde (8). Ozone was bubbled through a solution of alkene **7** (1.20 g, 1.63 mmol) in CH_2Cl_2 (20 mL) at −78 °C until it became slightly blue (over-exposure to ozone causes partial oxidation of the benzyl ethers to benzoates). The solution was purged with oxygen until colorless and was then treated with triphenylphosphine on polystyrene (1.13 g, 2.44 mmol) for 14 h, filtered, and concentrated to afford aldehyde **8** (1.15 g, 96%): $[\alpha]_D = -2.1$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.68 (s, 1H, CHO), 7.39−7.26 (m, 20H, Ph), 4.95 and 4.63 (2d, 2H, *J* = 10.9 Hz, PhC*H*$_2$O), 4.94 and 4.65 (2d, 2H, *J* = 11.8 Hz, PhC*H*$_2$O), 4.75 and 4.68 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.47 and 4.43 (2d, 2H, *J* = 11.8 Hz, PhC*H*$_2$O), 3.99 (d, 1H, *J* = 1.4 Hz, H-4), 3.66 (t, 1H, *J* = 10.1 Hz, $SiOCH_2$), 3.65 (t, 1H, *J* = 8.9 Hz, H-2), 3.59 (dd, 1H, *J* = 9.3, 2.3 Hz, H-3), 3.54 (2d, 2H, *J* = 7.1, 5.8 Hz, H-6), 3.48 (q, 1H, *J* = 6.4 Hz, H-5), 3.38 (dd, 1H, *J* = 10.1, 7.2 Hz, $SiOCH_2$), 3.24 (t, 1H, *J* = 9.8 Hz, H-1), 2.50−2.39 (m, 2H, $SiOCH_2CH$, CH_2CHO), 2.37−2.28 (m, 1H, CH_2CHO), 1.86−1.78 (m, 1H, $SiOCH_2CHCH_2$), 1.63−1.49 (m, 1H, $SiOCH_2CHCH_2$), 0.88 (s, 9H, $SiCCH_3$), 0.02 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.1 (CHO), 84.9 (C-3), 79.3 (C-2), 77.4 (C-1), 76.9 (C-5), 75.6 (Ph*C*H_2O), 74.6 (Ph*C*H_2O), 73.7 (C-4), 73.6 (Ph*C*H_2O), 72.4 (Ph*C*H_2O), 69.0 (C-6), 67.0 ($SiOCH_2$), 46.0 (*C*H_2-CHO), 33.6 ($SiOCH_2CHCH_2$), 33.4 ($SiOCH_2CH$), 26.0 ($SiCCH_3$), 18.4 ($SiCCH_3$), −5.4 ($SiCH_3$); HR-MS (FAB) calcd for $C_{45}H_{58}NaO_7Si$ 761.3849 $[M + Na]^+$, found 761.3857.

(5*S*,*Z*)-2-Benzyloxycarbonylamino-(*tert*-butyldimethylsilanyloxymethyl)-6-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-hex-2-enoic Acid Methyl Ester (9). DBU (798 μL, 5.33 mmol) was added dropwise to a solution of $(MeO)_2P(O)CH(NHCbz)CO_2CH_3$ (1.77 g, 5.33 mmol) in CH_2Cl_2 (10 mL) and stirred for 10 min. This solution was transferred to aldehyde **8** (3.14 g, 4.26 mmol) in CH_2Cl_2 (10 mL). After being stirred for 30 min, the solution was concentrated and the residue was purified by flash column chromatography (*n*-heptane/EtOAc 9:1) to provide enamide ester **9** (3.70 g, 92%) as a colorless oil (*E*/*Z* >98:2 according to ^1H NMR spectroscopy): $[\alpha]_D = -7.8$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.24 (m, 25H, Ph), 6.91 (brs, 1H, NH), 6.55 (t, 1H, *J* = 8.1 Hz, NCCH), 5.13 and 5.10 (2d, 2H, *J* = 12.3 Hz, $NCOOCH_2$), 4.93 and 4.62 (2d, 2H, *J* = 10.8 Hz, PhC*H*$_2$O), 4.92 and 4.63 (2d, 2H, *J* = 11.8 Hz, PhC*H*$_2$O), 4.72 and 4.65 (2d, 2H, *J* = 11.7 Hz, PhC*H*$_2$O), 4.46 and 4.41 (2d, 2H, *J* = 11.8 Hz, PhC*H*$_2$O), 3.93 (d, 1H, *J* = 2.6 Hz, H-4), 3.70 (brs, 3H, OCH_3), 3.62 (t, 1H, *J* = 9.2 Hz, H-2), 3.60−3.53 (m, 3H, $SiOCH_2$, H-3, H-5), 3.53−3.45 (m, 2H, H-6), 3.35−3.26 (m, 2H, H-1, $SiOCH_2$), 2.41−2.32 (m, 1H, $NCCHCH_2$), 2.30−2.20 (m, 1H, $NCCHCH_2$), 2.06−1.96 (m, 1H, $SiOCH_2CH$), 1.77 (dt, 1H, *J* = 12.4, 1.7 Hz, $SiOCH_2CHCH_2$), 1.38 (ddd, 1H, *J* = 14.4, 10.3, 4.1 Hz, $SiOCH_2CHCH_2$), 0.85 (s, 9H, $SiCCH_3$), 0.01 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1 (*C*$OOCH_3$), 154.5 (NCO), 85.0 (C-3), 79.4 (C-2), 77.5 (C-1), 77.2 (C-5), 75.6 (Ph*C*H_2O), 74.5 (Ph*C*H_2O), 73.7 (C-4), 73.5 (Ph*C*H_2O), 72.4 (Ph*C*H_2O), 69.2 (C-6), 67.2 ($NCOOCH_2$), 66.2 ($SiOCH_2$), 52.2 (OCH_3), 36.9 ($SiOCH_2CH$), 33.2 ($SiOCH_2CHCH_2$), 28.0 ($NCCHCH_2$), 26.0 ($SiCCH_3$), 18.4 ($SiCCH_3$),

−5.3 ($SiCH_3$); HR-MS (FAB) calcd for $C_{56}H_{69}NNaO_{10}Si$ 966.4588 $[M + Na]^+$, found 966.4577.

(5*S*)-*N*-Benzyloxycarbonyl-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosylmethyl)-2,3-dehydropiperidine 2-Methyl Ester (12). PPh_3 (52 mg, 200 μmol) and DEAD (35 mg, 200 μmol) were added to a solution of enamide ester **10** (76 mg, 90.7 μmol) in THF (4 mL). After 2 min, diphenylphosphoryl azide (21 μL, 136 μmol) was added. After 15 min of stirring, the solution was concentrated, and the residue was purified by flash column chromatography (*n*-heptane/EtOAc 2:1 → 1:1) to provide dehydropiperidine **12** (66 mg, 90%) as a colorless oil: ^{1}H NMR δ 7.40−7.24 (m, 25H, Ph), 6.01 (t, 1H, *J* = 3.7 Hz, NCCH), 5.13 and 5.07 (2d, 2H, *J* = 12.2 Hz, $NCOOCH_2$), 4.93 and 4.65 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.92 and 4.58 (2d, 2H, *J* = 10.7 Hz, $PhCH_2O$), 4.75 and 4.67 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.44 and 4.41 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.11 (dd, 1H, *J* = 12.9, 2.5 Hz, $CbzNCH_2$), 3.99 (d, 1H, *J* = 2.0 Hz, H-4), 3.63 (t, 1H, *J* = 9.2 Hz, H-2), 3.61−3.46 (m, 4H, H-3, H-5, H-6, H-6), 3.53 (s, 3H, OCH_3), 3.26 (t, 1H, *J* = 9.2 Hz, H-1), 2.91 (t, 1H, *J* = 11.5 Hz, $CbzNCH_2$), 2.34 (dt, 1H, *J* = 19.3, 5.0 Hz, NC═CHCH_2), 2.18−2.06 (m, 1H, $CbzNCH_2CH$), 1.83 (dd, 1H, *J* = 19.3, 3.5 Hz, NC═CHCH_2), 1.67 (t, 1H, *J* = 11.7 Hz, C-1CH_2), 1.57−1.47 (m, 1H, C-1CH_2); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 165.2 (NCO), 154.1 ($COOCH_3$), 122.6 (NC*C*H), 84.9 (C-3), 79.2 (C-2), 77.3 (C-1), 77.2 (C-5), 75.7 ($PhCH_2O$), 74.6 ($PhCH_2O$), 73.6 ($PhCH_2O$), 73.6 (C-4), 72.3 ($PhCH_2O$), 69.0 (C-6), 68.0 ($CbzNCOOCH_2$), 52.0 (OCH_3), 49.2 (N_3CH_2), 35.3 ($CbzNCH_2CHCH_2$), 30.5 ($CbzCH_2CH$), 29.1 ($CbzNCCHCH_2$); LC-MS calcd for $C_{50}H_{56}NO_9^+$ 814.4 $[M + H]^+$, found 814.5.

(2*S*,5*S*)-2-Benzyloxycarbonylamino-5-(*tert*-butyldimethylsilanyloxymethyl)-6-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)-hexanoic Acid Methyl Ester (13). Enamide ester **9** (217 mg, 230 μmol) was dissolved in *i*-PrOH (2.5 mL), the solution was flushed with nitrogen for 10 min, and then was [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (3.5 mg, 4.8 μmol) added. After 5 vacuum-H_2 cycles, the solution was heated at 70 °C with microwave irradiation in a sealed tube for 40 min. Concentration and purification of the residue by flash column chromatography (*n*-heptane/EtOAc 3:1) gave **13** (206 mg, 95%) as a colorless oil (d.e. = 99.7): $[\alpha]_D$ = 3.7 (*c* 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.24 (m, 25H, Ph), 5.33 (d, 1H, *J* = 8.2 Hz, NH), 5.12 and 5.09 (2d, 2H, *J* = 12.1 Hz, $NCOOCH_2$), 4.95 and 4.66 (2d, 2H, *J* = 11.2 Hz, $PhCH_2O$), 4.95 and 4.64 (2d, 2H, *J* = 11.2 Hz, $PhCH_2O$), 4.74 and 4.65 (2d, 2H, *J* = 11.8 Hz, $PhCH_2O$), 4.48 and 4.41 (2d, 2H, *J* = 11.8 Hz, $PhCH_2O$), 4.36−4.28 (m, 1H, C*H*$COOCH_3$), 3.98 (d, 1H, *J* = 2.4 Hz, H-4), 3.70 (s, 3H, OCH_3), 3.67−3.48 (m, 6H, H-2, H-3, H-5, H-6, H-6, $SiOCH_2$), 3.39 (dd, 1H, *J* = 10.1, 5.4 Hz, $SiOCH_2$), 3.25 (t, 1H, *J* = 9.4 Hz, H-1), 1.89−1.75 (m, 3H, CH_2CHCOOCH$_3$, $SiOCH_2CH$, C-1CH_2), 1.73−1.64 (m, 1H, CH_2CHCOOCH$_3$), 1.50−1.35 (m, 3H, C-1CH_2, CH_2CH$_2$CHCOOCH$_3$), 0.88 (s, 9H, $SiCCH_3$), 0.02 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1 ($COOCH_3$), 156.0 (NCO), 85.0 (C-5), 79.6 (C-2), 78.1 (C-1), 77.5 (C-3), 75.6 ($PhCH_2O$), 74.5 ($PhCH_2O$), 73.8 (C-4), 73.5 ($PhCH_2O$), 72.4 ($PhCH_2O$), 69.1 (C-6), 67.0 ($NCOOCH_2$), 66.0 ($SiOCH_2$), 54.2 ($CCOOCH_3$), 52.3 (OCH_3), 36.6 ($SiOCH_2CH$), 33.6 (CH_2CH_2-CHCOOCH$_3$), 29.3 (C-1CH_2), 26.0 ($SiCCH_3$), 25.5 (CH_2CH-COOCH$_3$), 18.4 ($SiCCH_3$), −5.5 ($SiCH_3$); HR-MS (FAB) calcd for $C_{56}H_{71}NNaO_{10}Si$ 968.4745 $[M + Na]^+$, found 968.4745.

(2*S*,5*S*)-2-Benzyloxycarbonylamino-5-(hydroxymethyl)-6-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)hexanoic Acid Methyl Ester (14). Tetrabutylammonium fluoride monohydrate (173 mg, 550 μmol) was added to a solution of **13** (400 mg, 423 μmol) in THF (20 mL), and the resulting solution was stirred for 30 min. Then the solution was concentrated and the residue was purified by flash column chromatography (*n*-heptane/EtOAc 1:1) to provide alcohol **14** (330 mg, 94%) as a colorless oil: $[\alpha]_D$ = −2.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.23 (m, 25H, Ph), 5.26 (d, 1H, *J* = 8.2 Hz, NH), 5.10 (s, 2H, $NCOOCH_2$), 4.95 and 4.64 (2d, 2H, *J* = 10.9 Hz, $PhCH_2O$), 4.92 and 4.60 (2d, 2H, *J* = 11.8 Hz, $PhCH_2O$), 4.74 and 4.67 (2d, 2H, *J* = 11.8 Hz, $PhCH_2O$), 4.48 and 4.32 (2d, 2H, *J* = 11.9 Hz, $PhCH_2O$), 4.35−4.28 (m, 1H, C*H*$COOCH_3$), 3.90 (d, 1H, *J* = 2.4 Hz, H-4), 3.70 (s, 3H, OCH_3), 3.60−3.49 (m, 5H, H-2, H-3, H-5, H-6, CH_2OH), 3.45−3.36 (m, 2H, H-6, CH_2OH), 3.25 (t, 1H, *J* = 9.1 Hz, H-1), 2.83 (br s, 1H, OH), 1.89−1.75 (m, 2H, CH_2-CHCOOCH$_3$), 1.70−1.51 (m, 3H, CH_2CH$_2$CHCOOCH$_3$, C*H*CH_2-OH, C-1CH_2), 1.43−1.21 (m, 2H, C-1CH_2, CH_2CH$_2$CHCOOCH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0 ($COOCH_3$), 156.0 (NCO), 85.0 (C-5), 79.7 (C-1), 78.9 (C-2), 77.4 (C-3), 75.7 ($PhCH_2O$), 74.5 ($PhCH_2O$), 73.6 (C-4), 73.6 ($PhCH_2O$), 72.5 ($PhCH_2O$), 69.3 (C-6), 67.1 ($NCOOCH_2$), 65.8 (CH_2OH), 54.2 ($CHCOOCH_3$), 52.4 (OCH_3), 39.8 ($CHCH_2OH$), 34.4 ($CH_2CH_2CHCOOCH_3$), 29.3 (C-1CH_2), 28.2 ($CH_2CHCOOCH_3$); HR-MS (FAB) calcd for $C_{50}H_{57}$-$NNaO_{10}$ 854.3880 $[M + Na]^+$, found 854.3873.

(2*S*,5*S*)-2-Benzyloxycarbonylamino-5-(azidomethyl)-6-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)hexanoic Acid Methyl Ester (15). PPh_3 (131 mg, 500 μmol) and DEAD (79 μL, μmol) was added to a solution of alcohol **14** (320 mg, 385 μmol) in THF (15 mL). After 2 min, diphenylphosphoryl azide (107 μL, 500 μmol) was added. After 15 min of stirring, the solution was concentrated and the residue was purified by flash column chromatography (*n*-heptane/EtOAc 6:1→2:1) to provide azide **15** (307 mg, 93%) as a colorless oil: $[\alpha]_D$ = −1.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.23 (m, 25H, Ph), 5.30 (d, 1H, *J* = 8.2 Hz, NH), 5.09 (s, 2H, $NCOOCH_2$), 4.94 and 4.64 (2d, 2H, *J* = 10.9 Hz, $PhCH_2O$), 4.91 and 4.61 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.72 and 4.62 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.46 and 4.38 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.34−4.29 (m, 1H, C*H*$COOCH_3$), 3.93 (d, 1H, *J* = 2.4 Hz, H-4), 3.72 (s, 3H, OCH_3), 3.58−3.51 (m, 5H, H-2, H-3, H-5, H-6, H-6), 3.33 (dd, 1H, *J* = 12.6, 4.9 Hz, CH_2N_3), 3.23−3.15 (m, 2H, H-1, CH_2N_3), 1.86−1.69 (m, 2H, C-1CH_2, C*H*CH_2N_3), 1.68−1.58 (m, 1H, CH_2CHCOOCH$_3$), 1.47−1.30 (m, 4H, C-1CH_2, CH_2CH$_2$CHCOOCH$_3$, CH_2CHCOOCH$_3$, CH_2CH$_2$-CHCOOCH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8 ($COOCH_3$), 156.0 (NCO), 84.9 (C-5), 79.1 (C-1), 78.1 (C-2), 77.4 (C-3), 75.6 ($PhCH_2O$), 74.5 ($PhCH_2O$), 73.7 (C-4), 73.6 ($PhCH_2O$), 72.4 ($PhCH_2O$), 69.3 (C-6), 67.1 ($NCOOCH_2$), 55.4 (CH_2N_3), 54.0 ($CCOOCH_3$), 52.4 (OCH_3), 35.3 ($CHCH_2OH$), 34.0 (CH_2CH_2-CHCOOCH$_3$), 29.2 (C-1CH_2), 26.7 ($CH_2CHCOOCH_3$); HR-MS (FAB) calcd for $C_{50}H_{56}N_4NaO_9$ 879.3945 $[M + Na]^+$, found 879.3936.

(2*S*,5*S*)-2-Benzyloxycarbonylamino-5-(*tert*-butoxycarbonylaminomethyl)-6-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranosyl)hexanoic Acid Methyl Ester (16). PPh_3 (40 mg, 157 μmol) was added to a solution of azide **15** (106 mg, 117 μmol) in moist THF (3 mL). After the mixture was heated under microwave irradiation at 130 °C for 15 min (or stirring overnight at rt), Boc_2O (33 mg, 157 μmol) and triethylamine (16 μL, 117 μmol) were added, and stirring was continued for 30 min. The solution was concentrated, and the residue was purified by flash column chromatography (*n*-heptane/EtOAc 4:1→3:1) to provide amide **16** (106 mg, 97%) as a white amorphous solid: $[\alpha]_D$ = −1.3 (*c* 2.1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43−7.23 (m, 25H, Ph), 5.95 (d, 1H, *J* = 7.0 Hz, NHCbz), 5.16 (t, 1H, *J* = 5.0, N*H*Boc), 5.10 (s, 2H, OCH_2Ph) 4.96 and 4.94 (2d, 2H, *J* = 10.8 Hz, $PhCH_2O$), 4.76 and 4.70 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.66 and 4.64 (2d, 2H, *J* = 11.1 Hz, $PhCH_2O$), 4.50 and 4.38 (2d, 2H, *J* = 11.7 Hz, $PhCH_2O$), 4.23−4.13 (m, 1H, C*H*$COOCH_3$), 3.90 (s, 1H, H-4), 3.72 (s, 3H, OCH_3), 3.67−3.54 (m, 3H, H-2, H-3, H-6), 3.53−3.47 (m, 1H, H-5), 3.36 (dd, 1H, *J* = 8.7, 4.9 Hz, H-6), 3.30−3.14 (m, 2H, H-1, CH_2NHBoc), 3.00−2.91 (m, 1H, CH_2NHBoc), 1.95−1.77 (m, 2H, C*H*CH_2NHBoc, CH_2CH$_2$CHCOOCH$_3$), 1.73 (dd, 1H, *J* = 14.3, 5.5 Hz, CH_2CHCOOCH$_3$), 1.50−1.22 (m, 12H, C-1CH_2, CH_2CHCOOCH$_3$, CH_2CH$_2$CHCOOCH$_3$, *t*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 ($COOCH_3$), 157.1 (NCO), 156.6 (NCO), 85.0 (C-5), 79.3 (C-1), 79.0 (C-2), 78.6 (C-5), 75.6 ($PhCH_2O$), 74.6 ($PhCH_2O$), 73.8 (C-4), 73.7 ($PhCH_2O$), 72.6 ($PhCH_2O$), 69.8 (C-6), 66.9 ($NCOOCH_2$), 54.5 ($CHCOOCH_3$), 52.3 (OCH_3), 41.5 (CH_2-NHBoc), 37.7 ($CHCH_2$NHBoc), 34.0 (C-1CH_2), 30.4 (CH_2-

$CHCOOCH_3$), 29.3 ($CH_2CH_2CHCOOCH_3$); HR-MS (FAB) calcd for $C_{55}H_{66}N_2NaO_{11}$ 953.4564 $[M + Na]^+$, found 953.4550.

(2*S*,5*S*)-5-(*tert*-Butoxycarbonylaminomethyl)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-6-(β-D-galactopyranosyl)hexanoic Acid (1). Aqueous LiOH (71 μL, 71 μmol, 1.0 M) was added to a solution of **16** (63 mg, 68 μmol) in THF (2 mL). After 15 min of stirring, the mixture was extracted with CH_2Cl_2, the organic phase was washed with HCl (0.2 M, aq), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in AcOH (10 mL), and Pd−C (60 mg, 5%) was added. The suspension was aggitated under an atmosphere of H_2 (75 psi) for 16 h and filtered through a pad of Celite, and the solvent was evaporated. The solid residue was dissolved in a 1:1 mixture of Na_2CO_3 (10% aq) and MeCN (3 mL in total), Fmoc-succinimide (25 mg, 74 μmol) was added, and enough H_2O (ca 0.5 mL) was then added until a clear solution was obtained. After being stirred for 16 h, the solution was acidified with AcOH (1 mL), and the solvents were evaporated. Purification of the residue on reversed-phase HPLC (H_2O/MeCN (+0.2% TFA) gradient 100:0 → 0:100 during 60 min) afforded **1** (24 mg, 56%) as a white solid: $[\alpha]_D = 3.5$ (*c* 0.2, MeOH); ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.79 (d, 2H, *J* = 7.5 Hz, Fmoc-arom.), 7.71−7.60 (m, 2H, Fmoc-arom), 7.38 (t, 2H, *J* = 7.5 Hz, Fmoc-arom.), 7.31 (t, 2H, *J* = 7.5 Hz, Fmoc-arom), 4.41−4.29 (m, 2H, $NHCOOCH_2$), 4.22 (t, 1H, *J* = 7.0 Hz, Fmoc-C*H*), 4.10−4.00 (m, 1H, $CHCOOCH_3$), 3.87−3.81 (m, 1H, H-4), 3.72 (dd, 1H, *J* = 11.2, 7.0 Hz, H-6), 3.64 (dd, 1H, *J* = 11.2, 4.9 Hz, H-6), 3.46−3.32 (m, 3H, H-2, H-3, H-5), 3.14 (t, 1H, *J* = 9.5 Hz, H-1), 3.06 (d, 2H, *J* = 3.9 Hz, $BocNHCH_2$), 1.96−1.89 (m, 1H, C-1CH_2), 1.84−1.67 (m, 3H, $CH_2CHCOOCH_3$, $CH_2CH_2CHCOOCH_3$, $BocNHCH_2CH$), 1.50−1.35 (m, 12H, C-1CH_2, $CH_2CH_2CHCOOCH_3$, $CH_2CHCOOCH_3$, *t*-Bu); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 173.1 (COOH), 159.9 (NCO), 159.7 (NCO), 81.2 (C-2), 81.0 (C-5), 77.5 (C-3), 74.4 (Fmoc-CH_2), 72.0 (C-4), 69.0 (Fmoc-*C*H), 64.0 (C-6), 49.5 (*C*HCOOH), 46.6 ($BocNHCH_2$), 37.8 ($BocNHCH_2CH$), 36.3 ($CH_2CHCOOH$), 31.2 (C-1CH_2), 29.9 (*t*-Bu), 26.3 ($CH_2CH_2CHCOOH$); HR-MS (FAB) calcd for $C_{33}H_{43}N_2Na_2O_{11}$ 689.2662 $[M + 2Na - H]^+$, found 689.2664.

Glycyl-L-isoleucyl-L-alanylglycyl-L-phenylalanyl-(5*S*)-(β-D-galactopyranosylmethyl)-L-lysylglycyl-L-glutam-1-yl-L-glutaminglycyl-L-prolyl-L-lysylglycyl-L-glutam-1-y-L-threonine (18). Residues Gly265-Glu272 were coupled on Tentagel-S-TRT-Thr-Fmoc resin essentially as descibed elsewhere.[17] N^{α}-Fmoc amino acids with standard side chain protecting groups were used (4 equiv). Couplings were accomplished with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 4 equiv) and diisopropylethylamine (DIPEA, 8 equiv) in DMF. Building block **1** was coupled using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 1.2 equiv), HOBt (1.2 equiv), and DIPEA (2.4 equiv) as coupling reagents. Residues Gly259-Phe263 were coupled as their pentafluorophenyl esters by mixing the amino acid, DIC (3 equiv), and pentafluorophenol (5 equiv) in DMF for 2 h.[56] Fmoc-deblocking was achieved by treating the resin with 20% piperidine in DMF for 10 min. Cleavage of the peptide from the resin with trifluoroacetic acid/water/thioanisole/ethanedithiol (35:2:2:1)/ and subsequent workup was performed essentially as described elsewhere:[17] After cleavage from the solid phase, purification by reversed-phase HPLC (0 → 100% MeCN in H_2O, with 0.1% TFA in both eluents, during 60 min) followed by lyophilization gave peptide **18** as a white amorphous solid (6 mg, 7%); ^{1}H NMR (H_2O/D_2O, 500 MHz) see Table 2; MS (MALDITOF) calcd 1651.8 ($M + H^+$), found 1651.8.

TABLE 2. ^{1}H NMR Chemical Shifts for C-Linked Glycopeptide 18 in Water Containing 10% D_2O[a]

residue	HN	Hα	Hβ	Hγ	other
Gly^{259}	*b*	*b*			
Ile^{260}	8.45	4.17	1.82	0.88 (CH_3) 1.15;1.42	0.81 (δCH_3)
Ala^{261}	8.48	4.29	1.34		
Gly^{262}	8.29	3.86			
Phe^{263}	8.04	4.57	3.04		7.24 (Hδ); 7.33 (Hϵ) 7.31 (Hζ)
Hyl^{264}	8.36	4.2	1.65; 1.78	1.36	1.7 (Hδ); 1.39[c,d] 2.98 (Hϵ)
Gly^{265}	7.83	3.86			
Glu^{266}	8.19	4.38	2.1; 1.93	2.43	
Gln^{267}	8.47	4.35	2.08; 1.95	2.33	
Gly^{268}	8.26	4.1; 3.97			
Pro^{269}		4.38	2.27; 1.98	1.89	3.59 (Hδ)
Lys^{270}	8.44	4.26	1.8; 1.66	1.42	1.8 (Hδ); 2.96 (Hϵ)
Gly^{271}	8.34	3.91			
Glu^{272}	8.18	4.44	2.1; 1.93	2.44	
Thr^{273}	8.19	4.46	4.33	1.16	

[a] Spectra were recorded at 500 MHz, 298 K. [b] N-terminal (Gly^{259}) not assigned due to spectral overlap. [c] CH_2-bridge to C-galactose. [d] Chemical shifts for the galactose moiety: δ = 3.92 (H-4), 3.69 and 3.58 (H-5, H-6, H-6), 3.56 (H-3), 3.36 (H-2), 3.23 (H-1).

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Supporting Information Available: General methods and materials as well as ^{1}H NMR and ^{13}C NMR spectra for all new isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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