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Preparation of Building Blocks for Glycopeptide Synthesis by Glycosylation of Fmoc Amino Acids Having Unprotected Carboxyl Groups

Lourdes A. Salvador, Mikael Elofsson and Jan Kihlberg*

Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Abstract: N^{α}-Fmoc amino acids with an unprotected α-carboxyl group have been glycosylated with carbohydrate 1,2-*trans* peracetates using Lewis acids as promoters. Aliphatic and phenolic *O*- and *S*-glycosides of amino acids, with a 1,2-*trans* anomeric configuration, were obtained as products in 34-65% yields. The glycosylated building blocks have the protective groups of choice (*i.e.* *O*-acetyl and N^{α}-Fmoc) for direct use in stepwise synthesis of glycopeptides. The starting materials are readily available and the method does not require an extensive experience in synthetic carbohydrate chemistry.

INTRODUCTION

The carbohydrate moieties of glycoproteins are known to influence the properties of the parent protein in many and diverse ways (reviewed in refs 1 and 2). For instance, glycosylation provides protection against proteolysis, influences uptake of serum proteins by the liver, affects intracellular transport of enzymes to lysosomes, determines human blood groups, and regulates leukocyte trafficking to sites of inflammation. Based on these observations glycosylation has recently been used in efforts to modify the biological function of peptides which are not glycosylated in nature. Thus, enkephalins which displayed substantially increased analgetic activity[3], or were able to cross the blood-brain barrier[4], were obtained. Glycosylation has also been found to increase the absorption of peptides from the small intestine[5], decrease excretion[6], and provide protection against enzymatic degradation[5,7]. Substantial efforts towards synthesis of glycopeptides have therefore recently been undertaken to delineate the biological functions of glycoproteins and glycopeptides, and also to investigate the conformational preferences of glycopeptides (reviewed in refs 8 and 9).

Convergent synthesis of *O*-linked glycopeptides by attachment of an oligosaccharide fragment to a peptide has been restricted by the low solubility of peptides under conditions used for glycoside synthesis, and by problems in obtaining satisfactory regio- and stereoselectivity.[9] The alternative approach, according to which suitably protected *O*-glycosylated amino acids are used as building blocks in stepwise assembly of glycopeptides, has been shown to be more reliable and efficient, and is also well suited for synthesis on solid

phase. Protective groups used for the glycosylated amino acid building blocks have to be chosen considering both the lability of glycosidic bonds towards acids and the tendency of peptides glycosylated on serine and threonine to undergo β-elimination on treatment with strong base.[8,9] Preferably, the fluoren-9-ylmethoxycarbonyl (Fmoc) group[10] is used for protection of the α-amino group, whereas the hydroxyl groups of the carbohydrate should carry acetyl or benzoyl groups that stabilize the glycosidic bonds towards the acidic conditions used for cleavage from the resin and side-chain deprotection. Fears of β-elimination or racemization during the mild basic conditions used for N^{α}-Fmoc deprotection and removal of *O*-acyl groups have been shown to be exaggerated.[11,12]

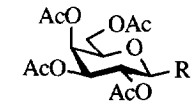
Previous approaches to glycosylated amino acids have all relied on glycosylation of amino acids protected at both the α-carboxyl and α-amino groups.[8,9] In most cases several subsequent steps, which lowered the overall yield, such as exchange of protective groups used for the α-amino group and the carbohydrate hydroxyl groups, and selective removal of the α-carboxyl protective group followed by activation, were then required to produce the desired building block in a form suitable for further use in glycopeptide synthesis. An attractive alternative which avoids such manipulations of protective groups involves glycosylation of N^{α}-Fmoc protected amino acid pentafluorophenyl esters.[9] The pentafluorophenyl ester serves as a protective group during the glycosylation but is reactive enough to allow formation of an amide bond.

It occurred to us that glycosylation of reactive hydroxyl and mercapto groups in N^{α}-Fmoc amino acids, without prior protection of the α-carboxyl group, would give a simple and convenient route to glycosylated amino acids. If commercial, or readily available[13,14], 1,2-*trans* 1-*O*-acetyl sugars were used as glycosyl donors in the presence of a Lewis acid promoter, 1,2-*trans* glycosylated amino acids carrying the protective groups of choice for glycopeptide synthesis would be formed as main products. Glycosyl esters formed in reactions between the carboxyl group of the amino acid and the glycosyl donor should, in the presence of the Lewis acid, rearrange to the desired *O*- and *S*-glycosylated amino acids. Previously, 1,2-*trans*-1-*O*-acetylated saccharides have been used for preparation of β-*O*-glycosides in the D-galactose and glucose series and also for synthesis of α-D-mannosides, using a range of Lewis acids as promotors.[15]

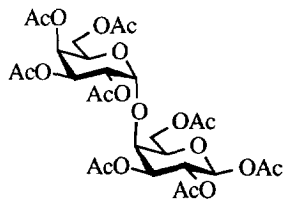
RESULTS

In a model study[16], glycosylation of 3-mercaptopropionic acid with β-D-galactose pentaacetate (**1**) gave the β-thioglycoside **2**[17] in 90% yield when boron trifluoride etherate[18] was used as promoter. The propionate **3** was formed as an intermediate in the glycosylation, but rearranged to the thioglycoside **2** within 1 h. Molecular sieves should be avoided in the reaction since they prevented rearrangement of **3**, most likely due to adsorption of the boron trifluoride etherate. Attempts to use a carbohydrate peracetate with a 1,2-*cis*-galacto configuration as glycosyl donor for coupling to 3-mercaptopropionic acid resulted in a lowering of both yield and stereoselectivity in the reaction[16], in agreement with previous observations[19].

Using boron trifluoride etherate as promoter 3-mercaptopropionic acid glycosides of the disaccharides cellobiose, lactose, and galabiose were obtained in 62-90% yields from the corresponding disaccharide β-D-octaacetates.[20] The 3-mercaptopropionic acid glycosides were then used in solid phase synthesis of glycosylated derivatives of helper-T-cell immunogenic peptides.[20]



1 R = OAc
2 R = $S(CH_2)_2CO_2H$
3 R = $OOC(CH_2)_2SH$



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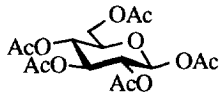

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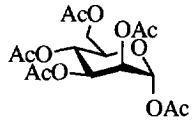

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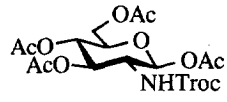

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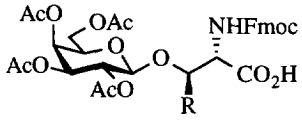
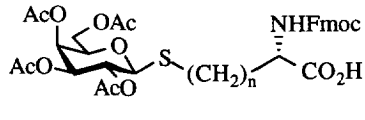
Troc = 2,2,2-Trichloroethoxycarbonyl

Glycosylation of amino acids were investigated in a series of reactions of β-D-galactose pentaacetate (**1**) with N^{α}-Fmoc serine, threonine, cysteine (**8**) and homocysteine (**9**), respectively (Table 1). In these reactions boron trifluoride etherate[18] and tin(IV) chloride[21] were used as promoters in combinations with dichloromethane and acetonitrile as solvents. In general, reactions reached completion within 1 h using either of the promoters. Only minor variations in yields were obtained for the *O*-linked glycosides of serine and threonine, **10** and **11**, but acetonitrile was preferred as solvent since it dissolved the Fmoc amino acids better than dichloromethane. The synthesis of compounds **10** and **11** revealed that both primary and secondary amino acid alcohols could be glycosylated in satisfactory yields (50-60%). For the *S*-linked glycosides of cysteine and homocysteine, **12** and **13**, use of tin(IV) chloride in dichloromethane was found to give significantly better yields (59 and 65%, respectively) than when tin(IV) chloride in acetonitrile or boron trifluoride etherate in dichloromethane were used. When carbohydrate peracetates have been used in boron trifluoride etherate promoted glycosylations of derivatives of serine and threonine protected at both the α-amino and the α-carboxyl group, lower yields (based on the glycosyl donor) were obtained[5,22,23] than in the present study.

The silver salt catalyzed Koenigs-Knorr reaction of glycopyranosyl bromides has been commonly employed for preparation of β-*O*-glycosylated amino acids.[8,9] The procedure gives high yields in glycosylations of amino acids protected at both the amino and carboxyl groups. Silver trifluoromethanesulfonate promoted coupling of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with N^{α}-Fmoc serine was therefore attempted. However, the desired glycoside **10** was obtained in only 28% yield, revealing the advantage of using carbohydrate 1,2-*trans* peracetates as glycosyl donors in glycosylations of Fmoc amino acids having unprotected carboxyl groups.



10 R = H (Ser)
11 R = Me (Thr)



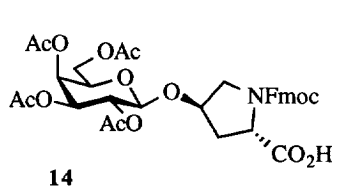
12 n = 1 (Cys)
13 n = 2 (homoCys)

Table 1. Influence of Promoter and Solvent on the Glycosylation of *N*α-Fmoc-Ser, Thr, Cys, and homoCys with β-D-Galactose Pentaacetate (**1**).[a]

Promoter	Solvent	Yield[b] (%) **10**	**11**	**12**	**13**
$BF_3{\cdot}Et_2O$	CH_2Cl_2	49	-[c]	34	45
$BF_3{\cdot}Et_2O$	CH_3CN	<u>53</u>	50	-[c]	-[c]
$SnCl_4$	CH_2Cl_2	-[c]	-[c]	<u>59</u>	<u>65</u>
$SnCl_4$	CH_3CN	46	<u>58</u>	33	-[c]

[a]The pentaacetate **1** was reacted with 1.2 molar equivalents of Fmoc amino acid and either 3 equivalents of $BF_3{\cdot}Et_2O$ or 1.3 equivalents of $SnCl_4$. Reactions were terminated after 1h. Detailed reaction conditions are given in the experimental. [b]Yields were determined after purification with reversed phase HPLC. The best yields for each product are underlined. [c]Not attempted.

The syntheses of compounds **14-23** were undertaken to further exemplify the versatility of boron trifluoride etherate promoted glycosylations of Fmoc amino acids with 1,2-*trans* sugar peracetates as a direct route to glycosylated amino acid building blocks (Table 2). The glycosylated amino acids **14-23** were chosen as model compounds since they occur in glycopeptides and glycoproteins of biological importance. For instance, incorporation of *trans*-4-hydroxyproline carrying a β-D-galactosyl residue (cf. **14**) in the opioid agonist morphiceptin was found to increase the analgetic activity 200—2000-fold.[3] T-cell immunogenic glycopeptides containing the disaccharide galabiose [Galα(1-4)Gal] linked to serine (cf. **15**) have been shown to give a carbohydrate specific helper T cell response in mice.[24] In bovine blood clotting factor a novel connection of a trisaccharide to the main polypeptide chain by a β-D-glucosyl-*O*-serine linkage (cf. **16**) has been identified.[25] The glycosylated analogue of human insulin-like growth factor-I, expressed from yeast together with the native form, was found to contain an α-D-mannosyl-*O*-threonine linkage (cf. **17**).[26] Multiple 2-acetamido-2-deoxy-β-D-glucopyranosyl-*O*-serine residues (cf. **19**) are common in glycoproteins found in the cytoplasm and the nucleus.[27] Finally, cell surface layer (S-layer) glycoproteins of anaerobic eubacteria carry oligosaccharides in which β-D-galactose and β-D-glucose residues are linked to the phenolic hydroxyl group of tyrosine (cf. **21** and **23**).[28,29]



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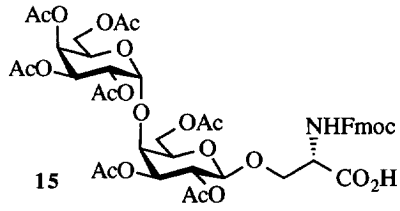

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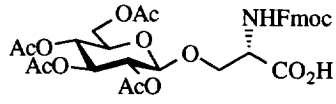

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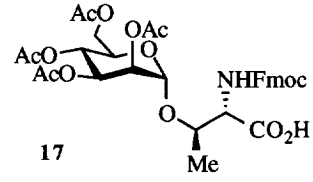

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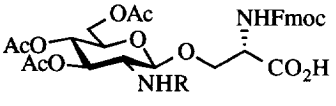
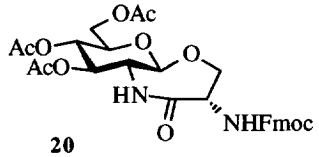


18 R = Troc
19 R = Ac



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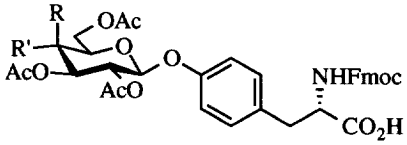

21 R = AcO, R' = H
23 R = H, R' = AcO

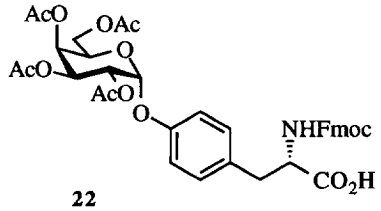

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Table 2. Glycosylation of Fmoc Amino Acids using Boron Trifluoride Etherate Promotion.[a]

Entry	Fmoc Amino Acid	Carbohydrate Peracetate	Solvent	Reaction Time (h)	Product (%)	Yield[b]
1	Fmoc-Hyp-OH	**1** (Gal)	CH_3CN	1.5	**14**	51
2	Fmoc-Ser-OH	**4** (GalGal)	CH_3CN	1.25	**15**[20]	64
3	Fmoc-Ser-OH	**5** (Glc)	CH_2Cl_2	18.5	**16**	37
4	Fmoc-Thr-OH	**6** (Man)	CH_2Cl_2	20	**17**	42
5	Fmoc-Ser-OH	**7** (GlcN)	CH_2Cl_2	5	**18/19**	70[c]/33[d]
6	Fmoc-Tyr-OH	**1** (Gal)	CH_2Cl_2	4	**21**	34
7	Fmoc-Tyr-OH	**1** (Gal)	CH_3CN	3	**22/21**	19/10
8	Fmoc-Tyr-OH	**5** (Glc)	CH_2Cl_2	8	**23**	41

[a]The carbohydrate peracetates were reacted with 1.2 molar equivalents of Fmoc amino acid and 3 equivalents of BF_3-Et_2O. Detailed reaction conditions are given in the experimental. [b]Yields were determined after purification by reversed phase HPLC. [c]Yield of **18** based on the carbohydrate peracetate **7**. [d]Yield of **19** based on **7**.

Boron trifluoride etherate promoted glycosylation of the secondary hydroxyl group in N^{α}-Fmoc-*trans*-4-hydroxyproline with β-D-galactose pentaacetate **1** gave the β-glycoside **14** (Table 2, entry 1). Acetonitrile was used as solvent due to the low solubility of the hydroxyproline in dichloromethane and **14** was obtained in a yield (51%) comparable to those obtained for the galactosides of serine, **10**, and threonine, **11**, under identical reaction conditions. A significant amount (15-20%) of *O*-acetylated hydroxyproline [N^{α}-Fmoc-Hyp(OAc)-OH] was obtained as a side product in the glycosylation. This indicates an orthoester as an intermediate in the glycosylation since orthoesters have been shown to rearrange with *O*-acetylation of the glycosyl acceptor under Lewis acid catalysis.[30,31] When a threefold excess of pentaacetate **1** was used, *O*-acetylation of Fmoc-hydroxyproline increased and the yield of **14** decreased to 30%. The β-glycoside **14** has previously been prepared in a lower overall yield via a multi-step procedure involving manipulations of protective groups both at the α-amino and α-carboxyl groups.[32]

Glycosylation of N^{α}-Fmoc serine with β-D-galabiose octaacetate (**4**), under conditions identical to those described in the present paper, has previously been reported[20] to give **15** (64%, Table 2, entry 2). This illustrates that larger peracetylated saccharides give similar, or even higher, overall yields in glycosylations of Fmoc amino acids as monosaccharides.

When β-D-glucose pentaacetate (**5**) was used for glycosylation of N^{α}-Fmoc serine to give **16**, a longer reaction time was required and a lower yield (37%) was obtained, than in the formation of the analogous galactoside (**10**) (compare Table 2, entry 3 with Table 1). In comparison, a higher yield (62%) was reported[33] when the disaccharide 1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-β-D-glucopyranose was used in a boron trifluoride etherate mediated glycosylation of Fmoc serine. This again illustrates that disaccharides give at least as high yields in the glycosylations, and provides yet another example of the well known sensitivity of glycosylations to the pattern of substituents on the reacting components[15,34].

Neighbouring group participation in the coupling of α-D-mannose pentaacetate **6** to N^{α}-Fmoc threonine gave the α-glycoside **17** (42%, Table 2, entry 4). The stereochemistry of the *O*-glycosidic linkage in **17** was determined from the $^{1}J_{C\text{-}1,H\text{-}1}$ coupling constant which has been found[35] to be *ca.* 170 Hz for α-glycosides and *ca.* 160 Hz for β-glycosides (172 Hz was obtained for **17**). The progress of reaction between **6** and Fmoc threonine was monitored by analytical HPLC, and at short reaction times the glycoester 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl N^{α}-Fmoc-threoninoate was formed as the major product as revealed by ^{1}H NMR spectroscopy ($\delta_{H\text{-}1}$ = 6.16 ppm, as compared to 4.94 ppm in **17**). Conversion of the glycoester to the desired α-mannoside **17** was achieved by use of a larger than normal excess of boron trifluoride etherate (9 equivalents) and a prolonged reaction time (20 h). Dichloromethane was preferred as solvent since substantial *O*-acetylation of N^{α}-Fmoc-Thr-OH occurred in acetonitrile.

The *N*-trichloroethoxycarbonyl (Troc) glucosamine 1-*O*-acetate **7** was recently shown to be a most versatile glycosyl donor in boron trifluoride etherate promoted glycosylations[36], and gave the β-glycoside **18** in high yield on reaction with N^{α}-Fmoc serine (Table 2, entry 5). Reductive cleavage of the Troc-group using zinc in acetic acid followed by *N*-acetylation with acetic anhydride then gave the GlcNAc-*O*-serine building block **19** (33% from **7**, 47% from **18**). During the *N*-acetylation the lactam **20** was formed (25% from **18**) as a side product. The direct boron trifluoride etherate promoted glycosylation of Fmoc serine with 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose was recently reported to give **19** in a slightly lower yield, based on the amount of glycosyl donor used in the reaction.[37]

The lower nucleophilicity of a phenolic, as compared to an aliphatic hydroxyl group, makes glycosylations of tyrosine more difficult than of serine and threonine. As expected, glycosylation of N^{α}-Fmoc tyrosine with β-D-galactose pentaacetate (**1**) required longer time to reach completion, and gave a lower yield (34%), as compared to the glycosylations of Fmoc serine and threonine (compare Table 2, entry 6 with Table 1). Unlike the glycosylations of aliphatic hydroxyl groups in amino acids, the anomeric ratio of the product was significantly affected by the solvent. In dichloromethane, the β-galactoside **21** was obtained as the main product, and the β/α ratio was 45/2 according to analytical HPLC. In contrast, when acetonitrile was used as solvent the β- and α-glycosides **21** and **22** were obtained in a 1:2 ratio (Table 2, entry 7) together with an appreciable amount (20%) of *O*-acetylated tyrosine [N^{α}-Fmoc-Tyr(OAc)-OH]. A similar loss of stereoselectivity has previously been observed on replacement of dichloromethane with acetonitrile as solvent in the silver triflate promoted reactions of allyl and pentafluorophenyl esters of Fmoc tyrosine with perbenzoylated or peracetylated glucosyl bromides.[38]

To avoid loss of diastereoselectivity and problems with *O*-acetylation of the glycosyl acceptor, dichloromethane was used as solvent in the coupling of β-D-glucose pentaacetate **5** to N^{α}-Fmoc tyrosine and the β-glucoside **23** was obtained as the main product (41%, Table 2, entry 8). A longer reaction time was required for coupling of glucose pentaacetate **5** to Fmoc tyrosine than for galactose pentaacetate **1**, as was also observed in the synthesis of the corresponding glycosides of Fmoc serine (**16** and **10**).

DISCUSSION

In the present work we have shown that hydroxyl and mercapto groups in the side chains of Fmoc amino acids can be glycosylated without prior protection of the amino acid carboxyl group when Lewis acids are used as promoters. The Fmoc amino acids and carbohydrate 1,2-*trans* peracetates which were used as starting materials are either commercially available, or can be readily prepared[13,14]. Formation of *O*- and *S*-glycosides was performed under standardized conditions with boron trifluoride etherate[18] (*O*-glycosides) or tin(IV) chloride[21] (*S*-glycosides) as promoter and dichloromethane or acetonitrile as solvent. Dichloromethane was preferred to acetonitrile, which led to more *O*-acetylation of the Fmoc amino acid, but acetonitrile had to be used in cases when the Fmoc amino acid was sparingly soluble in dichloromethane. Products were preferably purified by chromatography on reversed phase and not on silica gel. Under these conditions glycosylated building blocks with the protective groups of choice (*i.e.* *O*-acetyl and N^{α}-Fmoc) for direct use in stepwise glycopeptide synthesis, in solution or on solid phase, were obtained without further manipulations of protective groups. The simplicity of the method thus allows glycosylated amino acid building blocks to be prepared also in research groups with no previous experience of the diverse array of variables (protective groups, types of glycosyl donors, catalysts, etc.) that normally need to be fine tuned by the synthetic carbohydrate chemist.

Yields in the direct glycosylations of Fmoc amino acids ranged from 34 to 65%, and in general lower yields were obtained for glycosylations of Fmoc tyrosine than for aliphatic amino acids. When used as glycosyl donor, β-D-galactose pentaacetate **1** gave higher yields than the peracetates of glucose and mannose, **5** and **6**. Interestingly, disaccharide peracetates were found to give at least as high yields as monosaccharide peracetates. Comparison of yields with methods that require manipulations of protective groups after the glycosylation in order to give useful building blocks is difficult. On the other hand, glycosylation of N^{α}-Fmoc

protected amino acid pentafluorophenyl esters[9], in common with the method presented here, gives building blocks that can be used directly for synthesis of glycopeptides. Recently, the pentafluorophenyl ester corresponding to compound **23** was prepared[38] in a yield almost identical to that obtained for **23**, after taking into account that an excess of glycosyl donor was used for glycosylation of the pentafluorophenyl ester. Pentafluorophenyl ester analogues of compounds **16** and **21** carrying benzoyl protective groups on the carbohydrate moieties have also been prepared.[39,40] As expected[41], the use of benzoyl protective groups led to increased yields (~10% higher, when based on the glycosyl donor) than obtained in the syntheses of **16** and **21** where acetyl protective groups were employed.

The synthesis of 1,2-*trans* glycosides from glycosyl halides that have participating acyl protective groups at O-2 is considered to involve orthoesters as intermediates.[30,31] Rearrangement of the orthoester can occur via a cyclic 1,2-*cis* dioxocarbenium ion, which directs formation of the 1,2-*trans* glycoside, or via a pathway leading to acylation of the glycosyl acceptor.[30,31] The observation of *O*-acetylation in the preparations of **14**, **17** and **21**, as well as the predominant formation of 1,2-trans glycosides, suggests that orthoesters are intermediates in the boron trifluoride etherate mediated glycosylations of Fmoc amino acids.

The formation of the glycoester 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl N^{α}-Fmoc-threoninoate as an intermediate in the synthesis of the mannoside **17** revealed that the unprotected carboxyl group of the Fmoc amino acid competes with the hydroxyl group for attack on the 1,2-*cis* dioxocarbenium ion, but that the glycoester is sufficiently reactive to rearrange to the desired product on prolonged reaction. It is also noteworthy that when formed, β-glycosides of amino acids do not undergo Lewis acid mediated anomerization to the thermodynamically more stable α-glycosides. Such a stability has also been observed[42] for *O*-acetylated dibromoisobutyl and bromoethyl glycosides in contrast to ordinary alkyl glycosides which undergo more facile anomerization.

According to Paulsen[34], the cyclic 1,2-*cis* dioxocarbenium ion is in equilibirum with the less stable oxocarbenium ion, which in the presence of only moderately reactive alcohols reacts to give a mixture of α- and β-glycosides[34,31]. Polar solvents tend to give increased amounts of α-glycosides which may be related to their greater ability to stabilize the oxocarbenium ion.[31] The preferred formation of the α-glycoside **22** from N^{α}-Fmoc tyrosine and β-D-galactose pentaacetate (**1**) in acetonitrile may be due to the lower nucleophilicity of the phenolic hydroxyl group as compared to aliphatic alcohols, and to the greater ionizing power of acetonitrile relative to dichloromethane. As suggested for silver triflate promoted reactions of esters of N^{α}-Fmoc tyrosine with perbenzoylated or peracetylated glucosyl bromides the formation of anomeric product mixtures may also involve nitrilium-nitrile complexes.[38]

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Varian XL-300 spectrometer or at 500 MHz, with a Bruker ARX-500 spectrometer, for solutions in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) and $CDCl_3$ (δ_C 77.0 ppm) as internal standards], acetone-d_6 [residual acetone-d_5 (δ_H 2.05 ppm) and acetone-d_6 (δ_C 29.8 ppm)], and Me_2SO-d_6 [residual Me_2SO-d_5 (δ_H 2.50 ppm)]. First-order chemical shifts and coupling constants were obtained from one-dimensional spectra and proton resonances were assigned from COSY[43] experiments. Proton resonances that could not be assigned are not reported. Optical rotations were measured in $CHCl_3$, except when otherwise indicated, using a Perkin-Elmer 141

polarimeter. High resolution positive fast atom bombardment mass spectra (HRMS) were recorded on a Jeol SX 102 mass spectrometer. Ions were produced by a beam of xenon atoms (6 keV) from a matrix of 3-nitrobenzyl alcohol.

Preparative HPLC separations were performed on a Beckman System Gold HPLC using a Kromasil C-8 column (1000 Å, 20 x 250 mm) with a flow rate of 10-16 mL/min and detection at 214 nm. Solvent systems A: 0.1% aqueous trifluoroacetic acid and B: 0.1% trifluoroacetic acid in acetonitrile were used. A Kromasil C-8 column (4.6 x 250 mm) and a flow rate of 1.5 mL/min was used for analytical HPLC separations. Thin layer chromatography was performed on silica gel 60 F_{254} (Merck) with detection by UV light and charring with sulfuric acid. Immediately before being used, CH_2Cl_2 was dried by distillation from calcium hydride, and CH_3CN was passed through a column of neutral aluminium oxide (activity 1). Organic solutions were dried over Na_2SO_4.

N^{α}-Fmoc-L-serine, -L-threonine, -L-tyrosine and -L-cystine were purchased from Bachem Feinchemikalien AG (Switzerland) and L-homocystine was purchased from Fluka (Switzerland). N^{α}-Fmoc-*trans*-4-hydroxy-L-proline[44] (N^{α}-Fmoc-Hyp-OH) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2',2',2'-trichloroethoxycarbonylamino)-β-D-glucopyranose[36] (**7**) were prepared as reported previously in the literature.

General procedure for glycosylation of N^{α}*-Fmoc amino acids.*

The Lewis acid ($SnCl_4$: 20 µL, 170 µmol or $BF_3{\cdot}Et_2O$: 49 µL, 390 µmol, except for **17** where 154 µL $BF_3{\cdot}Et_2O$ was used) was added to the 1,2-*trans* peracetylated monosaccharide (50.7 mg, 130 µmol) and the N^{α}-Fmoc amino acid (156 µmol) in dry CH_2Cl_2 (2-2.5 mL) or CH_3CN (1.5 mL) under a nitrogen atmosphere at room temperature. The reaction was monitored by TLC and analytical HPLC. When the reaction did not progress further, the mixture was diluted with CH_2Cl_2 (8 mL), washed with 1 M aqueous HCl (1 mL) and water (1 mL), dried, and concentrated. The residue was purified in two portions by preparative HPLC.

N^{α}*-(9-Fluorenylmethoxycarbonyl)-*L*-cysteine (**8**).* A mixture of N^{α}-Fmoc-L-cystine (0.5 g, 0.72 mmol) and zinc (1.0 g, 15.3 mmol) in HOAc (10 ml) and MeOH (20 ml) was stirred at room temperature for 3 days. During the reaction a white precipitate formed. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with 2 M aqueous HCl (30 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried, filtered, and concentrated to give **8** (0.5 g): ^{1}H NMR (300 MHz, acetone-d_6) δ 3.00 (m, 2H, H-β), 4.26 (t, 1H, J = 7.6 Hz, Fmoc CHAr), 4.38 (d, 2H, J = 7.2 Hz, Fmoc OCH_2), 4.49 (m, 1H, H-α), 6.80 (d, 1H, J = 7.1 Hz, NH).

N^{α}*-(9-Fluorenylmethoxycarbonyl)-*L*-homocysteine (**9**).* A solution of 9-fluorenylmethyl chloroformate (78 mg, 300 µmol) in dioxane (650 µL) was added dropwise during 15 min to a solution of L-homocystine (40 mg, 149 µmol) in 10% aqueous Na_2CO_3 (900 µL) and dioxane (450 µL) at 0 °C. The solution was stirred at 0 °C for 1 h and at room temperature for a further 2 h. The solution was diluted with EtOAc (8 mL) and washed with 2 M aqueous HCl (8 mL). The aqueous phase was extracted with EtOAc (3 x 8 mL) and the combined organic phases were dried, filtered, and concentrated. Precipitation from EtOAc and heptane gave amorphous Fmoc-L-homocystine (86 mg, 121 µmol) which was dissolved in HOAc (1 mL) and MeOH (2.5 mL), then treated with zinc (200 mg, 3.06 mmol) at room temperature for 3 days. During the reaction a white precipitate formed. The reaction was washed as described for **8** to give **9** (83 mg, 78%): ^{1}H NMR (300 MHz, acetone-d_6)

δ 2.66 (m, 2H, H-γ), 4.25 (t, 1H, *J* = 7.1 Hz, Fmoc CHAr), 4.36 (d, 2H, *J* = 7.2 Hz, Fmoc OCH_2), 4.45 (m, 1H, H-α), 6.81 (d, 1H, *J* = 7.1 Hz, NH).

N^{α}-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*galactopyranosyl)-*L-*serine* ***(10)***. Compound **10** was prepared by reaction of monosaccharide **1** (50 mg, 128 μmol) with N^{α}-Fmoc-Ser-OH (50.3 mg, 154 μmol) for 1 h 5 min in CH_3CN (1.5 mL) under $BF_3{\cdot}Et_2O$ promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 45% B in A) gave **10** (45 mg, 53%): $[\alpha]^{20}_D$ +0.8° (*c* 0.6); ^1H NMR (500 MHz, acetone-d_6) δ 1.92, 1.98, 1.98, and 2.12 (4s, 3H each, Ac), 3.97 (dd, 1H, *J* = 4.0, 10.6 Hz, H-β), 4.14 (2d, 1H each, *J* = 5.8 and *J* = 7.3 Hz, H-6,6'), 4.20 (t, 1H, *J* = 6.0 Hz, H-5), 4.23 (dd, 1H, *J* = 4.9, 9.5 Hz, H-β), 4.27 (t, 1H, *J* = 7.2 Hz, Fmoc CHAr), 4.40 (m, 1H, Fmoc OCH_2), 4.47 (m, 1H, H-α), 4.77 (d, 1H, *J* = 6.9 Hz, H-1), 5.09-5.15 (m, 2H, H-2,3), 5.39 (dd, 1H, *J* = 1.2, 3.1 Hz, H-4), 6.32 (d, 1H, *J* = 8.2 Hz, NH); HRMS $(M + H)^+$ calcd 658.2136, obsd 658.2132.

N^{α}-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*galactopyranosyl)-*L-*threonine* ***(11)***. Compound **11** was prepared by reaction of monosaccharide **1** (50 mg, 128 μmol) with N^{α}-Fmoc-Thr-OH (52.5 mg, 154 μmol) for 1 h in CH_3CN (1.5 mL) under $SnCl_4$ promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 45% B in A) gave **11** (50 mg, 58%): $[\alpha]^{20}_D$ -9.5° (*c* 0.7); ^1H NMR (500 MHz, acetone-d_6) δ 1.27 (d, 3H, *J* = 6.3 Hz, H-γ), 1.92, 1.98, 2.04, and 2.11 (4s, 3H each, Ac), 4.12 (d, 2H, *J* = 11.0 Hz, H-6), 4.20 (t, 1H, *J* = 6.8 Hz, H-5), 4.28 (t, 1H, *J* = 7.2 Hz, Fmoc CHAr), 4.31 (dd, 1H, *J* = 2.4, 9.1 Hz, H-α), 4.37 (d, 2H, *J* = 7.3 Hz, Fmoc OCH_2), 4.51 (bdd, 1H, *J* = 2.6, 6.2 Hz, H-β), 4.83 (d, 1H, *J* = 7.9 Hz, H-1), 5.07 (dd, 1H, *J* = 7.9, 10.5 Hz, H-2), 5.16 (dd, 1H, *J* = 3.5, 10.5 Hz, H-3), 5.39 (d, 1H, *J* = 2.9 Hz, H-4), 6.03 (d, 1H, *J* = 9.0 Hz, NH); HRMS $(M + H)^+$ calcd 672.2292, obsd 672.2291.

N^{α}-*(9-Fluorenylmethoxycarbonyl)-3-*S-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*galactopyranosyl)-*L-*cysteine* ***(12)***. Compound **12** was prepared by reaction of monosaccharide **1** (50 mg, 128 μmol) with **8** (52.8 mg, 154 μmol) for 1 h in CH_2Cl_2 (2.0 mL) under $SnCl_4$ promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 50% B in A) gave **12** (48 mg, 59%): $[\alpha]^{20}_D$ +1.7° (*c* 4.0); ^1H NMR (500 MHz, acetone-d_6) δ 1.93, 1.95, 2.00, and 2.10 (4s, 3H each, Ac), 3.01 (dd, 1H, *J* = 8.8, 14.1 Hz, H-β), 3.43 (dd, 1H, *J* = 3.7, 14.2 Hz, H-β), 4.13 (d, 2H, *J* = 8.0 Hz, H-6,6'), 4.21 (t, 1H, *J* = 6.4 Hz, H-5), 4.29 (t, 1H, *J* = 7.0 Hz, Fmoc CHAr), 4.34 (dd, 1H, *J* = 7.2, 10.4 Hz, Fmoc OCH_2), 4.40 (dd, 1H, *J* = 7.2, 10.3 Hz, Fmoc OCH_2), 4.54 (m, 1H, H-α), 4.90 (d, 1H, *J* = 9.3 Hz, H-1), 5.19 (dd, 1H, *J* = 3.2, 10.0 Hz, H-3), 5.23 (t, 1H, *J* = 9.1 Hz, H-2), 5.43 (d, 1H, *J* = 2.3 Hz, H-4), 6.79 (d, 1H, *J* = 8.0 Hz, NH); HRMS $(M + H)^+$ calcd 674.1908, obsd 674.1907.

N^{α}-*(9-Fluorenylmethoxycarbonyl)-4-*S-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*galactopyranosyl)-*L-*homocysteine* ***(13)***. Compound **13** was prepared by reaction of monosaccharide **1** (35.6 mg, 91.2 μmol) with **9** (39.1 mg, 109 μmol) for 1 h in CH_2Cl_2 (1.4 mL) under $SnCl_4$ promotion (14 μL, 119 μmol) according to the general procedure. Purification of the crude product by HPLC (isocrat, 48% B in A) gave **13** (41 mg, 65%): $[\alpha]^{20}_D$ -0.5° (*c* 2.7); ^1H NMR (500 MHz, acetone-d_6) δ 1.93, 1.97, and 2.03 (3s, 3H each, Ac), 2.12 (s, 4H, Ac and H-β), 2.29 (m, 1H, H-β), 2.76 (m, 1H, H-γ), 2.96 (m, 1H, H-γ), 4.08-4.14 (m, 2H, H-6,6'), 4.21 (t, 1H, *J* = 6.4 Hz, H-5), 4.25 (t, 1H, *J* = 7.1 Hz, Fmoc CHAr), 4.36 (m, 2H, Fmoc OCH_2), 4.44 (m, 1H, H-α), 4.85 (d, 1H, *J*

= 9.0 Hz, H-1), 5.17 (dd, 1H, J = 3.3, 9.9 Hz, H-3), 5.20 (t, 1H, J = 9.9 Hz, H-2), 5.43 (dd, 1H, J = 1.0, 3.0 Hz, H-4), 6.78 (d, 1H, J = 8.1 Hz, NH); HRMS (M + H)$^+$ calcd 688.2064, obsd 688.2058.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-4-*O-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*galactopyranosyl)-*trans-*4-hydroxy-*L-*proline (14)* . Compound **14** was prepared by reaction of monosaccharide **1** (50.3 mg, 129 μmol) with N^{α}-Fmoc-Hyp-OH (55.1 mg, 156 μmol) for 1h 35 min in dry CH_3CN (1.5 mL) under $BF_3{\cdot}Et_2O$ promotion according to the general procedure. Purification of the crude product by HPLC (gradient, 25-80% B in A during 40 min) gave **14** (45 mg, 51%): ^{1}H and ^{13}C NMR data were in agreement with those reported[32]; HRMS (M + H)$^+$ calcd 684.2292, obsd 684.2316.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2,3,4,6-tetra-*O-*acetyl-β-*D-*glucopyranosyl)-*L *-serine (16).* Compound **16** was prepared by reaction of monosaccharide **5** (50.9 mg, 130 μmol) and N^{α}-Fmoc-L-serine (51.5 mg, 156 μmol) for 18.5 h in CH_2Cl_2 (2.5 mL) under $BF_3{\cdot}Et_2O$ promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 50% A in B) gave **16** (31.4 mg, 37%): $[\alpha]^{20}_D$ +21° (*c* 0.91); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.94, 1.96, 1.99, and 2.01 (4s, 3H each, Ac), 4.12 (dd, 1H, J = 12.3, 2.4 Hz, H-6), 4.45 (m, 1H, H-α), 4.82 (d, AB type, 1H, J = 8.1 Hz, H-1), 4.89 (dd, AB type, 1H, J = 9.3, 8.0 Hz, H-2), 5.03 (t, 1H, J = 9.7 Hz, H-4), 5.26 (t, 1H, J = 9.4 Hz, H-3), 6.42 (d, 1H, J = 8.0 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 47.1 (Fmoc CHAr), 61.7 (C-6), 67.1, 68.3, 69.8, 71.1, 71.9, and 72.5 (C-2,3,4,5, Fmoc OCH_2, C-β), 101.2 (C-1); HRMS (M + H)$^+$ calcd 658.2136, obsd 658.2161.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2,3,4,6-tetra-*O-*acetyl-α-*D-*mannopyranosyl)-*L-*threonine (17)* . Compound **17** was prepared by reaction of monosaccharide **6** (53.1 mg, 136 μmol) and N^{α}-Fmoc-L-threonine (56.1 mg, 164 μmol) for 20 h in CH_2Cl_2 (2.5 mL) under $BF_3{\cdot}Et_2O$ promotion (154 μL,1.23 mmol) according to the general procedure. Purification of the crude product by HPLC (isocrat, 50% A in B) gave **17** (38.5 mg, 42%): $[\alpha]^{20}_D$ +41° (*c* 0.67); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.4 Hz, H-γ), 1.99, 2.03, 2.08, and 2.12 (4s, 3H each, Ac), 4.54 (bd, 1H, J = 9.0 Hz, H-α), 4.94 (bs, 1H, H-1), 5.08 (bs, 1H, H-2), 5.23-5.29 (complex, 2H, H-3,4), 5.96 (d, 1H, J = 9.6 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 17.9 (C-γ), 47.1 (Fmoc CHAr), 62.5 (C-6), 66.1 (C-4), 67.4 (Fmoc OCH_2), 69.1, 69.8, and 76.8 (C-2,3,5), 77.8 (C-β), 98.7 (C-1, $^1J_{CH}$ = 172 Hz), 156.7 (carbamate); HRMS (M + H)$^+$ calcd 672.2292, obsd 672.2297.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2-deoxy-2-(2',2',2'-trichloroethoxycarbonylamino)-3,4,6-tri-*O-*acetyl-β-*D-*glucopyranosyl)-*L-*serine (18).* Compound **18** was prepared by reaction of monosaccharide **7** (68.4 mg, 131 μmol) and N^{α}-Fmoc-L-serine (51.7 mg, 157 μmol) for 5 h in CH_2Cl_2 (2.5 mL) under $BF_3{\cdot}Et_2O$ promotion (49.5 μL, 394 μmol) according to the general procedure. Purification of the crude product by HPLC (gradient, 40-100% B in A during 50 min) gave **18** (72.6 mg, 70%). Spectral data were in agreement with those reported.[36]

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2-acetamido-2-deoxy-3,4,6-tri-*O-*acetyl-β-*D-*glucopyranosyl)-*L-*serine (19)* and N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)-3-*O-*(2-amino-2-deoxy-3,4,6-tri-*O-*acetyl-β-*D-*glucopyranosyl)-*L-*serine 1,2'-lactam (20).* A mixture of compound **18** (63.8 mg, 81 μmol) and zinc dust (113 mg) in acetic acid (1.6 mL) was stirred at room temperature for 8.5 h. Then acetic anhydride (1.6 mL) was

added and after 13h the mixture was filtered, the residue washed with acetic acid (5 mL) and the combined filtrates were concentrated. Purification of the residue by flash column chromatography (heptane-ethyl acetate, 1:2 then heptane-ethyl acetate-acetic acid, 2:17:1) gave **19** (25 mg, 47%, 33% from **7**) and the lactam **20** (12 mg, 25%).

Compound **19** had $[\alpha]^{20}_D$ -7.9° (*c* 0.70, MeOH) [lit.[37] $[\alpha]^{22}_D$ +27.8° (*c* 1, MeOH)]; ^{1}H NMR (500 MHz, Me_2SO-d_6) δ 1.73 (s, 3H, NAc), 1.90, 1.97, and 2.00 (3s, 3H each, Ac), 3.69 (q, 1H, *J* = 10 Hz, H-2), 3.83 (brd, 1H, *J* = 9.0 Hz, H-5), 4.71 (d, 1H, *J* = 8.6 Hz, H-1), 4.83 (t, 1H, *J* = 9.7 Hz, H-4), 5.09 (t, 1H, *J* = 9.9 Hz, H-3), 7.85 (d, 1H, *J* = 8.8 Hz, NHAc); HRMS $(M + Na)^+$ calcd 679.2115, obsd 679.2140. Since the optical rotation for **19** did not agree with that previously reported[37], **19** was converted to the corresponding pentafluorophenyl ester which had ^{1}H NMR data and optical rotation as reported in the literature[45].

Compound **20** had $[\alpha]^{20}_D$ +29° (*c* 0.86); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 and 2.12 (2s, 3H and 6H, Ac), 3.64-3.68 (m, 2H, H-β and H-2), 3.76 (m, 1H, H-5), 4.42 (d, 2H, *J* = 6.1 Hz, Fmoc OCH_2), 4.55 (d, 1H, *J* = 7.4 Hz, H-1), 4.61 (brs, 1H, H-α), 5.08 (t, 1H, *J* = 9.7 Hz, H-3), 5.17 (t, 1H, *J* = 9.5 Hz, H-4), 5.96 (brs, 1H, NHFmoc), 6.40 (brs, (1H, NHAc); HRMS $(M + H)^+$ calcd 597.2084, obsd 597.2093.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)*-O$^{\zeta}$-*(2,3,4,6-tetra*-O-*acetyl*-*β*-D-*galactopyranosyl)*-L-*tyrosine (21).* Compound **21** was prepared by reaction of monosaccharide **1** (53.5 mg, 137 μmol) with *N*$^{\alpha}$-Fmoc-Tyr-OH (71.8 mg, 169 μmol, freeze dried twice from 1.5 mL dioxane) for 4 h in CH_2Cl_2 (2.6 mL) under BF_3·Et_2O promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 55% B in A) gave **21** (33.8 mg, 34%): $[\alpha]^{20}_D$ +22° (*c* 0.73); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02, 2.02, 2.03, and 2.17 (4s, 3H each, Ac), 3.06 (dd, AB type, 1H, *J* = 13.6, 6.5 Hz, H-β), 3.17 (dd, AB type, 1H, *J* = 14.1, 4.9 Hz, H-β), 3.92 (m, 1H, H-5), 4.32 (m, 1H, Fmoc CHAr), 4.44 (m, 1H, Fmoc OCH_2), 4.66 (m, 1H, H-α), 4.93 (d, 1H, *J* = 8.0 Hz, H-1), 5.07 (dd, 1H, *J* = 10.5, 3.4 Hz, H-3), 5.29 (d, 1H, *J* = 8.2 Hz, NH), 5.42 (bs, 1H, H-4), 5.45 (dd, 1H, *J* = 10.3, 7.9 Hz, H-2), 6.91 and 7.08 (ABq, 4H, H-δ,ε); ^{13}C NMR ($CDCl_3$) δ 37.0 (C-β), 47.1 (Fmoc CHAr), 54.6 (C-α), 61.3 (C-6), 66.9, 67.2, 68.6, 70.8, and 70.9 (C-2,3,4,5, Fmoc OCH_2), 99.6 (C-1), 117.3 (C-ε), 130.5 (C-γ,δ); HRMS $(M + H)^+$ calcd 734.2449, obsd 734.2474.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)*-O$^{\zeta}$-*(2,3,4,6-tetra*-O-*acetyl*-α-D-*galactopyranosyl)*-L-*tyrosine (22).* Compound **22** was prepared by reaction of monosaccharide **1** (51.2 mg, 131 μmol) with *N*$^{\alpha}$-Fmoc-Tyr-OH (62.7 mg, 155 μmol) for 3h 10 min in CH_3CN (1.5 mL) under BF_3·Et_2O promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 55% B in A) gave **22** (18.2 mg, 19%): $[\alpha]^{20}_D$ +117° (*c* 0.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91, 2.03, 2.06, and 2.16 (4s, 3H each, Ac), 3.06 (dd, AB type, 1H, *J* = 14.4, 6.2 Hz, H-β), 3.15 (dd, AB type, 1H, *J* = 14.7, 3.2 Hz, H-β), 4.67 (m, 1H, H-α), 5.24 (d, 1H, *J* = 8 Hz, NH), 5.27 (dd, 1H, *J* = 10.9, 3.3 Hz, H-3), 5.50 (bs, 1H, H-4), 5.55 (dd, 1H, *J* = 10.8, 3.4 Hz, H-2), 5.73 (d, 1H, *J* = 3.4 Hz, H-1), 6.97 and 7.06 (ABq, 4H, H-δ,ε); ^{13}C NMR ($CDCl_3$) δ 36.9 (C-β), 47.1 (Fmoc CHAr), 54.6 (C-α), 61.4 (C-6), 67.0, 67.5, and 67.8 (C-2,3,4,5, Fmoc OCH_2), 94.8 (C-1), 116.8 (C-ε), 130.1 and 130.6 (C-γ,δ); HRMS $(M + H)^+$ calcd 734.2449, obsd 734.2422.

N$^{\alpha}$-*(9-Fluorenylmethoxycarbonyl)*-O$^{\zeta}$-*(2,3,4,6-tetra*-O-*acetyl*-*β*-D-*glucopyranosyl)*-L-*tyrosine (23).* Compound **23** was prepared by reaction of monosaccharide **5** (53.5 mg, 137 μmol) with *N*$^{\alpha}$-Fmoc-Tyr-OH (68.7 mg, 162 μmol, freeze dried twice from 1.5 mL dioxane) for 8 h in CH_2Cl_2 (2.5 mL) under BF_3·Et_2O

promotion according to the general procedure. Purification of the crude product by HPLC (isocrat, 55% B in A) gave **23** (41.0 mg, 41%): $[\alpha]^{20}_D$ +11° (*c* 0.98); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.97, 1.99, 2.00, and 2.02 (4s, 3H each, Ac), 2.98 (dd, 1H, *J* = 13.9, 9.5 Hz, H-β), 3.23 (dd, 1H, *J* = 13.9, 4.5 Hz, H-β), 4.49 (m, 1H, H-α), 5.08 (t, 1H, *J* = 9.4 Hz, H-4), 5.14 (dd, 1H, *J* = 9.5, 8.0 Hz, H-2), 5.24 (d, 1H, *J* = 8.0 Hz, H-1), 5.34 (t, 1H, *J* = 9.5 Hz, H-3), 6.74 (d, 1H, *J* = 8.8 Hz, NH), 6.98 (d, 2H, *J* = 8.7 Hz, H-ε), 7.28 (d, 2H, *J* = 8.1 Hz, H-δ); ^{13}C NMR ($CDCl_3$) δ 37.0 (C-β), 47.1 (Fmoc CHAr), 54.5 (C-α), 61.9 (C-6), 67.1, 68.2, 71.2, 71.9, and 72.7 (C-2,3,4,5, Fmoc OCH_2), 99.0 (C-1), 117.3 (C-ε), 130.5 and 130.6 (C-γ,δ); HRMS $(M + H)^+$ calcd 734.2449, obsd 734.2440.

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