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Synthesis of well-defined ADP-Ribosylated biomolecules

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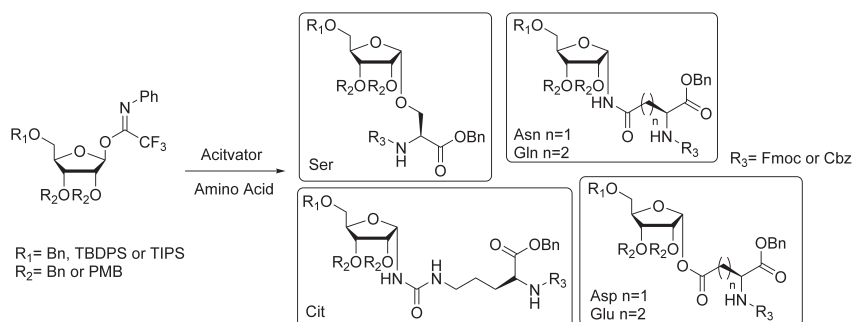
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Chapter 2

Stereoselective Ribosylation of Amino Acids



Abstract: The glycosylation properties of ribofuranosyl *N*-phenyltrifluoroacetimidates toward side chains of asparagine, glutamine, citrulline, serine, glutamic acid and aspartic acid were investigated. Conditions were found that promote nearly exclusive formation of the α -anomerically configured, *N*-ribosylated, asparagine and glutamine while citrulline proved to be less α -selective. Furthermore, ribosylation of serine with these *N*-phenyltrifluoroacetimidates proved to be completely α -selective and, for the first time, α -ribosylated glutamic- and aspartic acid, the naturally occurring sites for poly-ADP-ribosylation, were synthesized. The strategy allows for the synthesis of Fmoc-amino acids suitably modified for future solid phase peptide synthesis (SPPS) and the preparation of ADP-ribosylated peptides.

Part of this chapter has been published:

Kistemaker, H. A. V.; van der Heden van Noort, G. J.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V., *Org. Lett.*, **2013**, 15 (9), 2306-9.

Introduction

Glycosylation of proteins is a post-translational modification that plays a significant role in many biological processes.^{1,2} Adenosine diphosphate ribosylation (ADPr) (Figure 1) is a peculiar type of protein glycosylation that occurs in both monomeric and polymeric form and is considered to play an important role in a wide range of biological processes including cell proliferation, immune response, DNA repair, transcription regulation, and apoptosis.³⁻⁶ The process of ADP-ribosylation requires the enzymatic transfer of a single ADP-ribose moiety from β -NAD⁺ to the nucleophilic side chain of an amino acid forming an α -glycosidic linkage (dotted box, Figure 1). Poly-ADP-ribose polymerase (PARP) enzymes that are able to transfer additional ADP-ribosyl units to the 2'-OH of the adenosine moiety effect the formation of *poly*-ADP-ribose (Figure 1). The various identified sites amenable to ADP-ribosylation are asparagine, glutamic acid, aspartic acid, arginine, serine and cysteine.^{3,7} The construction of well-defined ADP-ribosylated peptides and analogues thereof would be of significant help in gaining a better understanding of the role and function of ADP-ribosylation.^{8,9}

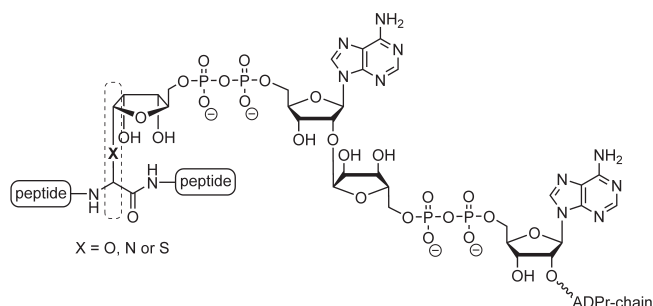


Figure 1. Poly-ADP-ribose polymer linked to a peptide.

One of the crucial steps in the synthesis of ADP-ribosylated peptides is the construction of an α -glycosidic linkage between the ribofuranosyl moiety and the amino acid side chain. The first fully synthetic approach to ADP-ribosylated peptides, reported by van der Heden-van Noort et al., involved the synthesis of such an α -ribosyl containing glutamine or asparagine building block.¹⁰ Incorporation of these building blocks in a peptide by solid phase peptide synthesis (SPPS), followed by installment of the adenosine diphosphate linkage resulted in the formation of ADP-ribosylated peptides. The ribosylated amino acids were prepared via the reduction of a ribofuranosyl azide and *in situ* condensation of the formed amine to the side chain of suitably protected glutamic acid or aspartic acid derivatives.^{10,11} The condensation products in this key amide bond formation were obtained as an anomeric mixture (75/25; α/β).¹⁰

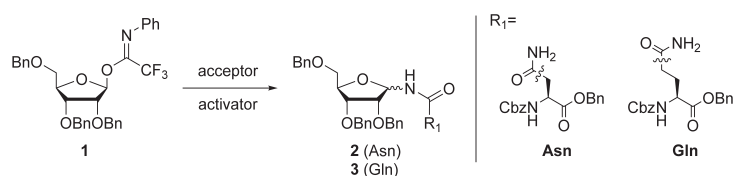
It was reasoned that the preparation of side-chain ribosylated amino acids might proceed with better α -selectivity when using acid-catalysed glycosylation. Furthermore, such an approach would allow for the use of other amino acids thereby expanding the scope to O-glycosides. Trifluoroacetimidate chemistry¹² was deemed to be the most viable for introducing the crucial α -linkage between

the ribosyl moiety and the amino acids.¹²⁻¹⁴ Moreover, it is known from literature that nonparticipating benzyl protection on the ribofuranosyl donor predominantly renders the α -product in glycosylation reactions.^{13,15,16} The results of the use of ribofuranosyl trifluoroacetimidates for the α -selective construction of a series of ribosylated amino acids corresponding to the sites of ADP-ribosylation are described in this chapter.

Results and discussion

Donor **1**¹³ was selected for its reported α -directing properties and allowed to react with either *N*-Cbz-asparagine-OBn (Asn, Table 1) or *N*-Cbz-glutamine-OBn (Gln, Table 1) under various reaction conditions. Ribosylation of asparagine using donor **1** and TMSOTf as activator gave an excellent α -selectivity (entry 1, Table 1). Application of identical conditions for glutamine resulted in a decrease in selectivity (entry 3, Table 1). Lowering the reaction temperature improved the α -selectivity but also led to a lower yield (entry 2, Table 1). Changing the solvent to nitromethane¹⁴ (CH₃NO₂) did improve the yield but the α -selectivity remained poor (entry 4, Table 1). The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures and of the purified anomeric mixtures, and identical ratios were observed in both measurements. The stereochemistry of the two products could not be determined from the coupling constants of the anomeric proton signals (H1'), since these were almost similar for both anomers. Therefore, HSQC-HECADE (Heteronuclear couplings from ASSCI-Domain Experiments with E.COSY-type cross peaks) NMR experiments were performed to determine which anomeric signal corresponds with the alpha and beta product respectively.¹⁷ From these NMR experiments the coupling constants between H1' and C2' (²J_{C2,H1'}) from the 2D-spectra could be obtained in which a value below 0.0 Hz indicated the H1'-H2' to be trans orientated (beta product) and a value above 0.0 Hz a cis orientation (alpha product).

Table 1. Ribosylation of asparagine and glutamine.

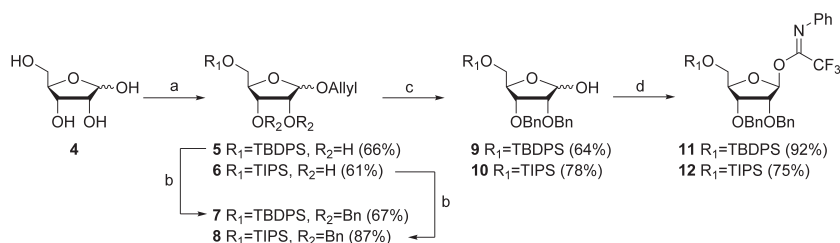


no.	acceptor (R ₁)	solvent	TMSOTf (equiv)	temp (°C)	yield (%)	ratio (α/β) ¹⁷
1	Asn	CH ₂ Cl ₂	0.2	-20 to rt	58	96/4
2	Gln	CH ₂ Cl ₂	0.3	-78 to rt	38	87/13
3	Gln	CH ₂ Cl ₂	0.2	-20 to rt	56	69/31
4	Gln	CH ₃ NO ₂	0.3	0	67	77/23

Reaction conditions: 1 equiv acceptor (50 mM), 1.25 equiv donor, 1.5 hours.

Improvement of the selectivity was anticipated by introducing a more bulky substituent at the 5'-position. For this reason two new donors with tert-butyldiphenylsilyl (TBDPS), **11**, or triisopropylsilyl (TIPS), **12**, at the 5'-position were synthesized (Scheme 1). A new synthesis route had to be devised because acidic removal of an anomeric methoxy protecting group, as in the synthesis of donor **1**, would not be compatible with the silyl protecting groups. Therefore, the anomeric position of D-ribose **4** was first protected with an allyl group using allyl alcohol and in situ generated HCl followed by silylation with TBDPS chloride to give compound **5** or TIPS chloride to give compound **6** in good yields over two steps (61 - 66%). The two compounds were benzylated with the use of benzyl bromide and sodium hydride yielding compounds **7** and **8** in 67% and 87% respectively. Next, isomerization of the allyl group with a catalytic amount of $\text{Ir}(\text{COD})(\text{Ph}_2\text{MeP})_2\text{PF}_6$ and subsequent cleavage of the enol ether with iodine and aqueous NaHCO_3 furnished **9** in 64% yield and **10** in 78% yield. Installation of the trifluoroacetimidate at the anomeric alcohol was achieved with the use of trifluoroacetimidoyl chloride ($\text{Cl}(\text{C}=\text{NPh})\text{CF}_3$) and cesium carbonate resulting in mostly β -configured imidate donors **11** and **12** in 92% and 75% yield, respectively.

Scheme 1. Synthesis of 5'-silylated imidate donors.



Reagents and conditions: a) i. allyl alcohol, acetyl chloride, rt; ii. TBDPS-Cl or TIPS-Cl, imidazole, DMF, rt; b) benzyl bromide, NaH, DMF, 0 °C to rt; c) i. $\text{Ir}(\text{COD})(\text{Ph}_2\text{MeP})_2\text{PF}_6 \cdot \text{H}_2$ (cat.), THF, rt; ii. I_2 , aq. NaHCO_3 (sat.); d) $\text{Cl}(\text{C}=\text{NPh})\text{CF}_3$, Cs_2CO_3 , acetone, H_2O , rt.

To investigate the glycosylation properties of donor **11** and **12**, *N*-Cbz-Glutamine-OBn was reacted with these under various conditions. The most favorable conditions for the ribosylation of glutamine turned out to be activation at -20 °C with 0.2 eq. TMSOTf (entry 1 and 2, Table 2). Although lower temperatures (~ -50 °C) resulted in highly α -selective ribosylations (>98% α), yields were fairly low (<20%). Silylation of glutamine, before ribosylation, with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) was employed in order to increase the solubility but this did not improve the solubility or yield. Replacing the benzyl by 2-naphthylmethyl ethers or by a 2',3'-cyclic carbonate moiety did also not improve the yield or selectivity. Using either of the two 5'-silylated donors, **11** and **12**, greatly improved the α -selectivity compared to the use of 5'-benzylated donor **1** (95/5 vs. 87/13, α/β). Ribosylation of asparagine with TIPS-donor **12** still gave a higher α -selectivity than that of glutamine although the difference in selectivity was greatly reduced compared to the tri-*O*-benzyl donor (entry 3, Table 2). Compounds **13**, **14** and **15** were isolated as anomeric mixture after silica gel column chromatography and separation of the anomers can only be

achieved after protecting group manipulation of the 2'- and 3'-OH functionalities, as will be described in chapter 3.

Table 2. Ribosylation of glutamine and asparagine with 5'-silylated donors.

11 (R_1=TBDPS) 12 (R_1=TIPS) 13 (R_1=TBDPS, R_2=Gln) 14 (R_1=TIPS, R_2=Gln) 15 (R_1=TIPS, R_2=Asn) R_2= Asn Gln						
no.	acceptor	donor	product	temp (°C)	yield (%)	ratio (α/β) ^a
1	Gln	11	13	-20 to rt	57	95/5
2	Gln	12	14	-20 to rt	66	95/5
3	Asn	12	15	-20 to rt	68	98/2

Reaction conditions: 1 equiv acceptor (50 mM), 1.25 – 1.5 equiv donor, 0.2 equiv TMSOTf, DCM, 1.5 hours. ^a The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures and of the purified anomeric mixtures.

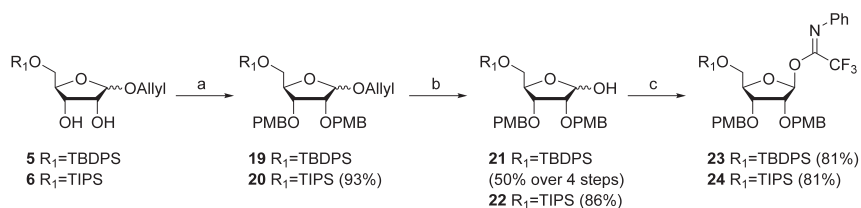
At this stage in the synthetic investigations it became clear that direct ribosylation of Fmoc-amino acids would give more straightforward access to the target building blocks required for SPPS. The feasibility of this approach was first tested in the ribosylation of *N*-Fmoc-asparagine-OBn with donor **11**. Due to the poor solubility of the Fmoc-amino acid in DCM, the solvent system had to be changed to DCM/dioxane (1/1; v/v). The ribosylation went almost completely α -selective but in a moderate yield when performed at 0 °C (entry 1, Table 3). At room temperature the stereoselectivity only slightly decreased while the yield significantly increased (entry 2, Table 3). The yield and selectivity are comparable with respect to the *N*-Cbz protected asparagine derivative and this approach circumvents tedious protecting group manipulations. However, these promising results did not transfer to the ribosylation of *N*-Fmoc-glutamine-OBn, which gave a modest excess of the α -anomer and an average yield at 0 °C (entry 3, Table 3). Replacing the benzyl ester protecting group of glutamine with 4-methoxy benzyl (PMB), in an attempt to increase the solubility of the amino acid, did not improve the outcome of the reaction in any way (compound **38**, experimental section). Therefore, we investigated the use of perchloric acid on silica ($\text{HClO}_4\text{-SiO}_2$) as activator, for it has been used with glycosylations in the presence of dioxane at room temperature.^{18,19} The $\text{HClO}_4\text{-SiO}_2$ reagent was prepared according to literature procedure²⁰ and added to a mixture of *N*-Fmoc-glutamine-OBn and donor **12** at room temperature. The stereoselectivity increased considerably along with a good yield (entry 4, Table 3).

Table 3. Ribosylation of Fmoc-asparagine- and Fmoc-glutamine-benzyl esters.

	11 (R_1 =TBDPS) 12 (R_1 =TIPS)		16 (R_1 =TBDPS, R_2 =Asn) 17 (R_1 =TBDPS, R_2 =Gln) 18 (R_1 =TIPS, R_2 =Gln)		$R_2 =$		
no.	donor	acceptor	product	activator	temp (°C)	yield (%)	ratio (α/β) ^a
1	11	Asn	16	TMSOTf	0	44	97/3
2	11	Asn	16	TMSOTf	rt	63	93/7
3	11	Gln	17	TMSOTf	0	49	72/28
4	12	Gln	18	HClO ₄ -SiO ₂	rt	59	96/4

Reaction conditions: 1 equiv acceptor (50 mM), 1.5 equiv donor, 0.2 equiv activator, dioxane/DCM (1/1; v/v), 1.5 hours. ^a The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures and of the purified anomeric mixtures.

The hydrogenolysis of benzyl ethers at the ribosyl moiety was found to be incompatible with the integrity of the Fmoc protection. Therefore, it was decided to introduce the acid sensitive 4-methoxybenzyl (PMB) at the 2'- and 3'-position (Scheme 2). The previously described compounds **5** and **6** (Scheme 1) were treated with PMB chloride and sodium hydride to afford **20** in 93% yield and **19** was used in the next step without purification. For the allyl ether cleavage, palladium(II) chloride (PdCl₂) was used as catalyst instead of iridium which reduced the cost of this transformation significantly (PdCl₂ = 1.2-1.6 euro/mmol substrate using 15-20 mol% and Ir(COD)(Ph₂MeP)₂PF₆ = 18-35 euro/mmol substrate using 1.4-3 mol%). Compound **22** was obtained in 86% and compound **21** in 50% (starting from D-ribose). Finally, formation of the imidate was straightforward using the previously described conditions to afford donor **23** and donor **24** in good yields (81%).

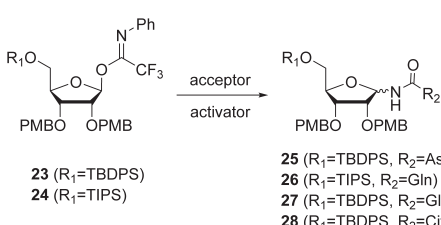
Scheme 2. Synthesis of 5'-silyl-3'-2'-bis-PMB imidate donors.

Reagents and conditions: a) PMB chloride, NaH, DMF, 0 °C to rt; b) i. PdCl₂, CHCl₃/H₂O (3/1; v/v), 45 °C, O₂; ii. I₂, aq. NaHCO₃ (sat.); c) Cl(C=NPh)CF₃, Cs₂CO₃, acetone, H₂O, rt.

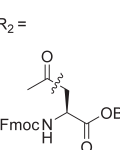
Ribosylation of *N*-Fmoc-asparagine-OBn with donor **23** and HClO₄-SiO₂ gave compound **25** in a highly α -selective manner (97/3; α/β) and in 56% yield (entry 1,

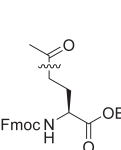
Table 4). Changing the activator to TBSOTf gave similar stereochemical outcomes (97/3; α/β) and the yields ranged from 52% to 79% (entry 2, Table 4). The ribosylation of *N*-Fmoc-glutamine-OBn with donor **24** in the presence of TMSOTf (entry 3, Table 4) resulted in a comparable yield and α -selectivity as for the benzylated donor **11** (entry 3, Table 3). The influence of Fmoc protection was investigated by reacting donor **24** with *N*-Cbz-glutamine-OBn to give compound **37** (see experimental section) in comparable yield (52%) and selectivity (85/15 α/β). The selectivity could be increased significantly by activation with $\text{HClO}_4\text{-SiO}_2$ (entry 6, Table 4) as was demonstrated before. However, closer inspection of the reaction conditions revealed that by adding less TMSOTf (5 mol% vs. 20 mol%) at the start of the reaction helped to restore the α -selectivity of the reaction (entry 4, Table 4). Screening other activators showed TfOH,

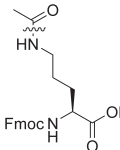
Table 4. Ribosylation of Fmoc-asparagine, Fmoc-glutamine and Fmoc-citrulline.



$R_2 =$


Asn


Gln


Cit

no.	donor	equiv	acceptor	activator	equiv	product	yield (%)	ratio (α/β) ^e
1	23	1.2	Asn	$\text{HClO}_4\text{-SiO}_2$	0.12	25	56	97/3
2	23	1.2	Asn	TBSOTf	0.06	25	52-79 ^a	97/3
3	24	1.5	Gln	TMSOTf	0.20	26	60	78/22
4	24	1.2	Gln	TMSOTf	0.25 ^b	26	59	92/8
5	24	3	Gln	TMSOTf	0.05	26	88	90/10
6	24	1.5	Gln	$\text{HClO}_4\text{-SiO}_2$	0.10	26	69	93/7
7	24	1.5	Gln	Pyr.OTf	0.56	26	45	98/2
8	24	1.5	Gln	TfOH	0.05	26	55	98/2
9	24	3	Gln	TfOH	0.05	26	89	87/13
10	24	1.2	Gln	TBSOTf	0.20 ^c	26	51	98/2
11	23	1.25	Gln	TBSOTf	0.06	27	61	94/6
12	23	1.05	Cit	TBSOTf	0.30 ^d	28	40	78/22

Reaction conditions: 1 equiv acceptor (50-100 mM), donor, dioxane/DCM (1/1; v/v), -10 °C to rt, 2-4 hours. ^a Three identical experiments; ^b added in 4 equal portions over 4 hours; ^c added in 3 equal portions over 3 hours; ^d added in 6 equal portions over 6 hours. ^e The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures and of the purified anomeric mixtures.

TBSOTf and pyridinium triflate (Pyr.OTf) to be useful activators showing comparable results as well, in terms of yield and stereoselectivity (entries 7, 8, 10 and 11, Table 4). Finally, higher yields could be obtained by using a larger excess of donor (3 equiv) but with a small decrease in α -selectivity (entries 5 and 9, Table 4). So, this approach was abandoned as it did not outweigh the loss of valuable donor material. The scope of *N*-ribosylated amino acids was also extended to citrulline, which was selected as isostere for arginine, one of the major sites of ADPriboseylation. Ribosylation of *N*-Fmoc-citrulline-OBn proved to be difficult and coupling with donor **23** resulted in a moderate yield and a modest stereoselectivity (entry 12, Table 4).

Next, the ribosylation properties of donors **1**, **11** and **12** with serine, glutamic acid and aspartic acid were investigated. The observed anomeric ratio for the ribosylation of *N*-Cbz-serine-OBn with tribenzyl-donor **1** (entry 1, Table 5) was comparable to the results obtained for glutamine (entries 2 and 3, Table 1) and also in agreement with previously reported data.^{21,22} Ribosylation with the 5'-silylated donors **11** and **12**, on the other hand, gave exclusively α -ribosylated serine and this result is the first example of a completely α -selective ribosylation of an amino acid. (entries 2 and 3, Table 5). Subjecting donor **12** and suitably protected glutamic acid to the same reaction conditions resulted in a partial loss of stereoselectivity giving an anomeric ratio of 77/23 (α/β) (entry 4, Table 5). In the case of aspartic acid no selectivity was

Table 5. Ribosylation of Serine, Glutamic- and Aspartic acid.

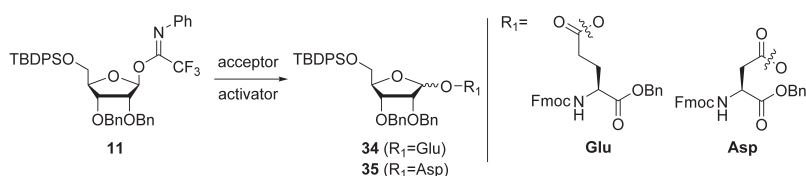
no.	donor	acceptor	product	activator	temp (°C)	yield (%)	ratio (α/β) ^b
1	1	Ser	29	TMSOTf	-50	78	75/25
2	11	Ser	30	TMSOTf	-50	60	100/0
3	12	Ser	31	TMSOTf	-50	56	100/0
4	12	Glu	32	TMSOTf	-50	84	77/23
5	12	Glu	32	HClO ₄ -SiO ₂	-50	73	60/40 ^a
6	12	Asp	33	TMSOTf	-70	63	50/50
7	12	Asp	33	HClO ₄ -SiO ₂	-78	74	43/57 ^a

Reaction conditions: 1 equiv acceptor (50 mM), 1.25 equiv donor, 0.2 equiv activator (^a 0.05 equiv), DCM, 1.5 hours. ^b The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures.

observed resulting in a 50/50 (α/β) anomeric mixture (entry 6, Table 5). Moreover, using $\text{HClO}_4\text{-SiO}_2$ as activator did not improve the outcome of the ribosylations (entries 5 and 7, Table 5). Nevertheless, both anomers could be separated at this stage by silica gel chromatography to afford α -ribosylated glutamic acid (**32**) and aspartic acid (**33**) derivatives.

However, closer examination of the reaction conditions for glutamic acid and aspartic acid revealed spontaneous product formation during the co-evaporation process of the donor and acceptor. This effect was attributed to the carboxylic side-chain being able to function as activator at elevated temperatures along with reduced pressure. Therefore, the donor and acceptor were co-evaporated separately for the ribosylation reactions with *N*-Fmoc-glutamic acid-OBn and *N*-Fmoc-aspartic acid-OBn. Subsequently, the donor and acceptor were dissolved together in DCM and stored with molecular sieves for 16 hours to remove traces of water. In doing so, product formation occurred again as was observed by TLC analysis before the addition of activator. The observed anomeric ratios after completion of the reactions were similar to the previously reported ratios (entries 2 and 4, Table 6). Finally, the selectivity could be restored by cooling the dissolved donor and acceptor separately to -78°C before mixing which resulted in an almost complete α -selective outcome for both acceptors (entries 1 and 3, Table 6).

Table 6. Ribosylation of Fmoc-glutamic- and Fmoc-aspartic acid.

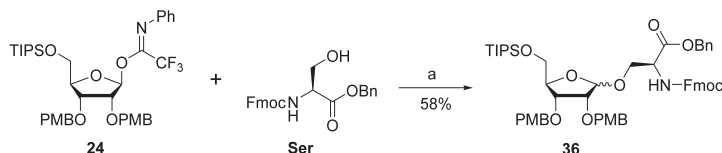


no.	donor	acceptor	activator	product	yield (%)	ratio (α/β) ^b
1	11	Glu	TMSOTf	34	51	98/2
2	11	Glu	TBSOTf	34	65	66/34 ^a
3	11	Asp	TMSOTf	35	59	98/2
4	11	Asp	TBSOTf	35	74	41/59 ^a

Reaction conditions: 1 equiv acceptor (50 mM), 1.2 - 1.5 equiv donor, -78°C , 0.05 equiv activator, DCM, 15-30 minutes. ^a donor/acceptor mixture stored with mol. sieves at rt for 16 hours. ^b The anomeric ratios were determined by NMR spectroscopic analysis of the crude reaction mixtures.

Finally, *N*-Fmoc-Serine-OBn was ribosylated with donor **24** to yield only α -ribosylated serine **36** (Scheme 3).

Scheme 3. Ribosylation of Fmoc-serine.



Reagents and conditions: a) 1 equiv acceptor (50 mM), 1.25 equiv donor, 0.05 equiv TMSOTf, DCM, -50 °C 1.5 hours.

Conclusion

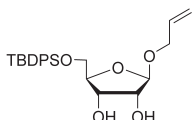
This chapter describes the preparation of a number of ribofuranosyl imidate donors with different non-participating protecting groups at the 2'-, 3'- and 5'-position. The glycosylation properties of these donors were closely investigated using different amino acids as acceptor. Optimizing the reaction conditions and tuning the protective group at the 5'-position resulted in a highly α -selective outcome. Installation of the more bulky TIPS or TBDPS for benzyl protection gave an almost complete α -selective ribosylation for glutamine, asparagine, serine, aspartic acid and glutamic acid, while the selectivity for citrulline was only moderate. Initially, the choice of activator appeared to be critical with an α -selective outcome using $\text{HClO}_4\text{-SiO}_2$ as activator and moderate selectivity with TMSOTf. However, closer investigation of the conditions showed that careful addition of activator, using lower amounts at the start, allowed all the standard activators to be used with equal stereoselective outcome and similar yields. Based on the above described investigation an efficient synthesis protocol toward six Fmoc protected ribosylated amino amino acid building blocks, suitable for SPPS (see Chapter 3), was developed.

Experimental Section

General procedures

All solvents used under anhydrous conditions were stored over 4Å molecular sieves except for methanol which was stored over 3Å molecular sieves. Solvents used for workup and column chromatography were of technical grade from Sigma Aldrich and used directly. Unless stated otherwise, solvents were removed by rotary evaporation under reduced pressure at 40 °C. All chemicals were used as received unless stated otherwise. Reactions were monitored by TLC-analysis using Merck 25 DC plastikfolien 60 F254 with detection by spraying with 20% H_2SO_4 in EtOH, $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (25 g/L) and $(\text{NH}_4)_4\text{Ce}(\text{SO}_4)_4\cdot 2\text{H}_2\text{O}$ (10 g/L) in 10% sulfuric acid or by spraying with a solution of ninhydrin (3 g/L) in EtOH / AcOH (20/1 v/v), followed by charring at approx. 150 °C. Column chromatography was performed on Fluka silicagel (0.04 – 0.063 mm) or by automation using a Biotage® Isolera™ Spektra Four machine. For LC-MS analysis a JASCO HPLC-system (detection simultaneously at 214 and 254 nm) coupled to a PE/SCIEX API 165 single quadrupole mass spectrometer (Perkin-

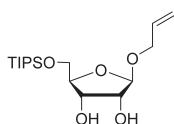
Elmer) using an analytical Gemini C18 column (Phenomex, 50 x 4.60 mm, 3 micron) in combination eluents A: H₂O; B: MeCN and C: 0.1 M aq. NH₄OAc or a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer with an electrospray ion source coupled to Surveyor HPLC system (Thermo Finnigan) using an analytical Gemini C18 column (Phenomex, 50 x 4.60 mm, 3 micron) in combination with eluents A: H₂O; B: MeCN and C: 1% aq. TFA as the solvent system. High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylphthalate (m/z = 391.2842) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). ¹H-, ¹³C- and ³¹P-NMR spectra were measured on a Brüker AV-400 (400 MHz) or a Brüker AV-500 (500 MHz), AVIII-Brüker DMX-600 (600 MHz) or a Bruker Ascend 850 (850 MHz) and all individual signal were assigned using 2D-NMR spectroscopy. HSQC-HECADE (Heteronuclear couplings from ASSCI-Domain Experiments with E.COSY-type cross peaks) NMR experiments were performed to determine which anomeric signal corresponds with the alpha and beta product respectively.¹⁷ The coupling constants between H1' and C2' (²J_{C2,H1}) from the 2D-spectra could be obtained in which a value below 0.0 Hz indicated the H1'-H2' to be trans orientated being the beta product and a value above 0.0 Hz a cis orientation being the alpha product. Chemical shifts are given in ppm (δ) relative to TMS (0 ppm) or indirectly referenced to H₃PO₄ (0.00 ppm) in D₂O via the solvent residual signal and coupling constants are given in Hz. Stereoisomers were, when possible, separated by silica gel column chromatography for analytical purposes.



1-O-allyl-5-O-tert-butyldiphenylsilyl-α,β-D-ribofuranoside (5)

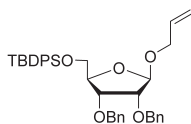
Allyl α,β-D-ribofuranoside²³ (1.90 g, 10 mmol) was used without further purification and after coevaporation with toluene dissolved in dry DMF (50 mL). Imidazole (1.36 g, 20 mmol) and TBDPSCI (2.86 mL, 11 mmol) were added and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched upon addition of water and concentrated *in vacuo*. The residue was taken up in Et₂O and washed with H₂O, dried (MgSO₄) and concentrated. Column chromatography (Pentane/EtOAc, 85/15 – 60/40) yielded the title compound (2.84 g, 6.63 mmol, 66%) as a colorless oil. α-anomer: ¹H-NMR (400 MHz, MeOD) δ: 7.79 – 7.70 (m, 4H, TBDPS, arom.), 7.48 – 7.32 (m, 6H, TBDPS, arom.), 5.87 (dddd, J = 17.2, 10.5, 6.0, 5.2 Hz, 1H, CH₂CHCH₂), 5.24 (dq, J = 17.2, 3.5, 1.7 Hz, 1H, CHCH₂), 5.11 (ddd, J = 10.5, 3.1, 1.3 Hz, 1H, CHCH₂), 4.75 (d, J = 4.6 Hz, 1H, H1'), 4.14 (ddt, J = 13.0, 5.2, 1.5 Hz, 1H, OCH₂CH), 3.99 (ddt, J = 13.0, 6.0, 1.4 Hz, 1H, OCH₂CH), 3.90 – 3.88 (m, 1H, H3'), 3.87 – 3.84 (m, 1H, H4'), 3.52 – 3.44 (m, 2H, H5'), 3.44 – 3.41 (m, 1H, H2'), 1.10 – 1.07 (m, 9H, t-Bu, TBDPS). ¹³C-NMR (100 MHz, MeOD) δ: 137.09, 136.87 (arom.), 135.46 (CH₂CHCH₂), 134.57, 133.73 (Cq. arom.), 131.19, 131.16, 128.89, 128.84 (arom.), 117.37 (CHCH₂), 101.36 (C1'), 72.80 (C4'), 72.63 (C2'), 70.01 (OCH₂CH), 69.25 (C3'), 64.05 (C5'), 27.42 (t-Bu, TBDPS), 20.04 (Cq. t-Bu). β-anomer: ¹H-NMR (400 MHz, MeOD) δ: 7.77 – 7.69 (m, 4H, TBDPS arom.), 7.48 – 7.33 (m, 6H, TBDPS arom.), 5.89 – 5.76 (dddd, J = 16.8, 10.9, 5.9, 5.1 Hz, 1H, CH₂CHCH₂), 5.18 (dq, J = 17.2, 3.5, 1.8 Hz, 1H, CHCH₂), 5.08 (ddd, J = 10.4, 3.2, 1.4 Hz,

1H, CHCH₂), 4.93 (d, *J* = 0.6 Hz, 1H, H1'), 4.21 (dd, *J* = 6.9, 4.7 Hz, 1H, H3'), 4.16 (ddt, *J* = 13.0, 5.0, 1.6 Hz, 1H, OCH₂CH), 4.05 (ddt, *J* = 6.9, 5.5, 3.2 Hz, 1H, H4'), 3.96-3.95 (m, 1H, H2'), 3.95 - 3.91 (m, 1H, OCH₂CH), 3.87 (AB, *J* = 11.1, 3.2 Hz, 1H, H5'), 3.70 (AB, *J* = 11.1, 5.4 Hz, 1H, H5'), 1.08 - 1.02 (m, 9H, t-Bu, TBDPS). ¹³C-NMR (100 MHz, MeOD) δ: 136.74, 136.72 (arom.), 135.63 (CH₂CHCH₂), 134.60, 134.57 (Cq. arom.), 130.82, 128.76 (arom.), 117.06 (CHCH₂), 107.86 (C1'), 84.71 (C4'), 76.31 (C2'), 72.28 (C3'), 69.36 (OCH₂CH), 66.31 (C5'), 27.34 (t-Bu, TBDPS), 20.09 (Cq. t-Bu). $[\alpha]_D^{25}$ MeOH = +49.8 ° (α), $[\alpha]_D^{25}$ CHCl₃ = -30.4 ° (β). IR: 3388, 2931, 2858, 1473, 1428, 1112, 1048, 991, 949, 823, 786, 738, 701, 614. HRMS [C₂₄H₃₂O₅Si + Na]⁺: 451.1910 found, 451.1911 calculated.



1-O-allyl-5-O-triisopropylsilyl-α,β-D-ribofuranoside (6)

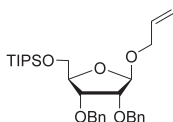
Allyl α,β-D-ribofuranoside²³ (1.90 g, 10 mmol) was used without further purification and after coevaporation with toluene dissolved in dry DMF (50 mL). Imidazole (1.36 g, 20 mmol) and TIPSCI (2.35 mL, 11 mmol) were added and the reaction mixture was stirred at room temperature for 6 hours. After concentration *in vacuo* the residue was taken up in Et₂O and washed with water, dried (MgSO₄) and concentrated. Column chromatography (Pentane/EtOAc, 90/10 - 70/30) yielded the title compound (2.08 g, 6.0 mmol, 60%) as a colorless oil. α-anomer: ¹H-NMR (400 MHz, MeOD) δ: 5.96 (dddd, *J* = 17.2, 10.5, 6.1, 5.1 Hz, 1H, CH₂CHCH₂), 5.32 (dq, *J* = 17.3, 3.4, 1.7 Hz, 1H, CHCH₂), 5.17 (ddd, *J* = 10.4, 3.2, 1.4 Hz, 1H, CHCH₂), 4.99 (d, *J* = 4.0 Hz, 1H, H1'), 4.26 (ddt, *J* = 11.6, 5.0, 3.2, 1.6 Hz, 1H, OCH₂CH), 4.11 - 4.05 (m, 1H, OCH₂CH), 4.05 - 4.01 (m, 3H, H2', H3', H4'), 3.87 - 3.80 (m, *J* = 3.2, 1.4 Hz, 2H, H5'), 1.12 - 1.07 (m, 21H, TIPS). ¹³C-NMR (100 MHz, MeOD) δ: 135.89 (CH₂CHCH₂), 117.32 (CHCH₂), 102.70 (C1'), 86.86 (C4'), 73.35 (C2'), 71.45 (C3'), 69.71 (OCH₂CH), 65.07 (C5'), 18.43 (CH, TIPS), 18.41 (CH, TIPS), 13.17 (CH₃, TIPS). β-anomer: ¹H-NMR (400 MHz, MeOD) δ: 5.89 (dddd, *J* = 17.0, 10.7, 5.9, 5.1 Hz, 1H, CH₂CHCH₂), 5.24 (dq, *J* = 17.3, 3.5, 1.8 Hz, 1H, CHCH₂), 5.13 (ddd, *J* = 10.5, 3.2, 1.4 Hz, 1H, CHCH₂), 4.89 (d, *J* = 0.6 Hz, 1H, CHCH₂), 4.21 (dddd, *J* = 11.6, 5.1, 3.2, 1.6 Hz, 1H, OCH₂CH), 4.18 - 4.13 (dd, *J* = 6.8, 4.8 Hz, 1H, H3'), 3.99 - 3.96 (m, 1H, OCH₂CH), 3.96 - 3.93 (m, 1H, H4'), 3.93 - 3.92 (m, 1H, H2'), 3.92 - 3.98 (m, 1H, H5'), 3.77 (AB, *J* = 10.8, 5.5 Hz, 1H, H5'), 1.13 - 1.08 (m, 21H, TIPS). ¹³C-NMR (100 MHz, MeOD) δ: 135.75 (CH₂CHCH₂), 116.91 (CHCH₂), 107.84 (C1'), 85.01 (C4'), 76.31 (C2'), 72.31 (C3'), 69.29 (OCH₂CH), 66.11 (C5'), 18.49 (CH, TIPS), 13.19 (CH₃, TIPS). $[\alpha]_D^{25}$ MeOH = +74.2 ° (α), -30.8 ° (β). IR: 3406, 2943, 2866, 1460, 1116, 1050, 993, 949, 882, 776, 682, 632. HRMS [C₁₇H₃₄O₅Si + Na]⁺: 369.2067 found, 369.2068 calculated.



1-O-allyl-2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl-α,β-D-ribofuranoside (7)

Compound **5** (1.99 g, 4.65 mmol) was dissolved in dry DMF (25 mL). The reaction mixture was stirred at 0 °C and sodium hydride (60% in mineral oil, 0.47 g, 11.6 mmol) was slowly added. After hydrogen generation ceased, benzyl bromide (1.38 mL, 11.6 mmol) was added under argon atmosphere. The reaction mixture was stirred for 16 h and allowed to reach room temperature. The reaction was carefully quenched with water and extracted with Et₂O. The organic layer was dried (MgSO₄), concentrated and purified by silica

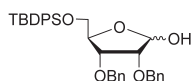
gel column chromatography (Pentane/EtOAc, 100/0 – 80/20). The title compound (1.88 g, 3.1 mmol, 67%) was obtained as a colorless oil. **α -anomer:** $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.57 (ddd, $J = 18.3, 7.9, 1.3$ Hz, TBDPS arom.), 7.46 – 7.24 (m, 16H, arom.), 6.05 – 5.93 (m, 1H, CH_2CHCH_2), 5.35 (dd, $J = 17.2, 1.5$ Hz, 1H, CHCH_2), 5.20 (dd, $J = 10.4, 1.4$ Hz, 1H, CHCH_2), 5.07 (d, $J = 4.3$ Hz, 1H, $\text{H}1'$), 4.72 – 4.52 (m, 4H, CH_2 Bn), 4.34 – 4.26 (m, 1H, OCH_2CH), 4.20 (q, $J = 3.3$ Hz, 1H, $\text{H}4'$), 4.18 – 4.12 (m, 1H, OCH_2CH), 3.98 (dd, $J = 6.5, 2.9$ Hz, 1H, $\text{H}3'$), 3.84 (dd, $J = 6.5, 4.3$ Hz, 1H, $\text{H}2'$), 3.62 (AB, $J = 11.1, 3.7$ Hz, 1H, $\text{H}5'$), 3.54 (AB, $J = 11.1, 3.3$ Hz, 1H, $\text{H}5'$), 0.94 (bs, 9H, t-Bu TBDPS). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 138.53, 138.06 (Cq. arom.), 135.72, 135.65 (arom.), 134.90 (CH_2CHCH_2), 133.31, 133.19 (Cq. arom.), 129.84 – 127.62 (arom.), 117.39 (CHCH_2), 100.14 ($\text{C}1'$), 83.53 ($\text{C}4'$), 78.13 ($\text{C}2'$), 75.32 ($\text{C}3'$), 72.55, 72.41 (CH_2 Bn), 68.72 (OCH_2CH), 64.20 ($\text{C}5'$), 26.85 (t-Bu, TBDPS), 19.26 (Cq. t-Bu). **β -anomer:** $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.69 (ddd, $J = 7.9, 3.3, 1.6$ Hz, 4H, TBDPS arom.), 7.41 – 7.21 (m, 16H, arom.), 5.81 (dddd, $J = 16.7, 10.5, 6.1, 5.2$ Hz, 1H, CH_2CHCH_2), 5.19 (ddd, $J = 17.2, 3.2, 1.6$ Hz, 1H, CHCH_2), 5.14 – 5.09 (m, 1H, CHCH_2), 5.11 (d, $J = 1.0$ Hz, 1H, $\text{H}1'$), 4.63 (dd, $J = 26.6, 12.1$ Hz, 2H, CH_2 Bn), 4.51 (dd, $J = 28.2, 11.8$ Hz, 2H, CH_2 Bn), 4.31 (dt, $J = 7.0, 4.2$ Hz, 1H, $\text{H}4'$), 4.23 – 4.18 (m, 1H, $\text{H}3'$), 4.06 (dddd, $J = 77.7, 6.5, 5.1, 1.2$ Hz, 1H, OCH_2CH), 3.94 – 3.91 (m, 1H, $\text{H}2'$), 3.85 (AB, $J = 11.1, 3.9$ Hz, 1H, $\text{H}5'$), 3.74 (AB, $J = 11.1, 4.5$ Hz, 1H, $\text{H}5'$), 1.05 (bs, 9H, t-Bu TBDPS). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 137.93, 137.88 (Cq. arom.), 135.63, 135.62 (arom.), 134.12 (CH_2CHCH_2), 133.43, 133.39 (Cq. arom.), 129.69 – 127.71 (arom.), 117.26 (CHCH_2), 104.39 ($\text{C}1'$), 82.07 ($\text{C}4'$), 80.06 ($\text{C}2'$), 77.87 ($\text{C}3'$), 72.40, 72.30 (CH_2 Bn), 68.45 (OCH_2CH), 64.44 ($\text{C}5'$), 26.87 (t-Bu, TBDPS), 19.30 (Cq. t-Bu). $[\alpha]_D^{25}(\text{CHCl}_3) = +60.4^\circ$ (α), $+2.6^\circ$ (β). IR: 2930, 2857, 1454, 1427, 1265, 1103, 1026, 945. HRMS $[\text{C}_{38}\text{H}_{44}\text{O}_5\text{Si} + \text{Na}]^+$: 631.2849 found, 631.2850 calculated.



1-O-allyl-2,3-di-O-benzyl-5-O-triisopropylsilyl- α,β -D-ribofuranoside (8)

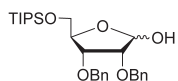
Compound **6** (1.14 g, 3.3 mmol) was dissolved in dry DMF (20 mL). The reaction mixture was stirred at 0°C and sodium hydride (60% in mineral oil, 0.33 g, 8.3 mmol) was slowly added. After hydrogen generation ceased, benzyl bromide (0.98 mL, 8.3 mmol) was added. The reaction mixture was stirred under argon for 16 hours and allowed to reach room temperature. The reaction was carefully quenched with water and extracted with Et_2O . The organic layer was dried (MgSO_4), concentrated and purified by silica gel column chromatography (Pentane/EtOAc, 100/0 – 80/20). The title compound (1.51 g, 2.86 mmol, 87%) was obtained as a colorless oil. **α -anomer:** $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.42 – 7.21 (m, 10H, arom), 5.98 (dddd, $J = 17.1, 10.5, 6.5, 4.8$ Hz, 1H, CH_2CHCH_2), 5.38–5.30 (m, 1H, CHCH_2), 5.21–5.15 (m, 1H, CHCH_2), 5.03 (d, $J = 4.3$ Hz, 1H, $\text{H}1'$), 4.75 – 4.60 (m, 4H, CH_2 Bn), 4.30 (ddt, $J = 13.4, 4.7, 1.4$ Hz, 1H, OCH_2CH), 4.19 (dd, $J = 6.4, 3.3$ Hz, 1H, $\text{H}4'$), 4.18 – 4.11 (m, 1H, OCH_2CH), 3.95 (dd, $J = 6.5, 2.7$ Hz, 1H, $\text{H}3'$), 3.77 (dd, $J = 6.4, 4.4$ Hz, 1H, $\text{H}2'$), 3.63 (AB, $J = 10.8, 3.9$ Hz, 1H, $\text{H}5'$), 3.58 (AB, $J = 10.8, 3.3$ Hz, 1H, $\text{H}5'$), 0.97 (s, 21H, TIPS). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 138.53, 137.99 (Cq. arom.), 134.86 (CH_2CHCH_2), 128.34 – 127.53 (arom.), 117.18 (CHCH_2), 100.03 ($\text{C}1'$), 83.76 ($\text{C}4'$), 77.91 ($\text{C}2'$), 75.16 ($\text{C}3'$), 72.33, 72.28 (CH_2 , arom), 68.58 (OCH_2CH), 63.79 ($\text{C}5'$), 17.94 (CH, TIPS), 17.92 (CH, TIPS), 11.87 (CH_3 , TIPS). **β -anomer:** $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.40 – 7.23 (m, 10H, arom.), 5.86 (dddd, $J = 16.6, 10.5, 6.1, 5.2$ Hz, 1H, CH_2CHCH_2), 5.23 (dq, $J = 17.2, 1.6$ Hz, 1H, CHCH_2), 5.15 (ddd, $J = 10.4, 2.8, 1.3$ Hz,

¹H, CHCH₂), 5.07 (d, *J* = 1.3 Hz, 1H, H1'), 4.64 (q, *J* = 12.1 Hz, 2H, CH₂ Bn), 4.58 - 4.48 (m, 2H, CH₂ Bn), 4.25 - 4.21 (m, 1H, H4'), 4.18 (ddt, *J* = 5.2, 4.7, 1.8 Hz, 1H, OCH₂CH), 4.15 (dd, *J* = 6.5, 4.7 Hz, 1H, H3'), 3.98 - 3.91 (m, 1H, OCH₂CH), 3.90 (dd, *J* = 4.6, 1.4 Hz, 1H, H2'), 3.81 (AB, *J* = 10.8, 4.3 Hz, 1H, H5'), 3.77 (AB, *J* = 10.8, 4.5 Hz, 1H, H5'), 1.09 - 1.01 (m, 21H, TIPS). ¹³C-NMR (100 MHz, CDCl₃) δ: 138.11, 138.01 (Cq. arom.), 134.30 (CH₂CHCH₂), 128.47 - 127.77 (arom.), 117.22 (CHCH₂), 104.42 (C1'), 82.42 (C4'), 80.26 (C2'), 77.96 (C3'), 72.46, 72.35 (CH₂, arom.), 68.46 (OCH₂CH), 64.15 (C5'), 18.09 (CH, TIPS), 12.02 (CH₃, TIPS). [α _D²⁰CHCl₃] = +64.8 ° (α), -2.2 ° (β). IR: 2942, 2865, 1498, 1456, 1130, 1098, 882. HRMS [C₃₁H₄₆O₅Si + Na]⁺: 549.3003 found, 549.3007 calculated.



2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl-D-ribose (9)

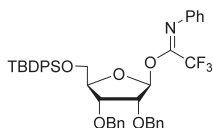
Dry 3 Å molecular sieves were added to a solution of compound **7** (1.92 g, 3.15 mmol) in dry THF (20 mL). The solution was stirred under argon at room temperature for 1 hour. After the addition of Ir(COD)(Ph₂MeP)₂PF₆ (81 mg, 0.095 mmol) the solution was purged with hydrogen for ~10s. After stirring under argon for 3 hours, the mixture was diluted with THF (15 mL) and sat. aq. NaHCO₃ (30 mL). Upon addition of I₂ (1.23 g, 4.7 mmol), the mixture was allowed to stir at room temperature for 1.5 hours. The mixture was then diluted with EtOAc (50 mL) and washed with sat. aq. Na₂S₂O₃ (50 mL) and brine (50 mL), respectively. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Silica gel column chromatography (Pentane/EtOAc, 100/0 - 70/30) afforded the desired alcohol (1.15 g, 2.1 mmol, 64%) as a pale yellow oil. ¹H-NMR (400 MHz, MeOD) δ: 7.70 - 7.63 (m, 4H, TBDPS-β, arom.), 7.63 - 7.53 (m, 4H, TBDPS-α, arom.), 7.45 - 7.21 (m, 32H, arom.), 5.33 (d, *J* = 2.3 Hz, 1H, H1'-β), 5.31 (d, *J* = 4.1 Hz, 1H, H1'-α), 4.71 - 4.47 (m, 8H, CH₂ Bn), 4.22 (q, *J* = 3.3 Hz, 1H, H4'-α), 4.16 - 4.08 (m, 2H, H4'-β, H3'-β), 4.05 (dd, *J* = 5.6, 3.1 Hz, 1H, H3'-α), 3.97 (dd, *J* = 5.6, 4.2 Hz, 1H, H2'-α), 3.82 (dd, *J* = 4.1, 2.3 Hz, 1H, H2'-β), 3.78 - 3.68 (m, 2H, H5'-β), 3.60 (qd, *J* = 11.2, 3.5 Hz, 2H, H5'-α), 1.01 (s, 9H, t-Bu, TBDPS-β), 0.93 (s, 9H, t-Bu, TBDPS-α). ¹³C-NMR (100 MHz, MeOD) δ: 139.27, 139.22, 139.17 (Cq. arom.), 136.78, 136.73, 136.71, 136.64 (arom.), 134.46, 134.42, 134.26, 134.14 (Cq. arom.), 130.99 - 128.80 (arom.), 101.11 (C1'-β), 97.42 (C1'-α), 83.90 (C4'-α), 82.98 (C4'-β), 82.29 (C2'-β), 79.09 (C2'-α), 78.99 (C3'-β), 77.77 (C3'-α), 73.54, 73.30, 73.22 (CH₂ Bn), 66.20 (C5'-β), 65.13 (C5'-α), 27.37 (t-Bu, TBDPS-β), 27.31 (t-Bu, TBDPS-α), 20.06 (Cq. t-Bu-β), 19.97 (Cq. t-Bu-α). IR: 3431, 2930, 2857, 1454, 1422, 1113, 1026, 941. HRMS [C₃₅H₄₀O₅Si + NH₄]⁺: 586.2989 found, 586.2983 calculated.



2,3-di-O-benzyl-5-O-triisopropylsilyl-D-ribose (10)

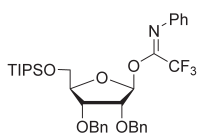
Dry 3 Å molecular sieves were added to a solution of compound **8** (1.89 g, 3.6 mmol) in dry THF (20 mL). The solution was stirred under argon at room temperature for 1 hour. After the addition of Ir(COD)(Ph₂MeP)₂PF₆ (47 mg, 0.054 mmol) the solution was purged with hydrogen for ~10s. After stirring under argon for 1 hour, the mixture was diluted with EtOAc (10 mL) and sat. aq. NaHCO₃ (10 mL). Upon addition of I₂ (1.37 g, 5.4 mmol), the mixture was allowed to stir at room temperature for 30 minutes. The mixture was then diluted with EtOAc (50 mL) and washed with sat. aq. Na₂S₂O₃ (50 mL) and brine (50 mL), respectively. The organic layer was dried over MgSO₄ and concentrated *in vacuo*.

Silica gel column chromatography (Pentane/EtOAc, 100/0 – 80/20) afforded the desired alcohol (1.36 g, 2.8 mmol, 78%) as a pale yellow oil. $^1\text{H-NMR}$ (400 MHz, MeOD) δ : 7.38 – 7.23 (m, 10H, arom.), 5.32 (d, $J = 2.4$ Hz, 1H, H1'- β), 5.26 (d, $J = 4.2$ Hz, 1H, H1'- α), 4.69 – 4.56 (m, 4H, CH₂ Bn), 4.52 (q, $J = 11.8$ Hz, 4H, CH₂ Bn), 4.23 (q, $J = 3.3$ Hz, 1H, H4'- α), 4.14 – 4.05 (m, 2H, H4'- β , H3'- β), 4.03 (dd, $J = 5.5$, 2.5 Hz, 1H, H3'- α), 3.93 (dd, $J = 5.4$, 4.3 Hz, 1H, H2'- α), 3.82 (dd, $J = 4.3$, 2.4 Hz, 1H, H2'- β), 3.76 (d, $J = 4.5$ Hz, 2H, H5'- β), 3.65 (d, $J = 3.5$ Hz, 2H, H5'- α), 1.08 – 1.03 (m, 21H, TIPS- β), 1.01 – 0.97 (m, 21H, TIPS- α). $^{13}\text{C-NMR}$ (100 MHz, MeOD) δ : 138.85, 138.83, 138.81, 138.76 (Cq. arom.), 129.28 – 128.69 (arom.), 100.78 (C1'- β), 97.09 (C1'- α), 83.99 (C4'- α), 83.07 (C4'- β), 81.91 (C2'- β), 78.72 (C3'- β), 78.63 (C2'- α), 77.55 (C3'- α), 73.42, 73.18, 73.08, 73.06 (CH₂ Bn), 65.76 (C5'- β), 64.68 (C5'- α), 18.46, 18.40, 18.38 (CH₃, TIPS), 12.89, 12.88, 12.80 (CH₃, TIPS). IR: 3420, 2941, 2864, 1454, 1119, 1069, 1026, 1012. 997, 881. HRMS [$\text{C}_{28}\text{H}_{42}\text{O}_5\text{Si} + \text{NH}_4$] $^+$: 504.3141 found, 504.3140 calculated.



1-O-((N-Phenyl)-2,2,2-trifluoroacetimido))-2,3-di-O-benzyl-5-O-tert-butylidiphenylsilyl- α,β -D-ribofuranose (11)

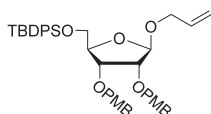
Compound **9** (1.42 g, 2.5 mmol) was dissolved in acetone (15 mL) and water (100 μL). Cs_2CO_3 (1.3 g, 4.0 mmol,) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (0.81 g, 3.9 mmol) were added and the reaction mixture was stirred at room temperature for 16 hours. After filtration over celite, the solvents were removed and the residue was purified using silica gel column chromatography (Pentane/EtOAc, 100/0 – 90/10) to afford the title compound as a pale yellow oil (1.69 g, 2.3 mmol, 92%). β -anomer: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.67 (dd, $J = 10.8$, 4.0 Hz, 4H, TBDPS arom.), 7.56 (d, $J = 7.8$ Hz, 4H, TBDPS arom.), 7.44 – 7.21 (m, 15H, arom.), 7.11 (t, $J = 7.4$ Hz, 1H, NPh), 6.80 (d, $J = 7.6$ Hz, 2H, NPh), 6.32 (bs, 1H, H1'), 4.83 – 4.58 (m, 2H, CH₂ Bn), 4.51 (q, $J = 11.6$ Hz, 2H, CH₂ Bn), 4.38 (dt, $J = 7.1$, 3.5 Hz, 1H, H4'), 4.29 – 4.21 (m, 1H, H3'), 4.12 (d, $J = 3.7$ Hz, 1H, H2'), 3.91 (AB, $J = 11.5$, 2.8 Hz, 1H, H5'), 3.78 (AB, $J = 11.5$, 4.0 Hz, 1H, H5'), 1.04 (s, 9H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 143.99, 137.71, 137.54 (Cq. arom.), 135.81, 135.72, 135.67 (TBDPS, arom.), 133.48, 133.24 (Cq. arom.), 129.84 – 127.84 (arom.), 126.52, 124.34 (NPh), 120.63 (TBDPS, arom.), 119.71, 102.84 (NPh), 102.84 (C1'), 83.60 (C4'), 79.07 (C2'), 76.69 (C3'), 72.79, 72.41 (CH₂ Bn), 63.50 (C5'), 26.85 (CH₃, t-Bu), 19.35 (Cq. t-Bu). IR: 3319, 2933, 2860, 1704, 1602, 1550, 1498, 1454, 1428, 1349, 1318, 1286, 1242, 1208, 1155, 1114, 1028, 922, 824, 756, 732, 695. HRMS [$\text{C}_{43}\text{H}_{44}\text{F}_3\text{NO}_5\text{Si} + \text{Na}$] $^+$: 762.2829 found, 762.2833 calculated.



1-O-((N-Phenyl)-2,2,2-trifluoroacetimido))-2,3-di-O-benzyl-5-O-triisopropylsilyl- α,β -D-ribofuranose (12)

Compound **10** (630 mg, 1.3 mmol) was dissolved in acetone (10 mL) and water (100 μL). Cs_2CO_3 (593 mg, 1.8 mmol,) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (374 mg, 1.8 mmol) were added and the reaction mixture was stirred at room temperature for 16 hours. After filtration over celite, the solvents were removed and the residue was purified using silica gel column chromatography (Pentane/EtOAc, 100/0 – 95/5) to afford the title compound as a white solid (637 mg, 0.97 mmol, 75%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.37 – 7.22 (m, 12H, 2xBn, NPh), 7.10 (t, $J = 7.4$ Hz, 1H, NPh), 6.79 (d, $J = 7.7$ Hz, 2H, NPh), 6.27 (bs, 1H, H1'), 4.77 – 4.60 (m, 2H, CH₂ Bn), 4.59 – 4.50 (m, 2H, CH₂ Bn), 4.36

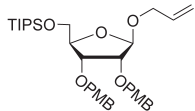
- 4.30 (m, 1H, H4'), 4.28 - 4.20 (m, 1H, H3'), 4.08 (d, $J = 4.4$ Hz, 1H, H2'), 3.94 (AB, $J = 11.2, 2.9$ Hz, 1H, H5'), 3.83 (AB, $J = 11.3, 3.9$ Hz, 1H, H5'), 1.12 - 1.02 (m, 21H, TIPS). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 144.03, 137.81, 137.58 (Cq. arom.), 128.81 - 119.69 (arom.), 102.52 (C1'), 84.94 (C4'), 79.14 (C2'), 76.52 (C3'), 72.80, 72.40 (CH_2 Bn), 63.08 (C5'), 18.06, 12.00 (TIPS). IR: 2943, 2866, 1712, 1600, 1455, 1328, 1206, 1128, 1089, 1027, 929, 883, 735, 695, 632. HRMS [$\text{C}_{28}\text{H}_{42}\text{O}_5\text{Si} + \text{Na}$] $^+$: 680.2988 found, 680.2990 calculated.



1-O-allyl-2,3-bis-O-(4-methoxybenzyl)-5-O-tert-butylidiphenylsilyl- α,β -D-ribofuranoside (19)

D-Ribose (15 g, 100 mmol) and allyl alcohol (250 mL) were stirred and acetyl chloride (1.43 mL, 20 mmol) was added.

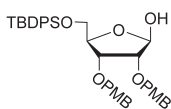
The reaction was stirred at room temperature for 1 hour and quenched upon addition of pyridine (2 mL). The reaction mixture was concentrated under reduced pressure, co-evaporated with toluene and dried under high vacuum. Crude allyl α,β -D-ribofuranoside was dissolved in DCM (250 mL) after which imidazole (10.2 g, 150 mmol) and TBDPSCl (27.3 mL, 105 mmol) were added. The reaction mixture was stirred at room temperature for 30 minutes and quenched upon addition of water. The water layer was extracted with DCM and the combined organic layers washed with brine. The organics were dried (MgSO_4) and concentrated *in vacuo*. The crude mixture was dissolved in dry DMF (275 mL), cooled to 0° C and sodium hydride (250 mmol, 10.0 g, 60% dispersion in mineral oil) was added in small portions. After hydrogen generation ceased, 4-methoxybenzyl chloride (34 mL, 250 mmol) was added. The reaction mixture was stirred under argon for 1 hour and allowed to reach room temperature. The reaction was carefully quenched with water and extracted with Et_2O . The organic layer was dried (MgSO_4), concentrated and a small portion was subjected to silica gel column chromatography (Pentane/ EtOAc , 95/5 - 85/15) to obtain the title compound as a pale yellow oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.74 - 7.60 (m, 4H, arom.), 7.47 - 7.31 (m, 6H, arom.), 7.29 (d, $J = 8.6$ Hz, 2H, arom.), 7.19 (d, $J = 8.6$ Hz, 2H, arom.), 6.87 (d, $J = 8.6$ Hz, 2H, arom.), 6.81 (d, $J = 8.6$ Hz, 2H, arom.), 5.88 - 5.71 (m, 1H, CH_2CHCH_2), 5.22 - 5.09 (m, 2H, CH_2CHCH_2), 5.06 (s, 1H, H1'), 4.60 (d, $J = 11.7$ Hz, 1H, CH_2 PMB), 4.54 (d, $J = 11.7$ Hz, 1H, CH_2 PMB), 4.46 (d, $J = 11.4$ Hz, 1H, CH_2 PMB), 4.38 (d, $J = 11.4$ Hz, 1H, CH_2 PMB), 4.27 - 4.21 (m, 1H, OCH_2CH), 4.19 - 4.11 (m, 2H, H3', H4'), 3.93 (dd, $J = 12.9, 6.3$ Hz, 1H, H2'), 3.88 (d, $J = 4.6$ Hz, 1H, H5'), 3.80 (s, 3H, CH_3 PMB), 3.78 (s, 3H, CH_3 PMB), 3.69 (AB, $J = 11.1, 4.6$ Hz, 1H, H5'), 1.03 (s, 9H, CH_3 TBDPS). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 159.42, 159.31 (Cq. arom.), 135.74, 134.26 (arom.), 133.55, 130.15, 130.08 (Cq. arom.), 129.76, 129.50, 127.78 (arom.), 117.36 (CH_2CHCH_2), 113.89, 113.83 (arom.), 104.50 (C1'), 82.19 (C4'), 79.71 (C2'), 77.53 (C3'), 72.10, 72.02 (CH_2 PMB), 68.52 (OCH_2CH), 64.55 (C5'), 55.40, 55.37 (CH_3 PMB), 26.93 (CH_3 TBDPS), 19.39 (Cq. TBDPS).



1-O-allyl-2,3-bis-O-(4-methoxybenzyl)-5-O-triisopropylsilyl- α,β -D-ribofuranoside (20)

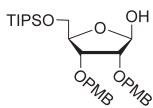
Compound **6** (5.2 g, 15 mmol) was dissolved in dry DMF (70 mL). The reaction mixture was stirred at 0° C and sodium hydride (60% in mineral oil, 1.26 g, 31.5 mmol) was slowly added. After hydrogen generation ceased, 4-methoxybenzyl chloride (4.27 mL, 31.5 mmol) was added. The

reaction mixture was stirred under argon for 16 hours and allowed to reach room temperature. The reaction was carefully quenched with water and extracted with Et₂O. The organic layer was dried (MgSO₄), concentrated and purified by silica gel column chromatography (Pentane/EtOAc, 100/0 – 70/30). The title compound (8.19 g, 13.9 mmol, 93%) was obtained as a colorless oil. **β-anomer**: ¹H-NMR (400 MHz, CDCl₃) δ: 7.34 – 7.18 (m, 4H, arom.), 6.92 – 6.76 (m, 4H, arom.), 5.86 (ddt, *J* = 16.5, 10.8, 5.6 Hz, 1H, CH₂CHCH₂), 5.28 – 5.11 (m, 2H, CHCH₂), 5.04 (s, 1H, H1'-β), [4.99 (d, *J* = 4.3 Hz, H1'-α)], 4.65 – 4.51 (m, 2H, CH₂ PMB), 4.45 (d, *J* = 6.8 Hz, 2H, CH₂ PMB), 4.22 – 4.14 (m, 2H, OCH₂CH, H4'), 4.14 – 4.08 (m, 1H, H3'), 3.94 (dd, *J* = 13.4, 5.3 Hz, 1H, OCH₂CH), 3.87 (d, *J* = 4.5 Hz, 1H, H2'), 3.77 (s, 8H, H5', CH₃ PMB), 1.05 (d, *J* = 4.8 Hz, 21H, TIPS-β), [0.98 (s, TIPS-α)]. ¹³C-NMR (100 MHz, CDCl₃) δ: 159.32, 159.27 (Cq. arom.), 134.29 (CH₂CHCH₂), 130.16, 130.03 (Cq. arom.), 129.62, 129.49, 129.39 (arom.), 117.04 (CHCH₂), 113.77, 113.72 (arom.), 104.37 (C1'-β), [100.16 (C1'-α)], 82.36 (C4'), 79.75 (C2'), 77.41 (C3'), 71.98, 71.88 (CH₂, arom.), 68.32 (OCH₂CH), 64.07 (C5'), 55.22 (CH₃ PMB), 18.02 (CH, TIPS), 11.95 (CH₃, TIPS). IR: 2940, 2864, 1612, 1512, 1464, 1246, 1013, 910, 881. HRMS [C₃₃H₅₀O₇Si + Na]⁺: 609.3214 found, 609.3218 calculated.



2,3-bis-O-(4-methoxybenzyl)-5-O-tert-butyldiphenylsilyl-D-ribose (21)

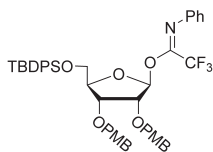
Crude compound **19** was dissolved in CHCl₃/H₂O (500 mL; 3/2 v/v%) and PdCl₂ (3.5 g, 20 mol%) was added. The mixture was vigorously stirred at 45 °C under O₂ atmosphere for 48 hours. To cleave the remaining isomerized allyl ether, sat. aq. NaHCO₃ (100 mL) and I₂ (0.6 eq.) were added. The organic layer was washed with sat. aq. Na₂S₂O₃, brine, dried over MgSO₄ filtered over celite and concentrated *in vacuo*. Silica gel column chromatography (Pentane/EtOAc, 90/10 – 70/30) afforded the desired alcohol (31.1 g, 49.5 mmol, 50% over 4 steps) as a brown oil. ¹H-NMR (400 MHz, CDCl₃) δ 7.68 – 7.53 (m, 8H, arom.), 7.48 – 7.33 (m, 12H, arom.), 7.33 – 7.15 (m, 8H, arom.), 6.90 – 6.80 (m, 8H, arom.), 5.32 – 5.21 (m, 2H, H1'-α, H1'-β), 4.68 – 4.44 (m, 8H, CH₂ PMB), 4.31 – 4.10 (m, 3H, H4'-α, H3'-β, H4'-β), 4.05 (dd, *J* = 5.0, 1.8 Hz, 1H, H3'-α), 4.00 – 3.92 (m, 1H, H2'-α), 3.87 – 3.82 (m, 2H, H2'-β, H5'-β), 3.82 – 3.76 (m, 13H, CH₃ PMB, H5'-β), 3.67 – 3.54 (m, 2H, H5'-α), 1.01 (s, 9H, CH₃ TBDPS-β), 0.94 (s, 9H, CH₃ TBDPS-α). ¹³C-NMR (101 MHz, CDCl₃) δ 159.54, 159.48 (Cq. arom.), 135.81, 135.73, 135.65 (arom.), 133.23, 133.00, 132.69 (Cq. arom.), 130.10, 129.97, 129.93, 129.88 (arom.), 129.81, 129.75 (Cq. arom.), 129.65, 129.61, 129.57, 129.95, 129.90, 129.88, 114.02, 113.97, 113.94 (arom.), 100.19 (C1'-β), 96.38 (C1'-α), 82.61 (C4'-α), 82.29 (C4'-β), 80.23 (C2'-β), 77.85 (C3'-β), 77.51 (C2'-α), 76.16 (C3'-α), 72.61, 72.14, 72.03 (CH₂, PMB), 64.10 (C5'-β), 63.35 (C5'-α), 55.40, 55.39 (CH₃ PMB), 26.94 (CH₃ TBDPS), 19.31 (Cq. TBDPS).



2,3-bis-O-(4-methoxybenzyl)-5-O-triisopropylsilyl-D-ribose (22)

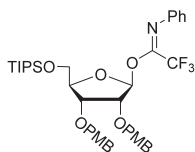
Compound **20** (8.19 g, 13.9 mmol) was dissolved in 60 mL CHCl₃/H₂O (3/1; v/v) and PdCl₂ (0.37 g, 15 mol%) was added. The mixture was vigorously stirred at 45 °C under O₂ atmosphere for 48 hours after which the mixture was concentrated *in vacuo*. EtOAc (50 mL), sat. aq. NaHCO₃ (50 mL) and I₂ (1 eq.) were added to convert the remaining isomerized allyl ether into the free alcohol. The organic layer was washed with sat. aq. Na₂S₂O₃ (50 mL), brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Silica gel column chromatography

(Pentane/EtOAc, 90/10 – 70/30) afforded the desired alcohol (6.52 g, 11.9 mmol, 86%) as a colorless oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.38 – 7.11 (m, 8H, arom.), 6.94 – 6.74 (m, 8H, arom.), 5.29 – 5.18 (m, 1H, H1'- β , H1'- α), 4.68 – 4.38 (m, 8H, CH_2 PMB), 4.32 – 4.15 (m, 4H, H4'- β , H2'- α , H3'- α , H4'- α), 4.04 (dd, J = 4.9, 1.5 Hz, 1H, H3'- β), 3.93 (t, J = 4.6 Hz, 1H, H2'- β), 3.83 (AB, J = 10.8, 3.0 Hz, 1H, H5'- β), 3.80 – 3.77 (m, 13H, H5'- β , CH_3 PMB), 3.69 (AB, J = 10.8, 3.0 Hz, 1H, H5'- α), 3.59 (AB, J = 10.8, 5.0 Hz, 1H, H5'- α), 1.11 – 0.94 (m, 42, TIPS- β , TIPS- α). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 159.41, 159.38, 129.89 (Cq. arom.), 129.81 (arom.), 129.73 (Cq. arom.), 129.65, 129.57, 129.48, 113.82 (arom.), 99.91 (C1'- β), 96.25 (C1'- α), 82.80 (C4'- α), 82.43 (C4'- β), 80.25 (C2'- β), 77.49 (C3'- β), 77.24 (C2'- α), 75.71 (C3'- α), 72.42, 71.96, 71.87 (CH_2 , arom.), 63.70 (C5'- β), 62.43 (C5'- α), 55.27 (CH_3 PMB), 17.96, 17.92 (CH, TIPS), 11.86 (CH_3 , TIPS). IR: 3306, 2941, 2866, 1612, 1514, 1464, 1246, 1206, 1152, 1128, 1086, 1034. HRMS $[\text{C}_{30}\text{H}_{46}\text{O}_7\text{Si} + \text{Na}]^+$: 569.2905 found, 569.2905 calculated.



1-O-((N-Phenyl)-2,2,2-trifluoroacetimido)-2,3-bis-O-(4-methoxybenzyl)-5-tert-butyldiphenylsilyl- α,β -D-ribofuranose (21)

Compound **21** (6.29 g, 10.0 mmol) was dissolved in acetone (50 mL) and water (1.0 mL). Cs_2CO_3 (4.87 g, 15.0 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (2.18 g, 10.5 mmol) were added and the reaction mixture was stirred at room temperature for 1 hour. The mixture was filtered over celite, concentrated *in vacuo* and the residue was purified using silica gel column chromatography (Pentane/EtOAc, 99/1 – 95/5) to afford the title compound as a pale yellow oil (6.35 g, 8.1 mmol, 81%). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 7.68 (t, J = 7.1 Hz, 4H), 7.64 – 7.51 (m, 3H), 7.49 – 7.32 (m, 10H), 7.32 – 7.22 (m, 7H), 7.15 – 6.99 (m, 2H), 6.91 – 6.73 (m, 8H), 6.44 (bs, H1'- α), 6.27 (bs, 1H, H1'- β), 4.75 – 4.55 (m, 2H, CH_2 PMB), 4.52 – 4.40 (m, 2H, CH_2 PMB), 4.37 – 4.27 (m, 1H, H4'), 4.25 – 4.20 (m, 1H, H3'), 4.15 – 4.03 (m, 1H, H2'), 3.90 (d, J = 11.7 Hz, 1H, H5'), 3.80 – 3.73 (m, 7H, CH_3 PMB, H5'), 3.70 – 3.55 (m, H5'- α), 1.05 (s, 9H, CH_3 , TBDPS- β), 0.97 (s, CH_3 TBDPS- α). $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ : 159.57, 159.52, 159.49, 159.25, 144.34, 143.98 (Cq. arom.), 135.76, 135.69, 135.67, 135.62 (arom.), 133.47, 133.22, 133.12, 132.84 (Cq. arom.), 130.51, 129.97, 129.93, 129.79, 129.77 (arom.), 129.58 (Cq. arom.), 129.55, 129.46, 129.39, 129.31, 128.80, 128.74, 127.89, 127.86, 127.80, 127.79, 126.36, 124.27, 120.63, 119.66, 114.02, 113.94, 113.91, 113.80 (arom.), 102.91 (C1'- β), 85.77 (C4'- α), 83.55 (C4'- β), 78.79 (C2'- α), 78.59 (C2'- β), 76.16 (C3'- β), 75.37 (C3'- α), 72.94, 72.37, 72.30, 72.04 (CH_2 , PMB), 63.85, 63.44 (C5'- β), 55.33, 55.31, 55.29 (CH_3 PMB), 26.88 (CH_3 TBDPS), 19.32, 19.27 (Cq. TBDPS).



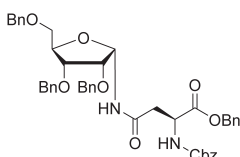
1-O-((N-Phenyl)-2,2,2-trifluoroacetimido)-2,3-bis-O-(4-methoxybenzyl)-5-O-triisopropylsilyl- α,β -D-ribofuranose (22)

Compound **22** (3.2 g, 5.8 mmol) was dissolved in acetone (30 mL) and water (1 mL). Cs_2CO_3 (2.83 g, 8.7 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (1.3 mL, 8.8 mmol) were added and the reaction mixture was stirred at room temperature for 16 hours. After filtration over celite, the solvents were removed and the residue was purified using silica gel column chromatography (Pentane/EtOAc, 100/0 – 95/5) to afford the title compound

as a pale yellow oil (2.49 g, 4.71 mmol, 81%). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.55 (d, $J = 7.9$ Hz, 2H, arom.), 7.41 – 7.16 (m, 4H, arom.), 7.09 (t, $J = 7.4$ Hz, 1H, arom.), 6.85 (dd, $J = 12.6, 8.5$ Hz, 4H, arom.), 6.78 (d, $J = 7.6$ Hz, 2H, arom.), 6.22 (bs, 1H, H1'), 4.74 – 4.52 (m, 2H, CH_2 PMB), 4.52 – 4.38 (m, 2H, CH_2 PMB), 4.36 – 4.25 (m, 1H, H4'), 4.25 – 4.15 (m, 1H, H3'), 4.04 (d, $J = 3.6$ Hz, 1H, H2'), 3.94 – 3.90 (m, 1H, H5'), 3.83 – 3.80 (m, 1H, H5'), 3.79 – 3.73 (m, 6H, CH_3 PMB), 1.06 (bs, 21H, TIPS). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 159.50, 159.44, 143.96 (Cq. arom.), 129.93 (arom.), 129.79 (Cq. arom.), 129.63 (arom.), 129.51 (Cq. arom.), 129.30, 128.73, 126.30, 124.17, 120.66, 119.57, 113.85, 113.72 (arom.), 102.47 (C1'), 83.76 (C4'), 78.53 (C2'), 75.82 (C3'), 72.33, 71.97 (CH_2 PMB), 62.86 (C5'), 55.28 (CH_3 PMB), 17.98 (CH, TIPS), 11.89 (CH_3 , TIPS). IR: 2941, 2866, 1711, 1612, 1514, 1464, 1248, 1206, 1153, 1128, 1085, 1034. HRMS [$+\text{NH}_4$] $^+$: 740.3200 found, 740.3201 calculated.

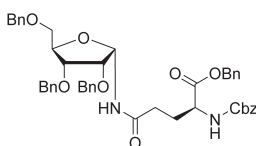
General procedure A

The trifluoroacetimidate donor (**1**, **11**, **12** or **24**) (1.25 – 1.5 eq.) and Cbz-Gln-OBn or Cbz-Asn-OBn (1.0 eq.) were co-evaporated with 1,4-dioxane (2x) and DCE (1x), dissolved in dry DCM and stirred with freshly activated 3 Å molecular sieves at room temperature for 1 h under argon to remove traces of water. The solution was then cooled to -20°C and TMSOTf (0.2 eq.) was added to the reaction mixture. After being stirred at the same temperature for 5 – 10 min, the acceptor started to precipitate and the reaction mixture was allowed to warm to room temperature. The reaction was stirred at room temperature for 60 – 90 min and quenched by the addition of triethylamine. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo* and purified.



N^γ -(2,3,5-tri-O-benzyl- α -D-ribose)- N^α -benzyloxycarbonyl asparagine benzyl ester (**2**)

General procedure A using donor **1** (148 mg, 0.25 mmol), Cbz-Asn-OBn (71 mg, 0.20 mmol), TMSOTf (7.0 μL , 40 μmol) and DCM (3 mL) afforded the title compound (88 mg, 115 μmol , 58% yield) after silica gel chromatography (Pentane/ EtOAc , 90/10 – 60/40). $^1\text{H-NMR}$ (600 MHz, MeOD-CDCl_3) δ : 7.34 – 7.18 (m, 25H), 5.74 (d, $J = 5.4$ Hz, 1H, H1'- α), [5.62 (d, $J = 3.3$ Hz, H1'- β)], 5.20 – 4.96 (m, 4H, CH_2 Bn, CH_2 Cbz), 4.61 – 4.39 (m, 7H, CH_2 Bn, CH α -Asn), 4.17 – 4.11 (m, 1H, H4'), 4.06 (t, $J = 5.2$ Hz, 1H, H2'), 3.98 – 3.93 (m, 1H, H3'), 3.42 (d, $J = 4.2$ Hz, 2H, H5'), 2.81 – 2.63 (m, 2H, CH_2 β -Asn). $^{13}\text{C-NMR}$ (150 MHz, MeOD-CDCl_3) δ : 172.08, 171.43 (CO α -Asn, CO γ -Asn), 157.63 (CO Cbz), 138.61, 138.29, 138.16, 137.16, 136.30 (Cq. arom.), 129.20 – 128.43 (arom.), 82.01 (C4'), 79.81 (C1'), 78.62 (C3'), 77.28 (C2'), 74.18, 73.70, 73.37 (CH_2 Bn), 70.70 (C5'), 68.02, 67.58 (CH_2 Bn, CH_2 Cbz), 51.68 (CH α -Asn), 38.47 (CH_2 β -Asn). IR: 3400, 3320, 2926, 2866, 1717, 1678, 1497, 1454, 1329, 1209, 1042, 1026, 910. HRMS [$\text{C}_{45}\text{H}_{46}\text{N}_2\text{O}_9 + \text{Na}$] $^+$: 848.3801 found, 848.3800 calculated.

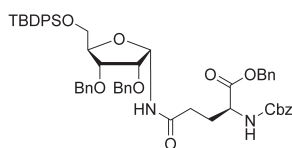


N^δ -(2,3,5-tri-O-benzyl- α -D-ribose)- N^α -benzyloxycarbonyl glutamine benzyl ester (**3**)

General procedure A using donor **1** (266 mg, 0.45 mmol), Cbz-Gln-OBn (111 mg, 0.30 mmol), TMSOTf (10.9 μL , 60 μmol) and DCM (6 mL) afforded the title compound (130

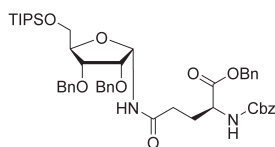
mg, 170 μ mol, 56% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 60/40). **¹H-NMR** (400 MHz, MeOD-CDCl₃) δ : 7.39 – 7.15 (m, 25H), 5.74 (d, J = 5.4 Hz, 1H, H1'- α), [5.63 (d, J = 3.1 Hz, H1'- β)] 5.18 – 4.98 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.64 – 4.39 (m, 6H, CH₂ Bn), 4.24 (dd, J = 8.9, 4.9 Hz, 1H, CH α -Gln), 4.19 (q, J = 4.1 Hz, 1H, H4'), 4.09 (t, J = 5.3 Hz, 1H, H2'), 3.99 (dd, J = 5.1, 3.0 Hz, 1H, H3'), 3.43 (d, J = 4.0 Hz, 2H, H5'), 2.23 (t, J = 7.5 Hz, 2H, CH₂ γ -Gln), 2.17 – 2.02 (m, 1H, CH₂ β -Gln), 2.01 – 1.82 (m, 1H, CH₂ β -Gln). **¹³C-NMR** (100 MHz, CDCl₃) δ : 172.28, 171.90 89 (CO α -Gln, CO δ -Gln), 156.19 (CO Cbz), 138.00, 137.77, 137.45, 136.37, 135.39 (Cq. arom.), 128.74 – 127.71 (arom.), 81.61 (C4'), 78.73 (C1'), 78.16 (C3'), 76.79 (C2'), 73.70, 72.79, 72.68 (CH₂ Bn), 70.24 (C5'), 67.35, 67.10 (CH₂ Bn, CH₂ Cbz), 53.91 (CH α -Gln), 32.61 (CH₂ γ -Gln), 27.64 (CH₂ β -Gln). **IR**: 2926, 2866, 1717, 1684, 1670, 1497, 1454, 1420, 1339, 1211, 1080, 1045, 1026, 912. **HRMS** [C₄₆H₄₈N₂O₉ + Na]⁺: 795.3250 found, 795.3252 calculated.

2



N⁶-(2,3-di-O-benzyl-5-O-tert-butylidiphenylsilyl- α -D-ribose)-N ^{α} -benzyloxycarbonyl glutamine benzyl ester (13)

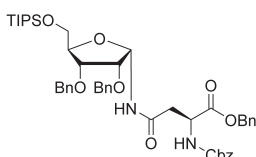
General procedure A using donor **11** (185 mg, 0.25 mmol), Cbz-Gln-OBn (62 mg, 0.167 mmol), TMSOTf (6.0 μ L, 33 μ mol) and DCM (6 mL) afforded the title compound (88 mg, 96 μ mol, 57% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 65/35). **¹H-NMR** (400 MHz, MeOD) δ : 7.61 – 7.53 (m, 4H, TBDPS arom.), 7.44 – 7.31 (m, 6H, TBDPS arom.), 7.31 – 7.20 (m, 20H, arom.), 5.79 (d, J = 5.4 Hz, 1H, H1'- α), [5.65 (d, J = 4.2 Hz, H1'- β)] 5.15 – 4.97 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.63 – 4.42 (m, 4H, CH₂ Bn), 4.25 (dd, J = 8.9, 4.9 Hz, 1H, CH α -Gln), 4.16 – 4.07 (m, 2H, H4', H2'), 4.08 – 4.05 (m, 1H, H3'), 3.58 (d, J = 3.6 Hz, 2H, H5'), 2.23 (t, J = 7.5 Hz, 2H, CH₂ γ -Gln), 2.16 – 2.08 (m, 1H, CH₂ β -Gln), 1.98 – 1.89 (m, 1H, CH₂ β -Gln), 0.95 (s, 9H, t-Bu). **¹³C-NMR** (100 MHz, MeOD) δ : 174.12, 172.89 (CO α -Gln, CO δ -Gln), 157.92 (CO Cbz), 138.38, 138.16, 137.29 (Cq. arom.), 136.33, 136.25 (TBDPS arom.), 133.69, 133.49 (Cq. arom.), 130.66, 130.61 (TBDPS arom.), 129.28 – 128.49 (arom.), 83.64 (C4'), 79.68 (C1'), 78.44 (C3'), 77.58 (C2'), 73.54, 73.35 (CH₂ Bn), 67.76, 67.49 (CH₂ Bn, CH₂ Cbz), 64.69 (C5'), 54.56 (CH α -Gln), 33.21 (CH₂ γ -Gln), 27.78 (CH₂ β -Gln), 27.24 (t-Bu), 19.73 (Cq. t-Bu). **IR**: 3410, 3309, 2926, 2857, 1722, 1680, 1506, 1499, 1454, 1244, 1111, 1045. **HRMS** [C₄₈H₆₂N₂O₉Si + Na]⁺: 943.3961 found, 943.3960 calculated.



N⁶-(2,3-di-O-benzyl-5-O-triisopropylsilyl- α -D-ribose)-N ^{α} -benzyloxycarbonyl glutamine benzyl ester (14)

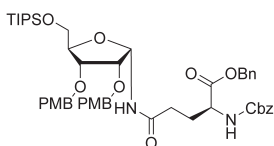
General procedure A using donor **12** (493 mg, 0.75 mmol), Cbz-Gln-OBn (214 mg, 0.58 mmol), TMSOTf (21.0 μ L, 116 μ mol) and DCM (15 mL) afforded the title compound (323 mg, 385 μ mol, 66% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 70/30). **¹H-NMR** (400 MHz, MeOD) δ : 7.40 – 7.20 (m, 20H, arom.), 5.76 (d, J = 5.4 Hz, 1H, H1'- α), [5.63 (d, J = 4.8 Hz, H1'- β)] 5.17 – 4.99 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.69 – 4.51 (m, 4H, CH₂ Bn), 4.24 (dd, J = 9.1, 5.1 Hz, 1H, CH α -Gln), 4.18 – 4.10 (m, 2H, H4', H2'), 4.08 (dd, J = 5.0, 2.4 Hz, 1H, H3'), 3.69 – 3.63 (m, 2H, H5'), 2.25 (t, J = 7.5 Hz, 2H, CH₂ γ -Gln), 2.19 – 2.05 (m, 1H, CH₂ β -Gln), 1.98 – 1.86 (m, 1H, CH₂ β -Gln), 1.00 (s, 21H, TIPS). **¹³C-NMR** (100 MHz, MeOD) δ : 174.60, 173.33

(CO α -Gln, CO δ -Gln), 158.54 (CO Cbz), 139.16, 138.95, 138.06, 137.19 (Cq. arom.), 129.58 - 128.80 (arom.), 84.28 (C4'), 80.25 (C1'), 78.78 (C3'), 77.87 (C2'), 73.70, 73.55 (CH₂ Bn), 67.91, 67.67 (CH₂ Bn, CH₂ Cbz), 64.94 (C5'), 55.00 (CH α -Gln), 33.44 (CH₂ γ -Gln), 28.10 (CH₂ β -Gln), 18.46, 13.05 (CH, CH₃, TIPS). IR: 3408, 3311, 2941, 2864, 1720, 1682, 1497, 1454, 1211, 1045, 1026, 881. HRMS [C₄₈H₆₂N₂O₉Si + Na]⁺: 861.4120 found, 861.4117 calculated.



N^γ-(2,3-di-O-benzyl-5-O-triisopropylsilyl- α -D-ribose)-N^α-benzyloxycarbonyl asparagine benzyl ester (15)

General procedure A using donor **12** (165 mg, 0.25 mmol), Cbz-Asn-OBn (71 mg, 0.20 mmol), TMSOTf (7.0 μ L, 40 μ mol) and DCM (3 mL) afforded the title compound (112 mg, 136 μ mol, 68% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 - 60/40). ¹H-NMR (600 MHz, MeOD-CDCl₃) δ : 7.39 - 7.18 (m, 20H, arom.), 5.75 (d, J = 5.6 Hz, 1H, H1'- α), [5.63 (d, J = 4.8 Hz, H1'- β)], 5.17 - 4.99 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.66 - 4.57 (m, 3H, CH α -Asn, CH₂ Bn), 4.56 - 4.51 (m, 2H, CH₂ Bn), 4.13 - 4.07 (m, 2H, H4', H2'), 4.06 - 4.02 (m, 1H, H3'), 3.67 - 3.59 (m, 2H, H5'), 2.81 - 2.64 (m, 2H, CH₂ β -Asn), 0.98 (s, 21H, TIPS). ¹³C-NMR (150 MHz, MeOD-CDCl₃) δ : 172.30, 171.65 (CO α -Asn, CO γ -Asn), 157.88 (CO Cbz), 138.62, 138.39, 137.43, 136.59 (Cq. arom.), 129.43 - 128.69 (arom.), 84.22 (C4'), 79.96 (C1'), 78.51 (C3'), 77.62 (C2'), 73.60, 73.56 (CH₂ Bn), 68.20, 67.75 (CH₂ Bn, CH₂ Cbz), 64.69 (C5'), 51.97 (CH α -Asn), 38.75 (CH₂ β -Asn), 18.54, 18.49, 18.47, 12.81 (CH, CH₃, TIPS). IR: 3405, 2941, 2864, 1721, 1678, 1497, 1454, 1329, 1211, 1082, 1043, 1026, 881. HRMS [C₄₇H₆₀N₂O₉Si + Na]⁺: 847.3957 found, 847.3960 calculated.



N^δ-(2,3-bis-O-(4-methoxybenzyl)-5-O-triisopropylsilyl- α -D-ribose)-N^α-benzyloxycarbonyl glutamine benzyl ester (37)

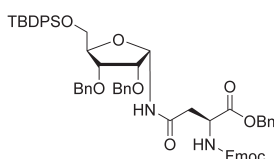
General procedure A using donor **24** (215 mg, 0.30 mmol), Cbz-Gln-OBn (74 mg, 0.20 mmol), TMSOTf (7.2 μ L, 40 μ mol) and DCM (4 mL) afforded the title compound (93 mg, 103 μ mol, 52% yield, 85/15 α/β) after silica gel chromatography (Pentane/EtOAc, 90/10 - 75/25). ¹H-NMR (400 MHz, MeOD-CDCl₃) δ : 7.38 - 7.15 (m, 14H, arom.), 6.86 (t, J = 8.7 Hz, 4H, PMB arom.), 5.72 (d, J = 5.4 Hz, 1H, H1'- α), [5.60 (d, J = 4.8 Hz, H1'- β)], 5.17 - 4.97 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.61 - 4.38 (m, 4H, CH₂ PMB), 4.24 (dd, J = 8.8, 5.2 Hz, 1H, CH α -Gln), 4.14 - 4.04 (m, 2H, H4', H2'), 4.04 - 4.00 (m, 1H, H3'), 3.74 (d, J = 1.6 Hz, 6H, CH₃ PMB), 3.66 - 3.28 (m, 2H, H5'), 2.24 (t, J = 7.6 Hz, 2H, CH₂ γ -Gln), 2.18 - 2.03 (m, 1H, CH₂ β -Gln), 1.98 - 1.82 (m, 1H, CH₂ β -Gln), 0.99 (bs, 21H, TIPS). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ : 174.56, 173.32 (CO α -Gln, CO δ -Gln), 160.99 (Cq. arom.), 158.50 (CO Cbz), 138.04, 137.17 (Cq. arom.), 130.97 - 130.76 (arom.), 129.56 - 128.78 (arom.), 114.92 - 114.75 (PMB arom.), 84.26 (C4'), 80.23 (C1'), 78.28 (C3'), 77.34 (C2'), 73.28, 73.17 (CH₂ PMB), 67.91, 67.67 (CH₂ Bn, CH₂ Cbz), 64.91 (C5'), 55.71 (CH₃ PMB), 55.00 (CH α -Gln), 33.45 (CH₂ γ -Gln), 28.11 (CH₂ β -Gln), 18.48, 13.04 (CH, CH₃, TIPS). IR: 3410, 3312, 2940, 2864, 1732, 1717, 1684, 1512, 1456, 1248, 1034. HRMS [C₅₀H₆₆N₂O₁₁Si + Na]⁺: 921.4328 found, 921.4328 calculated.

General procedure B

The trifluoroacetimidate donor (**11**, **12**, **23** or **24**) and Fmoc-amino acid-OR (1.0 eq.) were co-evaporated with 1,4-dioxane (3x), dissolved in dry DCM/Dioxane (1/1; v/v) and stirred with freshly activated 3 Å molecular sieves at room temperature for 1 h under argon to remove traces of water. The temperature was adjusted as desired and activator was added to the reaction mixture. The reaction mixture was stirred at the same temperature and upon complete consumption of donor, as indicated by TLC, quenched by the addition of triethylamine. The mixture was filtered through a pad of Celite, concentrated *in vacuo* and purified by silica gel chromatography.

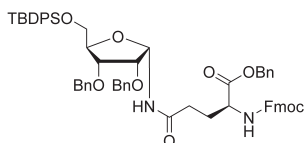
Preparation $\text{SiO}_2\text{-HClO}_4$ ²⁰

Silica gel (5g, 200 mesh) was suspended in Et_2O (15 mL) and HClO_4 (172 μL , 70% aqueous solution, 2 mmol) was added to the silica gel slurry. The mixture was stirred at room temperature for 30 minutes and the solvents removed *in vacuo*. The resulting powder was dried at 110 °C for 2 h under reduced pressure and the powder was used directly or stored under an argon atmosphere and protected against light.



N^{γ} -(2,3-di-O-benzyl-5-O-*tert*-butyldiphenylsilyl- α -D-ribose)- N^{α} -fluorenylmethoxycarbonyl asparagine benzyl ester (16**)**

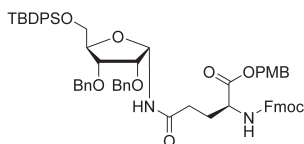
General procedure B, at room temperature, using donor **11** (296 mg, 0.40 mmol), Fmoc-Asn-OBn (89 mg, 0.20 mmol), TMSOTf (3.6 μL , 20 μmol) and Dioxane/DCM (6 mL) afforded the title compound (125 mg, 126 μmol , 63% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 75/25). $^1\text{H-NMR}$ (400 MHz, MeOD-CDCl_3) δ : 7.73 (d, J = 7.5 Hz, 2H, Fmoc arom.), 7.64 – 7.49 (m, 6H, Fmoc, TBDPS arom.), 7.45 – 7.18 (m, 25H, arom.), 5.80 (d, J = 5.4 Hz, 1H, $\text{H1}'$ - α), [5.65 (d, J = 4.8 Hz, $\text{H1}'$ - β)], 5.14 (bs, 2H, CH_2 Bn), 4.62 (t, J = 6.1 Hz, 1H, CH α -Asn), 4.61 – 4.50 (m, 4H, CH_2 Bn), 4.33 (AB, J = 10.4, 7.2 Hz, 1H, CH_2 Fmoc), 4.22 (AB, J = 10.4, 7.2 Hz, 1H, CH_2 Fmoc), 4.17 – 4.08 (m, 3H, CH Fmoc, $\text{H2}'$, $\text{H3}'$), 4.08 – 4.03 (m, 1H, $\text{H4}'$), 3.61 – 3.51 (m, 2H, $\text{H5}'$), 2.78 (d, J = 6.1 Hz, 2H, CH_2 β -Asn), 0.94 (s, 9H, *t*-Bu). $^{13}\text{C-NMR}$ (100 MHz, MeOD-CDCl_3) δ : 172.28, 171.82 (CO α -Asn, CO δ -Asn), 157.94 (CO Fmoc), 144.82, 142.22, 138.60, 138.44 (Cq. arom.), 136.48, 136.40 (TBDPS arom.), 133.87, 133.68 (Cq. arom.), 130.74, 129.38 – 127.93, 126.04, 125.99, 120.67 (arom.), 83.72 ($\text{C4}'$), 80.05 ($\text{C1}'$), 78.46 ($\text{C3}'$), 77.76 ($\text{C2}'$), 73.74, 73.48 (CH_2 Bn), 68.12, 68.01 (CH_2 Bn, CH_2 Fmoc), 64.78 ($\text{C5}'$), 52.03 (CH α -Asn), 47.99 (CH Fmoc), 38.63 (CH_2 β -Asn), 27.28 (*t*-Bu), 19.83 (Cq. *t*-Bu). IR: 3405, 2930, 2859, 1722, 1682, 1497, 1452, 1331, 1215, 1105, 1042, 1026. HRMS [$\text{C}_{61}\text{H}_{62}\text{N}_2\text{O}_9\text{Si} + \text{Na}$]⁺: 1017.4122 found, 1017.4117 calculated.



N^{δ} -(2,3-di-O-benzyl-5-O-*tert*-butyldiphenylsilyl- α -D-ribose)- N^{α} -fluorenylmethoxycarbonyl glutamine benzyl ester (17**)**

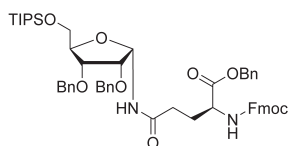
General procedure B, at 0 °C, using donor **11** (222 mg, 0.30 mmol), Fmoc-Gln-OBn (92 mg, 0.20 mmol), TMSOTf (7.2 μL , 40 μmol) and Dioxane/DCM (5 mL) afforded the title compound (98 mg, 97 μmol , 49% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 70/30). $^1\text{H-NMR}$ (400 MHz, MeOD-CDCl_3) δ : 7.72 (d, J = 7.5 Hz, 2H,

Fmoc arom.), 7.61 – 7.49 (m, 6H, Fmoc, TBDPS arom.), 7.43 – 7.18 (m, 25H, arom.), 5.80 (d, $J = 5.5$ Hz, 1H, H1'- α), 5.66 (d, $J = 4.2$ Hz, 1H, H1'- β), 5.11 (d, $J = 3.3$ Hz, 2H, CH₂ Bn), 4.65 – 4.44 (m, 4H, CH₂ Bn), 4.43 – 4.22 (m, 2H, CH₂ Fmoc, CH α -Gln), 4.18 – 4.02 (m, 6H, CH Fmoc, H4'- α , H2'- α , H3'- α , H3'- β , H4'- β), 3.86 – 3.80 (m, 1H, H2'- β), 3.77 – 3.64 (m, 2H, H5'- β), 3.58 (d, $J = 3.5$ Hz, 2H, H5'- α), 2.22 (t, $J = 7.3$ Hz, 2H, CH₂ γ -Gln), 2.18 – 2.02 (m, 2H, CH₂ β -Gln), 1.99 – 1.77 (m, 2H, CH₂ β -Gln), 0.98 (s, 9H, tBu- β), 0.95 (s, 9H, tBu- α). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ : 174.06, 173.82, 172.76, 172.74 (CO α -Gln, CO δ -Gln), 157.93, 157.78 (CO Fmoc), 144.64, 144.60, 144.42, 144.37, 142.00, 141.98, 138.24, 138.15, 138.00 (Cq. arom.), 136.25, 136.17, 136.12 (TBDPS arom.), 133.58, 133.44, 133.39 (Cq. arom.), 130.58, 130.54, 129.21 – 127.72, 125.82, 125.74, 125.70, 120.49 (arom.), 83.60 (C4'- α), 83.55 (C1'- β), 82.57 (C4'- β), 80.32 (C2'- β), 79.55 (C1'- α), 78.34 (C3'- α), 77.51 (C2'- α), 76.52 (C3'- β), 73.46, 73.28 (CH₂ Bn α), 72.78, 72.55 (CH₂ Bn β), 67.78, 67.72, 67.58 (CH₂ Bn, CH₂ Fmoc), 64.62 (C5'- α), 64.26 (C5'- β), 54.46 (CH α -Gln α), 54.39 (CH α -Gln β), 47.82 (CH Fmoc α), 47.76 (CH Fmoc β), 33.23 (CH₂ γ -Gln α), 32.71 (CH₂ γ -Gln β), 27.91 (CH₂ β -Gln β), 27.67 (CH₂ β -Gln α), 27.34 (t-Bu β), 27.21 (t-Bu α), 19.84 (Cq. t-Bu β), 19.67 (Cq. t-Bu α). IR: 3310, 2920, 2853, 1740, 1686, 1651, 1497, 1445, 1427, 1321, 1260, 1215, 1105, 1082, 1037. HRMS [C₆₂H₆₄N₂O₉Si + Na]⁺: 1031.4272 found, 1031.4273 calculated.



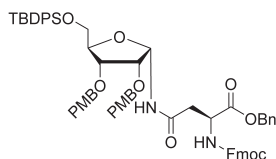
N⁶-(2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl- α -D-ribose)-N ^{α} -fluorenylmethoxycarbonyl glutamine (4-methoxybenzyl) ester (38**)**

General procedure B, at 0 °C, using donor **11** (222 mg, 0.30 mmol), Fmoc-Gln-OPMB (98 mg, 0.20 mmol), TMSOTf (7.0 μ L, 40 μ mol) and Dioxane/DCM (5 mL) afforded the title compound (95 mg, 91 μ mol, 49% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 70/30). ¹H-NMR (400 MHz, MeOD-CDCl₃) δ : 7.78 – 7.65 (m, 2H, arom.), 7.63 – 7.50 (m, 4H, arom.), 7.45 – 7.14 (m, 24H, arom.), 6.81 – 6.68 (m, 2H, PMB arom.), 5.79 (d, $J = 5.4$ Hz, 1H, H1'- α), 5.65 (d, $J = 4.4$ Hz, 1H, H1'- β), 5.12 – 4.96 (m, 2H, CH₂ Bn), 4.64 – 4.38 (m, 4H, CH₂ Bn), 4.34 (AB, $J = 10.5, 6.9$ Hz, 1H, CH₂ Fmoc), 4.28 – 4.18 (m, 2H, CH₂ Fmoc, CH α -Gln), 4.18 – 4.00 (m, 7H, CH Fmoc, H4'- α , H2'- α , H3'- α , H3'- β , H4'- β), 3.84 (t, $J = 4.7$ Hz, 1H, H2'- β), 3.73 – 3.63 (m, 4H, H5'- β , CH₃ PMB), 3.63 – 3.53 (m, 2H, H5'- α), 2.22 (t, $J = 7.4$ Hz, 2H, CH₂ γ -Gln), 2.19 – 2.03 (m, 1H, CH₂ β -Gln), 1.98 – 1.75 (m, 1H, CH₂ β -Gln), 0.98 (s, 9H, tBu- β), 0.94 (s, 10H, tBu- α). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ : 174.33, 174.23, 173.02, 173.00 (CO α -Gln, CO δ -Gln), 160.74, 160.71 (Cq. arom. PMB), 158.22, 158.07 (CO Fmoc), 144.92, 144.89, 144.64, 144.59, 142.21, 142.17, 138.54, 138.44, 138.33 (Cq. arom.), 136.43, 136.38, 136.35 (TBDPS arom.), 134.09, 133.80, 133.70, 133.62 (Cq. arom.), 130.88, 130.75, 130.70, 129.35 – 128.51, 127.89, 127.87, 126.04, 125.93, 125.89, 120.64, 114.61 (arom.), 83.73 (C4'- α), 83.65 (C1'- β), 82.76 (C4'- β), 80.57 (C2'- β), 79.84 (C1'- α), 78.49 (C3'- α), 77.71 (C2'- α), 76.87 (C3'- β), 73.63, 73.40 (CH₂ Bn α), 73.00, 72.69 (CH₂ Bn β), 67.86, 67.75, 67.69 (CH₂ PMB, CH₂ Fmoc), 64.79 (C5'- α), 64.59 (C5'- β), 55.54 (CH₃ PMB), 54.69 (CH α -Gln α), 54.65 (CH α -Gln β), 48.01 (CH Fmoc α), 47.96 (CH Fmoc β), 33.36 (CH₂ γ -Gln α), 32.91 (CH₂ γ -Gln β), 28.02 (CH₂ β -Gln β), 27.82 (CH₂ β -Gln α), 27.39 (t-Bu β), 27.27 (t-Bu α), 19.93 (Cq. t-Bu β), 19.79 (Cq. t-Bu α). IR: 3314, 2926, 2855, 1734, 1695, 1653, 1580, 1520, 1446, 1252, 1175, 1082, 1036, 963. HRMS [C₆₃H₆₆N₂O₁₀Si + Na]⁺: 1061.4381 found, 1061.4379 calculated.



N⁶-(2,3-di-O-benzyl-5-O-triisopropylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl glutamine benzyl ester (18)

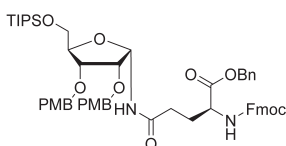
General procedure B, at room temperature, using donor **12** (171 mg, 0.26 mmol), Fmoc-Gln-OBn (92 mg, 0.20 mmol), SiO₂-HClO₄ (50 mg, 0.02 mmol HClO₄) and Dioxane/DCM (4 mL) afforded the title compound (110 mg, 119 μmol, 59% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 70/30). ¹H-NMR (400 MHz, MeOD-CDCl₃) δ: 7.73 (d, *J* = 7.5 Hz, 2H, Fmoc arom.), 7.60 (dd, *J* = 7.2, 2.2 Hz, 2H, Fmoc arom.), 7.35 (t, *J* = 7.5 Hz, 2H, arom.), 7.33 – 7.19 (m, 17H, arom.), 5.76 (d, *J* = 5.5 Hz, 1H, H1'-α), [5.64 (d, *J* = 4.6 Hz, H1'-β)], 5.17 – 5.07 (m, 2H, CH₂ Bn), 4.61 (bs, 2H, CH₂ Bn), 4.53 (bs, 2H, CH₂ Bn), 4.36 (AB, *J* = 10.5, 6.9 Hz, 1H, CH₂ Fmoc), 4.32 – 4.21 (m, 2H, CH₂ Fmoc, CH α-Gln), 4.19 – 4.12 (m, 2H, CH Fmoc, H4'), 4.10 (t, *J* = 5.4 Hz, 1H, H2'), 4.07 (dt, *J* = 5.0, 2.5 Hz, 1H, H3'), 3.66 (AB, *J* = 11.1, 2.8 Hz, 1H, H5'), 3.61 (AB, *J* = 11.0, 4.0 Hz, 1H, H5'), 2.23 (t, *J* = 7.4 Hz, 2H, CH₂ γ-Gln), 2.18 – 2.06 (m, 1H, CH₂ β-Gln), 2.00 – 1.87 (m, 1H, CH₂ β-Gln), 0.98 (s, 21H, TIPS). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ: 174.18, 172.88 (CO α-Gln, CO δ-Gln), 157.96 (CO Fmoc), 144.77, 144.57, 142.12, 138.42, 138.16, 136.40 (Cq. arom.), 129.28 – 127.80 (arom.), 125.91, 125.85, 120.58 (Fmoc arom.), 84.05 (C4'), 79.64 (C1'), 78.35 (C3'), 77.41 (C2'), 73.38, 73.33 (CH₂ Bn), 67.77 (CH₂ Bn), 67.68 (CH₂ Fmoc), 64.52 (C5'), 54.55 (CH α-Gln), 47.94 (CH Fmoc), 33.30 (CH₂ γ-Gln), 27.74 (CH₂ β-Gln), 18.34, 12.62 (CH, CH₃, TIPS). IR: 3405, 2941, 2864, 1719, 1674, 1502, 1452, 1329, 1213, 1045, 953. HRMS [C₅₅H₆₆N₂O₉Si + Na]⁺: 949.4432 found, 949.4430 calculated.



N^γ-(2,3-di-O-(4-methoxybenzyl)-5-O-tert-butylidiphenylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl asparagine benzyl ester (25)

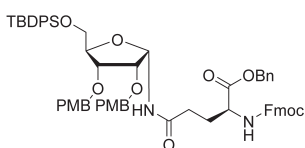
General procedure B using donor **23** (2.82 g, 3.6 mmol), Fmoc-Asn-OBn (3.0 mmol), DCM/Dioxane (30 mL) and TBSOTf (41 μL, 0.18 mmol) was executed at -10 °C. Precipitation was observed and the mixture was allowed to reach room temperature and stirred for 30 minutes. The product was obtained by silica gel chromatography (Pentane/EtOAc, 80/20 – 70/30 – 60/40) as a white foam (2.50 g, 2.37 mmol, 79%, 97/3 α/β). ¹H-NMR (500 MHz, MeOD-CDCl₃) δ 7.71 (d, *J* = 7.6 Hz, 2H, arom.), 7.62 – 7.50 (m, 6H, arom.), 7.46 – 7.10 (m, 19H, arom.), 6.80 (t, *J* = 8.0 Hz, 4H, arom.), 5.77 (d, *J* = 5.3 Hz, 1H, H1'-α), [5.63 (d, *J* = 4.4 Hz, H1'-β)], 5.18 – 5.08 (m, 2H, CH₂ Bn), 4.62 (t, *J* = 5.9 Hz, 1H, CH α-Asn), 4.54 – 4.40 (m, 4H, CH₂ PMB), 4.31 (AB, *J* = 10.4, 7.2 Hz, 1H, CH₂ Fmoc), 4.21 (AB, *J* = 10.0, 7.7 Hz, 1H, CH₂ Fmoc), 4.14 – 4.08 (m, 1H, CH Fmoc), 4.08 – 4.04 (m, 1H, H2'), 4.04 – 3.98 (m, 2H, H3', H4'), 3.76 – 3.66 (m, 6H, CH₃ PMB), 3.54 (AB, *J* = 11.3, 2.7 Hz, 1H, H5'), 3.53 – 3.47 (m, 1H, H5'), 2.78 (d, *J* = 5.9 Hz, 2H, CH₂ β-Asn), 0.94 (s, 9H, CH₃ TBDPS). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ 172.24, 171.75 (CO α-Asn, CO γ-Asn), 160.60 (Cq. PMB), 157.85 (CO Fmoc), 144.81, 144.76, 142.19, 136.57 (Cq. arom.), 136.46, 136.38 (arom.), 133.93, 133.72 (Cq. arom.), 130.75, 130.71, 130.61, 130.51 (arom.), 130.38 (Cq. arom.), 129.29, 129.00, 128.86, 128.65, 128.61, 128.50, 127.91, 126.03, 125.97, 120.66, 114.75 (arom.), 83.72 (C4'), 80.02 (C1'), 77.99 (C3'), 77.32 (C2'), 73.33, 73.10 (CH₂ PMB), 68.09, 68.01 (CH₂ Bn, CH₂ Fmoc), 64.79 (C5'), 55.66,

55.61 (CH₃ PMB), 52.02 (CH α-Asn), 47.97 (CH Fmoc), 38.67 (CH₂ β-Asn), 27.30 (CH₃ TBDPS), 19.83 (Cq. TBDPS). HRMS [C₆₃H₆₆N₂O₁₁Si + H]⁺: 1055.4513 found, 1055.4509 calculated.



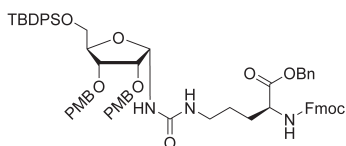
N^δ-(2,3-bis-O-(4-methoxybenzyl)-5-O-triisopropylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl glutamine benzyl ester (26)

General procedure B, at -10 °C, using donor **24** (215 mg, 0.30 mmol), Fmoc-Gln-OBn (92 mg, 0.20 mmol), SiO₂-HClO₄ (50 mg, 0.02 mmol HClO₄) and Dioxane/DCM (4.5 mL) afforded the title compound (137 mg, 139 μmol, 69% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 60/40). ¹H-NMR (400 MHz, MeOD-CDCl₃) δ: 7.72 (d, *J* = 7.5 Hz, 2H, Fmoc arom.), 7.63 – 7.55 (m, 2H, Fmoc arom.), 7.35 (t, *J* = 7.3 Hz, 2H, arom.), 7.31 – 7.11 (m, 10H, arom.), 6.83 (t, *J* = 8.1 Hz, 4H, PMB arom.), 5.73 (d, *J* = 5.3 Hz, 1H, H1'-α), [5.62 (d, *J* = 4.4 Hz, H1'-β)], 5.18 – 5.06 (m, 2H, CH₂ Bn), 4.58 – 4.49 (m, 2H, CH₂ PMB), 4.48 – 4.41 (m, 2H, CH₂ PMB), 4.39 – 4.27 (m, 2H, CH₂ Fmoc), 4.27 – 4.21 (m, 1H, CH α-Gln), 4.14 (t, *J* = 6.9 Hz, 1H, CH Fmoc), 4.09 (bs, 1H, H4'), 4.07 – 3.99 (m, 2H, H2', H3'), 3.73 (s, 6H, CH₃ PMB), 3.64 – 3.56 (m, 2H, H5'), 2.22 (t, *J* = 7.3 Hz, 2H, CH₂ γ-Gln), 2.18 – 2.05 (m, 1H, CH₂ β-Gln), 2.01 – 1.88 (m, 1H, CH₂ β-Gln), 0.98 (s, 21H, TIPS). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ: 174.03, 172.77 (CO α-Gln, CO δ-Gln), 160.35 (Cq. PMB), 157.79 (CO Fmoc), 144.68, 144.48, 142.01, 136.27 (Cq. arom.), 130.49 (arom.), 130.31 (Cq. arom.), 130.25 (arom.), 130.03 (Cq. arom.), 129.16 – 127.75 (arom.), 125.84, 125.79, 120.51 (Fmoc arom.), 114.54 (PMB arom.), 83.95 (C4'), 79.52 (C1'), 77.83 (C3'), 76.86 (C2'), 72.90, 72.89 (CH₂ PMB), 67.71 (CH₂ Bn), 67.59 (CH₂ Fmoc), 64.43 (C5'), 55.58, 55.56 (CH₃ PMB), 54.49 (CH α-Gln), 47.85 (CH Fmoc), 33.26 (CH₂ γ-Gln), 27.67 (CH₂ β-Gln), 18.33, 18.30, 12.54 (CH, CH₃, TIPS). IR: 2941, 2864, 1717, 1684, 1612, 1514, 1420, 1331, 1248, 1173, 1034, 883. HRMS [C₅₇H₇₀N₂O₁₁Si + H]⁺: 987.4830 found, 987.4822 calculated.



N^δ-(2,3-bis-O-(4-methoxybenzyl)-5-O-tert-butylidiphenylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl glutamine benzyl ester (27)

General procedure B, at -10 °C, using donor **23** (2.94 g, 3.75 mmol), Fmoc-Gln-OBn (1.38 g, 3.0 mmol), TBSOTf (43 μL, 0.19 mmol) and Dioxane/DCM (30 mL) afforded the title compound (1.95 g, 139 μmol, 61% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 80/20 – 70/30). ¹H-NMR (400 MHz, MeOD) δ: 7.73 (d, *J* = 7.5 Hz, 2H, Fmoc arom.), 7.63 – 7.53 (m, 6H, arom.), 7.44 – 7.15 (m, 19H, arom.), 6.90 – 6.75 (m, 4H, PMB arom.), 5.77 (dd, *J* = 8.9, 5.4 Hz, 1H, H1'), 5.18 – 5.05 (m, 2H, CH₂ Bn), 4.55 – 4.42 (m, 4H, CH₂ PMB), 4.38 – 4.22 (m, 2H, CH₂ Fmoc), 4.18 – 3.99 (m, 5H, CH α-Gln, CH Fmoc, H4', H2', H3'), 3.76 – 3.66 (m, 6H, CH₃ PMB), 3.61 – 3.50 (m, 2H, H5'), 2.23 (t, *J* = 7.2 Hz, 2H, CH₂ γ-Gln), 2.18 – 2.08 (m, 1H, CH₂ β-Gln), 1.99 – 1.87 (m, 1H, CH₂ β-Gln), 0.95 (s, 9H, CH₃ TBDPS). HRMS [C₆₄H₆₈N₂O₁₁Si + H]⁺: 1069.6673 found, 1069.4665 calculated.

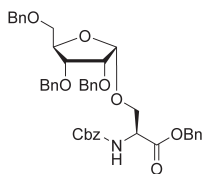


***N*^ω-(2,3-di-*O*-(4-methoxybenzyl)-5-*O*-tert-butyl-diphenylsilyl- α -D-ribose)-*N*^α-fluorenylmethoxycarbonyl citrulline benzyl ester (**28**)**

General procedure B using donor **23** (5.0 g, 6.4 mmol), Fmoc-Cit-OBn (2.93 g, 6.0 mmol), DCM/Dioxane (60 mL) and TBSOTf (73 μ L, 0.32 mmol) was executed at -15 °C and additional TBSOTf (365 μ L, 1.6 mmol) was added over a period of 6 hours in 6 equal portions. The mixture was purified by silica gel chromatography (Pentane/EtOAc, 60/40 - 50/50 - 40/60) to obtain the title compound as a white foam (2.64 g, 2.41 mmol, 40%, 78/22 α/β). ¹H-NMR (400 MHz, MeOD-CDCl₃) δ 7.72 (d, *J* = 7.5 Hz, 2H, arom.), 7.63 - 7.57 (m, 6H, arom.), [7.57 - 7.52 (m, 2H, arom- β)], 7.45 - 7.13 (m, 19H, arom.), 6.86 - 6.75 (m, 4H), 5.73 (d, *J* = 4.3 Hz, 1H, H1'- α), [5.54 (d, *J* = 5.9 Hz, H1'- β)], 5.14 - 5.06 (m, 2H, CH₂ Bn), 4.55 - 4.38 (m, 4H, CH₂ PMB), 4.35 - 4.24 (m, 2H, CH₂ Fmoc), 4.24 - 4.15 (m, 1H, CH α -Cit), 4.15 - 4.07 (m, 1H, CH Fmoc), 4.07 - 3.98 (m, 3H, H2', H3', H4'), [3.96 (dd, *J* = 5.2, 3.9 Hz, H3'- β)], 3.74 - 3.71 (m, 3H, CH₃ PMB), 3.70 (s, 3H, CH₃ PMB), [3.62 (d, *J* = 4.1 Hz, H5'- β)], 3.59 - 3.48 (m, 2H, H5'), 3.15 - 2.99 (m, 2H, CH₂ δ -Cit), 1.89 - 1.75 (m, 1H, CH₂ β -Cit), 1.75 - 1.60 (m, 1H, CH₂ β -Cit), 1.58 - 1.43 (m, 2H, CH₂ γ -Cit), [0.98 (s, CH₃ TBDPS- β)], 0.94 (s, 9H, CH₃ TBDPS). ¹³C-NMR (100 MHz, MeOD-CDCl₃) δ 173.66 (CO α -Cit), 160.72 (Cq. PMB), 159.69 (CO Fmoc), 158.43 (CO ω -Cit), 145.10, 144.94, 142.39, 136.93 (Cq. arom.), 136.61, 136.52 (arom.), 134.14, 133.97, 130.94 (Cq. arom.), 130.86, 130.81, 130.76, 130.72, 130.68, 130.57, 129.42, 129.15, 129.04, 128.80, 128.77, 128.73, 128.64, 128.05, 128.03, 126.15, 126.11, 120.78, 114.78, 114.77, 114.73, 114.69 (arom.), 84.90 (C1'- β), 83.22 (C4'- α), 82.73 (C4'- β), 81.70 (C1'- α), 80.70 (C2'- β), 78.25 (C3'- α), 77.24 (C2'- α), 76.66 (C3'- β), 73.17, 73.10 (CH₂ PMB- α), 72.82, 72.39 (CH₂ PMB- β), 67.84, 67.77 (CH₂ Bn, CH₂ Fmoc), 65.21 (C5'- β), 65.06 (C5'- α), 55.68, 55.66, 55.64 (CH₃ PMB), 55.35 (CH α -Cit), 48.21 (CH Fmoc), 40.23 (CH₂ δ -Cit), 29.70 (CH₂ β -Cit), 27.50 (CH₂ γ -Cit), 27.43, 27.34 30 (CH₃ TBDPS), 20.00, 19.92 (Cq. TBDPS). HRMS [C₆₅H₇₁N₃O₁₁Si + H]⁺: 1098.4944 found, 1098.4931 calculated.

General procedure C

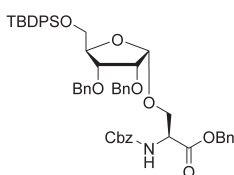
The trifluoroacetimidate donor (**1**, **11**, **12** or **24**) (1.25 eq.) and acceptor (1.0 eq.) were co-evaporated with 1,4-dioxane (2x) and DCE (1x), dissolved in dry DCM and stirred with freshly activated 3 Å molecular sieves at room temperature for 1 h under argon to remove traces of water. The solution was then cooled to -50 °C, TMSOTf (0.2 eq.) was added to the reaction mixture and stirred at the same temperature for 60 - 90 min. The reaction was quenched by the addition of triethylamine, filtered through a pad of Celite, concentrated *in vacuo* and purified by silica gel chromatography.



***O*^β-(2,3,5-tri-*O*-benzyl- α -D-ribose)-*N*^α-benzyloxycarbonyl serine benzyl ester (**29**)**

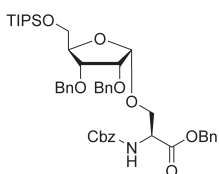
General procedure C using donor **1** (177 mg, 0.30 mmol), Cbz-Ser-OBn (79 mg, 0.24 mmol), TMSOTf (8.8 μ L, 48 μ mol) and DCM (4 mL) afforded the title compound (137 mg, 187 μ mol, 78% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 - 65/35). ¹H-NMR (400 MHz, CDCl₃) δ : 7.41 - 7.16 (m, 25H), 6.45 (d, *J* = 9.0

Hz, 1H, NH- α), [6.13 (d, J = 8.6 Hz, NH- β)], 5.18 – 5.04 (m, 4H, CH₂ Bn, CH₂ Cbz), [4.97 (s, H1'- β)], 4.95 (d, J = 4.0 Hz, 1H, H1'- α), 4.68 – 4.33 (m, 7H, CH₂ Bn, CH α -Ser), 4.24 (q, J = 3.4 Hz, 1H, H4'), 4.15 (AB, J = 10.4, 3.0 Hz, 1H, CH₂ β -Ser), 3.97 (AB, J = 10.5, 3.1 Hz, 1H, CH₂ β -Ser), 3.87 (dd, J = 6.3, 3.0 Hz, 1H, H3'), 3.80 (dd, J = 6.3, 4.0 Hz, 1H, H2'), 3.43 (AB, J = 10.6, 3.8 Hz, 1H, H5'), 3.36 (AB, J = 10.6, 3.9 Hz, 1H, H5'). ¹³C-NMR (100 MHz, CDCl₃) δ : 170.44 (CO α -Ser), 156.51 (CO Cbz), 138.15, 137.91, 137.81, 136.59, 135.58 (Cq. arom.), 128.62 – 127.64 (arom.), 105.58 (C1'- β), 101.14 (C1'- α), 82.35 (C4'- α), 80.52 (C4'- β), 79.59 (C2'- β), 78.36 (C2'- α), 77.58 (C3'- β), 75.60 (C3'- α), 73.48, 72.48, 72.47 (CH₂ Bn), 69.90 (C5'), 67.69 (CH₂ β -Ser), 67.14, 66.83 (CH₂ Bn, CH₂ Cbz), 54.64 (CH α -Ser). IR: 3340, 2926, 2866, 1719, 1497, 1454, 1335, 1198, 1026, 910. HRMS [C₄₄H₄₅NO₉ + Na]⁺: 754.2985 found, 754.2987 calculated.



N^B-(2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl- α -D-ribose)-N ^{α} -benzyloxycarbonyl serine benzyl ester (30)

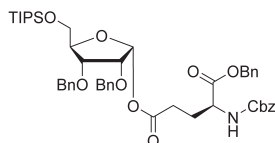
General procedure C using donor **11** (185 mg, 0.25 mmol), Cbz-Ser-OBn (66 mg, 0.20 mmol), TMSOTf (7.0 μ L, 40 μ mol) and DCM (3 mL) afforded the title compound (106 mg, 120 μ mol, 60% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 80/20). ¹H-NMR (400 MHz, CDCl₃) δ : 7.59 – 7.52 (m, 4H, TBDPS arom.), 7.42 – 7.14 (m, 26H, arom.), 6.47 (d, J = 9.0 Hz, 1H, NH), 5.15 – 5.00 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.93 (d, J = 4.1 Hz, 1H, H1'), 4.68 – 4.48 (m, 5H, CH₂ Bn, CH α -Ser), 4.18 – 4.07 (m, 2H, CH₂ β -Gln, H4'), 4.01 – 3.91 (m, 2H, CH₂ β -Gln, H3'), 3.83 (dd, J = 6.1, 4.1 Hz, 1H, H2'), 3.59 (AB, J = 11.3, 3.4 Hz, 1H, H5'), 3.48 (AB, J = 11.2, 2.9 Hz, 1H, H5'), 0.94 (s, 9H, t-Bu). ¹³C-NMR (100 MHz, CDCl₃) δ : 170.53 (CO α -Ser), 156.59 (CO Cbz), 138.31, 137.90 (Cq. arom.), 135.71, 135.62 (TBDPS arom.), 133.22, 133.03 (Cq. arom.), 129.91, 129.86, 128.60 – 127.63 (arom.), 101.12 (C1'), 84.01 (C4'), 78.90 (C2'), 75.65 (C3'), 72.63, 72.54 (CH₂ Bn), 67.63 (CH₂ β -Ser), 67.16, 66.86 (CH₂ Bn, CH₂ Cbz), 64.01 (C5'), 54.75 (CH α -Gln), 26.87 (t-Bu), 19.28 (Cq. t-Bu). IR: 3340, 2930, 2857, 1722, 1497, 1454, 1427, 1198, 1111, 1026, 822. HRMS [C₅₃H₅₇NO₉Si + Na]⁺: 902.3705 found, 902.3695 calculated.



N^B-(2,3-di-O-benzyl-5-O-triisopropylsilyl- α -D-ribose)-N ^{α} -benzyloxycarbonyl serine benzyl ester (31)

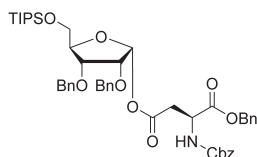
General procedure C using donor **12** (164 mg, 0.25 mmol), Cbz-Ser-OBn (66 mg, 0.20 mmol), TMSOTf (7.0 μ L, 40 μ mol) and DCM (3 mL) afforded the title compound (90 mg, 113 μ mol, 56% yield) after silica gel chromatography (Pentane/EtOAc, 90/10 – 80/20). ¹H-NMR (400 MHz, CDCl₃) δ : 7.38 – 7.15 (m, 20H, arom.), 6.51 (d, J = 9.0 Hz, 1H, NH), 5.18 – 5.00 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.90 (d, J = 4.1 Hz, 1H, H1'), 4.70 – 4.49 (m, 5H, CH α -Ser, CH₂ Bn), 4.16 (dd, J = 10.5, 3.1 Hz, 1H, CH₂ β -Ser), 4.13 (t, J = 2.8 Hz, 1H, H4'), 3.95 (dd, J = 6.1, 2.3 Hz, 1H, H3'), 3.92 (dd, J = 10.5, 3.2 Hz, 1H, CH₂ β -Ser), 3.78 (dd, J = 6.1, 4.1 Hz, 1H, H2'), 3.61 (AB, J = 11.0, 3.5 Hz, 1H, H5'), 3.54 (AB, J = 10.9, 2.8 Hz, 1H, H5'), 0.95 (s, 21H, TIPS). ¹³C-NMR (100 MHz, CDCl₃) δ : 170.52 (CO α -Ser), 156.58 (CO Cbz), 138.37, 137.91, 136.67, 135.69 (Cq. arom.), 128.58 – 127.60 (arom.), 101.14 (C1'), 84.30 (C4'), 78.74 (C2'), 75.50 (C3'), 72.60, 72.43 (CH₂ Bn), 67.75 (CH₂ β -Ser), 67.13, 66.83 (CH₂ Bn, CH₂ Cbz), 63.64 (C5'), 54.74 (CH α -Ser), 18.01, 17.98, 11.92 (CH, CH₃, TIPS). IR: 3035, 2941, 2864, 1724, 1510, 1497,

1454, 1333, 1290, 1163, 1113, 1063, 1028, 881. HRMS [$C_{46}H_{59}NO_9Si + Na$] $^+$: 820.3851 found, 820.3851 calculated.



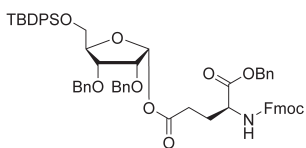
N⁶-(2,3-di-O-benzyl-5-O-triisopropylsilyl-α-D-ribofuranosyl)-N^α-benzyloxycarbonyl glutamic acid benzyl ester (32)

General procedure C, at -50°C, using donor **12** (132 mg, 0.20 mmol), Cbz-Glu-OBn (62 mg, 0.167 mmol), TMSOTf (6.0 μL, 33 μmol) and DCM (3 mL) afforded the title compound (115 mg, 137 μmol, 84% yield) and the anomers were separated by silica gel chromatography (Pentane/EtOAc, 80/20) to obtain the pure α-anomer (79 mg, 94 μmol, 56% yield). ¹H-NMR (400 MHz, CDCl₃) δ: 7.37 – 7.08 (m, 20H), 6.19 (d, *J* = 3.8 Hz, 1H, H1'-α), [6.11 (s, H1'-β)], 5.73 (d, *J* = 8.4 Hz, 1H, NH), 5.14 – 4.93 (m, 4H, Bn, CH₂ Cbz), 4.57 (q, *J* = 12.5 Hz, 2H, CH₂ Bn), 4.48 (bs, 2H, CH₂ Bn), 4.34 (td, *J* = 8.9, 4.7 Hz, 1H, CH α-Gln), 4.22 – 4.13 (m, 1H, H4'), 3.95 – 3.84 (m, 2H, H2', H3'), 3.49 (AB, *J* = 11.1, 3.4 Hz, 1H, H5'), 3.36 (AB, *J* = 10.9, 2.5 Hz, 1H, H5'), 2.43 (tq, *J* = 17.0, 8.2, 7.0 Hz, 2H, CH₂ γ-Gln), 2.15 (dq, *J* = 11.7, 6.9 Hz, 1H, CH₂ β-Gln), 2.01 (dq, *J* = 14.6, 7.1 Hz, 1H, CH₂ β-Gln), 0.85 (s, 21H, TIPS). ¹³C-NMR (100 MHz, CDCl₃) δ: 172.28, 171.95 (CO α-Gln, CO δ-Gln), 156.27 (CO Cbz), 138.08, 137.59, 136.30, 135.41 (Cq. arom.), 128.70 – 127.75 (arom.), 95.25 (C1'), 86.02 (C4'), 78.24 (C3'), 74.94 (C2'), 72.79, 72.46 (CH₂ Bn), 67.29, 67.17 (CH₂ Bn, CH₂ Cbz), 63.53 (C5'), 53.98 (CH α-Gln), 31.23 (CH₂ γ-Gln), 26.73 (CH₂ β-Gln), 17.95, 11.86 (CH, CH₃, TIPS). IR: 3345, 2941, 2864, 1724, 1516, 1497, 1454, 1250, 1207, 1113, 1061, 995, 881. HRMS [$C_{48}H_{61}NO_{10}Si + Na$] $^+$: 862.3961 found, 862.3957 calculated.



N^γ-(2,3-di-O-benzyl-5-O-triisopropylsilyl-α-D-ribofuranosyl)-N^α-benzyloxycarbonyl aspartic acid benzyl ester (33)

General procedure C, at -70°C, using donor **12** (132 mg, 0.20 mmol), Cbz-Asp-OBn (60 mg, 0.167 mmol), TMSOTf (6.0 μL, 33 μmol) and DCM (3 mL) afforded the title compound (87 mg, 105 μmol, 63% yield) and the anomers were separated by silica gel chromatography (Pentane/EtOAc, 85/15) to obtain the pure α-anomer (40 mg, 48 μmol, 29% yield). ¹H-NMR (400 MHz, CDCl₃) δ: 7.33 – 7.06 (m, 20H, arom.), 6.86 (d, *J* = 9.1 Hz, 1H, NH), 6.17 (d, *J* = 3.7 Hz, 1H H1'-α), [6.08 (s, H1'-β)], 5.06 – 4.90 (m, 4H, CH₂ Bn, CH₂ Cbz), 4.67 (dt, *J* = 9.1, 4.5 Hz, 1H, CH α-Asn), 4.62 – 4.35 (m, 4H, CH₂ Bn), 4.13 (bs, 1H, H4'), 3.88 – 3.74 (m, 2H, H2', H3'), 3.51 (AB, *J* = 11.0, 3.1 Hz, 1H, H5'), 3.37 (AB, *J* = 10.9, 1.9 Hz, 1H, H5'), 3.12 (AB, *J* = 17.0, 5.0 Hz, 1H, CH₂ β-Asn), 2.85 (AB, *J* = 17.0, 4.0 Hz, 1H, CH₂ β-Asn), 0.83 (s, 21H, TIPS). ¹³C-NMR (100 MHz, CDCl₃) δ: 170.38, 169.80 (CO α-Asn, CO γ-Asn), 156.61 (CO Cbz), 137.95, 137.46, 136.46, 135.60 (Cq. arom.), 128.62 – 127.84 (arom.), 95.27 (C1'), 86.76 (C4'), 78.18 (C3'), 74.65 (C2'), 72.77, 72.55 (CH₂ Bn), 67.34, 67.10 (CH₂ Bn, CH₂ Cbz), 63.40 (C5'), 50.75 (CH α-Asn), 37.17 (CH₂ β-Asn), 17.96, 11.85 (CH, CH₃, TIPS). IR: 3335, 2941, 2864, 1721, 1522, 1497, 1454, 1331, 1285, 1213, 1109, 1061, 993, 928. HRMS [$C_{47}H_{59}NO_{10}Si + Na$] $^+$: 848.3801 found, 848.3800 calculated.



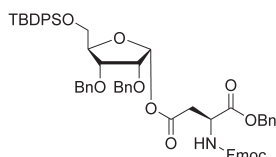
O⁶-(2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl glutamic acid benzyl ester (34**)**

A) Fmoc-Glu-OBn (127 mg, 0.27 mmol) dissolved in dry DCM (5 mL) and stored with freshly activated 3 Å molecular sieves at room temperature for 16 hours under argon to remove traces of water. The reaction mixture was cooled to -78 °C and the trifluoroacetimidate donor **11** (300 mg, 0.4 mmol; dissolved in DCM (1 mL) and cooled to -78 °C) was added. Next, TMSOTf (2 μL, 11 μmol) was added and the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was quenched by the addition of triethylamine, filtered, concentrated *in vacuo* and purified by silica gel chromatography (Pentane/EtOAc, 90/10 – 85/15) to obtain the title compound (139 mg, 0.14 mmol, 51%).

B) Fmoc-Glu-OBn (1.40 g, 3.0 mmol) and the trifluoroacetimidate donor **11** (2.66 g, 3.6 mmol) were co-evaporated with 1,4-dioxane (3x), dissolved in dry DCM (30 mL) and stored with freshly activated 3 Å molecular sieves at room temperature for 16 hours under argon to remove traces of water. The reaction mixture was cooled to -78 °C and TBSOTf (41 μL, 0.18 mmol) was added. The reaction mixture was stirred at -78 °C for 15 minutes and quenched by the addition of triethylamine. The mixture was filtered through a pad of Celite, concentrated *in vacuo* and purified by silica gel chromatography (Pentane/EtOAc, 90/10 – 85/15 – 80/20) to obtain the title compound as a white foam (1.31 g, 1.29 mmol, 43%) and the β-anomer separately (0.66 g, 0.66 mmol, 22%).

α-anomer: ¹H-NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 7.5 Hz, 2H, arom.), 7.57 (t, J = 8.4 Hz, 4H, arom.), 7.51 (d, J = 7.2 Hz, 2H, arom.), 7.45 – 7.19 (m, 25H, arom.), 6.37 (s, 1H, H1'), 5.67 (d, J = 8.3 Hz, 1H, NH), 5.19 – 5.07 (m, 2H, CH₂ Bn), 4.67 (AB, J = 12.3 Hz, 1H, CH₂ Bn), 4.62 – 4.53 (m, 3H, CH₂ Bn), 4.44 (q, J = 8.3 Hz, 1H, CH α-Glu), 4.41 – 4.31 (m, 2H, CH₂ Fmoc), 4.32 – 4.24 (m, 1H, H4'), 4.18 (t, J = 6.6 Hz, 1H, CH Fmoc), 4.05 (s, 2H, H2', H3'), 3.64 – 3.53 (m, 1H, H5'), 3.53 – 3.40 (m, 1H, H5'), 2.59 – 2.41 (m, 2H, CH₂ γ-Cit), 2.30 – 2.16 (m, 1H, CH₂ β-Cit), 2.15 – 2.04 (m, 1H, CH₂ β-Cit), 0.91 (s, 9H, CH₃ TBDPS). ¹³C-NMR (126 MHz, CDCl₃) δ 172.31 (CO α-Glu), 171.87 (CO δ-Glu), 156.16 (CO Fmoc), 143.96, 143.90, 141.35, 138.08, 137.55 (Cq. arom.), 135.64, 135.57 (arom.), 135.38, 133.01, 132.70 (Cq. arom.), 129.94, 129.92, 128.67, 128.62, 128.48, 128.31, 128.12, 128.09, 127.86, 127.76, 127.19, 125.23, 120.01 (arom.), 95.28 (C1'), 85.84 (C4'), 78.50, 75.22 (C2', C3'), 73.01, 72.55 (CH₂ Bn), 67.31, 67.08 (CH₂ Bn, CH₂ Fmoc), 63.88 (C5'), 53.71 (CH α-Glu), 47.26 (CH Fmoc), 31.00 (CH₂ γ-Glu), 26.91 (CH₂ β-Glu), 26.81 (CH₃ TBDPS), 19.19 (Cq. TBDPS). **β-anomer:** ¹H-NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 6.9 Hz, 2H, arom.), 7.68 – 7.58 (m, 4H, arom.), 7.55 (d, J = 6.7 Hz, 2H, arom.), 7.44 – 7.18 (m, 25H, arom.), 6.24 (s, 1H, H1'), 5.29 (d, J = 7.4 Hz, 1H, NH), 5.14 (q, J = 12.0 Hz, 2H, CH₂ Bn), 4.75 (d, J = 11.9 Hz, 1H, CH₂ Bn), 4.61 (d, J = 11.9 Hz, 1H, CH₂ Bn), 4.52 (d, J = 11.5 Hz, 1H, CH₂ Bn), 4.45 – 4.33 (m, 3H, CH₂ Bn, CH₂ Fmoc, CH α-Glu), 4.33 – 4.24 (m, 3H, CH₂ Fmoc, H3', H4'), 4.22 – 4.11 (m, 1H, CH Fmoc), 4.04 – 3.95 (m, 1H, H2'), 3.90 (d, J = 11.2 Hz, 1H, H5'), 3.76 (d, J = 10.6 Hz, 1H, H5'), 2.23 – 2.08 (m, 2H, CH₂ γ-Glu), 1.85 – 1.71 (m, 1H, CH₂ β-Glu), 1.69 – 1.53 (m, 1H, CH₂ β-Glu), 1.00 (s, 9H, CH₃ TBDPS). ¹³C-NMR (126 MHz, CDCl₃) δ 171.76, 171.67 (CO α-Glu, CO δ-Glu), 156.07 (CO Fmoc), 143.91, 143.75, 141.37, 137.73, 137.53 (Cq. arom.), 135.62 (arom.), 135.19, 133.43, 133.28 (Cq. arom.), 129.85, 129.76, 128.75, 128.64, 128.53, 128.50, 128.36, 128.22, 128.04, 127.91, 127.85, 127.77, 127.20, 125.17, 125.13, 120.09 (arom.), 99.37 (C1'),

83.03 (C4'), 79.13 (C2'), 76.08 (C3'), 72.51, 72.22 (CH₂ Bn), 67.47, 67.24 (CH₂ Bn, CH₂ Fmoc), 62.99 (C5'), 53.27 (CH α-Glu), 47.20 (CH Fmoc), 30.16 (CH₂ γ-Glu), 27.43 (CH₂ β-Glu), 26.90 (CH₃ TBDPS), 19.43 (Cq. TBDPS). HRMS [C₆₂H₆₃NO₁₀Si + H]⁺: 1010.4308 found, 1010.4294 calculated.



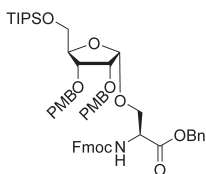
O^γ-(2,3-di-O-benzyl-5-O-tert-butyldiphenylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl aspartic acid benzyl ester (35)

A) Fmoc-Asp-OBn (134 mg, 0.3 mmol) dissolved in dry DCM (5 mL) and stored with freshly activated 3 Å molecular sieves at room temperature for 16 hours under argon to remove traces of water. The reaction mixture was cooled to -78 °C and the trifluoroacetimidate donor **11** (370 mg, 0.5 mmol; dissolved in DCM (1 mL) and cooled to -78 °C) was added. Next, TMSOTf (2 μL, 11 μmol) was added and the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was quenched by the addition of triethylamine, filtered, concentrated *in vacuo* and purified by silica gel chromatography (Pentane/EtOAc, 90/10 – 85/15) to obtain the title compound (177 mg, 0.18 mmol, 59%).

B) Fmoc-Asp-OBn (1.34 g, 3.0 mmol) and the trifluoroacetimidate donor **11** (2.66 g, 3.6 mmol) were co-evaporated with 1,4-dioxane (3x), dissolved in dry DCM (30 mL) and stored with freshly activated 3 Å molecular sieves at room temperature for 16 hours under argon to remove traces of water. The reaction mixture was cooled to -78 °C and TBSOTf (41 μL, 0.18 mmol) was added. The reaction mixture was stirred at -78 °C for 15 minutes and quenched by the addition of triethylamine. The mixture was filtered through a pad of Celite, concentrated *in vacuo* and purified by silica gel chromatography (Pentane/EtOAc, 90/10 – 85/15 – 80/20) to obtain the title compound as a white foam (0.68 g, 0.68 mmol, 23%) and the β-anomer separately (0.96 g, 0.97 mmol, 32%).

α-anomer: ¹H-NMR (500 MHz, CDCl₃) δ 7.65 (t, J = 7.5 Hz, 2H, arom.), 7.58 – 7.47 (m, 6H, arom.), 7.45 – 7.37 (m, 2H, arom.), 7.34 (t, J = 7.3 Hz, 4H, arom.), 7.31 – 7.14 (m, 19H, arom.), 6.89 (d, J = 9.0 Hz, 1H, NH), 6.35 (d, J = 3.1 Hz, 1H, H1'), 5.10 (d, J = 12.5 Hz, 1H, CH₂ Bn), 5.02 (d, J = 12.5 Hz, 1H, CH₂ Bn), 4.76 (dt, J = 9.0, 4.5 Hz, 1H, CH α-Asp), 4.61 (d, J = 12.8 Hz, 1H, CH₂ Bn), 4.58 – 4.48 (m, 3H, CH₂ Bn), 4.38 (AB, J = 10.7, 7.3 Hz, 1H, CH₂ Fmoc), 4.32 (AB, J = 10.7, 6.8 Hz, 1H, CH₂ Fmoc), 4.24 (s, 1H, H4'), 4.12 (t, J = 7.0 Hz, 1H, CH Fmoc), 4.05 – 4.00 (m, 2H, H2', H3'), 3.61 (AB, J = 11.4, 3.1 Hz, 1H, H5'), 3.46 (AB, J = 11.3, 2.2 Hz, 1H, H5'), 3.20 (AB, J = 17.1, 5.0 Hz, 1H, CH₂ β-Asp), 2.93 (AB, J = 17.1, 4.0 Hz, 1H, CH₂ β-Asp), 0.89 (s, 9H, CH₃ TBDPS). ¹³C-NMR (126 MHz, CDCl₃) δ 170.16 (CO α-Asp), 169.64 (CO γ-Asp), 156.37 (CO Fmoc), 143.96, 143.74, 141.23, 141.18, 137.75, 137.32 (Cq. arom.), 135.53, 135.46 (arom.), 132.80, 132.51 (Cq. arom.), 129.90, 128.58, 128.48, 128.38, 128.19, 128.15, 128.07, 127.97, 127.81, 127.78, 127.61, 127.58, 127.02, 126.98, 125.08, 119.89 (arom.), 95.12 (C1'), 86.39 (C4'), 78.38 (C2'), 74.78 (C3'), 72.81, 72.45 (CH₂ Bn), 67.25, 66.84 (CH₂ Bn, CH₂ Fmoc), 63.76 (C5'), 50.66 (CH α-Asp), 47.17 (CH Fmoc), 37.08 (CH₂ β-Asp), 26.70 (CH₃ TBDPS), 19.08 (Cq. TBDPS). β-anomer: ¹H-NMR (500 MHz, CDCl₃) δ 7.75 (d, J = 7.5 Hz, 2H, arom.), 7.64 (d, J = 6.6 Hz, 2H, arom.), 7.60 (d, J = 7.6 Hz, 2H, arom.), 7.56 (t, J = 8.1 Hz, 2H, arom.), 7.41 – 7.23 (m, 25H, arom.), 6.23 (s, 1H, H1'), 5.80 (d, J = 9.0 Hz, 1H, NH), 5.18 (d, J = 12.4 Hz, 1H, CH₂ Bn), 5.13 (d, J = 12.3 Hz, 1H, CH₂ Bn), 4.72 (d, J

= 12.0 Hz, 1H, CH₂ Bn), 4.63 – 4.56 (m, 2H, CH₂ Bn, CH α-Asp), 4.52 (d, J = 11.7 Hz, 1H, CH₂ Bn), 4.45 – 4.38 (m, 2H, CH₂ Bn, CH₂ Fmoc), 4.34 – 4.29 (m, 1H, H4'), 4.28 – 4.19 (m, 2H, H3', CH₂ Fmoc), 4.17 (t, J = 7.1 Hz, 1H, CH Fmoc), 3.94 (d, J = 4.3 Hz, 1H, H2'), 3.90 (AB, J = 11.7, 2.7 Hz, 1H, H5'), 3.76 (AB, J = 11.7, 3.1 Hz, 1H, H5'), 2.90 (AB, J = 17.6, 4.5 Hz, 1H, CH₂ β-Asp), 2.58 (AB, J = 17.5, 4.1 Hz, 1H, CH₂ β-Asp), 1.02 (s, 9H, CH₃ TBDPS). ¹³C-NMR (126 MHz, CDCl₃) δ 170.62 (CO α-Asp), 170.46 (CO γ-Asp), 156.09 (CO Fmoc), 143.92, 143.79, 141.36, 141.34, 137.64, 137.42 (Cq. arom.), 135.61 (arom.), 133.30, 133.19 (Cq. arom.), 129.91, 129.82, 128.69, 128.57, 128.53, 128.20, 128.11, 127.97, 127.86, 127.79, 127.19, 125.28, 125.22, 120.07 (arom.), 99.82 (C1'), 83.26 (C4'), 79.16 (C2'), 75.95 (C3'), 72.53, 72.24 (CH₂ Bn), 67.60, 67.47 (CH₂ Bn, CH₂ Fmoc), 62.78 (C5'), 50.35 (CH α-Asp), 47.16 (CH Fmoc), 36.52 (CH₂ β-Asp), 26.90 (CH₃ TBDPS), 19.42 (Cq. TBDPS). HRMS [C₆₁H₆₁NO₁₀Si + H]⁺: 996.4152 found, 996.4137 calculated.



N^β-(2,3-di-O-benzyl-5-O-triisopropylsilyl-α-D-ribose)-N^α-fluorenylmethoxycarbonyl serine benzyl ester (**36**)

General procedure C using donor **24** (0.9 g, 1.25 mmol), Fmoc-Ser-OBn (417 mg, 1.00 mmol), TMSOTf (11.3 μl, 0.06 mmol) and DCM (16 ml) afforded the title compound (0.54 g, 0.58 mmol, 58%) after silica gel chromatography (Pentane/EtOAc, 90/10 – 75/25). ¹H-NMR (400 MHz, CDCl₃) δ 7.74 – 7.71 (m, 2H, arom.), 7.56 (d, J = 7.5 Hz, 2H, arom.), 7.43 – 7.15 (m, 13H, arom.), 6.84 (d, J = 8.6 Hz, 2H, PMB arom.), 6.77 (d, J = 8.6 Hz, 2H, PMB arom.), 6.63 (d, J = 9.0 Hz, 1H, NH), 5.17 – 5.05 (m, 2H, CH₂ Bn), 4.91 (d, J = 4.1 Hz, 1H, H1'), 4.65 – 4.49 (m, 5H, CH₂ PMB, CH α-Ser), 4.39 (dd, 1H, J = 10.3, 6.8 Hz, CH₂ Fmoc), 4.21 – 4.13 (m, 3H, H4', CH₂ β-Ser, CH Fmoc), 4.00 – 3.93 (m, 2H, H3', CH₂ β-Ser), 3.82 – 3.73 (m, 8H, H2', CH₃ PMB), 3.68 – 3.57 (m, 2H, H5'), 1.11 – 0.91 (m, 21H, TIPS). ¹³C-NMR (101 MHz, CDCl₃) δ: 170.63 (CO α-Ser), 159.46, 159.27 (Cq. PMB), 156.46 (CO Fmoc), 144.78, 144.59, 142.13, 136.34, 129.89, 129.56 (Cq. arom.), 128.67, 128.27, 128.14, 127.69, 127.14, 125.53, 119.98, 113.83 (arom.), 101.18 (C1'), 84.47 (C4'), 78.47 (C2'), 75.22 (C3'), 72.38, 72.06 (CH₂ PMB), 67.24, 67.20 (CH₂ β-Ser, CH₂ Fmoc, CH₂ Bn), 63.77 (C5'), 55.32 (CH₃ PMB), 54.73 (CH α-Ser), 18.06, 11.98 (CH, CH₃, TIPS). HRMS [C₅₅H₆₇NO₁₁Si + Na]⁺: 968.4380 found, 968.4376 calculated.

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