Chemical Glycosylations for the Synthesis of Building Units of Post-translational modifications

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Abstract

In chemical glycosylation reactions, a glycosyl donor couple with glycosyl acceptor through glycosidic linkage. Most of the products end up with mixture due to the formation of stereogenic center at anomeric carbon. Activation with suitable Lewis acid and introduction of the non-participating protecting group on donor and acceptor results in a selective product. Herein, we used suitably protected donor and acceptor which produced orthogonally protected building block with α-selectivity. We used also donor for the synthesis of modified phosphoribosylated amino acid. The formation of glycoside products can be used to synthesize complex biologically important organic molecules.

Introduction

The glycosylations are considered to play a vital role in a wide range of regulatory processes and glycoside products can be used to synthesize complex organic molecules which are of vital importance for the maintenance of diverse cellular functions.[1] Poly-adenosine diphosphate (ADP) ribosylation is one of the complex polymeric post-translational modification (PTM) that occur at various functional groups in amino acid side chains (Fig. 1).[2-5] The carbohydrates occur as polysaccharides, glycoconjugates or glycosides and in their chemical synthesis, the main challenge is to build glycosidic linkages between the monomeric units with appropriate orientation and most of glycosylations give a mixture of the product.[6-9] The improvement of new methodologies for chemical glycosylation has emerged as an active area of research. Several types of new glycosyl donors for glycosylation reactions have been synthesized and applied. Diverse activation protocols have been established for the successful assembly of oligosaccharides from protected building blocks. Herein, we describe the glycosylation reactions resulted in synthesis of a ribosylated-amino acid **8**, and adenosine **9**. The glycosylation of adenosine gave an orthogonal bifunctional building block **9**, which may be used for future coupling reactions with amino acids and in the synthesis of PTMs (Fig. 1).

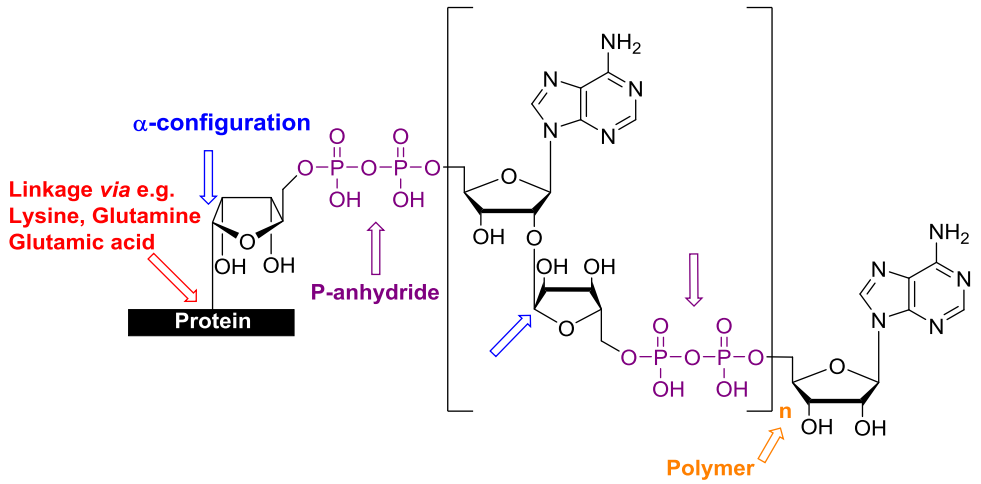
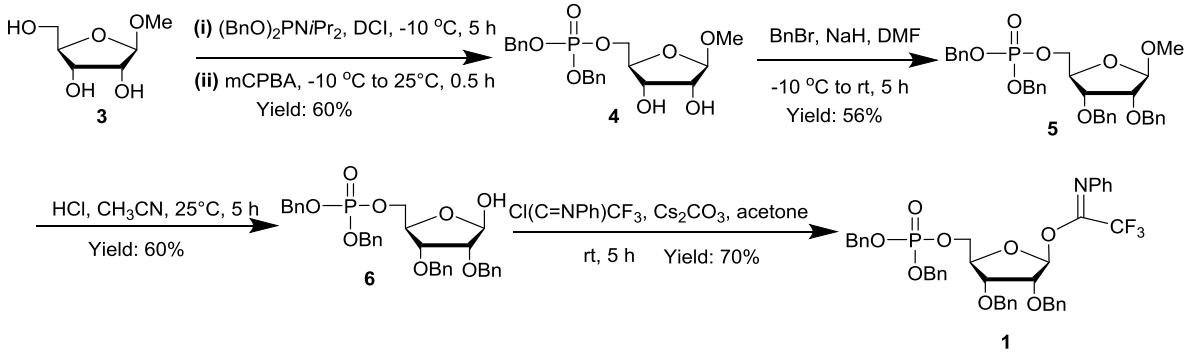


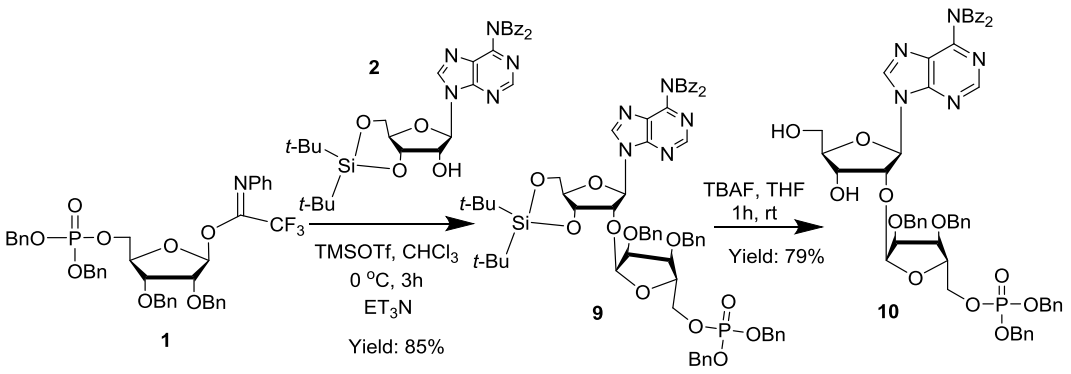
Figure 1. Post-translational protein modification (PTM): e.g; Poly-ADP-ribose polymer attached to protein.

We developed a synthetic route for the synthesis of benzyl protected phosphorylated ribofuranosyl *N*-phenyltrifluoroacetimidate **1** (Scheme 1) which was used in two representative glycosylation reactions; in synthesis of compounds **8** and **9**. The synthesis of **1** involved the following synthetic steps: i) synthesis of methyl D-ribofuranoside **3** according to the reported procedure,[10] ii) phosphorylation of methyl D-ribofuranoside **3** through using P-amidite chemistry,[11] iii) benzylation of phosphorylated methyl D-ribofuranoside **4** to protect the secondary hydroxyl groups,[6,7] iv) deprotection of the anomeric methoxy to hydroxyl group via hydrolysis to give **6**, v) and finally introduction of the (*N*-phenyl)-2,2,2-trifluoroacetimido group on the anomeric hydroxy function group (Scheme 1).[8,9]

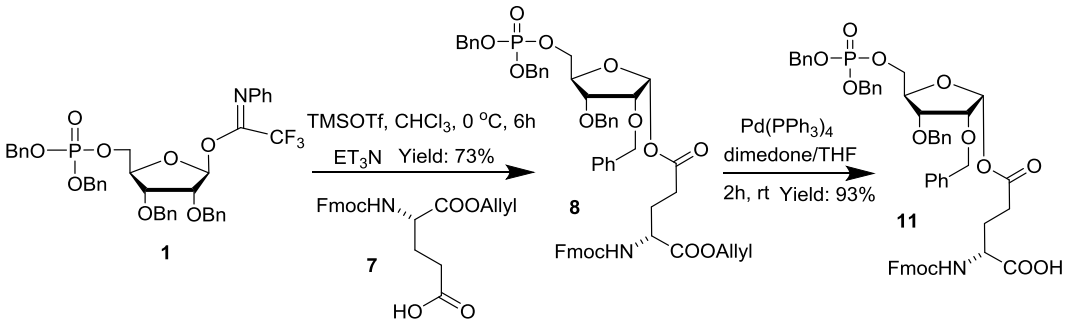


Scheme 1. Synthesis of benzyl-phosphorylated ribofuranosyl *N*-phenyltrifluoroacetimidate **1**.

After the synthesis of donor **1**, 3,5-O-di-*tert*-butylsilyl protected *N*-benzoyl adenosine **2** was synthesized in order to obtain a bifunctional building block **9**. The synthesis of compound **2** was achieved according to a reported procedure.[12-14] However, The phosphorylated donor **1** was also used for the preparation of ribosylated amino acid **8** (Scheme 3). [15,16] After the C-terminal deprotection of **8** by using 20 mol% $Pd(PPh_3)_4$ and excess dimedone in THF, give building block **11** with a terminal phosphoribose moiety which can be used in future for coupling reactions and phosphorylations with precise control over the number of modifications.[17,18]



Scheme 2. Synthesis of orthogonal bifunctional building blocks **9**, **10**.



Scheme 3. Synthesis of ribosyl amino acid derivatives **8**, **11**.

Generally, the synthesis of nucleosides with *O*-glycosylation on 2′-OH are considered difficult reactions., causing the formation of sideproducts in the reaction mixture and decreasing the yield of the desired *O*-glycosylated nucleoside.[6-8] Some reports containing examples of the glycolysation of nucleosides with pyranosyl moieties, shimofuridin,[19,20] and adenophostin,[21-23] possessing 2′-O-*β*-fucopyranosyl and 3′-O-α-glucopyranosyl respectively have been reported. A number of synthetic nucleosides with O-*β*-linked furanosyl groups are also reported.[24-26] However, very few examples have been reported for the synthesis of 2′-*O*-α-D-ribofuranosyladenosine which have 2′-O-α-ribosylated adenosine.[15-18,27] In one example, the synthesis of 2′-*O*-α-D-ribofuranosyladenosine involved selective *trans*-coupling of arabinofuranose to adenosine, then subsequent attachment of the 2′-O-acyl group, proceeding by inversion of the stereochemistry at the 2-position of the arabinofuranose *via* an oxidation reduction sequence. To significantly improve previous procedures, we utilized the building block, di-*tert*-butylsilyl-protected adenosine nucleoside (**2**, Scheme 2).[12-16] Using this block, and benzyl-phospho-ribofuranosyl *N*-phenyltrifluoroacetimidate as a donor **1**, it was possible to synthesize a α-riboside in excellent yield with orthogonal protective groups (Scheme 2). Filippov et al. reported similar kind of phosphorylated orthogonal building block in multiple steps synthesis (8-10 steps) using protecting and deprotecting chemistry and finished with laborious work up to provide free primary OH that was further functionalized with phosphoramidite group. [16] We synthesized phosphorylated orthogonal building block with free primary OH in two steps which possibly be functionalized with phosphoramidite group.

The imidate **1** activated with TMSOTf (Lewis acid) in the presence of acceptor **2** resulted in the formation of **9** with excellent α-selectivity in 85% yield (Scheme 2). The stereochemistry was assigned according to the literature.[28-30] The exocyclic amine of acceptor was dibenzoylated to avoid the side reaction. However, non-participating benzyl protection and (*N*-phenyl)-2,2,2-trifluoroacetimido group on the ribofuranosyl donor predominantly renders the α-product in glycosylation reactions. We deprotected silyl group of orthogonal bifunctional building block **9** to get compound **10** in 79% yield. However, the complete deprotection of **9** can be attempt by following the given literature.[6,7] We also synthesized phosphoribosylated amino acid **8** in 73% yield (Scheme 3) by using imidate **1** and glutamic acid **7**. For this glycosylation reaction, also the TMSOTf used as an activator. The compounds **10** and **11** can possibly be used for extension of phosphate and peptide chain for PTMs.[17,18]

Conclusions

We successfully synthesized ribosyl donor **1**, phosphoribosylated amino acid derivatives **8**, **11** and orthogonal bifunctional building blocks **9** and **10** which may provide an opportunity for the preparation of synthetic material for PTMs in a defined way.

Experimental Section

General

All chemicals were purchased from *Sigma-Aldrich* and *Merck*. Reactions were carried out under N_2 or Ar. Solvents for reactions were distilled prior to their use. Evaporation of the solvents *in vacuo* was done with the rotary evaporator. *Merck* silica gel 60 (40 – 63 μm) was used for column chromatography. *Merck* thin layer chromatography plates silica gel 60 on aluminum were used for the spots visualizing by UV light. $KMnO_4$ and *p*-anisaldehyde solutions were used for staining. For ^{1}H-NMR spectra; *Bruker AV-300* (300 MHz), Bruker *AV-400* (400 MHz) and Bruker *AV-500* (500 MHz) were used. For ^{13}C-NMR spectra; *Bruker AV-300* (75.5 MHz), *Bruker AV-400* (100 MHz) and *Bruker AV-500* (125 MHz) were used. For ^{31}P-NMR spectra; *Bruker AV-300* (75.5 MHz) or *Bruker AV-400* (161 MHz) were used.

Experimental

Synthesis of 4. 4,5-Dicyanoimidazole (DCI, 1.95 g, 16 mmol) was added to a soln. of **3** (2.464 g, 15 mmol) and $(BnO)_2PNiPr_2$ (technical grade, 90%, 5.76 g, 15 mmol) in DMF (15 mL) at –10°C. The soln. was stirred at –10°C. After 5 h mCPBA (70%, 4.04 g, 18 mmol) was added in small portions and after stirring for another 0.5 h at 25°C the reaction soln was diluted with Et_2O and washed with H_2O (3 x 30 mL). The aq. layer was extracted with Et_2O (3 x 30 mL) and the combined org. layer were dried with $MgSO_4$. Evaporation of solvent *in vacuo* delivered colorless solid as crude product of **4** (7.37 g). Filtration over silica gel (CH_2Cl_2/MeOH 10:0 to 10:1) delivered colorless oil of **4** (3.61 g, 9 mmol, 60%). ^{1}H-NMR (400 MHz, CDCl3): 7.41 – 7.30 (*m*, 2 x *Ph*), 5.05 – 5.03 (m, 2 x OC*H*2Ph), 4.67 (*s*, 1 H), 4.17 – 4.09 (*m*, 1 H), 3.99 – 3.88 (*m*, 3 H), 3.74 (*d*, *J* = 4.1, C1H), 3.19 (*s*, CH3), 2.89 (*s*, C3OH), 2.73 (broad *s*, C2OH). ^{13}C-NMR (100 MHz, DMSO): 136.1, 136.0 (2*s*, 2 x OCH2*Ph*), 128.5,

128.3, 127.8 (10*d*, 2 x OCH2*Ph*), 108.3 (*d*, C1), 80.6 (*d*, C4), 74.0 (*d*, C2), 70.6 (*d*, C3), 3 x 68.5 (3*t*, C5, 2 x *C*H2Ph), 54.3 (*q*, CH3). ^{31}P-NMR (161 MHz, CDCl3): –3.44 (*quin*). HR-ESI-MS (MeOH + NaOH): 447.11782 ($C_{20}H_{25}NaO_8P^+$, $[M + Na]^+$, calc. 447.11793, Δm = 0.2 ppm).

Synthesis of 5. NaH (60%, 0.64 g, 16 mmol) was added in small portions to a soln. of **4** (3.08 g, 7 mmol) in dry DMF (25 mL) at –10°C. Benzyl bromide (2.76 g, 16 mmol) was added after 5 min to the pale yellow and bubbling suspension. The reaction mixture was stirred for 1.5 h at -10°C before it was allowed to warm to 0°C. It was stirred for another 3.5 h at 0°C before TLC showed full consumption of **4** and the reaction was quenched by addition of H_2O (30 mL). The mixture was extracted with Et_2O (3 x 150 mL) and the collected org. layers were dried with $MgSO_4$. Evaporation of the solvent *in vacuo* delivered turbid pale yellow liquid as crude product of **5** (4.98 g). Purification by column chromatography (pentane/Et_2O 1:1 to 1:3) delivered colorless oil of **5** (3.36 g, 5 mmol, 56 %). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.10 (*m*, 4 x *Ph*), 5.08 (*s*, 1 H), 2 x 4.93 (2*d*, *J* = 7.8, 2 x POC*H*2Ph), 4.79 (*s*, 1 H), 4.52 (*q*, *J* = 12, 1 H), 4.42 (*d*, *J* = 11.7, 1 H), 4.32 (*d*, *J* = 11.7, 1 H), 4.27 – 4.16 (*m*, 1 H), 4.10 – 3.89 (*m*, C5H2, there in 3.99 – 3.96 (*t*-like *m*, C4H)), 3.73 (*d*, *J* = 4.5, C1H), 3.18 (*s*, CH3). ^{13}C-NMR (100 MHz, CDCl3): 137.8 (4*s*, Ph), 128.7, 3 x 128.6, 128.3, 128.1, 2 x 128.0 (20*d*, 4 x Ph), 106.4 (*d*, C1), 79.8 (*d*, C4), 79.6 (*d*, C2), 78.1 (*d*, C3), 72.7, 72.5 (2*t*, 2 x CO*C*H2Ph), 2 x 69.4 (2*t*, 2 x PO*C*H2Ph), 68.1 (*t*, C5), 55.1 (*s*, CH3). ^{31}P-NMR (161 MHz, CDCl3): –1.06 (*quin*). HR-ESI-MS (MeOH + NaOH): 627.21201 ($C_{34}H_{37}NaO_8P^+$, $[M + Na]^+$, calc. 627.21183, Δm = 0.3 ppm).

Synthesis of 6. 5.5 ml HCl was added to a solution of **5** (1.80 g, 3 mmol) in CH_3CN (55 mL). The solution was stirred at room temperature for 2 h. Then, ethyl acetate (excess) and brine solution were added to quench reaction. Organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The desired alcohol was purified by Silica gel column chromatography (CH_2Cl_2/EtOAC (50:1 to 50:10)) (1.20g, mmol, 60% yield) as a transparent oil.^{1}H-NMR (400 MHz, DMSO): 7.37 – 7.05 (*m*, 20 H), 5.05 – 4.85 (*m*, 4 H), 4.66 – 4.34 (*m*, 4 H), 4.25 – 3.96 (*m*, 4 H), 3.91 – 3.68 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 137.75, 135.62, 135.94, 135.90, 135.87, 135.83, 128.59, 128.46, 127.94 (arom), 106.31, 79.73, 77.98, 72.56, 69.34, 67.98. ^{31}P-NMR (161 MHz, DMSO): –0.71 (*quin*). ESI-MS (MeOH + NaOH): 613.2 ($C_{35}H_{35}NaO_8P^+$, $[M + Na]^+$, calc. 613.2).

Synthesis of 1. Compound **6** (120 mg, 0.2 mmol) was dissolved in acetone (3 mL) and 100 µL water. Cs_2CO_3 (71 mg, 0.2 mmol, 1.1 eq.) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride $ClC(=NPh)CF_3$ (30 µL, 0.2 eq.) were added and the reaction mixture was stirred at room temperature for 7 hours. After filtration over celite, the solvents were removed and the residue was purified using silica gel column chromatography (CH_2Cl_2/EtOAc (10:1) to afford the title compound as a colourless oil (107 mg, 70%).^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.52 – 7.16 (m, 22H, arom), 7.02 (m, 1H, arom), 6.71 (dd, *J* = 16.7, 7.5 Hz, 2H, arom), 6.20 (s, 1H, H1), 4.95 – 4.91 (m, 4H, CH2 Bn), 4.63 – 4.60 (m, 1H, H4') 4.54 – 4.33 (m, 4H, CH2 Bn), 4.15 – 4.11 (m, 1H, H3'), 4.08 – 4.01 (m, 1H, H2'), 3.96 (AB, *J* = 11.3, 4.3 Hz, 1H, H5'), 3.85 (AB, *J* = 11.3, 4.0 Hz, 1H, H5'). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.55,

136.17,134.79, 134.67, 128.24, 127.72, 127.51,127.11, 127.01, 126.91, 126.59, 125.15, 123.31, 119.57, 118.46, 101.11 (C1), 80.06 (C4), 77.25 (C2), 76.32 (C3), 71.77, 71.32, 68.38 (CH2 Bn), 65.73 (C5). ^{31}P-NMR (161 MHz, $CDCl_3$): –1.28. ESI-MS (MeOH + NaI): 762.8 ($C_{41}H_{39}F_3NO_8P^+$, [M + H]$^+$, calc. 761.7).

Synthesis of 9. The trifluoroacetimidate donor dissolved (**1**, 152mg, 0.2 mmol) in dry $CHCl_3$ (1ml), was added slowly at 0 ^{O}C to the solution of acceptor **2** (100mg, 0.16 mmol) and Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (9ul, 0.2 eq.) in dry $CHCl_3$ (1 ml) containing freshly activated 4 Å molecular sieves, and then solution was stirred under Nitrogen atmosphere for 3h at 0 ^{O}C and quenched by the addition of triethylamine (TEA, 200 ul). The reaction mixture was concentrated *in vacuo.* After evaporation of the solvent the crude material was purified using silica gel column chromatography (hexane/EtOAc (3:2) as white foam (202 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H, C2), 7.94 (s, 1H, C8), 7.88-7.25 (m, 30H, Arom. Bz , Bn), 6.06 (s, 1H, H1”), 5.40 (d, J = 4.0 Hz, 1H, H1’), 4.71 – 4.49 (m, 10H, CH2 Bn’s, C3”, C2”), 4.35-3.41 (m, 1H, C4”, C5”, C2’, C3’, C5’), 1.28 – 0.97 (m, 18H, t-butyl.). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.10, 149.40, 142.87, 131.86, 131.06, 127.47, 126.78, 126.53, 126.37, 126.30, 126.22, 126.02, 125.89, 125.85, 125.78, 90.47 (C1’), 86.31 (C1”), 71.81, 71.05, 67.21, 60.89, 34.10, 31.40. ^{31}P-NMR (161 MHz, $CDCl_3$): –1.17. ESI-MS (MeOH + NaI): 1189.5 ($C_{65}H_{71}N_5O_{13}PSi^+$, [M + H]$^+$, calc. 1188.4

Synthesis of 10. Compound **9** (120 mg, 0.1mmol) was dissolved in THF (5 mL). Treatment with TBAF (52.3mg, 2 eq.) at room temperature for one hour, concentration (Reaction was monitored by TLC, CH_2Cl_2: Methanol, 5:0.5) and purification using column chromatography (CH_2Cl_2: EtOAc, 3:4) afforded the title compound as a colourless syrup **10** (84 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H, C2), 8.01 (s, 1H, C8), 7.94-7.14 (m, 30H, Arom. Bz , Bn), 6.36 (d, J = 7.4 Hz 1H, H1”), 5.91 (s, 1H, C5” OH) 5.48 (d, J = 7.2 Hz, 1H, H1’), 5.19 4.71 – 4.49 (m, 4H, P-O-CH2 Bn’s) 4.91 – 4.80 (m, 5H, CH2 Bn’s, C4”), 4.75-4.32 (m, 5H, C2”, C3’, C5”, C4’) 4.28 (s, 1H, C3” OH), 4.05-3.78 (m, 4H, C3”, C2’, C5’). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.10, 152.24, 145.58, 137.47, 136.38, 134.62, 133.91, 130.09, 129.42, 129.36, 129.26, 129.18, 128.99, 128.99, 128.85, 128.64, 128.45, 126.11, 102.09 (C1’), 100.11 (C1”), 71.32, 70.05, 66.29, 63.40, 56.10. ^{31}P-NMR (161 MHz, $CDCl_3$): –1.24. ESI-MS (MeOH + NaI): 1048.35 ($C_{57}H_{55}N_5O_{13}P^+$, [M + H]$^+$, calc. 1048.35

Synthesis of 8. The trifluoroacetimidate donor dissolved (**1**, 38mg, 0.05 mmol) in dry $CHCl_3$ (0.5ml), was added slowly at 0 ^{O}C to the solution of glutamic acid **7** (20mg, 0.05 mmol) and Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2.5ul, 0.05 eq.) in dry $CHCl_3$ (0.5 ml) containing freshly activated 4 Å molecular sieves, and then solution was stirred under Nitrogen atmosphere for 6h at 0 ^{O}C and quenched by the addition of triethylamine (TEA, 200 ul). The reaction mixture was concentrated *in vacuo.* After evaporation of the solvent the crude material was purified using silica gel column chromatography (CH_2Cl_2/EtOAc (5:1) as white syrup (35 mg, 73% yield). ^{1}H-NMR (500 MHz, CDCl3) δ: 7.67 – 7.17 (m, 29H, arom), 6.16 (s, 1H, H1’-α), 5.78 –5.75 (m, 1H, -CH=), 5.78 – 5.75 (m, 1H, -CH=), 5.40-5.39 (d, 1H, =CH-), 5.23-3.22 (m, 19H, CH2 Bn, -CH2-, O-CH2-, -,-CH-,

H3', H4', H5'), 2.40-1.92 , (m, 4H, -CH2-CH2-). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.51, 171.28, 156.93, 144.01, 142.89, 138.14, 137.39, 136.15, 135.98, 132.07, 129.27-127.70 (arom.), 101.30, 100.11 (C1'), 99.35, 98.74, 95.57, 75.41, 73.63, 73.33, 73.08, 70.08, 66.69, 48.54, 47.77, 31.05, 27.22. ^{31}P-NMR (161 MHz, $CDCl_3$): –0.97. ESI-MS (MeOH + NaI): 1004.35 ($C_{57}H_{55}N_5O_{13}P^+$, [M + Na]$^+$, calc. 1004.34)

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