Protective group strategies in carbohydrate and peptide chemistry

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CHAPTER

6

Summary and future prospects

An efficient organic synthesis of fragments of biopolymers and analogues thereof cannot be reached without a proper use of protective groups. In oligonucleotide and oligopeptide synthesis the applied protective groups generally ensure the regioselective introduction of the phosphodiester and peptide linkages between the monomeric nucleosides and amino acids respectively, as well as minimization of unwanted side reactions en route to the target compounds. Thanks to the developed protective groups and improved coupling methods to introduce phosphate and peptide linkages, DNA and peptide fragments consisting of dozens of monomeric residues can be prepared with the aid of fully automated solid phase procedures. Despite these advances the search for new protective groups in the field of nucleic acid and peptide chemistry still goes on. For instance, improvement of the overall yield in the synthesis of RNA fragments and the synthesis of

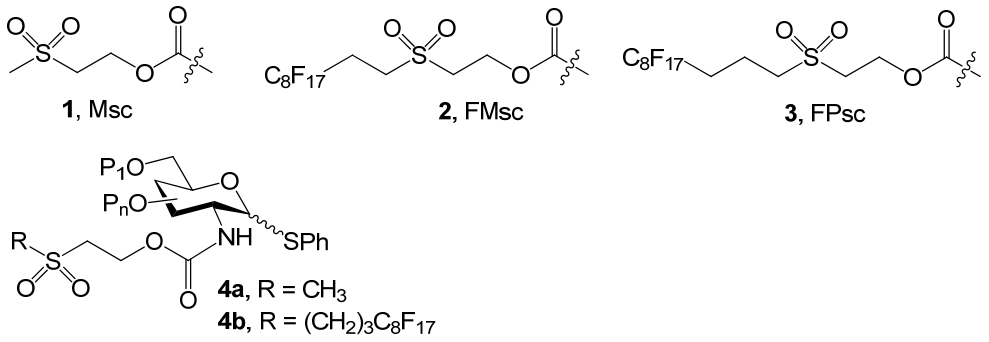
nucleic acid peptide conjugates may benefit from the development of new tailor made protective groups. Compared with the present state of the art in nucleic acid and peptide chemistry the synthesis of oligosaccharides has been relatively slow to mature, [1] which can be explained by the increased structural complexity of carbohydrates. Carbohydrates may occur either as straight or branched chains and may contain various monosaccharides differing in the number, nature and configuration of the substituents. Moreover, the glycosidic linkage between the constituting monosaccharides can occur in two diastereomeric forms. In the synthesis of naturally occurring and artificially designed oligosaccharides the protective group strategy[2] and the glycosylation procedure[3] play a decisive role to attain a productive and stereoselective glycosylation reaction. In this respect it is of interest to note that the protective groups installed on the glycosylating partners (donor and acceptor), not only dictate the regioselectivity[4] and the yield of the glycosylation reactions but also influence the stereoselective outcome.[5]

This thesis reports on the development of new protective groups that can be applied for the synthesis of biopolymer fragments with a focus on oligosaccharides. **Chapter 1** reviews recent advances on protective groups and protective group manipulations in the field of carbohydrate chemistry. With the objective to diminish the efforts to prepare sufficient amounts of suitably protected monosaccharides, several groups have reported on the development of one-pot protocols, entailing up to five reaction steps. One procedure starts from anomerically protected per-silylated carbohydrate monomers and gave access to a wide array of differentially protected monosaccharide donors and acceptors. A lot of attention has been paid to the design of protective groups for the C-2 hydroxyl, that are able to induce the stereoselective formation of 1,2-*cis* glycosidic bonds. An impressive example is presented by the development of two C-2 OH protecting groups capable of promoting the formation of 1,2-*cis* glycosidic bonds by neigbouring group participation, reported by the group of Boons. The discovery of Crich and co-workers that 4,6-benzylidene mannosyl donors react in a highly β-selective fashion was followed by studies on the influence of protecting groups at the C-2 and C-3 positions of these donors and led to the development of various propargyl ethers as minimally intrusive hydroxyl protecting groups. Silyl protecting groups are becoming increasingly popular in carbohydrate chemistry as exemplified by the introduction of the 4,6-di-*tert*-butylsilylene

(DTBS) as a more acid stabile alternative for the usual cylic ketals and acetals. A row of new *trans*-directing protecting groups for the glucosamine nitrogen function has also been reported. Contrary, Kerns and co-workers introduced oxazolidinone protected glucosamine donors that stereoselectively provided 1,2-*cis* linked products. Subsequent studies revealed that the stereochemical outcome of 2,3-oxazolidinone-*N*-acetyl and 2,3-oxazolidinone-*N*-benzyl protected glucosamine donors could be controlled by the (Lewis)-acidity of the employed activator systems.

Several types of protecting groups were published that not only mask a specific functional group on the carbohydrate core, but also add an extra functionality to the carbohydrate building block. For instance, protective groups have been developed which impart colour to the substrate, allowing an easy detection during purification procedures or monitoring of the glycosylation efficiency during automated synthesis. A number of protective groups provided with purification handles became available through the development of fluorous chemistry and ionic liquids.

Figure 1: The Msc protecting group and fluorous derivatives thereof.



Chapter 2 describes the first application of the methylsulfonylethoxycarbonyl (Msc) group (**1**, Figure 1) as protecting group for hydroxyl functions in oligosaccharide synthesis. The Msc group can be introduced using conditions, commonly used to install the 9-fluorenylmethyl carbonate (Fmoc). Contrary, the Msc group is less lipophilic, less bulky and slightly more stable than the Fmoc group. The Msc group can be cleaved *via* β-

elimination using mildly basic conditions and is orthogonal with the levulinoyl (Lev) group. The Msc group was used in donor and acceptor glycosides and was stable during glycosylation reactions. When the Msc group was placed at the C-2 hydroxyl, it provided anchimeric assistance while unwanted orthoester formation was prevented.

It would be interesting to evaluate the Msc group as an amino protecting group in oligosaccharide synthesis. Protection of the glucosamine nitrogen function with the Msc group would afford a glycosyl donor (e.g. **4a**, Figure 1), having a sterically unbiased, participating group.

In bioorganic chemistry fluorous solid phase extraction (FSPE) has emerged a new purification method. In this context a number fluorous protecting groups to facilitate the purification of oligopeptides, (oligo)nucleotides and oligosaccharides is reported. **Chapter 3** deals with the evaluation of fluorous counterparts of the Msc group as purification handles in carbohydrate chemistry. The [1H, 1H, 2H, 2H]-perfluorodecylsulfonylethoxycarbonyl (FMsc, **2**, Figure 1) group, known as a fluorous protective group for amines was found to be too labile for the protection of hydroxyl functions of carbohydrates. Increasing the distance between the sulfonyl functionality and the perfluoro moiety by an additional methylene group led to the development of the [1*H*,1*H*,2*H*,2*H*,3*H*,3*H*]-perfluoroundecylsulfonylethoxycarbonyl (FPsc, **3**, Figure 1) group as a sufficiently stable hydroxyl protecting group. The FPsc group was applied in the assembly of a trisaccharide and found to be orthogonal with levulinyl (Lev) group.

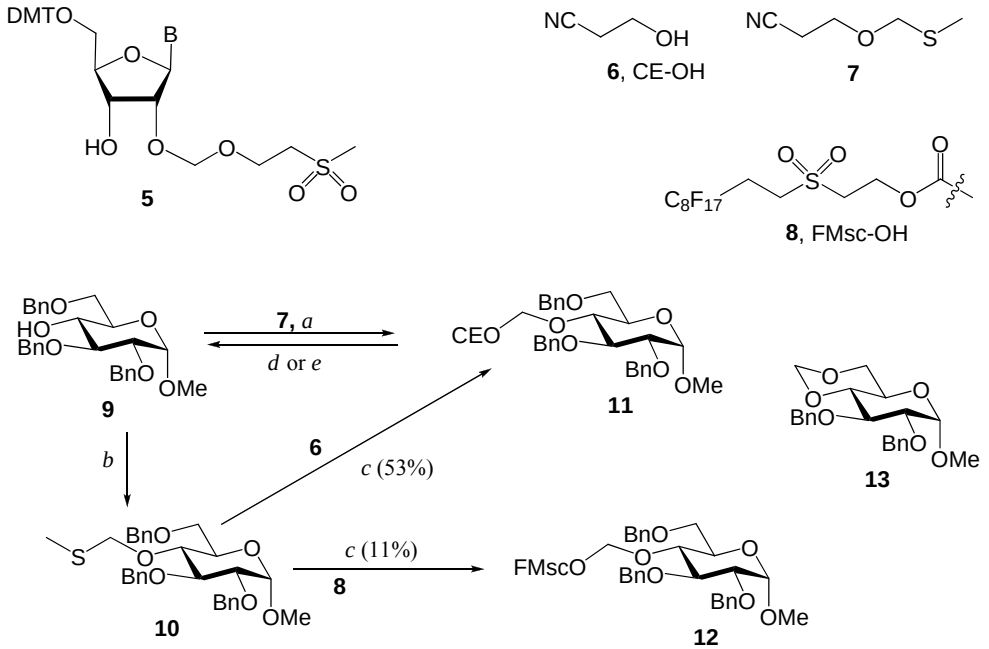
These results indicate that it is worthwhile to investigate whether the FPsc group can be applied for the purification of oligosaccharides and glycopeptides that are assembled by solid phase procedures. In this context the FPsc group can also be used as purification handle at amino functions such as in glucosamine derivative **4b** (Figure 1). In addition it would be interesting to investigate whether the FPsc can function as a fluorous handle to facilitate the purification of different classes of biomolecules, such as oligonucleotides and conjugates thereof.

Chapter 4 describes the methylsulfonylethoxymethyl (Msem) group as a new hydroxyl protecting group, that increases the palette of ether based protecting groups in carbohydrate chemistry. Several methods for the introduction of the Msem group were investigated. The Msem group can be introduced at primary and secondary hydroxyl

functions of *O*-glycosides using the thiomethylether of 2-(methylsulfonyl)ethanol and a thiophilic activator. Diol thioglycosides can be selectively protected by the conversion of the hydroxyl functions into dibutylstannylidene acetals followed by reaction with (methylsulfonylethoxy)methyl chloride (Msem-Cl). The Msem group proved to be relatively base stabile and could be easily removed by a catalytic amount of TBAF in the presence of piperidine as scavenger. Application of the Msem group in the synthesis of an all *cis*-linked 1,3-*O*-mannotrioside showed that this group is sterically unbiased and does not provide remote participation.

The properties of the Msem group indicate that is valuable to investigate whether the Msem group can function as a protecting group for the C-2-OH function in RNA synthesis. Accordingly, protected nucleoside **5** (Figure 2) may be accessible by the synthetic route devised for the introduction of the cyanoethoxymethyl group at the same position of RNA building blocks.[6]

Figure 2: The Msem protecting group, its fluorous derivatives and the cyanoethoxymethyl group.



Reagents and conditions; *a*) NIS, TMSOTf, DCM, -20 ºC to RT, 24h, 72%; *b*) NaH, Methylthiomethylchloride, DMF, 1h, 73%; *c*) IDCP, DCM, RT, 2h; *d*) DBU, DMF, 10h, 93%; *e*) THF, TBAF, 1h, 96%.

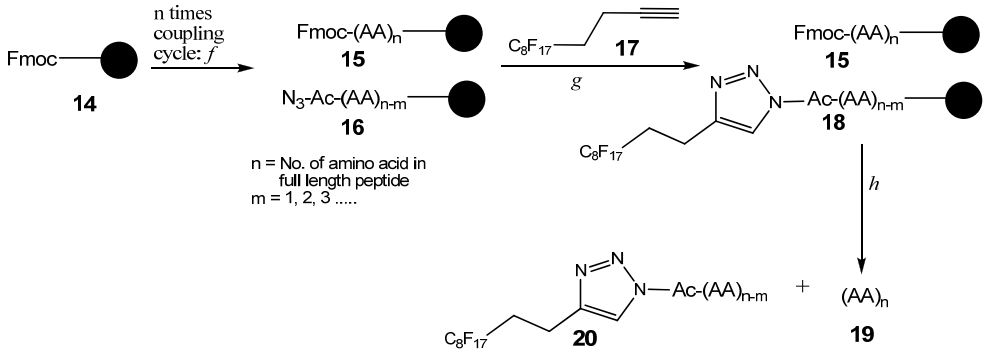
Conversely, it would be interesting to explore protecting groups that are specifically developed to improve RNA synthesis for their application in carbohydrate chemistry. Preliminary results on the use of the cyanoethoxymethyl group in carbohydrate chemistry are depicted in figure 2. The required 3-(methylthiomethoxy)propanenitrile **7** was prepared in 60% yield by treating cyanoethanol with dimethylsulfoxide, acetic acid and acetic anhydride. Condensation of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** with thiomethyl ether **7** under the agency of *N*-iodosuccinimide (NIS) and trimethylsilyltriflate (TMSOTf) produced cyanoethoxymethyl protected glucoside **11** in 72% yield (Figure 2). Alternatively, 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **9** was converted into methylthiomethyl ether **8** by treatment with sodium hydride and methylthiomethyl chloride (MTM-Cl) in DMF. Reaction of **10** and cyanoethanol under influence of IDCP (4 equivalents) as activating agent led to the isolation of the desired monosaccharide **11** (53% yield) together with side product **13**. The cyanoethoxymethyl group could be removed from 2,3,6-tri-*O*-benzyl-4-*O*-cyanoethoxymethyl-α-D-glucopyranoside **11** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 6h at room temperature to give **9** in 93% yield (Figure 2). Alternatively, treatment of **11** with tetrabutylammonium fluoride (TBAF, 0.1 equivalents) for 30 minutes led to the removal of the cyanoethoxymethyl group in 96% yield. The development of a fluorous version of the methylsulfonylethoxymethyl (Msem) group may be also be advantageous, as the Msem group is a non-participating and more base stabile in comparison with the perfluoroundecylsulfonylethoxycarbonyl (FPsc, see Chapter 3) group. In a preliminary experiment fluorous glucoside **12** could be prepared in 11% yield.

Two approaches can be distinguished for the application of fluorous techniques to purify fragments of biopolymers prepared with the aid of solid phase procedures In the first approach a suitable fluorous protecting group is used and installed in the final stage of the solid phase synthesis to give the fluorous target oligomer. Examples of such fluorous protecting groups are discussed in Chapter 1 and 3. In the second approach intermediate oligomers that resist elongation en route to the target compound are capped after every condensation step in the solid phase cycle with a fluorous reagent, making the truncated and deletion sequences fluorous and leaving the target compound untouched. **Chapter 5**

narrates the idea of a new two-step fluorous capping procedure. Five oligopeptides were prepared by regular solid phase peptide synthesis, in which the standard capping procedure was replaced by treatment with azidoacetic acid, HCTU and Dipea. After the completion of the synthesis of the target oligopeptide, the azides in the truncated and deletion sequences were reduced to amines and subsequently capped with (1H,1H,2H,2H)-perfluoroundecanoic acid. The fluorous sequences were separated from the target peptide by fluorous solid phase extraction (FSPE) or by Fluorous HPLC (F-HPLC).

It is envisaged that the number of reaction steps in this fluorous capping strategy can be reduced by replacing the azide reduction and ensuing capping with a fluorous carboxylic acid by a Huisgen 1,3-dipolar cycloaddition (click reaction) with a suitable alkyne.[7]

Figure 3: fluorous capping strategy using click chemistry.

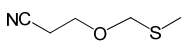


Reagents and conditions; *f*) i- Piperdine (20% in NMP)15 min.; ii- Fmoc-amino acid, HCTU, Dipea, NMP; iii- Azidoacetic acid, HCTU, NMP, 20 min; *g*) $CuSO_4$, Sodium ascorbat; *h*) i- TFA, TIS, H_2O, 45 min; ii- FSPE or F-HPLC.

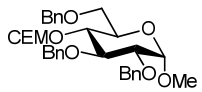
Following the same coupling cycle as described in Chapter 5, immobilized target oligopeptide **15** and a number of azido functionalized deletion sequences **16** will be obtained at the end of the synthesis (Figure 3). With the aid of alkyne **17** the deletion sequences **16** will be made fluorous by a copper catalyzed click reaction. Removal of the protecting groups and cleavage from the solid support will provide target oligopeptide **19** and fluorous sequences **20**. Target peptide **19** can be separated from the fluorous impurities using Fluorous HPLC.

Experimental:

General: Dichloromethane was refluxed with P_2O_5 and distilled before use. All other chemicals (Acros, Fluka, Merck, Fluorous Technologies Inc.) were used as received. Column chromatography was performed on Screening Devices silica gel 60 (0.040-0.063 mm). Compounds were visualized by UV absorption (245 nm), by spraying with an aqueous solution of $KMnO_4$ (20%) and K_2CO_3 (10%), by spraying with 20% H_2SO_4 in ethanol or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10g/L) in 10% $H_2SO_{4\ (aq)}$ followed by charring at ~150 ºC. IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotations were measured on a Propol automatic polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 MHz and 100 MHz respectively), AV 500 (500 MHz and 125 MHz respectively) or DMX 600 (600 MHz and 150 MHz respectively). NMR spectra were recorded in $CDCl_3$ unless stated otherwise. Chemical shift are relative to tetramethylsilane and are given in ppm. Coupling constants are given in Hz. All given ^{13}C spectra are proton decoupled. High resolution mass spectra were recorded on a LTQ-Orbitrap (thermo electron).



((Cyanoethoxy)methyl)methylsulfane (7) : To a solution of cyanoethanol **6** (4.16 ml, 58.4 mmol) in DMSO (18 ml, 234 mmol, 4 eq) was added acetic acid (7 ml, 117 mmol, 2 eq) and acetic anhydride (12 ml, 117 mmol, 2 eq). The reaction mixture was stirred for 48 hours. The mixture was neutralized by careful addition of $NaHCO_{3\ (s)}$, extracted using a large excess of EtOAc, dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to afford **7** (5.54 g, 30.0 mmol, 60%) as a yellow ~~a~~ oil. TLC (75% EtOAc in PE): R_f = 0.75; IR (neat, cm^{-1}): 730, 1129, 1286; ^1H NMR (400 MHz, ($CDCl_3$) δ = 2.16 (s, 3H, -$CH_2SC\underline{H}_3$), 2.66 (t, 2H, *J* = 6.0 Hz, $NCC\underline{H}_2CH_2OCH_2SCH_3$), 3.73 (t, 2H, *J* = 6.0 Hz, $NCCH_2C\underline{H}_2OCH_2SCH_3$), 4.68 (s, 2H, $NC(CH_2)_2OC\underline{H}_2SCH_3$); ^{13}C NMR (100 MHz, ($CDCl_3$) δ = 13.7 (-$CH_2S\underline{C}H_3$), 18.6 ($NC\underline{C}H_2CH_2OCH_2SCH_3$), 62.2 ($NCCH_2\underline{C}H_2OCH_2SCH_3$), 75.1 ($NC(CH_2)_2O\underline{C}H_2SCH_3$); HRMS $[M+Na]^+$ calculated for C_5H_9OSN 154.02971, found 154.02962.

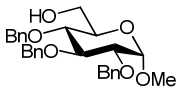


Methyl 2,3,6-tri-*O*-benzyl-4-*O*-cyanoethoxymethyl-α-D-glucopyranoside (11):

Method I: A solution of Methyl 2,3,6-tri-*O*-benzyl-4-*O*-methylthiomethyl-α-D-glucopyranoside **10** (0.203 g, 0.387 mmol) and cyanoethanol (66 µl, 0.968 mmol, 2.5 eq) in DCM (7.7 ml, 0.05M) was stirred over activated MS3Å for half an hour before Iodo dicollidine perchlorate (0.724 g, 1.548 mmol, 4eq) was added in dark. The mixture was stirred in dark for 24 hours. The reaction mixture was quenched with NH_4Cl, filtered, diluted with DCM and washed with $Na_2S_2O_3$. The aqueous layer was extracted with DCM thrice, the combined organic layer was washed with NH_4Cl, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to get compound **11** (0.113 g, 0.206 mmol, 53%);

Method II: A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** (70 mg, 0.15 mmol) and reagent **7** (30 mg, 0.23 mmol, 1.5 eq) in DCM (10.4 ml, 0.05 M) was stirred over activated MS3Å for 30 minutes before *N*-iodosuccinimide (40 mg, 1.85 mmol, 1.2 eq) was added. The mixture was cooled to -20 ºC followed by the addition of trimethylsilyltrifluoromethanesulfonate (10% in DCM, 55 µl, 30 µmol, 0.2 eq). The mixture was stirred for 2 hours. The reaction mixture was quenched with triethylamine (5 eq), filtered, diluted with DCM and washed with $Na_2S_2O_{3\ (aq)}$. The aqueous layer was extracted with DCM thrice, the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by silica gel column chromatography to get **11** (59 mg, 0.11 mmol, 72%).

TLC (50% EtOAc in PE): R_f = 0.6; $[\alpha]_D^{22}$: +59.0º (c = 0.4`, DCM); IR (neat, cm^{-1}): 689, 699, 738, 954, 1016, 1089, 1118, 1281, 1378; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.15-2.27 (m, 2H, NCC<u>H</u>$_2$CH$_2$OCH$_2$O-), 3.39 (s, 3H, OMe), 3.50 (mH-2 and NCCH$_2$C<u>H</u>$_2$OCH$_2$O-), 3.60 (m, 3H, H-4 and 2xH-6), 3.71 (m, 1H, H-5), 3.87 (t, 1H, *J* = 9.2 Hz, H-3), 4.62 (m, 6H, H-1, NC(CH$_2$)OCH<u>H</u>O- and 4xCH<u>H</u> Bn), 4.77 (m, 2H, NC(CH$_2$)OCH<u>H</u>O- and CH<u>H</u> Bn), 5.01 (d, 1H, *J* = 11.2 Hz, CH<u>H</u> Bn), 7.23-7.33 (m, 15H, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.4 (NC<u>C</u>H$_2$CH$_2$OCH$_2$O-), 55.2 (CH$_3$ OMe), 63.1 (NCCH$_2$<u>C</u>H$_2$OCH$_2$O-), 68.7 (C-6), 69.7 (C-5), 73.1 (CH$_2$ Bn), 73.3 (CH$_2$ Bn), 75.4 (CH$_2$ Bn), 75.5 (C-4), 79.9 (C-2), 81.1 (C-3), 96.5 (NC(CH$_2$)O<u>C</u>H$_2$O-), 97.8 (C-1), 117.6 (<u>C</u>N), 127.5-129.8 (CH arom), 137.8 (C_q Bn), 138.3 (C_q Bn); HRMS $[M+Na]^+$ calcd for $C_{32}H_{37}NO_7Na$ 570.24622 was found 570.24579.



Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (9) (Cleavage of Msem from 11):

Method I: To a solution of **11** (42 mg, 77 µmol) in DMF (0.8 ml, 0.1 M) was added DBU (0.067 M in DMF, 120 µl, 7.7 µmol, 0.1 eq) and the reaction mixture was stirred for 6 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography to afford methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **9** (33 mg, 71 µmol, 93%).

Method II: To a solution of **11** (52 mg, 95 µmol) in THF (1.0 ml, 0.1 M) was added TBAF (0.1 M in DMF, 100 µl, 9.5 µmol, 0.1 eq) and the reaction mixture was stirred for 1 hours. The reaction mixture was neutralized with $NH_4Cl_{(aq)}$, diluted with EtOAc, washed with $NH_4Cl_{(aq)}$, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography to afford methyl 2,3,6-*tri*-*O*-benzyl-α-D-glucopyranoside **9** (42 mg, 91 µmol, 96%).

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