One-Pot Synthesis of Asymmetrically Difunctionalized Oligomaltosides by Cyclodextrin Ring Opening

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The synthesis of pure difunctionalized hexa-, hepta- and octamaltosides was performed by one-pot chemical reaction from perbenzoylated cyclodextrin. Oligomaltosides with azide, propargyl or allyl on reducing end and an unprotected hydroxyl group on non-reducing end were obtained from perbenzoylated α-, β- and γ-cyclodextrin with 12 to 48% yields.

Oligosaccharides have many interests in food and health fields,[1–3] but also, more recently, in materials science and nanotechnologies for more extensive applications.[4–6]

Obtaining pure oligosaccharides both from natural sources,[7] and by multistep oligosaccharide synthesis,[8] remains challenging. On one hand, after the hydrolysis of a polysaccharide, the complex mixture of oligosaccharides must be fractionated by exclusion chromatography. On the other hand, total synthesis allowed to obtain pure compounds, but the yield of the sequential glycosylations strongly decreased with the growth of the oligosaccharide chain, limiting the quantity of the final product. Even the automated oligosaccharide synthesis is limited by the availability of building blocks.[9]

The synthesis of oligosaccharides by cyclodextrin (CD) ring opening is an efficient alternative to obtain them. Starting from α-, β-, or γ-CD, it can afford oligomaltosides containing 6, 7 or 8 glucose units, respectively. These oligosaccharides and derivatives have been used for many purposes such as the synthesis of cyclodextrin analogs for microenscapsulation,[10–12] as building blocks in linear[13–17] or graft[18–21] block copolymers for materials science and engineering, or as α-amylase biomarkers.[22,23]

The most used pathway to obtain those oligosaccharides is acetolysis of peresterified CD, with Ac_2O/H_2SO_4 (49:1), at 50–60 °C leading to icosa-O-acetylmaltohexaose in 46% yield from peracetylated α-cyclodextrin, for example.[24] Then, the method was extended to perbenzoylated α-, β- and γ-CD leading to 46, 41 and 52% yields respectively.[10] The conditions of this reaction were not versatile because acetolysis with chloroacetic and trifluoroacetic anhydrides were tested without success[25] just as the use of Lewis Acid,[22] instead of Brønsted Acid, which resulted in lower yields. Hoffmann *et al.* proposed a suitable alternative to open peracetylated CD, using Ac_2O/70% aqueous $HClO_4$ at 0 °C.[11] Lesur *et al.* extended the uses of these two methods to 6-bromo-6-deoxy peracetylated or perbenzoylated CD.[26]

Although acetolysis is an efficient way to open cyclodextrins, the resulting diacetylated perbenzoyl or 6-bromo-6-deoxy peresterified oligomaltosides may require many steps in order to functionalize them for further experiments,[10–13] reducing the overall yields.

Thus, the opening/glycosylation reactions were also investigated, such as thiolysis,[27] hydrolysis,[28] or chlorination using $TiCl_4$.[29] As these openings were performed on per-O-alkylated CD leading to per-O-alkylated oligomaltosides with all the hydroxyls substituted by alkyl groups.

As our studies require the efficient preparation of functionalized and unprotected oligomaltosides in high quantities, we have therefore investigated a new opening method of CDs. Here, we report the optimization of the synthesis of various easily graftable and non-protected oligomaltosides.

To perform this study, we first chose to work on the β-CD which is the less expensive of the three native CD.[30] The benzoate esters were selected as protecting groups for their easy introduction, removal and compatibility with many reactions and functional groups during their cleavage.[31,32]

Firstly, an opening inspired from acetolysis was carried out, using triflic anhydride instead of acetic anhydride.[10] This should lead to an easiest functionalization thanks to the lability of the triflate group. As triflic anhydride is quite expensive, it could not be used as a solvent compared with acetic anhydride in acetolysis reactions. Various polar aprotic solvents were tested. The sulfuric acid was chosen as Brønsted Acid because it contains less water than aqueous perchloric acid to prevent triflic anhydride from being hydrolyzed easily. Preliminary tests were operated on perbenzoylated β-CD **1b** (0.3 M) in THF, DMF, MeCN or DCM.

Unfortunately, in THF or DMF, further cleavages of glycosidic linkages were observed immediately after the beginning of the reaction, while conversion of **1b** was very low. In addition, oligosaccharides **2a** and **2b** were obtained together with lower DP byproducts as a crude. This crude could not be purified because of the similar Rf of these compounds in all the

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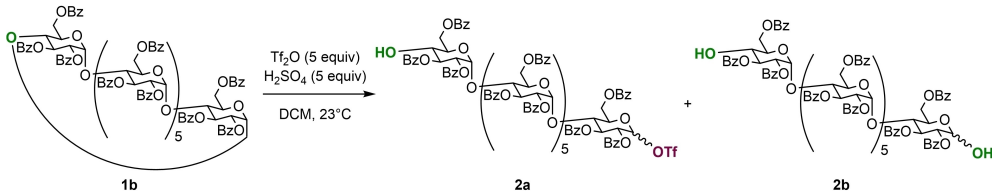


Scheme 1. Perbenzoylated β-cyclodextrin **1 b** opening using Tf_2O and H_2SO_4 in DCM. Reaction conditions: **1 b** (*C* 0.3 M) diluted in DCM, addition of Tf_2O (5 equiv.) then H_2SO_4 (5 equiv.) at 0 °C, warmed up to 23 °C for 3 h.

TLC systems tested. Contrary to THF and DMF, DCM and MeCN were promising.

In DCM (Scheme 1), we obtained a mixture of the monotriflated product **2 a** and the dihydroxylated compound **2 b**. Though it was not possible to separate them, the cleavage of other interglycosidic bonds was not observed before a few hours, so it is possible to control the reaction time to minimize this side reaction. Compound **2 a** could be easily functionalized at its reducing end and, in addition, its non-reducing end has the 4-hydroxyl unprotected, allowing further functionalization.

In MeCN, the formation of **2 a** was not observed but, in this opening reaction, the participation of the solvent led to a new product. Although hypothetical, the MS of the mixture (see Supporting Information, section 2.5, S6) suggested the presence of a N-acetylglucopyranosylamine, arising from the trapping of the glycosyl oxocarbenium intermediate by MeCN to give an acetonitrilium ion, as reported by Ratcliffe and Fraser-Reid.[33] We were not able to purify this product due to the presence of many byproducts, but this result suggested that the functionalization of the reducing end could be achieved in situ. We then tried to influence this substitution by introducing another nucleophile in the reaction mixture, leading to a functionalized oligosaccharide in one step. To avoid interactions with the solvent, we chose to use DCM in further experiments.

Our first attempt was to introduce an azide function. Anomeric azides are suitable for coupling by CuAAC but also precursors of amines, amides, and isothiocyanates. We performed two reactions in the conditions described before, in DCM, with the addition of either trimethylsilyl or sodium azide (6 equiv). These reactants were introduced in the reaction mixture before cooling to 0 °C and adding Tf_2O, then H_2SO_4. While the trial with trimethylsilyl azide showed a fast degradation of produced linear chains, from the beginning of the reaction, leading to non-separable different oligomers, the reaction with sodium azide, though insoluble in dichloromethane, produced the best results. Byproducts from chain degradations only started to appear after a few hours of reaction, so the workup of the reaction was performed before complete disappearance of starting material, allowing us to purify a monoazido maltoheptaose **3 b** with 24% yield (Table 1 entry 1).

Presence of the azido group was demonstrated by the signal in the IR spectrum (see Supporting Information, Figure S10, S23) of the absorption band at 2120 cm^{-1} corresponding to the asymmetric stretching (ν N=N=N), and confirmed by MS. In addition, ^{13}C NMR chemical shifts at 84.97 ppm and 87.82 ppm were assigned to the anomeric carbon of the reducing end C-1_α^I and C-1_β^I respectively, functionalized with azide group with a α/β ratio of 40:60. In the ^1H NMR spectrum, the triplet signal at 3.76 ppm corresponding to the H-4^{VII} (non-reducing end) with a coupling constant of 9.6 Hz is in accordance with the presence of an unprotected hydroxyl group with retention of the gluco configuration. This result suggested an opening mechanism similar to the one proposed by Vaitkus *et al.*[34] Glycosidic bond opening would take place between the anomeric carbon and the aglycone oxygen, which becomes the unprotected hydroxyl group on the non-reducing end, affording exclusively **3 b**.

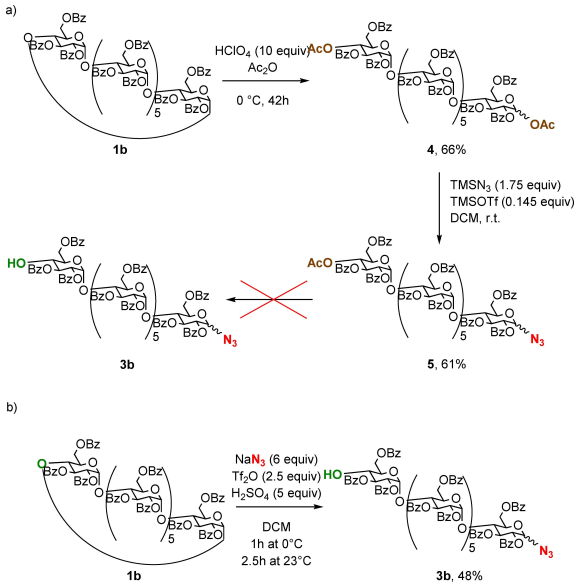
Table 1. Optimization of the reaction with NaN_3[a]

entry	Tf_2O [eq]	H_2SO_4 [eq]	temp [°C]	time [h]	**3 b** yield[b] [%]
1	5	5	23	3	24
2	5	2.5	23	24	0[c]
3	2.5	5	23	3.5	37
4	2.5	10	23	2	0[d]
5[e]	2.5	5	0 to 23	2.5	48

[a] Reaction conditions: **1 b** (0.3 M in DCM), NaN_3 (6 equiv.) addition of Tf_2O then H_2SO_4 at 0 °C, then stirring at 23 °C. [b] Isolated yield. [c] Only traces of **3 b**. [d] Impossible to separate **3 b** from degradation products. [e] Reaction stirred 1 h at 0 °C after addition of reagents then warmed up to 23 °C.

Other assays were performed by modifying either H_2SO_4 or Tf_2O proportions (Table 1). We first observed that reducing acid proportion decreased the reaction rate and the conversion of the starting material (entry 2). After 24 h of reaction, byproducts started to appear together with traces of **3 b**. The yield was increased decreasing Tf_2O to 2.5 equiv. (entry 3). Increasing the acid proportion to 10 equiv. produced more degradation byproducts (entry 4). Finally, keeping the mixture at 0 °C for one hour, instead of 10 minutes, delayed the formation of byproducts, making easier the purification and thus increasing the isolated yield. Starting from 5 g of **1 b**, reaction was stopped after 2 h30 at 23 °C, at the beginning of byproducts formation for easier purification. Thus, 2.45 g of **3 b** were obtained (48% yield, entry 5). 1.92 g of **1 b** were also recovered and could be used in another reaction.

To compare, we first tried, before this study, to synthesize **3 b** using a multistep sequence, from CD acetolysis (Scheme 2a). **3 b** could not be obtained this way due to the complexity to selectively cleave the acetate on C-4^{VII} and the difficulty to separate **3 b** from its byproducts (see Supporting Information, section 2.6, S7).

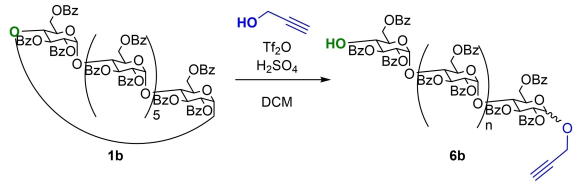


Scheme 2. Obtaining methods of **3b** by a) Acetolysis, glycosylation, deprotection and b) One-step opening.

We then tried to adapt this protocol to graft an alkyne group on our oligomaltosides. This terminal alkyne can give access to cycloadditions and also, for instance, additions, organometallic coupling reactions, or alkyne metathesis. To achieve this purpose, propargyl alcohol was used as nucleophile. This time, in order to prevent or reduce the transesterification side reactions, and the formation of propargyl triflate, the alcohol was added at 0 °C one hour after Tf_2O and H_2SO_4 (Table 2). Whereas **6b** was observed using 5 eq of Tf_2O or H_2SO_4 or 2.5 equiv. of both of them and 6 equiv. of propargyl alcohol (entries 6–9) the formation of byproducts was noticed right after warming the reactions mixture to 23 °C leading to poor yields.

Reducing the reaction temperature to 0 °C in these conditions lowered the conversion, so we tried to compensate this by using twice as much Tf_2O and H_2SO_4, but degradations were too abundant for this reaction to be a suitable alternative (entry 10). Finally, starting from 5 g of **1b**, with 2.5 equiv. of both Tf_2O and H_2SO_4 and 6 equiv. of propargyl alcohol at 0 °C, the reaction could be performed for 18 hours without the formation of byproducts, affording 1.92 g of **6b** (38% yield, entry 11). In this case the ratio α/β estimated by NMR was 10:90. 2.46 g of **1b** were also recovered and could be used in another reaction.

Table 2. Optimization of Reaction Conditions with propargyl alcohol.[a]



entry	Tf_2O [eq]	H_2SO_4 [eq]	temp [°C]	time [h]	Yield[b] [%]
6	5	5	23	3	0[c]
7	5	2.5	23	4	16
8	2.5	5	23	4	16
9	2.5	2.5	23	3	17
10	5	5	0	16	20
11	2.5	2.5	0	18	38

[a] Reaction conditions: **1b** (*C* 0.3 M) diluted in DCM, addition of Tf_2O then H_2SO_4 at 0 °C, stirred 1 h at 0 °C, addition of propargyl alcohol (6 equiv) before stirring at indicated temperature. [b] Isolated yield. [c] High byproducts quantity, **6b** non-isolated.

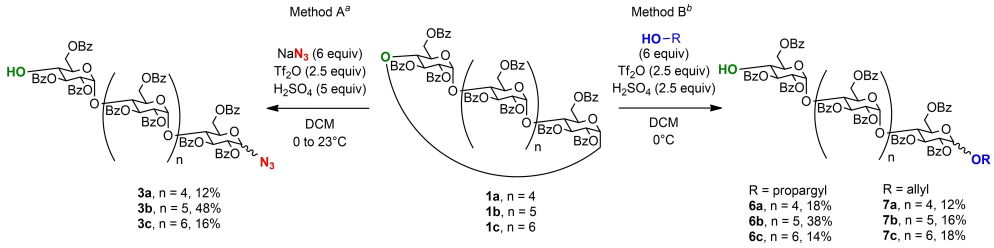
Regarding all these results, we tried to extend these new opening methods to perbenzoylated α- and γ-cyclodextrins, **1a** and **1c** (Table 3). Thus, we obtained **3a** and **3c** with 27 and 16% yields (entries 12 and 18) using the same method as **3b** (method A). We also obtained **6a** and **6c** with 18 and 14% yields (entries 13 and 19) using the method for the synthesis of **6b** (method B). These yields were lower than **3b** and **6b** because these trials were made on smaller quantities, leading to a greater loss during purification.

The allyl alcohol as nucleophile was also tested to complete the study, giving access to a key intermediate for reactions such as additions, cycloadditions, metathesis, oxidations, and polymerizations.

With allyl alcohol, the same reaction conditions optimized for propargyl alcohol were used. However, degradation byproducts appeared, even if reactions were cooled to 0 °C, increasing losses during purification and decreasing yields. Thus, **7a**, **7b** and **7c** were obtained with respectively 12, 16 and 18% yields from **1a**, **1b** and **1c** (entries 14, 17 and 20). The overall results of these reactions can be seen in Table 3. Although moderate, the yields remain very good because the reaction allows reducing 3 steps into 1 and the yields described in the literature are between 37 and 52% for the opening alone.[10,24] In the case of the hydrolysis opening, the yield drops to 31%.[28] Selectivity α/β is higher than the selectivity shown in literature for the opening/functionalization (1:1).[28] They are in the range of the α/β ratio of acetolysis products (8:2 or 9:1).[10,24] It should be noted that a different selectivity is observed depends on the nucleophile, α or β majority for allyl alcohol or propargyl alcohol and sodium azide respectively. This could be due to the formation of intermediary anomeric triflates which can isomerize the C-1[35] as a function of the temperature to give glycosides as α/β mixtures at 0 °C regardless of the substituent at C-2.

In conclusion, we developed a new strategy to obtain differentially substituted maltooligosaccharides from per-benzoylated CD. The methodology was successfully applied to α-, β-, and γ-CD allowing the selective preparation of 1-azide derivatives, propargyl and allyl glycosides by the regioselective opening of the corresponding perbenzoylated CD followed by their in situ glycosylation reaction with rather good yields and selectivity compared to results in the literature. Such oligomaltosides are precious building blocks as scaffolds in chemobiology or to synthesize biomimetic pseudo glycopeptides, but also as monomers for materials preparation. Regarding these results, we can also imagine that the use of other nucleophiles during the opening reaction could lead to more diversified substituted oligomaltosides.

Table 3. . Method extension.



entry	substrate	quantity [mmol]	method	reagent [6eq]	time [h]	product	ratio α/β[c]	Yield[d] [%]
12	**1a**	0.63	A	NaN_3	2	**3a**	1:9	27
13	**1a**	0.18	B	propargyl alcohol	18	**6a**	1:9	18
14	**1a**	1.8	B	allyl alcohol	18	**7a**	7:3	12
15	**1b**	1.5	A	NaN_3	2.5	**3b**	3:7	48
16	**1b**	1.5	B	propargyl alcohol	18	**6b**	1:9	38
17	**1b**	1.5	B	allyl alcohol	18	**7b**	7:3	16
18	**1c**	0.13	A	NaN_3	1.5	**3c**	3:7	16
19	**1c**	0.13	B	propargyl alcohol	18	**6c**	2:8	14
20	**1c**	1.3	B	allyl alcohol	18	**7c**	9:1	18

[a] Method A: substrate (0.3 M in DCM), NaN_3 (6 equiv.), addition of Tf_2O then H_2SO_4 at 0 °C, stirred 1 h at 0 °C then at 23 °C. [b] Method B: substrate (0.3 M in DCM), addition of Tf_2O then H_2SO_4 at 0 °C, stirred 1 h at 0 °C, addition of propargyl or allyl alcohol (6 equiv) and stirring at 0 °C. [c] According to NMR Spectra. [d] Isolated yield.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] S. I. Mussatto, I. M. Mancilha, *Carbohydr. Polym.* **2007**, *68*, 587–597.
[2] S. A. Belorkar, A. K. Gupta, *AMB Expr.* **2016**, *6*, 82.
[3] C. Zhong, C. Ukowitz, K. Domig, B. Nidetzky, *J. Agric. Food Chem.* **2020**, *68*, 8557–8567.
[4] C. Schatz, S. Lecommandoux, *Macromol. Rapid Commun.* **2010**, *31*, 1664–1684.
[5] S. Tallegas, T. Baron, G. Gay, C. Aggrafeil, B. Salhi, T. Chevolleau, G. Cunge, A. Bsiesy, R. Tiron, X. Chevalier, C. Navarro, K. Aissou, I. Otsuka, S. Halila, S. Fort, R. Borsali, *Phys. Status Solidi (c) Wiley* **2013**, *10*, 1195–1206.
[6] N. Hao, K. Neranon, O. Ramström, M. Yan, *Biosens. Bioelectron.* **2016**, *76*, 113–130.
[7] F. A. de Moura, F. T. Macagnan, L. P. da Silva, *Int. J. Food Sci. Technol.* **2015**, *50*, 275–281.
[8] L. Krasnova, C.-H. Wong, *J. Am. Chem. Soc.* **2019**, *141*, 3735–3754.
[9] C.-H. Hsu, S.-C. Hung, C.-Y. Wu, C.-H. Wong, *Angew. Chem. Int. Ed.* **2011**, *50*, 11872–11923.
[10] N. Sakairi, L.-X. Wang, H. Kuzuhara, *J. Chem. Soc. Perkin Trans. 1* **1995**, 437–443.
[11] B. Hoffmann, D. Zanini, I. Ripoche, R. Bürli, A. Vasella, *Helv. Chim. Acta* **2001**, *84*, 1862–1888.
[12] B. Hoffmann, B. Bernet, A. Vasella, *Helv. Chim. Acta* **2002**, *85*, 265–287.
[13] N. N. H. M. Eisink, J. Lohse, M. D. Witte, A. J. Minnaard, *Org. Biomol. Chem.* **2016**, *14*, 4859–4864.
[14] S. de Medeiros Modolon, I. Otsuka, S. Fort, E. Minatti, R. Borsali, S. Halila, *Biomacromolecules* **2012**, *13*, 1129–1135.
[15] I. Otsuka, K. Fuchise, S. Halila, S. Fort, K. Aissou, I. Pignot-Paintrand, Y. Chen, A. Narumi, T. Kakuchi, R. Borsali, *Langmuir* **2010**, *26*, 2325–2332.
[16] D. M. Haddleton, K. Ohno, *Biomacromolecules* **2000**, *1*, 152–156.
[17] Y.-C. Chiu, I. Otsuka, S. Halila, R. Borsali, W.-C. Chen, *Adv. Funct. Mater.* **2014**, *24*, 4240–4249.
[18] L. Bech, T. Meylheuc, B. Lepoittevin, P. Roger, *J. Polym. Sci. Polym. Chem. Ed.* **2007**, *45*, 2172–2183.
[19] Y. Ruff, E. Buhler, S.-J. Candau, E. Kesselman, Y. Talmon, J.-M. Lehn, *J. Am. Chem. Soc.* **2010**, *132*, 2573–2584.
[20] A. Narumi, H. Kaga, K. Kawasaki, Y. Taniguchi, T. Satoh, T. Kakuchi, *J. Polym. Sci. Polym. Chem. Ed.* **2001**, *39*, 4061–4067.
[21] T. Yoshida, T. Akasaka, Y. Choi, K. Hattori, B. Yu, T. Mimura, Y. Kaneko, H. Nakashima, E. Aragaki, M. Premanathan, N. Yamamoto, T. Uryu, *J. Polym. Sci. Polym. Chem. Ed.* **1999**, *37*, 789–800.
[22] E. Farkas, L. Jánossy, J. Harangi, L. Kandra, A. Lipták, *Carbohydr. Res.* **1997**, *303*, 407–415.
[23] H. Oka, T. Koyama, K. Hatano, D. Terunuma, K. Matsuoka, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1969–1971.
[24] N. Sakairi, L.-X. Wang, H. Kuzuhara, *J. Chem. Soc. Chem. Commun.* **1991**, 289–290.
[25] N. Sakairi, K. Matsui, H. Kuzuhara, *Carbohydr. Res.* **1995**, *266*, 263–268.
[26] D. Lesur, A. Gassama, V. Moreau, S. Pilard, F. Djedaïni-Pilard, *Carbohydr. Res.* **2005**, *340*, 1225–1231.
[27] N. Sakairi, H. Kuzuhara, *Carbohydr. Res.* **1996**, *280*, 139–143.
[28] T. Kida, T. Michinobu, W. Zhang, Y. Nakatsuji, I. Ikeda, *Chem. Commun.* **2002**, *15*, 1596–1597.
[29] A. Bösch, P. Mischnick, *Biomacromolecules* **2007**, *8*, 2311–2320.
[30] G. Crini, *Chem. Rev.* **2014**, *114*, 10940–10975.
[31] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis, Third Edition*; John Wiley & Sons, Inc.: New York, **1999**, Chapter 2, 779 pp.
[32] F. Cramer, G. Mackensen, K. Sensse, *Chem. Ber.* **1969**, *102*, 494–508.
[33] A. J. Ratcliffe, B. Fraser-Reid, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1805–1810.
[34] R. Vaitkus, G. Grincienė, E. Norkus, *Chemija* **2008**, *19*, 48–51.
[35] T. Nokami, A. Shibuya, Y. Saigusa, S. Manabe, Y. Ito, J. Yoshida, *Beilstein J. Org. Chem.* **2012**, *8*, 456–460.

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