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Efficient regioselective chemical modifications of maltotriose: an easy access to oligosaccharidic scaffold

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ABSTRACT

Regioselective chlorination of fully unprotected maltotriose has given in high yield $1^{I},2^{I-III},3^{I-III},4^{III}$-octa-*O*-acetyl-$6^{I-III}$-trichloro-$6^{I-III}$-trideoxymaltotriose. Moreover, regioselective ditritylation of methyl β-maltotrioside has provided the two regioselectively C_6-disubstituted trisaccharides. Selective deprotection of these new compounds gives the corresponding diol and halogenated analogues, respectively, in good yield. All compounds have been completely characterized and the substitution pattern in the oligosaccharidic sequence has been elucidated. A new family of amphiphilic carbohydrates, namely the 6-deoxy-6-alkylthiomaltotriose derivatives, bearing either two or three thioalkyl hydrophobic chains, respectively, has been synthesized. Critical micellar concentration (CMC) values as well as the antimicrobial properties have been evaluated for amphiphilic compounds.

1. Introduction

Carbohydrates are polyfunctionalized compounds that contain primary and secondary hydroxyl groups differing in terms of reactivity. Nevertheless, some chemical transformations of these functions have been shown to proceed regioselectively. For example, it is well known that the primary hydroxyl groups of sugar derivatives are in many cases more reactive towards halogenations than are secondary groups.[1] A variety of reagents have been developed for the direct replacement of primary hydroxyl groups of unprotected (or protected only at the anomeric position) alditols,[2] monosaccharides[3–5] and few disaccharides[6–9] by halogeno substituents. Moreover, perhalogenations at primary positions on polysaccharides such as amylose,[10,11] chitin[12] and cellulose[13,14] has been well described.

To our knowledge, no direct halogenation of maltotriose or higher acyclic maltodextrins has been described in the literature. We report here a method for synthesis of 6-deoxy-6-trichloro- and triiodomaltotriose derivatives **1** and **2** by direct chlorination of totally unprotected maltotriose (Fig. 1). Per-6-O-substitution gives access to the corresponding modified oligosaccharides but a regioselective disubstitution of maltotriose would provide new oligosaccharidic scaffolds which could serve as precursors of complex branched oligosaccharides or new amphiphilic carbohydrates for examples. We report also the synthesis of 6-deoxy-6-dichloro and diiodomaltotriose derivatives **10–11** and **12–13**, respectively, and of the corresponding diols **8–9** using a new method for the regioselective ditritylation[15] of methyl β-maltotrioside (Fig. 1).

As an example of their potential, compounds **2**, **10** and **13** served as precursors to a new family of amphiphilic carbohydrates, namely, the 6-deoxy-6-alkylthiomaltotriose derivatives **19** to **23**, **26** and **27** (Fig. 2) with the aim to study the influence of the position of alkyl chains on their properties. Amphiphilic carbohydrates are well known to show interesting applications in multiple areas. They display various biological and physiological properties. Amongst these can be cited their use as model biomembranes[16] or their potential antitumour activities.[17] They can also form liquid crystals[18] and have found practical uses as surfactants and non-ionic detergents.[19] It was generally recognized that *n*-alkyl glycosides containing a C_8 and C_{12} alkyl chain showed a broad spectrum of antimicrobial activity. Amongst them, those with *n*-dodecyl groups were particularly effective against Gram-positive strains as well as fungal strains.[20] Preliminary physico-chemical and antimicrobial data generated for the disubstituted derivatives **26** and **27** correlate not only with the number and the length but also the location of the grafted alkyl chains.

2. Results and discussion

2.1. Synthesis of 6^{I-III}-deoxy-6^{I-III}-trichloromaltotriose and 6^{I-III}-deoxy-6^{I-III}-triiodomaltotriose derivatives 1 and 2

Direct halogenation of the 6^{I}, 6^{II} and 6^{III} positions of maltotriose was first studied as an alternative to the multistep method[21] previously described for the synthesis of the desired target **1**. As

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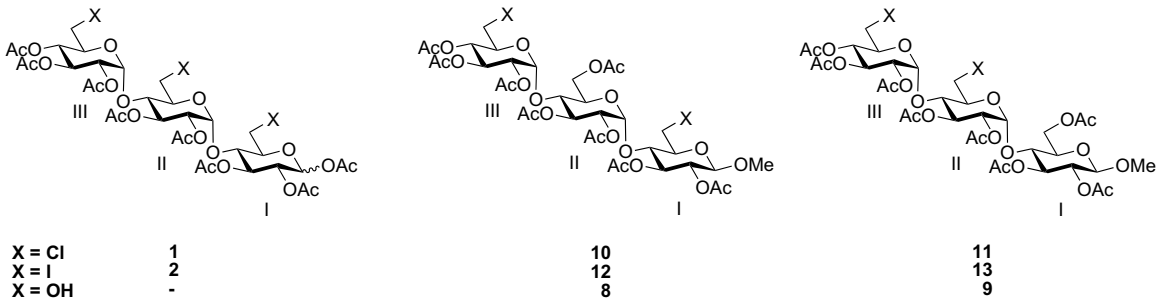


Figure 1. Structures of targets maltotriose derivatives **1**, **2**, **8**, **9** and **10** to **13** (roman numbers located below glucopyranosidic rings refer to each unit and are used to indicate their associated protons and carbons in the NMR data).

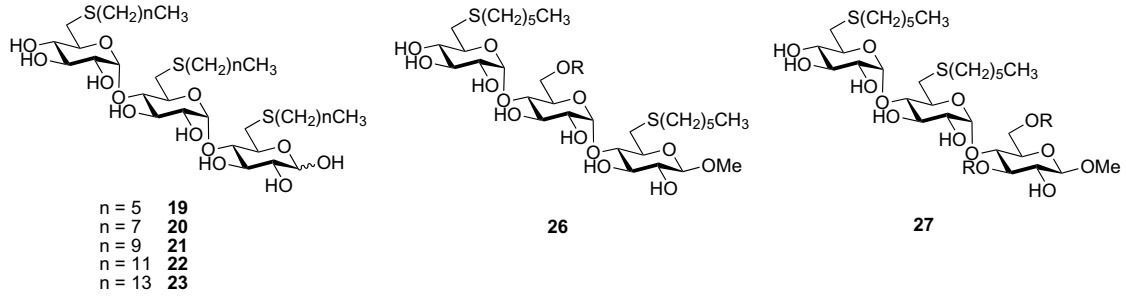
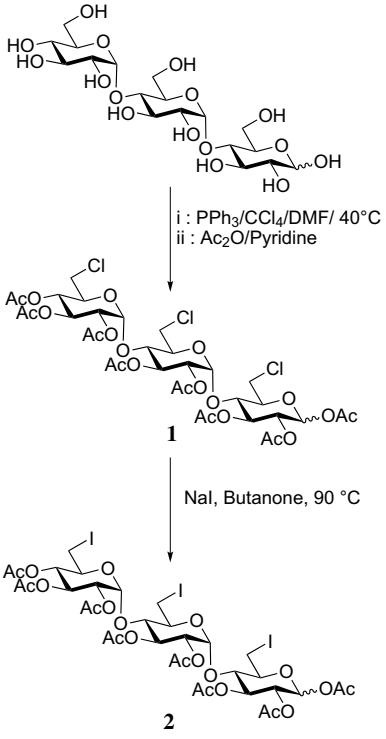


Figure 2. Structures of targets maltotriose derivatives **19** to **23**, **26** and **27**.

shown in Scheme 1, maltotriose was allowed to react with CCl_4 in presence of PPh_3 in DMF at 40 °C to give, after acetylation of the remaining free OH groups, the $1^{I},2^{I-III},3^{I-III},4^{III}$-octa-*O*-acetyl-$6^{I-III}$-trideoxy-$6^{I-III}$-trichloromaltotriose **1** in 95% yield. We found that ratio of PPh_3/maltotriose and CCl_4/maltotriose is crucial for the complete halogenation of all the primary positions. The use of less than 9 equivalents of each reagent leads to the mixtures of di- and trihalogenated maltotriose derivatives. Investigation of the direct bromination and iodination of fully unprotected maltotriose was also undertaken. Taking a lead from former work completed within our laboratory on monosaccharides,[5] a broad range of halogenous reagents were tested. Unfortunately, couples PPh_3/CBr_4, PPh_3/NBS, PPh_3/CI_4 or PPh_3/NIS under various conditions of temperature and time, gave only traces of a monohalogeno derivative as determined by mass spectroscopy. Consequently, the $1^{I},2^{I-III},3^{I-III},4^{III}$-octa-*O*-acetyl-$6^{I-III}$-trideoxy-$6^{I-III}$-triiodomaltotriose **2** was prepared from **1** which was allowed to react with sodium iodide in butanone. Using optimized conditions, compound **2** was obtained in the presence of an anhydro derivative which was readily separated by flash chromatography. The target product **2** was isolated in 85% yield (Scheme 1).



Scheme 1.

2.2. Synthesis of regioselectively difunctionalized methyl β-maltotrioside analogues 9 to 13

Methyl β-maltotrioside **5** was synthesized in 4 steps from maltotriose following the procedure reported by Takeo.[22] This latter route requires full acetylation of maltotriose, bromination of the anomeric position, Koenigs–Knorr condensation of the resulting 2^{I-III}, 3^{I-III}, 4^{III}, 6^{I-III}-deca-*O*-acetyl-α-maltotriosyl bromide **3** with methanol and, finally, deacetylation under Zemplén methanolysis (Scheme 2). The glycosylation step, slightly modified, was performed in the classical manner[23] using mercuric bromide and yellow mercuric oxide as promoters in dry dichloromethane to afford the desired methyl β-maltotrioside derivative **4** in 85% yield. Methyl β-maltotrioside **5** was allowed to react with 5 equivalents of trityl chloride at 40 °C for 4 days then treated with acetic anhydride. The ditritylated compounds **6** and **7** obtained were readily separated by column chromatography in 36% and 22% yields, respectively. Then, the ditritylated maltotrioside derivatives **6** and **7** were selectively deprotected using hydrated ferric chloride, which is known to prevent acetate migration,[24] to afford the corresponding diols **8** and **9** in 98% and 71% yields, respectively.