Synthesis of cyclogentiotriose by macrocyclization via a ring-closing glycosylation

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Synthesis of cyclogentiotriose by macrocyclization via a ring-closing glycosylation

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ABSTRACT

The synthesis of a benzylated cyclogentiotriose was achieved through the ring-closing glycosylation, which was developed by us recently. Moderate β-selectivity (3.3:1) was obtained in the 1,6 glycosidic linkage formation step. The α-acetoxy ether precursor was generated through the Rychnovsky reductive acetylation of a linear trisaccharide derived macrolactone.

Construction of complex oligosaccharides in a highly efficient and stereoselective manner is the central problem of synthetic carbohydrate chemistry. Due to the highly diverse structural feature of the oligosaccharides from the natural source, provision of an adequate amount of homogeneous oligosaccharide samples with well-defined structures for biological tests mainly relies on the chemical[1] and chemoenzymatic[2] synthesis approach. In the past century, great advances in chemical glycosylations have been witnessed by the scientific community.[3] A plethora of glycosylation reactions have been developed, based on the general mechanistic paradigm: activation of the glycosyl donor to generate the highly reactive oxocarbenium cation intermediate, followed by the nucleophilic attack of the glycosyl acceptor. In parallel with the development of new glycosyl donors or activators, we are interested in the design of a novel strategy towards the glycosidic construction via a different mechanism.

To the end, our group has recently developed a novel ring-closing glycosylation via non-glycosylating pathway (Fig. 1).[4] The sugar-derived acid was first coupled with a glycosyl acceptor through an ester bond, after which the glycosidic linkage was realized via (i) Rychnovsky's reductive acetylation of the ester[5] and (ii) trifluoromethanesulfonic acid (TfOH) mediated cyclization of the α-acetoxy ether. Moderate to high 1,2-*trans* selectivity was achieved in the construction of linear disaccharides through (1,2), (1,3), (1,4) and (1,6) linkages.

Encouraged by these results, we were eager to explore our strategy on the synthesis of more challenging cyclic oligosaccharide targets. The cyclic tri- and tetrasaccharides have attracted the extensive attention from carbohydrate chemists due to their interesting conformation and potent applications in the dendrimer synthesis.[6] The cyclic β(1→6)-D-triglucopyranose (cyclogentiotriose) peracetate has been synthesized via the $HgBr_2/Hg(CN)_2$ mediated cyclization of the glycosyl bromide derived from the linear trisaccharide.[6a] The β-configuration of the newly generated glycosidic bond was obtained by the neighboring group participation. Herein, we would like to report the synthesis of perbenzylated cyclogentiotriose **1** via our two-step glycosylation.

The retrosynthetic analysis of trisaccharide **1** is illustrated in Scheme 1. As the precursor of **1**, α-acetoxy ether **2** can be generated from the linear *seco*-acid **3** via macrolactonization and reductive acetylation. *seco*-Acid **3** can be assembled from monosaccharide building blocks **4**,[7] **5**[8] and **6**[9] via sequential glycosylations and further modifications, including protecting group manipulation and opening of the reducing pyranoside ring.

As shown in Scheme 2, the glycosylation between trichloroacetamide (TCA) donor **4** and **5** mediated by $BF_3{\cdot}OEt_2$ provided the desired disaccharide thioglycoside **7** in 93% yield, and the exclusive β-selectivity was obtained by the neighboring group participation. The second glycosylation between thioglycosyl donor **7** with **6** was mediated by *N*-iodosuccinimide (NIS) to generate the trisaccharide **8** in 75% yield. The benzoyl (Bz) group in donor **7** was critical for this step. If the Bz group was changed into an acetyl (Ac) group, the yield of this glycosylation decreased to 27% due to the formation of

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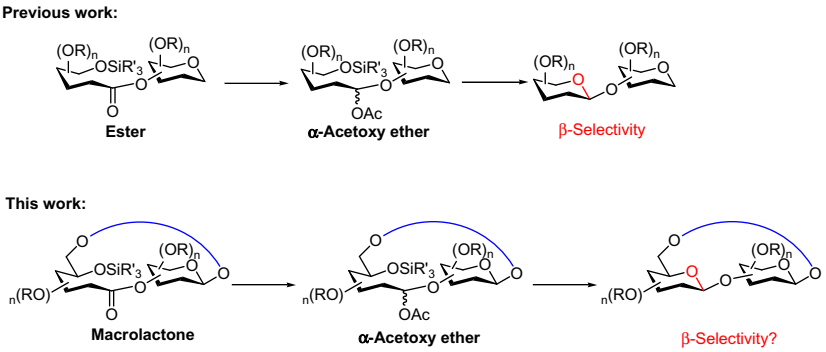
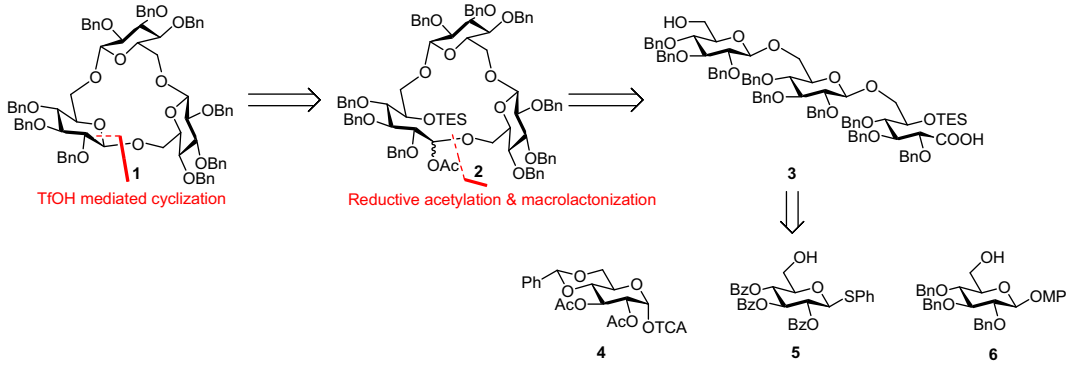


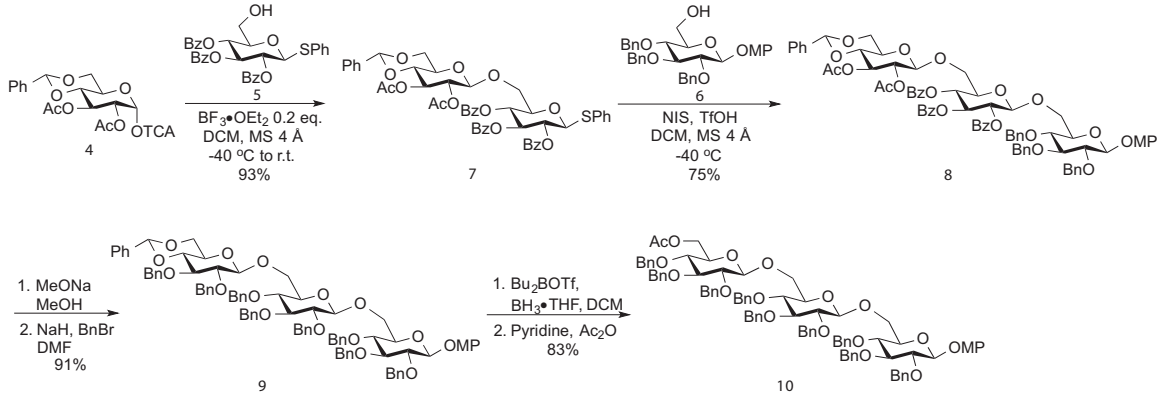
Figure 1. Two-step intramolecular glycosylation in linear and cyclic systems.

an orthoester side product. All of the acyl-type protecting groups on **8** were removed under Zemplén condition, and **9** was obtained after benzylation. The benzylidene group on **9** was regioselectively opened by *n*-Bu_2BOTf/BH_3–THF[10] at 0 °C, and the released primary hydroxyl was acetylated to give trisaccharide **10**.

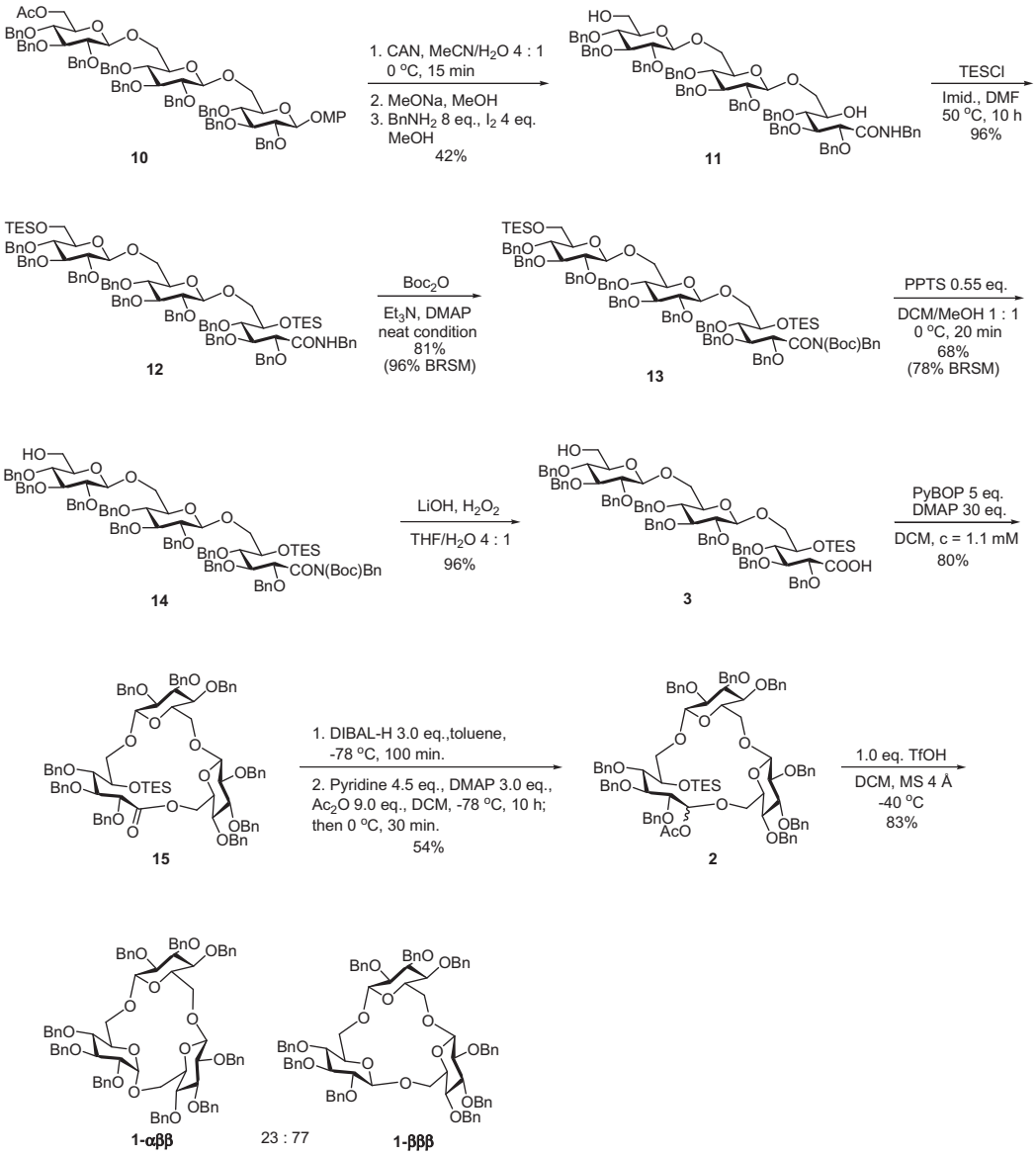
Further structural manipulations of linear trisaccharide **10** are shown in Scheme 3. To open the reducing pyranoside ring in **10**, the 4-methoxyphenyl (MP) group on the reducing end was first removed by ceric ammonium nitrate (CAN) treatment.[11] The reaction time and temperature were carefully controlled to minimize the side reaction. After removing the Ac group on the primary hydroxyl group, the lactol ring was opened under the oxidative condition, following Monk's procedure.[12] Due to the moderate solubility of the compound in methanol, the lower concentration (80 mM) and longer time (36 h) than Monk's condition were used. The desired amide **11** was obtained in 42% yield (3 steps). After protecting both of the two hydroxyl groups in **11** by triethylsilyl (TES) group, the amide bond in **12** was activated by imide formation, as we used in monosaccharide case.[13] However, the trisaccharide derived substrate was quite inert, and the solvent free condition (without THF) has to be used to obtain a good conversion. The product **13** was isolated in 81% yield, together with 16% recovered **12**. The TES group on the primary hydroxyl was selectively removed by PPTS at 0 °C to give alcohol **14** in 68% yield.[14] To minimize the over-deprotection, the reaction has to be quenched in 20 min, and the unreacted **13** was recovered. After the LiOOH (in situ generated from LiOH and H_2O_2) mediated cleavage of the imide,[15] the key *seco*-acid intermediate **3** was isolated in 96% yield. In the next macrolactonization step, the combination of PyBOP and large excess of DMAP recommended by Roush[16] gave the best result (80% yield)



Scheme 1. Retrosynthetic analysis of cyclogentiotriose.



Scheme 2. Synthesis of the linear trisaccharide intermediate.



Scheme 3. Structure manipulation of the linear trisaccharide and completion of cyclogentiotriose.

under high dilution condition (1.1 mM), while the Yamaguchi protocol and Mukaiyama reagent were less effective in this case. With the 17-membered macrolactone **15** in hand, the DIBAL-H mediated reductive acetylation[5] was attempted, following our previously used protocol.[4] To overcome the steric hindrance of the substrate, the amount of DIBAL-H and acetic anhydride was increased to 3.0 equiv and 9.0 equiv, respectively. The desired α-acetoxy ether **2** was isolated in 54% yield as the mixture of diastereomers.

Finally, the TfOH mediated glycosylation was tested under the optimized condition (1.0 equiv TfOH in DCM at −40 °C). To our delight, the reaction was quite clean, and two cyclized products were isolated (83% yield in total) and fully characterized by 1D and 2D NMR. The less polar compound (R_f = 0.25, CH_2Cl_2 as eluent) was confirmed to be **1**-**αββ**, and the other compound (R_f = 0.15, CH_2Cl_2 as eluent) was **1**-**βββ**.[17] The stereoselectivity in the last cyclization step was 23:77 and the β-anomer was favored.

In summary, we have synthesized a benzylated cyclogentiotriose through our macrolactonization/two-step intramolecular glycosylation process, in which the β-selectivity was obtained without relying on the neighboring group participation. Future efforts will be focused on the development of the second generation of ring-closing glycosylation based on more robust chemical transformations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.063.

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17. **1-βββ** is a symmetric compound, in which all three sugar units show the identical NMR signals.