THE SYNTHESIS OF OLIGOSACCHARIDE-BRANCHED CYCLODEXTRINS

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1. Introduction

Cyclodextrins (CDs) can be used in various drugs as an auxiliary additive such as a carrier, diluent, and solubilizer for tablet ingredients. The syntheses of natural oligosaccharide-branched CDs, which showed potential binding to lectin, have been studied for the development of a drug carrier for targeting drug delivery systems. We have already reported the chemo-enzymatic syntheses of three natural oligosaccharide-branched CDs by the transglycosylation of Fmoc-Asn(GlcNAc)-NH-β-CD (4) with

![Diagram of cyclodextrin synthesis](image)

Fig 1. The present syntheses (a) and previous syntheses (b) of oligosaccharide-branched CD.
glycosyl asparagines prepared from ovalbumin\textsuperscript{4} and human transferrin\textsuperscript{5} using \textit{endo-\(\beta\)-N-acetylglucosaminidase of \textit{Mucor hiemalis} (Endo-M)}.\textsuperscript{6} A large-scale synthesis of these CDs was required for the evaluation of these CDs. However, it is difficult to synthesize a large quantity of these CDs by this method, because of the availability limitations of Endo-M. In this paper, the large-scale chemical synthesis of high-mannose type oligosaccharide-branched CD (3) using glycosylasparagine, H-Asn(GlcNAc\textsubscript{2}Man\textsubscript{6})-OH (1)\textsuperscript{5} as the starting material, which was used as a transglycosylation substance of Endo-M, was described.

2. Experimental

2.1. MATERIALS

Glycosylasparagine, H-Asn(GlcNAc\textsubscript{2}Man\textsubscript{6})-OH (1) and 6-\textit{mono}-amino-6-deoxy-\(\beta\)-cyclodextrin (H\textsubscript{2}N-\(\beta\)-CD) were prepared according to the literature.\textsuperscript{5,7} Fmoc-OSu (9-Fluorenylmethyloxycarbonyl-oxysuccinimide) was used as the protecting reagent. The Amberlite XAD-2 (nonionic polymeric adsorbent) is commercially available (Organo Co.). PyBOP (Benzotriazole-1-yl-oxy-tris-pyrroridino-phosphonium hexafluorophosphate) or HBTU (2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)-HOBt (1-Hydroxybenzotriazole) as the condensing agents was used.

2.2. METHOD

Reversed-phase HPLC was performed on an Inertsil ODS-3 column (20 x 250mm) (GL Sciences Inc.) using a linear gradient of acetonitrile containing 0.1% TFA/H\textsubscript{2}O containing 0.1% TFA (10/91 to 35/65, v/v). The molecular interaction to immobilized concanavalin A (ConA) was examined using an optical biosensor equipped with a resonant mirror detector based on SPR,\textsuperscript{8-10} IAsys (FAST). Mass numbers were determined by MALDI-TOF mass spectrometry using a Voyager\textsuperscript{®} RP (PerSeptive Biosystems Inc.). Mass numbers were calculated and reported as average values. Fmoc-Asn(GlcNAc\textsubscript{2}Man\textsubscript{6})-OH (2): MALDI-TOF MS Found: \(m/z\) 1735 (M+H)+. Caled for (M+H)+ 1734. Fmoc-Asn(GlcNAc\textsubscript{2}Man\textsubscript{6})-NH-\(\beta\)-CD (3): MALDI-TOF MS Found: \(m/z\) 2870 (M+Na)+. Caled for (M+Na)+ 2871.

3. Results and discussion

3.1. INTRODUCTION OF FMOC GROUP TO GLYCOSYL-ASPARAGINE (1)

Natural oligosaccharides were planned as the starting materials for the synthesis of natural oligosaccharide-branched CDs. However, it is not very easy to use natural