A NEW SYNTHETIC STRATEGY OF CYCLOOLIGOSACCHARIDES.

CYCLODEXTRIN-DERIVED CYCLOALTRINS MADE UP FROM α (1→4)-LINKED ALTROPYRANOSES

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ABSTRACT

An effective synthetic strategy for preparing a new type of cyclooligosaccharide is proposed and along this plan, α-, β-, and γ-cycloaltrins, made up from six to eight α(1→4)-linked D-altropyranoses, have been prepared in 36, 52, and 37% overall yields from the corresponding cyclodextrins.

1. INTRODUCTION

For the syntheses of the novel cyclooligosaccharides uniformly composed of sugars other than glucose, there are two typical strategies. One is enzymatic cyclization reaction of naturally occurring open chain oligosaccharides and another is chemical cyclization of oligosaccharides which were elongated stepwise synthetically.

According to the former strategy, cyclofructans *etc.* have been prepared.[1] But, there are intrinsic disadvantages of the usual enzymatic reaction. Namely, specificity of the enzyme lowers the general applicability of this method and furthermore, enzymatic cyclization often lacks control of the reaction concerning the ring size of the products making various homologues which are difficult to isolate.

According to the latter strategy, α- , β- and γ- cyclomannins *etc.* are synthesized.[2] But, in these cases, there are difficulties of multi-step preparation. Furthermore, isolation of the pure oligomer in each steps requires a considerable endeavor.

To overcome these difficulties in the syntheses, we evolved a new synthetic strategy of cyclooligosaccharides using cyclodextrins as starting materials. This route might have a high possibility of the shortest approach to the aimed host molecules, because CDs are easily available in large amount and are free from the fear of contamination of different sized analogues.

Along this project, an approach to the cycloaltrins, which were made up from α-D-altropyranoses, was intended to go *via* per-2β,3-epoxy-cyclodextrins (**4a-c**)[3] as shown in Scheme 1.

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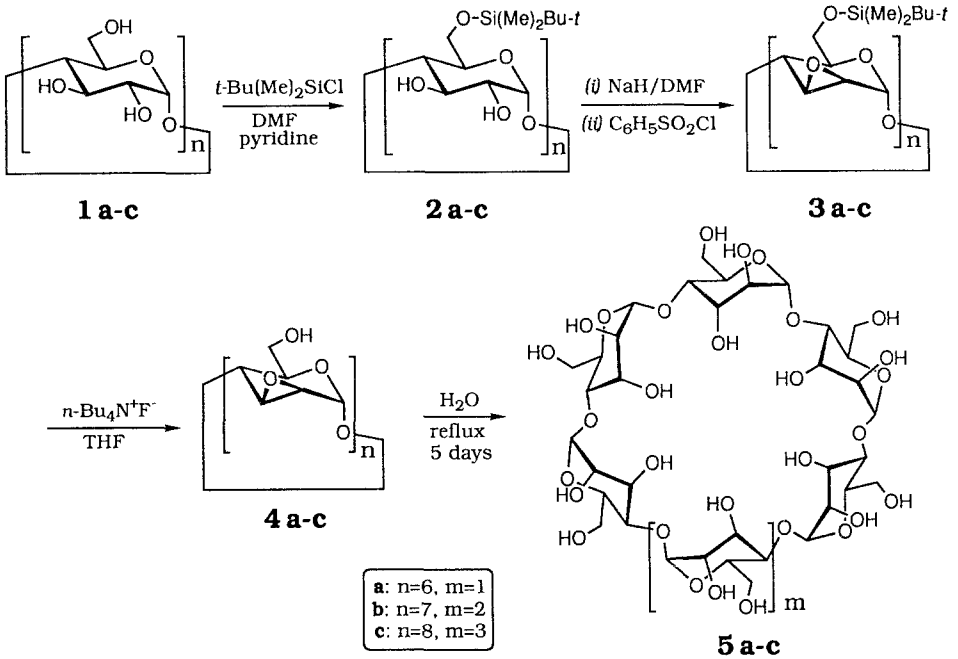

Scheme 1

2. MATERIAL AND METHODS

Compounds **2a-c** were obtained from corresponding cyclodextrins according to the reported methods[4] in 90%, 82%, and 85% yields, respectively.
Compound **2** was treated with NaH in dry dimethylformamide and the evolution of hydrogen gas ceased in 2 h (for **2a**) , 4 h (for **2b**) and 5.5 h (for **2c**) at 60°C. To the resulting oxyanion solution, benzenesulfonyl chloride was injected. The reaction was completed almost in 30 min at room temperature. After filtration, water was added to precipitate **3**. Compounds **3a-c** were characterized by elemental analyses and ^1H and ^{13}C NMR spectra.
Compound **3** was desilylated by treatment with tetrabutylammonium fluoride in tetrahydrofuran solution at 40°C for 4 h. Flash column chromatography of the crude product gave a pure sample of **4**. The yield of this step was almost quantitative. These compounds were characterized by FAB mass spectra and ^1H, ^{13}C NMR, C-H COSY, and H-H COSY spectra. Thus, per-2,3-anhydro-(2*S*)-α-, β-, or γ-cyclodextrin (**4a-c**) was obtained from **2a-c** in two steps in 59, 87, or 63% yields, respectively.
A solution of compound **4a-c** in distilled water was refluxed and the progress of the reaction was monitored by thin-layer chromatography. After five days, the starting material disappeared in favor of only one major product, which had distinctly different mobility from that of **4**. Reversed-phase column chromatography gave the novel cyclooligosaccharide, cycloaltrins **5a-c** in 68, 73 and 70 % yields, respectively.

3. RESULTS AND DISCUSSION

There are several methods[5] in the literature for converting glucoside units into altroside units. But, the yields of the conversion reported in these papers are too poor to employ, since, for our present purpose, six to eight glucoside units coexisting in one molecule must be converted by a single trial. We have already reported a general and convenient method for preparing altropyranoside from 2,3-manno-epoxide.[6] The transformation of this reaction is almost quantitative. By this method, an effective and useful synthesis of α-, β- and γ-cycloaltrins was achieved for the first time. (Overall yields of **5a-c** were 36, 52, and 37% from the corresponding CDs **1a-c**).

The FAB mass spectra showed **5** to have the same molecular weight as **1**; however, the NMR data are clearly different (Figure 1). The assignment of the signals of **5** relied on ^{1}H, ^{13}C, ^{1}H-^{13}C, and ^{1}H-^{1}H COSY (Figure 2) NMR spectra and indicates that **5** consists of altropyranoses. The major product of acid hydrolysis of **5** was a mixture of altrose and altrosan (1,6-anhydroaltropyranose), which is produced by acid treatment of altrose.

The coupling constants (e.g. $J_{H\text{-}1,H\text{-}2} = 4.5$Hz) indicate that **5b** is a mixture of at least two rapid interconverting conformations, $^1C_4$ and $^4C_1$ chair conformations, since the vicinal coupling constant $J_{H\text{-}1,H\text{-}2}$ is intermediate between that of α-methylaltropyranoside (2.0 Hz; $^4C_1$ chair conformation) and that of the α-altropyranose unit in 2^A(S),3^A(R)-β-cyclodextrin (6.6 Hz;[6] mainly $^1C_4$ chair conformation). Alternatively, **5** assumes a single fixed conformation, for example, in which the altropyranose unit have a twist conformation.

Further studies on the conformation, the inclusion properties, and the chemical modification of **5a-c** are currently in progress.

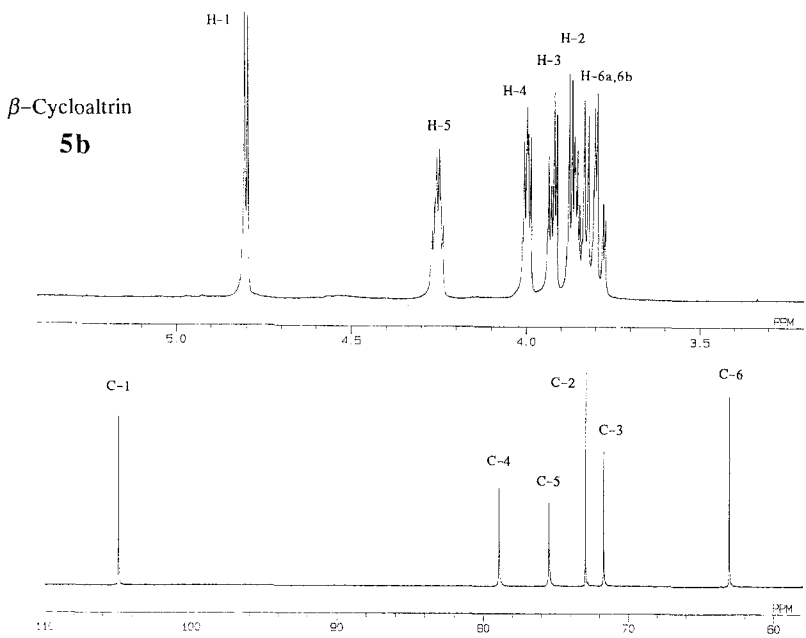

Figure 1. ^{1}H (500 MHz) and ^{13}H (125 MHz) NMR spectra of β-cycloaltrin **5b** in D_2O at 40°C

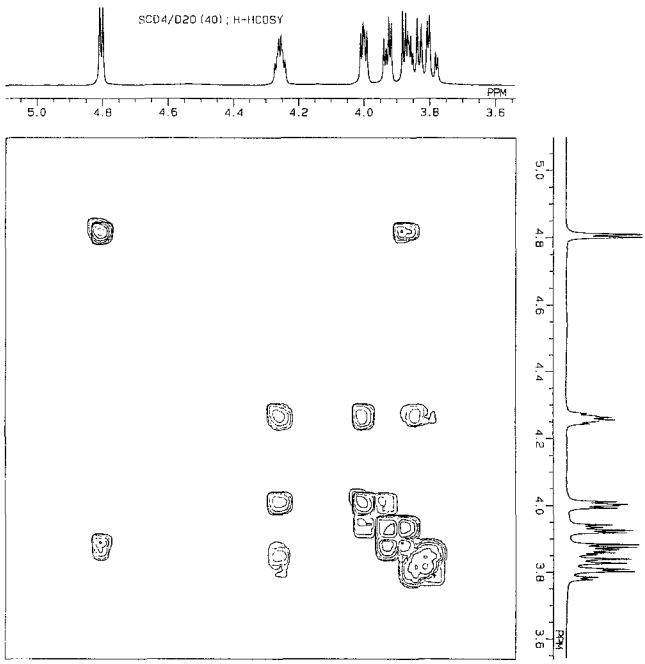

Figure 2. H-H COSY NMR spectrum of β-cycloaltrin **5b** (500 MHz, in D_2O at 40°C)

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