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Regiospecifically Multifunctional β-Cyclodextrins with Two or Three Glucose Residues Bearing Imidazolyl Groups at the C3 Positions

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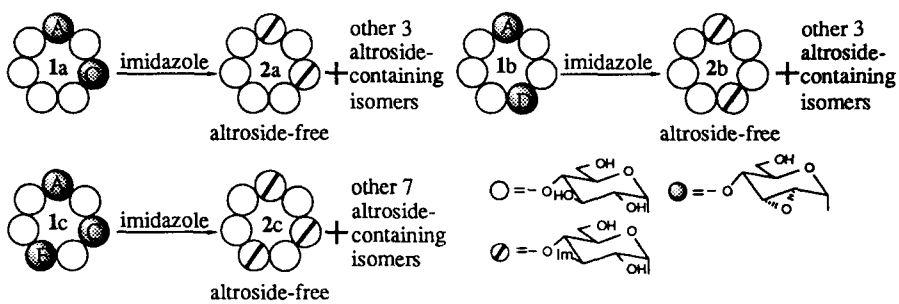
Abstract Two or three imidazolyl groups are incorporated to the C3 positions of β-cyclodextrin without altering the glucosidic structures of the functionalized sugar residues.

Regiospecific multifunctionalization of cyclodextrins (CDs) has attracted worldwide interests in biomimetic chemistry and host-guest chemistry since it proved to be an effective approach to artificial enzymes. By regiospecific introduction of two functional groups onto β-CD, bifunctional catalyses[1] have been successfully achieved. The regiospecific multifunctionalization of the secondary hydroxyl side, however, has been commonly recognized to be a complicate problem[2], and by now only two examples[3] on the regiospecific bifunctionalization have been reported. Even in these rare cases, the bifunctional cyclooligosaccharides have not kept but deformed the cavity of the native CD since the ring opening of mannoepoxide would give predominantly the functional altroside unit instead of the functional glucoside unit.[4] And there has been no report on the regiospecific bi- or tri-functionalization of the secondary hydroxyl side *with the retention of the cavity of the native CD*. The recent discovery of the abnormal ring opening of alloepoxido-β-CD[5] allows attaining such CD derivatives with the aid of an appropriate separation method. In



Scheme 1 Synthesis of Multifunctional Imidazolyl β-Cyclodextrins **2a-c**

the present report, we describe the first syntheses of regio-specifically multifunctional β-CDs with two or three glucose residues having imidazolyl groups at the C3 positions.

The syntheses of these multifunctional CDs were performed from the reaction of di- or tri-alloepoxido-β-CDs with imidazole in DMF (Scheme 1). As a typical example, a solution of $2^A,3^A$-, $2^C,3^C$-dialloepoxido-β-CD **1a** (190 mg) and imidazole (500 mg) in dry DMF (3 cm^3) was heated at 90℃ for 8 days. After dilution with water, the reaction mixture was chromatographed on a reverse-phase column (Lobar Column Lichroprep Rp-18, Size B, Merck) with an elution of water (1 dm^3) and then a linear gradient elution was performed ranging from water to 25% aqueous methanol (each 1 dm^3). The 20 cm^3-fractions from nos 43-63 were collected and rechromatographed under the same conditions as above, yielding **2a** (80 mg, 37.5%). In the same method, **2b** (135 mg, 31.7%) and **2c** (45 mg, 21%) were obtained from their corresponding dialloepoxide **1b** (430 mg) and trialloepoxide **1c** (180 mg), respectively.

Compounds **2a-c** exhibited correct FAB MS spectra with the *m/z* of $[M+1]^+$ being 1235, 1235 and 1285, respectively. ^1H- and ^{13}C- NMR spectra were also consistent with the given structures (Fig. 1, only the CD parts are shown). The chemical shift patterns of the modified sugar residues in **2a-c** have close resemblance to that of the 3-imidazolyl glucoside residue in 3-imidazolyl-β-CD,[5] indicating the 3-imidazolyl glucosidic structure for all these functional sugar residues. This fact was confirmed by the assignment of the NMR spectra with the aid of 2D COSY and ROESY experiments. Moreover, a predominant conformation of $^4C_1$ for all these modified glucoside residues could be derived from the vicinal ^1H-^1H coupling constants in Table 1. These facts suggest that there is no significant deformation of the hydrophobic cavities in **2a-c** from that of the native β-CD.

Table 1. Coupling Constants (Hz) of the Functional Sugar Residues in Compounds **2a-c**

Compound	**2a**		**2b**		**2c**		
	A	C	A(or D)	D(or A)	A(or C or E)	C(or E or A)	E(or A or C)
$J_{1,2}$	3.2	3.2	4.1	3.9	3.3	3.3	3.3
$J_{2,3}$	10.1	9.8	10.1	10.1	10.3	10.2	10.2
$J_{3,4}$	9.4	9.4	10.3	10.3	10.2	10.2	10.2

Separating an uniform CD derivative from its homologous and isomeric mixture is a discouraging task. Indeed, the success in the present syntheses relies upon the finding of the method for separating **2a-c** from the reaction mixtures. As the products of the reaction of mono(alloepoxido)-β-CD with imidazole, two products in a ratio of 3:1 are considered,[5] four or eight isomeric final products would be formed in the reaction of di- or tri(alloepoxido)-β-CD, respectively, even without the consideration of possible reaction

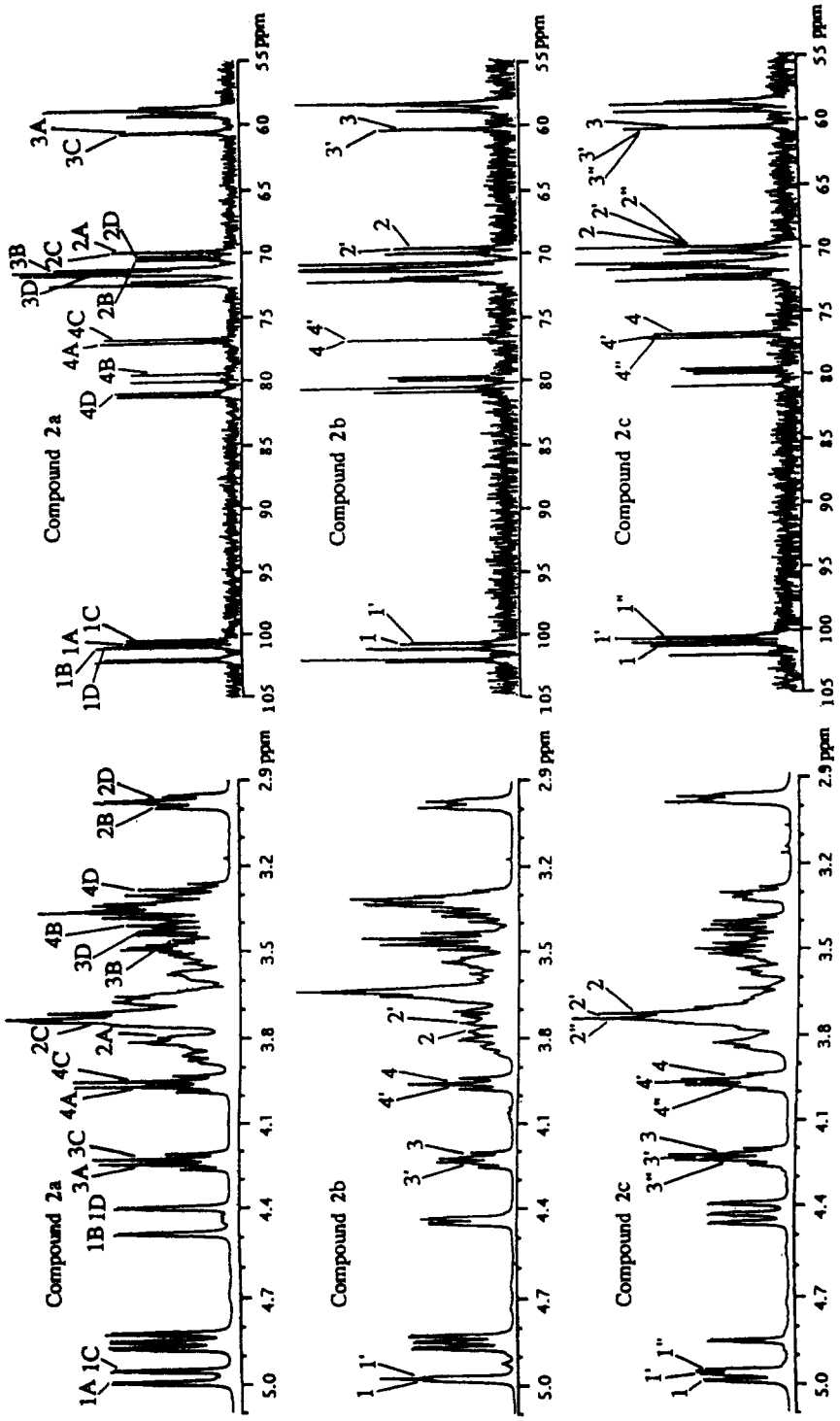


Fig. 1 ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra of 2a-c in $(CD_3)_2SO$-D_2O. The marked peaks in 2b-c and A, C of 2a correspond to the functional sugar residues and the specific residues in 2a are assigned by ROESY experiment.

intermediates or by-products. Neither column chromatography on Biogel and ion-exchange resin nor HPLC was proved to be effective enough to separate the desired products from their reaction mixtures. Fortunately, we found that, in the reverse-phase column chromatography on octadecyl silica gel, the functional β-CD with all its sugar units being of glucosidic type (*i.e.* altroside-free) had a longer retention time than its altroside-containing isomers, and this difference in retention time was large enough to enable us to obtain pure authentic CD derivatives. The altroside-containing isomers, however, had comparable retention time and could not be separated from each other. It was found that the purity of the starting epoxides was very important. If a di- or tri(alloepoxido)-CD contaminated by its homologous or isomeric derivatives or by other epoxides was used, the uniformity of the desired altroside-free product could not be attained. Furthermore, the completion of the reaction was required, otherwise any remaining intermediates of the reaction would interfere with the separation of the final products.

The present multifunctionalized β-CDs **2**a-c, which have two or three regiospecifically-positioned imidazolyl groups with restricted flexibility, are believed to possess very different potential of application in binding and catalyses from those functionalized on the primary hydroxyl side or those containing altrosides. Moreover, reactions of such alloepoxides with nucleophiles other than imidazole are expected to construct a variety of secondary regiospecific custom-designed CDs with desired functionalities. The availability of these CD derivatives will serve the nucleophilic ring opening of regiospecific alloepoxides as a generally applicable method to synthesize CD derivatives regiospecifically multifunctionalized on the secondary hydroxyl side and extend their chemistry and utility to new areas.

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