The first complete set of authentic functional β-cyclodextrins with one imidazolyl group specifically attached to C-2 or C-3

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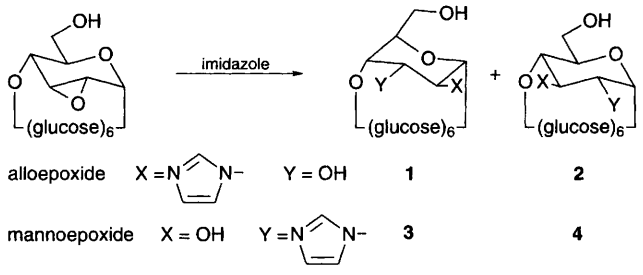
Imidazole is regio- and stereo-specifically incorporated to C-2 or C-3 of β-cyclodextrin.

Functional cyclodextrins (cyclodextrin is denoted as CD) have been extensively explored as efficient enzyme models and receptors, and have witnessed great development.[1] As enzyme models,[2] many functional CDs have been proved to be effective in mimicking the catalytic activities of a variety of natural enzymes such as transaminase, ribonuclease and chymotrypsin. As host molecules, some CD dimers can show a binding ability almost comparable to that of antibodies.[3] These studies, however, have been largely confined to the primary hydroxy side of CDs. Since the secondary side of a toroidal CD is more apparent in chirality, more diverse in chemistry, and therefore the preferential locus for selective binding and catalysis, secondary functional CDs could exhibit quite different properties from their primary side analogues. Unfortunately, efforts of incorporating a functional moiety directly to C-2 or C-3 in place of the secondary hydroxy group of a CD have seldom lead to success even after the explicit synthesis of the authentic β-CD-2-tosylate.[4] The secondary functional CDs synthesized from the ring opening of CD-2,3-mannoepoxide were not really of CD type in that the functional sugar units in these compounds are no longer glucosidic but altrosidic,[5] which would cause a decrease in binding ability.[6] On the other hand, an imidazole moiety can play an important role in bio-processes and imidazolyl functional CDs have attracted special attention.[2,7] These features prompted us to take the imidazole group as a representative functional moiety to search for methods of fabricating authentic secondary functional CDs. Here we describe the synthesis of the title compounds.

The synthetic sequence involved selective sulfonylation of one C-2 or C-3 hydroxy group in β-CD, conversion of the sulfonates to their corresponding manno- or allo-epoxide[4,8] and ring opening of the epoxides with imidazole (Scheme 1).

A solution of imidazole (500 mg) and β-CD alloepoxide (100 mg) in DMF (3 cm^3) was heated for 5 d at 90 °C. The reaction mixture was dissolved in water (500 cm^3), filtered and chromatographed on a reverse-phase column (Lobar Column



Scheme 1

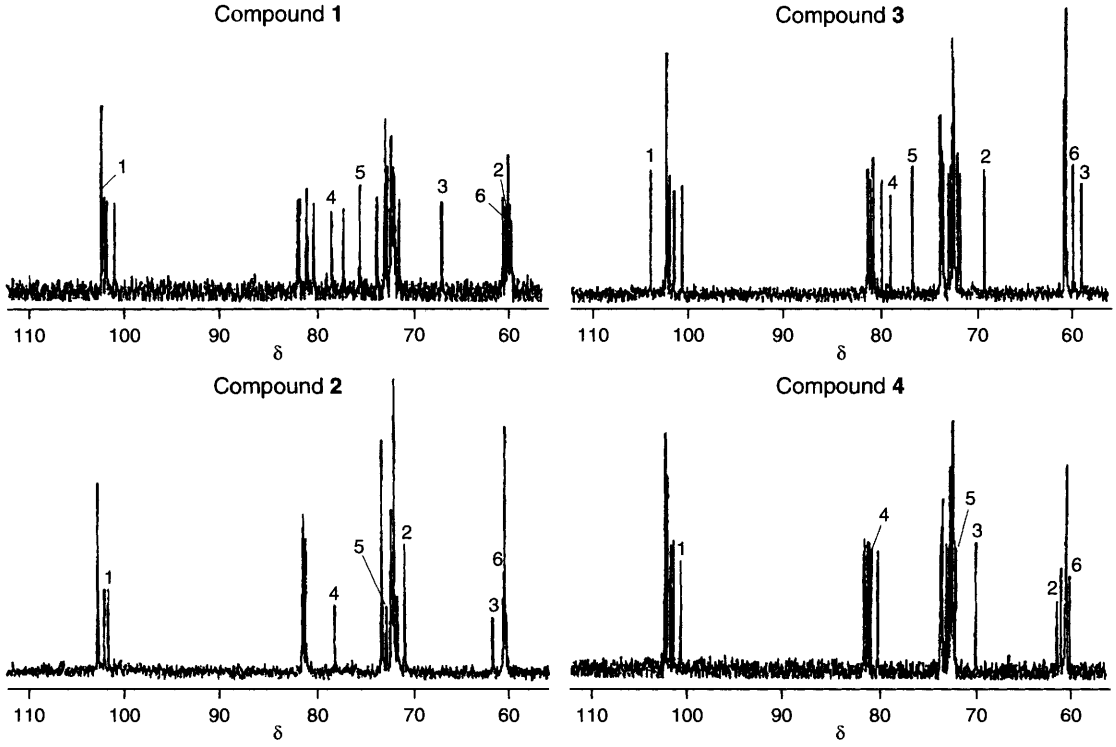


Fig. 1 ^{13}C NMR spectra (125 MHz) of imidazolyl cyclodextrins **1** in Me_2SO-[$^2H_6$] and **2**–**4** in D_2O. (The marked peaks correspond to functional sugar units).

Table 1 125 MHz ^{13}C NMR chemical shift differences and 500 MHz ^{1}H NMR coupling constants for the imidazolyl sugar units in **1–4**[a]

Compound	Chemical shift differences ($\delta_{fun}-\delta_{nor}$)					Coupling constants/Hz			Assignment	
	C-1	C-2	C-3	C-4	C-5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	Position of Im	Sugar type
1	0.2	−12.1	−5.9	−3.0	3.6	~6.4		~3.0	C-2	altroside
2	−1.2	−1.4	−11.6	−3.3	0.7	3.4	10.8	10.5	C-3	glucoside
3	1.6	−3.4	−14.4	−2.6	4.4	7.3	11.2	3.7	C-3	altroside
4	−1.7	−10.8	−3.7	−0.7	−0.4	3.7	11.2	8.7	C-2	glucoside

[a] δ_{fun} and δ_{nor} denote the chemical shifts for the imidazolyl sugar units in **1–4** and those for β-CD respectively. **1** was detected in Me_2SO-[$^2H_6$] (Me_4Si int), while **2–4** were detected in D_2O (MeCN as standard), and β-CD was measured under both conditions. All the NMR spectra were assigned by ^{1}H-^{1}H and ^{13}C-^{1}H COSY NMR. It should be pointed out that the assignment of the ^{13}C NMR spectrum of β-CD for C-2 and C-3 in literature[1a] must have been reversed. That is to say, the three peaks between δ 75 and 72 should have, from low field to high field, an order of C-3, C-2 and C-5 rather than that of C-2, C-3 and C-5.

LiChroprep Rp-18, size B, Merck) with H_2O (500 cm^3) and a gradient system from H_2O (1 dm^3) to 25% methanol (1 dm^3) as sequential eluents. The fractions containing imidazolyl CDs were identified by UV and TLC (by spotting on precoated silica gel plate and staining with 0.1% 1,3-dihydroxynaphthalene in EtOH–H_2O–H_2SO_4). The 20 cm^3-fractions from nos. 45–64 were combined and evaporated, furnishing **2** (59 mg, 55%). Fractions from nos. 28–44 were collected and rechromatographed with a gradient elution from H_2O (1 dm^3) to 20% methanol (1 dm^3) giving **1** (20 mg, 18%).

β-CD mannoepoxide (200 mg) was heated for 90 h at 75 °C in a pH 7.0 imidazole–HCl buffer (10 cm^3, containing 680 mg of imidazole). The reaction mixture was diluted to 100 cm^3 with water and chromatographed by the same procedures described above. The fractions from nos. 102–112 gave **4** (8 mg, 3.8%). Rechromatography of the fractions from nos. 57–85 with a gradient elution from H_2O (1 dm^3) to 20% methanol (1 dm^3) afforded **3** (177 mg, 83%).

All of compounds **1–4** showed the expected molecular ion peak [M+H$^+$] at *m/z* (FAB MS) 1185, and their NMR spectra also showed the expected signals from CD and imidazole moieties. The position of attachment of the imidazole moiety can be convincingly determined by ^{13}C NMR, since there is a large upfield shift for the nitrogen attached carbon (α-carbon) but a much smaller upfield shift for the β-carbon.[9] Fig. 1 and Table 1 demonstrate that both **1** and **4** exhibited these large upfield shifts of C-2 but much smaller upfield shifts of the neighbouring C-1 and C-3. While in **2** and **3**, great upfield shifts were observed for C-3, but much smaller upfield shifts for C-2 and C-4. Therefore, we assign the imidazolyl moiety to C-2 for **1** and **4**, but to C-3 for **2** and **3**. A clue to the stereochemistry of the functional sugar units in **1–4** was given by the proton NMR. Compound **3** showed axial–axial couplings for H-2 with both H-1 ($J_{1,2}$ 7.3 Hz) and H-3 ($J_{2,3}$ 11.2 Hz), indicating that H-1, H-2 and H-3 are all axial. The axial–equatorial coupling between H-3 and H-4 ($J_{3,4}$ 3.7 Hz) indicated an equatorial orientation of H-4. Therefore, the imidazolyl sugar unit in **3** should be an altroside type with a predominant conformation of $^{1}C_4$. In the case of **4**, the coupling constants suggested the axial orientation of H-2, H-3 and H-4 ($J_{2,3}$ 11.2, $J_{3,4}$ 8.7 Hz), and the equatorial orientation of H-1 ($J_{1,2}$ 3.7 Hz), implying a glucoside type unit having $^{4}C_1$ conformation. In the same way, a glucosidic type with $^{4}C_1$ conformation can also be evaluated for the imidazole modified unit in **2**, but an altrosidic type taking $^{1}C_4$ as the predominant conformation for **1**.

The key step in this synthesis has been the ring opening of CD epoxides. CD mannoepoxide was reported to undergo the diaxial opening[10] with the exclusive formation of an altroside unit substituted at C-3, while the reactions of CD alloepoxide have not yet been reported. In the present research, two products **3** and **4** were attained by reacting β-CD mannoepoxide with imidazole in a pH 7.0 buffer solution. The predominant **3** is the expected normal product having one imidazolyl group at C-3 of an altroside, whereas **4** has an imidazolyl group at C-2 of a glucoside ring which could not be derived from the normal diaxial opening rule. To the best of our knowledge, this represents the first exception to the normal opening for a CD mannoepoxide. This reaction did not take place in DMF. Rao[7b] claimed the synthesis of **4** from the reaction of β-CD-2-tosylate with imidazole. But unfortunately, we failed to reproduce this synthesis: instead of the imidazolyl CD, β-CD mannoepoxide (34%) was obtained together with the recovery of unreacted tosylate (52%). β-CD alloepoxide behaves quite differently. Its reaction with imidazole can be carried out in DMF, and the abnormal ring opening becomes predominant, giving the normal product **1** and abnormal one **2** in about 1 : 3.

The product distribution patterns in the ring opening of CD epoxides can be rationalized if a chair flip of the epoxido sugar ring to $^{1}C_4$ conformation and the repulsion between the nucleophile and the lone pair electron of the endo oxygen are taken into consideration.

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