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Simple Preparation of 3^I-O-Substituted β-Cyclodextrin Derivatives Using Cinnamyl Bromide

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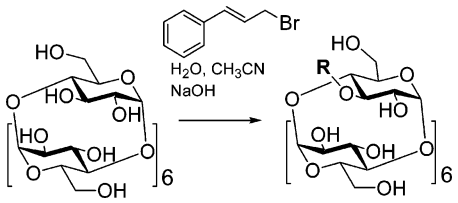

A new method for preparation of 3^I-O-substituted β-cyclodextrin derivatives was developed. Cinnamyl bromide reacts with β-cyclodextrin to form predominantly the 3^I-*O*-cinnamyl derivative (30% isolated yield, >90% regioselectivity). After protection of the remaining cyclodextrin hydroxyls by acetylation, the cinnamyl group can be easily transformed to many other groups (exemplified by transformation to 3^I-*O*-carboxymethyl derivative). Substitution pattern in singly modified CDs was unambiguously determined by a combination of 2D NMR techniques.

Cyclodextrins[1] (CDs) and their synthetic derivatives[2] attract much attention due to their complexation abilities. CDs consist of six, seven, or eight units of α-1,4-linked D-glucopyranose (named α-, β-, and γ-CD, respectively) and have the shape of truncated cones with secondary hydroxy groups at the 2 and 3 positions of glucose units arranged at the wider rim and primary hydroxy groups at the 6 position at the narrower rim. They have a hydrophobic cavity, consisting of C−H groups and glycosidic oxygens, which is capable of complexing guest molecules of appropriate size and shape. Hydroxy groups provide the resulting complex with hydrophilic character and also allow further synthetic transformations. Because of these features, CDs and their derivatives are being used as enzyme mimics,[3] drug delivery systems,[4] pseudophases in capillary electrophoresis,[5] stationary phases in GC and HPLC,[6] and in studies of host−guest interactions, self-assembled monolayers, and chemosensors.[7] In such studies, regioselectively monosubstituted CDs play an important role but their utility is limited by complicated and/or low-yielding preparation methods.

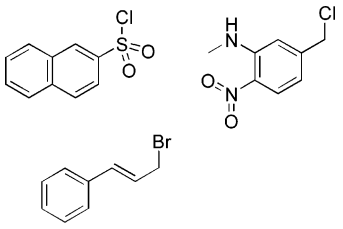

FIGURE 1. Reagents used for complexation-driven 3^I-O-derivatization of β-CD.

Among the monosubstituted[8] CD derivatives, the 6^I-monosubstituted ones are the easiest to prepare and most often used, due to the largest difference in reactivity between the primary 6-OH group and the secondary 2-OH and 3-OH groups. Also the 2^I-monosubstituted derivatives are quite common, since 2-OH is the most acidic hydroxyl. 3^I-Monosubstituted derivatives are the most difficult to prepare by direct derivatization, since 3-OH is the least reactive hydroxyl. They have been prepared by alkylation or sulfonylation with reagents that have been inserted into the CD cavity prior to the derivatization and oriented with the reactive site close to the 3-OH group. None of the reagents used (2-naphthalenesulfonyl chloride,[9] 3-methylamino-4-nitrobenzyl chloride[8]) offered the possibility to transform the attached substituent to any desired ether bond connected functionality without disturbing the already created bond to the CD glucose unit. Nevertheless, for the synthesis of 3^I-N-, 3^I-S-substituted or 3^I-halogen CD derivatives a general method based on nucleophilic cleavage of 2,3-anhydrocyclodextrins was already developed.[10]

Our work presents a simple method for the synthesis of the 3^I-*O*-alkyl-type derivatives of β-CD using cinnamyl bromide as the derivatizing reagent. It was chosen for its isostericity with the above complexation-driven derivatizing reagents (Figure 1), its high reactivity, and for offering further modification possibilities. Due to the presence of an allyl double bond, the cinnamyl group can be converted to many other substituents by several methods, without affecting the remainder of the β-CD. One such method, oxidation to a carboxymethyl group, is presented here. Another one, oxidation to the formylmethyl group and use in a Wittig reaction, is currently under study in our group.

Reaction of cinnamyl bromide with β-CD **1** and NaOH in a cold H_2O/CH_3CN solvent mixture yields the desired

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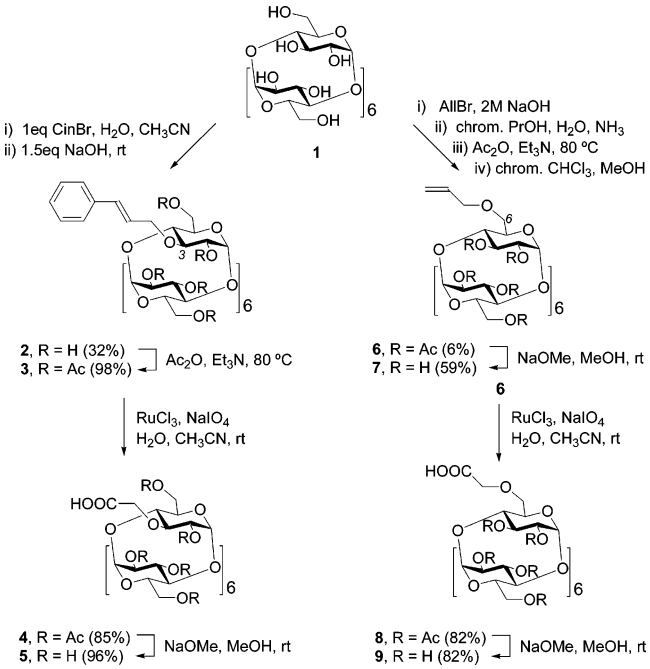
SCHEME 1. Synthesis of 3^I-O- and 6^I-O-Monosubstituted Derivatives of β-CD



3^I-*O*-cinnamyl-β-CD **2** in up to 30% isolated yield with more than 90% regioselectivity (Scheme 1). The crude reaction mixture also contains di- or trisubstituted derivatives and starting β-CD, but those can be easily separated on silica gel column using a 1-PrOH/H_2O/NH_3 elution mixture. The desired 3^I-O-derivative can be isolated from the resulting mixture of monosubstituted β-CDs by crystallization from water. To prove the utility of monocinnamyl-β-CD, the peracetylated derivative **3** was prepared and the cinnamyl double bond cleaved using $RuCl_3$/$NaIO_4$ in acetonitrile to afford peracetylated carboxymethyl-β-CD **4**, which was deprotected with sodium methoxide to give carboxymethyl-β-CD **5**.

We found out that peracetylated 3^I-*O*-carboxymethyl-β-CD derivative can be separated from peracetylated 2^I-*O*-carboxymethyl-β-CD (prepared in a similar way from 2^I-*O*-allyl-β-CD[11]) by TLC on silica gel using a $CHCl_3$/MeOH elution mixture. Therefore we decided, in addition to a 2D NMR structure proof, to confirm the location of the substituent in position 3 by the synthesis of the last possible regioisomer, peracetylated 6^I-*O*-carboxymethyl-β-CD **8**. We took advantage of the fact that in excess base the preferred outcome of the reaction of β-CD with allyl bromide will be substitution in position 6. The mixture of monoallyl regioisomers (containing 6 isomer as the main product) was again easily separated from the starting β-CD and more highly substituted derivatives by chromatography, but this time the separation of pure 6^I-*O*-allyl-β-CD **7** from its regioisomers was difficult. It was accomplished with peracetylated derivatives on silica gel with a $CHCl_3$/MeOH elution mixture. The resulting peracetyl 6^I-*O*-allyl-β-CD **6** was then used for preparation of **8** and its deacetylated derivative **9** and also for the preparation of the pure allyl derivative **7**.

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An unambiguous identification of monosubstituted regioisomers relied on a detailed NMR study. A standard set of two-dimensional techniques (COSY, TOCSY, HSQC, and HMBC) enabled us to make full assignment of all proton and carbon signals, especially for atoms in the modified ring of the CD molecule (ring I).

An accurate determination of the substituted position in the cyclodextrin derivatives is provided by an HMBC correlation between the carbon signal of C-1′ in the substituent and the corresponding proton signal of the substituted site in β-CD or/and by HMBC correlation between the proton signal of H-1′ in the substituent and the corresponding carbon signal in the substituted position in β-CD (for details see Supporting Information).

In conclusion, we have explored a novel synthetic approach utilizing cinnamyl bromide as a highly regioselective reagent for the preparation of 3^I-O-monosubstituted β-CD derivatives. The advantage of this procedure lies in the large synthetic potential of the cinnamyl moiety. The regioselectivity of the substitution was elucidated by 2D NMR techniques, which proved to be a reliable and unambiguous tool.

Experimental Section

3^I-*O*-Cinnamyl-β-CD 2. β-CD hydrate (5.6 g, 4.5 mmol) was dissolved in a mixture of water (150 mL) and acetonitrile (50 mL). The mixture was cooled to 0 °C, and a solution of cinnamyl bromide (975 mg, 5 mmol) in acetonitrile (3.0 mL) was added. After 5 min of stirring and cooling, the mixture changed from clear to milky white. Then solution of NaOH (400 mg, 10 mmol) in water (1.0 mL) was added. The mixture was stirred overnight at room temperature. The reaction was followed by TLC using two elution mixtures. Toluene/ethyl acetate (20/1) was used to test for the presence of unreacted cinnamyl bromide after extraction of the sample of the reaction mixture with toluene (UV detection). Elution mixture 1-propanol/water/ethyl acetate/concentrated aqueous ammonia (6/3/1/1) was used for observing β-CD derivatives (detection by carbonization). Reaction was quenched with acetic acid (3.2 mL). The reaction mixture was then evaporated to dryness. β-CD substitution products were extracted from the resulting solid with hot methanol (3 × 100 mL). The solid was first refluxed with methanol for 1 h and then filtered on a glass frit. Recrystallization from water (50 mL) yielded recovered β-CD (2.4 g, 43%). Methanol extracts were collected and evaporated. The resulting solid was dissolved in hot distilled water (200 mL), and silica gel (30 g) was added. The resulting suspension was evaporated to dryness and applied on silica gel column. The di- and monosubstituted β-CDs were then separated by elution with 1-propanol/water/concentrated aqueous ammonia (10/3/2). Fractions containing singly substituted derivatives were collected and evaporated to dryness. Pure 3^I-O-derivative **2** was obtained by crystallization of the solid (2.2 g) from water (90 mL). Yield 1.8 g (32%); mp 289−291 °C. MS (ESI) *m/z* 1276.6 $[M + Na]^+$. HRMS calcd for $C_{51}H_{78}O_{35}Na$: 1273.422135, found: 1273.426030. For ^1H NMR and ^{13}C NMR data, see Supporting Information Table 1.

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Supporting Information Available: Experimental procedures and NMR data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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