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Efficient regioselective functionalizations of cyclodextrins carried out under microwaves or power ultrasound

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Abstract—Regioselective syntheses of differently functionalized cyclodextrins (CDs) were efficiently carried out under ultrasound or microwave irradiation. 6^{I}-Deoxy-6^{I}-thio-β-CD, 6^{I}-deoxy-6^{I}-formyl-β-CD, and 6^{A},6^{D}-dideoxy-6^{A},6^{D}-dithio-β-CD were prepared under microwave irradiation. A new rapid and efficient ultrasound-assisted protocol is described for the synthesis of 3^{I}-azido-3^{I}-deoxy-α, -β, and -γ-CD by selective tosylation followed by azide substitution.

Cyclodextrins (CDs) have attracted worldwide interest in various research fields related to host–guest recognition.[1] It has been shown that functionalization of their hydroxyl groups can remarkably improve complexing and catalytic activities of CDs. However, as selective chemical modification of CDs still presents a challenge in the way of molecular design, much effort is being directed to developing new synthetic protocols that are both expeditious and regioselective.

Owing to the greater reactivity of primary C-6 hydroxyl groups toward electrophilic reagents, particularly when acyl groups or bulky substituents are being introduced, selective mono- and di-functionalizations have been relatively more studied,[2] although overall yields often remain unsatisfactory. Hydroxyl functionalization on the secondary face, that is larger than the primary face, is an important goal for its potential applications. It has however proved so difficult that attempts have been limited to a small selection of derivatives. In fact with small electrophiles substitution on the secondary face is favored. Secondary hydroxyl groups are more acidic than primary ones; this can affect their selective functionalization under basic conditions. The C-2 hydroxyl is accessible to direct derivatization, usually yielding a mixture of isomers.[3] On the other hand, selective derivatization at the C-3 hydroxyl groups is known to be very difficult because these are the least acidic and least accessible.[4] Many of the published protocols for the preparation of CD derivatives suffer from several limitations, such as low yields, poor regioselectivity, and long reactions times; products generally require time-consuming chromatographic purifications.

Although it is well known that many organic reactions are accelerated by ultrasound (US)[5] or microwave (MW)[6] irradiation, as witnessed by a vast literature on US- and MW-promoted reactions, only a couple of reports have so far concerned the modification of CDs under these non-conventional conditions.[7]

In recent papers we compared the outcomes of several CD functionalizations carried out both under conventional conditions and under US or MW. Results showed that these techniques are very advantageous in terms of yields and reaction times.[7] We found that the synthesis of 6^{I}-amino-6^{I}-deoxy-β-CD could be much improved by their application (Scheme 1).[7a] Not only were the yields higher, but also reaction times were dramatically cut down to a few minutes for the entire synthetic pathway.

Keywords: Cyclodextrin; Ultrasound-assisted synthesis; Microwave-assisted synthesis; Regioselectivity.
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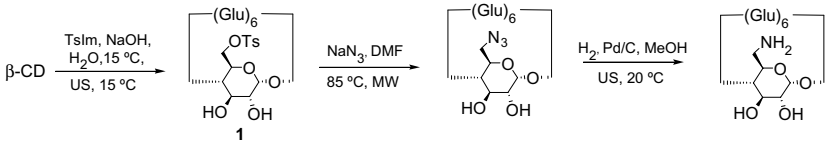
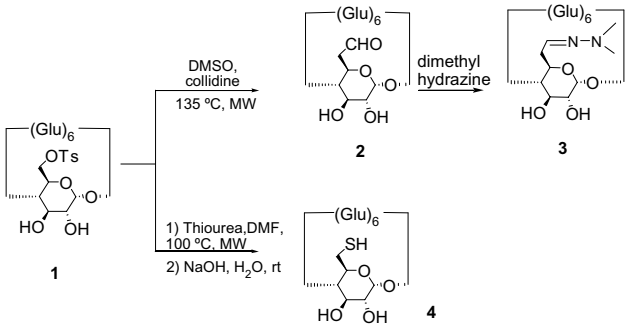


Scheme 1. Synthesis of 6^{I}-amino-6^{I}-deoxy-β-CD.

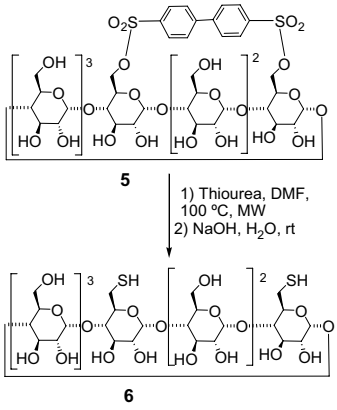
Using the same techniques we have now proceeded to carry out chemical modifications on the primary and secondary faces of CDs. The present Letter reports the syntheses of 6^{I}-formyl-β-CD, 6^{I}-deoxy-6^{I}-thio-β-CD, and 6^{A},6^{D}-dideoxy-6^{A},6^{D}-dithio-β-CD under MW irradiation. The synthesis of the 2^{I}-*O*-(*p*-toluenesulfonyl) derivatives of α-, β-, and γ-CD was strongly promoted by US. The latter products were further derivatized under MW irradiation to yield 3^{I}-deoxy-3^{I}-azido-*altro*-α-, β-, or γ-CD analogs.

6^{I}-*O*-(*p*-Toluenesulfonyl)-β-CD (**1**), synthesized in accordance with our previous protocol,[7a] was converted under MW to 6^{I}-formyl-β-CD (**2**) via DMSO oxidation[8] in the presence of collidine (Scheme 2). The aldehyde was obtained in 15 min at 110 W (135 °C), as a single, pure product, isolated by simple precipitation and characterized by NMR and mass spectrometry.[9] The ^{1}H NMR spectrum of compound **2** showed that the desired product was mainly present as covalent hydrate when dissolved in D_2O or in DMSO-d_6 (only a small aldehyde peak was seen at 9.3 ppm, whereas a broad peak at 5.3 ppm indicated the presence of the hydrate carbon). To confirm the identity of the product we synthesized the 6^{I}-deoxy-6^{I}-(1,1-dimethyl)hydrazone-β-CD (**3**). Compared to reported results of oxidation under conventional conditions, our protocol cut down the reaction time from 90 to 15 min.

The rate enhancement promoted by MW irradiation also occurred in the synthesis of 6^{I}-deoxy-6^{I}-thio-β-CD (**4**) and 6^{A},6^{D}-dideoxy-6^{A},6^{D}-dithio-β-CD (**6**), both carried out by displacement with thiourea of the primary sulfonic ester in C-6, followed by basic hydrolysis (Schemes 2 and 3). According to the literature,[10] treatment of $6^{A,D}$-capped-β-CD with thiourea in DMF gave the thiouronium salt after a 20-h heating at 90 °C. When we performed it under MW irradiation, complete conversion was observed after 1 h at 100 °C. 6^{I}-Deoxy-6^{I}-thiouronium-β-CD was synthesized from 6^{I}-*O*-(*p*-toluenesulfonyl)-β-CD in 20 min of MW irradiation at 100 °C. Both thiouronium salts were hydrolyzed to yield the desired products, that were isolated by crystallization and fully characterized.[11]



Scheme 2. Synthesis of 6^{I}-formyl-β-CD (**2**) and 6^{I}-deoxy-6^{I}-thio-β-CD (**4**).



Scheme 3. Synthesis of 6^{A},6^{D}-dideoxy-6^{A},6^{D} dithio-β-CD.

Table 1 quantifies the advantages of MW irradiation over conventional heating (oil bath) in the preparation of compounds **2**, **4** (Scheme 2), and **6** (Scheme 3).

Teranishi et al. reported a versatile preparation of 2^{I}-deoxy-2^{I}-*O*-(*p*-toluenesulfonyl)-α-, β-, and γ-CDs **7a**, **b**, **c** (Scheme 4) using a combination of *p*-toluenesulfonyl imidazole (TsIm) and molecular sieves in DMF[12] that proved to be remarkably regioselective. The reaction however was so slow, that it took several days to achieve substantial conversion.

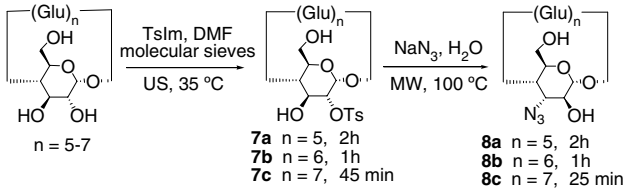
When we subjected α-, β-, and γ-CD to monotosylation under US, we obtained excellent yields in very short reaction times. Owing to different flexibilities of the three CDs, US did not influence their tosylation to the same degree: the reaction time was cut down to 2 h for α-CD, 1 h for β-CD and 45 min for γ-CD.[13]

2^{I}-*O*-(*p*-Toluenesulfonyl) derivatives (**7a**–**c**) were the key intermediates for the preparation of the corresponding azido derivatives. To the best of our knowledge 2- and 3-azido-α-CD have never been reported so far. Since it is known[3a] that nucleophilic attack to the secondary face of β- and γ-CD involves the formation of the 2,3-epoxide, we investigated the direct tosyl displacement, avoiding the isolation of the intermediate.

2^{I}-*O*-(*p*-Toluenesulfonyl)-α-CD (**7a**) was subjected to nucleophilic substitution by conventional heating with sodium azide in water. After 72 h the final product

Table 1. Conventional (oil bath) heating versus MW irradiation: a comparison of results

Entry	Conditions	Reaction time (h)	Yield (%)
2	Oil bath, 135 °C	1.5	60
2	MW, 135 °C, 110 W	0.25	68
4	Oil bath, 90 °C	18	55
4	MW, 100 °C, 100 W	0.3	69
6	Oil bath, 90 °C	20	58
6	MW, 90 °C, 100 W	1	79



Scheme 4. Synthesis of 3^{I}-azido-3^{I}-deoxy-*altro*-α-, β- and γ-CD.

was isolated in 75% yield and fully characterized as follows. To study the regioselectivity of this reaction, we resorted to 2D NMR experiments that enabled us to make detailed structural assignments. COSY and HMQC experiments were performed to determine whether the modified glucose unit was substituted in C-2 or C-3. Since the azido substituent is known to cause an upfield shift, in ^{13}C NMR spectra we expected a shifted signal from the modified position. The spectrum of compound **8a** showed upfield shifts of 2 ppm for the C-2 of the modified sugar and about 10 ppm for the C-3, as well as a downfield shift for C-1 (Fig. 1). Therefore, we concluded that we had obtained 3^{I}-azido-3^{I}-deoxy-*altro*-α-CD. After establishing the position of the modified hydroxyl, we inferred the stereochemistry of the sugar from that of the nucleophilic attack and confirmed it by examining the spin–spin coupling constants $^{3}J_{x,y}$.

The ^{1}H NMR spectrum of compound **8a** showed an axial–axial coupling of H-1 with H-2 ($J_{1,2} = 6.3$ Hz), and an axial–equatorial coupling between H-3 and H-4 ($J_{3,4} = 3.6$ Hz). The intramolecular substitution of 2^{I}-deoxy-2^{I}-(*p*-toluenesulfonyl)-α-CD regioselectively gave 3^{I}-deoxy-3^{I}-azido-α-CD through the epoxidic intermediate. From the inversion of the configuration we concluded that we had obtained 3^{I}-deoxy-3^{I}-azido-*altro*-α-CD.

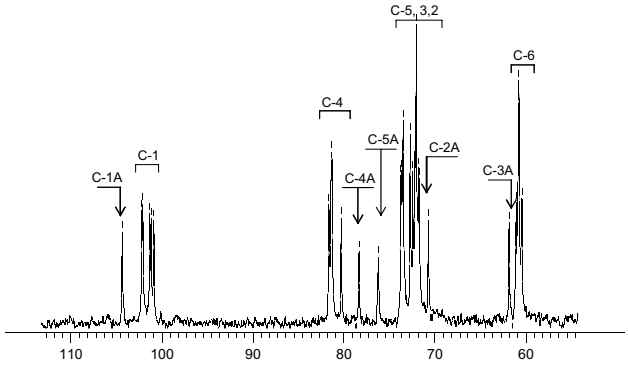


Figure 1. ^{13}C NMR spectrum of 3^{I}-azido-3^{I}-deoxy-*altro*-α-CD.

The same protocol was used starting from 2^{I}-(*p*-toluenesulfonyl)-β- and -γ-CD. From the characterization of the products we concluded that we had, respectively, synthesized 3^{I}-deoxy-3^{I}-azido-*altro*-β- and -γ-CD. The better to confirm this structure, we repeated the synthesis of 3^{I}-deoxy-3^{I}-azido-*altro*-β-CD as described in the literature:[3a] 2^{I}-*O*-(*p*-toluenesulfonyl)-β-CD was converted to 2,3-mannoepoxyde-β-CD and treated with sodium azide in water. After the product was isolated and characterized, we established that its NMR spectra were substantially identical to those of the product we had obtained by direct nucleophilic substitution. Our results unambiguously show that a previously reported selective synthesis of 2^{I}-deoxy-2^{I}-azido-β-CD by direct tosyl displacement,[14] yielded the 3- rather than the 2-derivative as claimed by the authors.

Finally the protocol for the synthesis of 3^{I}-deoxy-3^{I}-*altro*-azido-α-, β-, and γ-CD was optimized under MW. The reaction time was reduced from 72 h to 1 h for β-CD, and only 5 equiv of sodium azide were employed instead of the typical large excess. With γ-CD 25 min sufficed for complete conversion, while with α-CD the reaction was slower, taking 2 h to go to completion. ^{1}H NMR analysis of the crude product evidenced about 20% of 2,3-mannoepoxide-α-CD, which further confirmed that the epoxide was the intermediate product. A stoichiometric addition of acetic acid strongly promoted the nucleophilic attack to the latter,[15] thus bringing the reaction to completion.

To conclude, we showed that regioselective CD modification is strongly favored under US and MW irradiation. Good results were obtained in the preparations of 6^{I}-formyl-β-CD, 6^{I}-deoxy-6^{I}-thio-β-CD, and 6^{A},6^{D}-deoxy-6^{A},6^{D}-dithio-β-CD. In addition, we developed a new protocol for the synthesis of 3^{I}-deoxy-3^{I}-azido derivatives of α-, β-, and γ-CD, remarkably obtained as pure altrose isomers. US- and MW-assisted procedures proved very advantageous in terms of yields, reaction times and product purity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.104.

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9. *6^I-Formyl-β-CD* (**2**): The reaction was carried out under magnetic stirring in a professional MW oven (MicroSYNTH-Milestone), the temperature being monitored with a fibre-optic thermometer. 1 g (0.77 mmol) of 6^I-*O*-(*p*-toluenesulfonyl)-β-CD and 300 μl of collidine were dissolved in 10 ml DMSO. The mixture was irradiated with MW (110 W) for 15 min at 135 °C. 100 ml of acetone was then added; the precipitate was filtered off and recrystallized from water/acetone 1/15, yielding 600 mg of pure 6^Iformyl-β-CD (**2**) (yield 68%). To confirm the identity of product 2, the dimethylhydrazone was synthesized as follows. 1 ml of 1,1-dimethylhydrazine was added to 200 mg of 6^I-formyl-β-CD; the solution was stirred at room temperature for 12 h before it was evaporated to dryness. 5 ml of acetone was added and the product filtered off. 170 mg of 6^I-deoxy-6^I-(*N*,*N*-dimethyl)hydrazone-β-CD was recovered and characterized. Analytical data were in accordance with reported values.
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11. *General procedure for the synthesis of 6^I-deoxy-6^I-thio-β-CD* (**4**) *and 6^A,6^D-dideoxy-6^A, 6^D-dithio-β-CD* (**6**): The reaction was carried out under magnetic stirring in a professional MW oven (MicroSYNTH-Milestone), the temperature being monitored with a fibre-optic thermometer. 1.5 mmol of 6^I-*O*-(*p*-toluenesulfonyl)-β-CD (1) or of $6^{A,D}$-capped-β-CD (**5**) were dissolved in 16 ml of DMF and thiourea was added. The mixture was irradiated with MW (see detail in the synthesis of products **4** and **6**). The solvent was partially evaporated and 100 ml of acetone was added to precipitate the product. The thiouronium salt was dissolved in 15 ml of aq 0.25 N NaOH and stirred 10 min at 90 °C. The solution was cooled down to room temperature and 80 mg of $NaBH_4$ were added; the mixture was further cooled down to 0 °C and acidified with 7 ml of HCl 1 N. Finally 150 ml of acetone was added to precipitate the desired product.
6^I-Deoxy-6^I-thio-β-CD (**4**): The general procedure was followed starting with 2 g (1.55 mmol) of 6^I-*O*-(*p*-toluenesulfonyl)-β-CD and 1.17 g (15.4 mmol) of thiourea. After 20 min irradiation at 100 °C (100 W) 1.23 g of product **4** was obtained (yield 69%). Analytical data were in accordance with reported values.
6^A,6^D-Dideoxy-6^A,6^D-dithio-β-CD (**6**): The general procedure was followed starting with 2 g (1.44 mmol) of $6^{A,D}$-capped-β-CD (**5**) and 2 g (28.8 mmol) of thiourea. After 1 h irradiation at 90 °C (100 W) 1.32 g of product **6** was obtained (yield 79%). Analytical data were in accordance with reported values.
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13. *Typical procedure for the synthesis of 2^I-O-(p-toluenesulfonyl)-CDs*: 1 mmol of α-, β- or γ-CD was dissolved in 12 ml of DMF and 0.9 mmol of TsIm with 1 g of powder molecular sieves 4A were added, After sonication (immersion-horn, 50 W, 20.4 kHz), molecular sieves were removed by filtration through a Celite® pad and the filtrate was evaporated to dryness under reduced pressure. The filtrate was purified by reverse-phase chromatography with a gradient from water/methanol 95:5 to 25% methanol.
2^I-O-(p-Toluenesulfonyl)-α-CD (**7a**): The general procedure was followed starting with 1 g (1.02 mmol) of α-CD. Sonication for 2 h gave 406 mg of product (36%). Analytical data were in accordance with reported values.
2^I-O-(p-Toluenesulfonyl)-β-CD (**7b**): The general procedure was followed starting with 1 g (0.88 mmol) of β-CD. Sonication for 1 h gave 454 mg of product (40%). Analytical data were in accordance with reported values.
2^I-O-(p-Toluenesulfonyl)-γ-CD (**7c**): the general procedure was followed starting with 1 g (0.77 mmol) of γ-CD. Sonication for 45 min gave 501 mg of product (46%). Analytical data were in accordance with reported values.
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15. *Typical procedure for the synthesis of 3^I-azido-3^I-deoxy-altro-CD*: The reaction was carried out under magnetic stirring in a professional MW oven (MicroSYNTH-Milestone), the temperature being monitored with a fibre-optic thermometer. 0.1 mmol of 2^I-*O*-(*p*-toluenesulfonyl)-CD derivative and 0.5 mmol of NaN_3 were dissolved in 1 ml of H_2O. The mixture was irradiated with MW (100 W) at 100 °C till complete conversion of the starting material. The mixture was evaporated to dryness under reduced pressure. The product was purified by chromatography on reverse phase with a gradient from water to 10% methanol.
3^I-Deoxy-3^I-azido-altro-α-CD (**8a**): The general procedure was followed starting with 100 mg of 2^I-*O*-(*p*-toluenesulfonyl)-α-CD. The mixture was irradiated for 1 h, then 20 μl of acetic acid was added and irradiation was resumed (100 W) at 100 °C for 1 h to give 110 mg of **8a** (yield 95%) as a white solid. ^{1}H NMR (300 MHz, D_2O) δ: 5.12 (d, $J = 3.9$ Hz 1H), 5.08–5.01 (m, 4H), 4.92 (d, $J = 6.6$ Hz, 1H), 4.30–4.22 (m, 1H), 4.10 (t, $J =$ about 3.6 Hz, 1H), 4.05–3.72 (m, 23H), 3.70–3.49 (m, 11H). ^{13}C NMR (D_2O

*t*BuOH int)104.54, 102.30, 102.15, 101.41, 101.20, 100.87, 81.66, 81.49, 81.38, 81.26, 80.25, 78.42, 76.25, 73.80, 73.67, 73.66, 73.55, 73.52, 73.44, 72.71, 72.68, 72.42, 72.41, 72.24, 72.09, 72.06, 72.02, 71.85, 71.69, 70.74, 61.84, 61.15, 61.00, 60.79, 60.74, 60.45. ESI-MS: 1020.8 $[M+Na]^+$.

3^I-Azido-3^I-deoxy-altro-β-*CD* (**8b**): The general procedure was followed starting with 100 mg of 2^I-*O*-(*p*-toluenesulfonyl)-β-CD. Irradiation for 1 h gave 110 mg of **8b** (yield 95%) as a white solid. ^{1}H NMR (300 MHz, D_2O) δ; 5.18–5.13 (m, 2H), 5.11–5.03 (m, 4H), 4.93 (d, $J = 6.0$ Hz, 1H), 4.32–4.23 (m, 1H), 4.13 (t, $J =$ about 3.9 Hz, 1H), 4.07–3.74 (m, 28 H), 3.72–3.52 (m, 12 H). ^{13}C NMR (D_2O, CH_3CN int.) δ: 103.4, 102.2, 101.7, 101.5, 81.9, 81.8, 81.7, 81.6, 81.4, 80.67, 78.37, 75.41, 74.15, 74.06, 73.9, 73.74, 73.39, 73.02, 72.99, 73.02, 72.99, 72.89, 72.82, 72.67, 72.45, 72.42, 72.39, 70.71, 62.46,61.32,61.27,61.24,60.54. ESI-MS: 1182.82 $[M+Na]^+$, 602.8 $[M+Na_2]^{2+}$.

3^I-Azido-3^I-deoxy-altro-γ-*CD* (**8c**): The general procedure was performed starting with the 2^I-*O*-(*p*-toluenesulfonyl)-γ-CD and irradiated for 25 min to give 129 mg of **8c** (yield 98%) as a white solid ^{1}H NMR (300 MHz, D_2O) δ; 5.22 (d, $J =$ about 4 Hz, 1H), 5.16–4.94 (m, 6H), 4.93 (d, $J = 4.8$ Hz, 1H), 4.26–4.17 (m, 1H), 4.16–4.09 (m, 1H), 4.05–3.74 (m, 32H), 3.72–3.52 (m, 14H). ^{13}C NMR (D_2O *t*BuOH int). δ: 103.4, 102.32, 102.11, 101.74, 100.95, 80.96, 79.63, 76.91, 74.18, 73.81, 73.58, 73.15, 72.99, 72.91, 72.51, 72.34, 72.24, 72.14, 69.94, 62.0, 60.78, 60.30. ESI-MS: 1344.7 $[M+Na]^+$, 683.8 $[M+Na_2]^{2+}$.