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Smart regioselectivity towards mono 6-hydroxyl α -cyclodextrin amphiphilic derivatives†

Yanli Cui,^{ID}*^{ab} Yangyi Mao,^c Jianwei Mao^e and Yongmin Zhang^{ID}*^{ad}

Following the trend of eco-friendly development, a smart regioselective modification is described herein, for mono 6-hydroxyl and penta-alkyl coexistence on the primary face of α -cyclodextrins with no additional catalysis or no enzyme process, just *via* the adjustment of the ratio of alkali to alkylation agent, with good yields. The novel procedure minimized the tedious protection, deprotection steps and provided useful intermediates for further cutting edge research. Thus, the scope of green and economical access is extended from penta-pentenyl substitution to C₄–C₆ alkyl group substitution. It was speculated that the mechanism might be controlled by the concentration of alkali in the system and the steric effects of the electrophilic reagent RBr.

1. Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides derived from starch enzymolysis that possess molecular cavities with topological structures. CDs and their cyclodextrin derivatives (CDDs) have attracted widespread attention for their increasingly expanding applications from traditional to cutting edge research in fields such as: cosmetics, food additives, drug carriers, analysis and catalysis technologies, and recently in stimuli-responsive carriers, cyclodextrin–graphene, supramolecular systems and other CD-based biomolecules.^{1–7} The monosubstituted CDs are synthesized by introducing a desired functional group or biomolecule to the single hydroxyl, or the mono hydroxyl on cyclodextrins connected with another biological macromolecule or polymer. Monosubstituted derivatives were also utilized in the synthesis of defined CD dimers and oligomers, which exhibit stronger binding constants towards guest molecules than the corresponding monomers due to the cooperative inclusion.⁸

The CD molecule has numerous hydroxyl groups in three different positions that make tiny differences to its reaction activity. The selective derivatization is often a tough task, involving elaborate multistep protection-deprotections, with

a low overall yield. In 1998, D'Souza reviewed strategies for selective modification of CDs, including regioselective mono-modifications, but nevertheless, the methods used were traditional.⁹ Traditionally the most popular method for monomodifications at the 6-position of CDs is *via* nucleophilic attack from a reagent containing the appropriate group on a mono-6-sulfonylcyclodextrin. These monosulfonates are prepared by reacting 1 equiv. of *p*-toluenesulfonyl chloride with CD in pyridine. However, monotosylation of CD is often a nonselective process and produces a mixture of primary as well as secondary side tosylated products together with di- or tri-tosylated derivatives.⁹ Alternatively, from the opposite point of view, an approach has been developed over the years, which involves the deprotection of the protected CDs. The methodology uses diisobutylaluminium hydride (DIBAL-H) as a dealkylating reagent and has been successfully applied to benzylated CDs,¹⁵ allowing access to polyhetero-functionalized CDs containing two, three or even six different functionalities.¹⁶ For example, when perbenzylated α -CD was treated with excess DIBAL-H at room temperature, the mono-debenzylated product was formed in 64% yield, the hydroxyl group being on the primary face.¹⁵ The mono-demethylation could also occur on the primary face of hexakis(2,3-di-*O*-benzyl)-6-hexa-*O*-methyl- α -CD, but with a low yield (30%).¹⁷ Recently Ghosh *et al.* applied this methodology to per-6-*O*-*tert*-butyldimethylsilylated CDs to produce mono- and di-*O*-desilylated CDs,¹⁸ for example, the mono-*O*-desilylated- α -CD product was isolated in 71% yield.

Herein a one-pot approach is reported for the preparation of a novel series of mono 6-hydroxyl α -CDs with a variety of alkyl groups on the primary face using no additional catalysis or no enzyme process. However, the efficient method and unique structure of the substrates have not been reported as far as is known. Among the linkages (*e.g.*, sulfide,^{10,11} amine,¹²

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ester,¹³ ether,¹⁴ etc.) available for the attachment of functional groups to CDs, ether bonds are the most desirable, because they are less susceptible to degradation by oxidation or hydrolysis and obtained by a single nucleophilic reaction of a hydroxyl group of the CDs with an appropriate electrophile. The CD ethers either serve as amphiphilic sections, ene-end CDDs for further functionalization, or act as reaction intermediates of click reactions, or are converted into artificial enzymes, and others. In other words, the published substrates can provide versatile variation for fast CD-based research.

2. Materials and methods

2.1. General methods

Analytical grade chemicals were used for all reactions and all solvents were dried over standard drying agents and freshly distilled prior to use. Optical rotations were measured at 20 ± 2 °C with a PerkinElmer model 241 digital polarimeter, using a 10 cm, 1 mL cell. Electrospray ionization (ESI)-time-of-flight mass spectra were obtained with a Micromass (UK) LCT ESI-TOF spectrometer. The NMR spectra (¹H, ¹³C) were recorded on a Bruker DRX-400, DMX-500 instrument (Karlsruhe, Germany) at ambient temperature with tetramethylsilane as an internal standard and the coupling constants are represented in Hz. Assignments were aided by carrying out correlated spectroscopy (COSY) experiments. The reactions were monitored by thin-layer chromatography (TCL) on a precoated plate of Merck silica gel 60 F₂₅₄ (layer thickness: 0.2 mm, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

2.2. Per-2,3-di-O-benzyl-α-cyclodextrin (4)

A solution of 3 (100 mg, 0.04335 mmol) in 5 mL of 0.05 M NaOMe (dry dichloromethane and dry methanol, 1 : 1) was stirred under argon for 24 h at room temperature. The Amberlite IR 120/H⁺ resin was then added, and this mixture was stirred until the pH became neutral. The mixture was filtered, and the resin was washed with a mixture of dichloromethane and methanol (1 : 1). The filtrate was then concentrated. The residue was purified by silica gel chromatography (dichloromethane : methanol, 15 : 1) to provide the title compound 4 (88.01 mg, 99.00%) as a white powder. The $R_f = 0.43$ (dichloromethane : methanol, 15 : 1); $[\alpha]_D = +50$ (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.20–7.30 (m, 10H, Ph), 5.16, 4.88 (dd, 2H, $J = 11.6$ Hz, CH₂Ph), 5.08 (d, 1H, $J_{1,2} = 3.52$ Hz, H₁), 4.88 (1H, OH), 4.65, 4.49 (dd, 2H, $J = 12.27$ Hz, CH₂Ph), 4.17–4.07 (m, 2H, H₃, H_{6a}), 3.96–3.90 (m, 1H, H₅), 3.78–3.67 (m, 2H, H₂, H_{6b}), 3.54 (dd, 1H, $J_{1,2} = 3.52$ Hz, $J_{2,3} = 9.81$ Hz, H₂). ¹³C-NMR (100 MHz, CDCl₃) δ 139.12 (C, Ph), 138.21 (C, Ph), 128.17 (CH, Ph), 127.98 (CH, Ph), 127.68 (CH, Ph), 127.46 (CH, Ph), 127.29 (CH, Ph), 126.95 (CH, Ph), 98.00 (C₁), 80.80 (C₃), 79.56 (C₄), 78.93 (C₂), 75.39 (CH₂Ph), 73.20 (C₅), 73.01 (CH₂Ph), 63.00 (C₆).

2.3. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-pentyl- (per-2,3-di-O-benzyl)-α-cyclodextrin (5e) and per-6-O-(pentyl-1)-per-2,3-di-O-benzyl-α-cyclodextrin (6e)

To a solution of 4 (51 mg, 0.02485 mmol) in 7 mL of dry DMF, was added 60% NaH (13.90 mg, 0.3479 mmol) under argon at room temperature, then 5-bromo-1-pentene (88.91 mg, 0.5964 mmol) was added. The mixture was stirred at room temperature until the starting product 4 had disappeared, and was then hydrolyzed by MeOH (7 mL) and evaporated. The residue was dissolved in dichloromethane. The organic phase was washed with saturated NaCl and water, dried over anhydrous magnesium sulfate, filtered, and then concentrated. The residue was purified by silica gel chromatography (cyclohexane : ethyl acetate, 5 : 1) to give the title compounds 5e (39.1 mg, 65.81%) and 6e (19.50 mg, 31.94%) as white powders.

5e. The $R_f = 0.18$ (cyclohexane/ethyl acetate, 5 : 1); $[\alpha]_D = +27.6$ (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.40–7.10 (m, 60H, Ph), 5.92–5.76 (m, 5H, 5 × CH=CH₂), 5.71 (d, 1H, $J_{1,2} = 3.86$ Hz, H₁), 5.67 (d, 1H, $J_{1,2} = 3.76$ Hz, H₁'), 5.53, 5.47 (dd, 2H, $J = 10.5$ Hz, CH₂Ph), 5.25 (dd, 2H, $J = 10.7$ Hz, CH₂Ph), 5.16 (d, $J_{1,2} = 3.48$ Hz, H₁), 5.08–4.97 (m, 2H, CH=CH₂), 4.57, 4.50 (dd, 2H, $J = 12.6$ Hz, CH₂Ph), 4.22–4.16 (m, 1H, H₅), 4.09–4.00 (m, 2H, H₄, H_{6a}), 3.98–3.92 (m, 1H, H₃), 3.60–3.50 (m, 3H, H₂, H_{6b}, H-(O-CH₂)), 3.43–3.36 (m, 1H, H-(O-CH₂')), 2.20–2.01 (m, 10H, CH₂-CH=CH₂), 1.78–1.63 (m, 10H, CH₂CH₂-CH=CH₂). ¹³C-NMR (100 MHz, CDCl₃) δ 139.41, 139.33, 139.29, 139.25, 139.16, 138.63, 138.49, 138.44, 138.22, 138.10, 137.96, (C, Ph), 138.16, 138.02, 137.93, 137.89 (CH=CH₂), 128.16–126.34 (CH, Ph), 114.88, 114.87, 114.84, 114.78, 114.71 (CH=CH₂), 98.87, 98.20, 98.14, 98.10, 98.09, 97.73 (C₁), 81.60, 81.49, 81.37, 81.19, 81.11, 80.89, 80.84, 80.68, 80.50, 80.20, 79.79, 79.60, 79.17, 79.05, 78.15, 77.69, 75.49, 74.28, 71.94, 71.83, 71.74, 71.41, 71.34, 71.10 (C₂, C₃, C₄, C₅), 76.32, 76.17, 76.00, 75.98, 74.15, 74.10, 73.31, 73.22, 73.12, 72.94, 72.35, 72.30, 71.56, 71.21, 71.01, 70.98, 61.05, 61.00 (CH₂Ph, O-CH₂, C₆). 30.28, 30.23, 30.19, 30.18, 30.16 (CH₂-CH=CH₂), 29.01, 28.84, 28.81, 28.60, 28.58 (CH₂CH₂-CH=CH₂). HRMS (MALDI-TOF, M + Na⁺) m/z calcd for C₁₄₅H₁₇₂O₃₀Na 2416.1826, found 2416.1944.

6e. The $R_f = 0.43$ (cyclohexane : ethyl acetate, 5 : 1); $[\alpha]_D = +25$ (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.30–7.20 (m, 10H, Ph), 5.89–5.78 (m, 1H, CH=CH₂), 5.24, 4.92 (dd, 2H, $J = 11.01$ Hz, CH₂Ph), 5.16 (d, 1H, $J_{1,2} = 3.48$ Hz, H₁), 5.08–4.97 (m, 2H, CH=CH₂), 4.57, 4.50 (2d, 2H, $J = 12.60$ Hz, CH₂Ph), 4.19 (dd, 1H, $J_{2,3} = 9.59$ Hz, $J_{3,4} = 8.34$ Hz, H₃), 4.09–4.00 (m, 2H, H₄, H_{6a}), 3.97–3.92 (m, 1H, H₅), 3.60–3.50 (m, 3H, H₂, H_{6b}, one of O-CH₂), 3.43–3.36 (m, 1H, one of O-CH₂'), 2.19–2.03 (m, 2H, CH₂-CH=CH₂), 1.73–1.66 (m, 2H, CH₂CH₂-CH=CH₂). ¹³C-NMR (100 MHz, CDCl₃) δ 139.38 (C, Ph), 138.37 (C, Ph), 138.01 (CH=CH₂), 128.13 (CH, Ph), 127.96 (CH, Ph), 127.74 (CH, Ph), 127.40 (CH, Ph), 127.24 (CH, Ph), 126.89 (CH, Ph), 114.79 (CH=CH₂), 98.60 (C₁), 81.09 (C₃), 79.18 (C₄), 78.99 (C₂), 75.52 (CH₂Ph), 72.77 (CH₂Ph), 71.39 (C₅), 71.08 (O-CH₂), 69.56 (C₆), 30.25 (CH₂-CH=CH₂), 28.86 (CH₂CH₂-CH=CH₂). HRMS (FAB⁺, M + Na⁺) m/z calcd for C₁₅₀H₁₈₀O₃₀Na 2484.2457, found 2484.2475.



2.4. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-pentyl- α -cyclodextrin (7e) and per-6-O-pentyl- α -cyclodextrin (8e)

To a solution of **5e** (61.01 mg, 0.02476 mmol) in a mixture of methanol/AcOH (1 : 1, 12 mL) was added Pd-C (10%, 42.10 mg), and the resulting mixture was then stirred under an atmosphere of H₂ for 12 h at room temperature. The results of the TLC (cyclohexane : ethyl acetate, 5 : 1) indicated that the starting product had disappeared. The catalyst was removed by filtration and was washed with a mixture of dichloromethane and methanol (1 : 1). The filtrate was then concentrated. The residue was purified by silica gel chromatography (dichloromethane : methanol, 8 : 1) to give the title compound **7e** (27.61 mg, 80.02%) as a white powder. The R_f = 0.54 (dichloromethane : methanol, 6 : 1); $[\alpha]_D$ = +66.7 (*c* 1, CHCl₃/MeOH, 7 : 3); ¹H-NMR (400 MHz, pyridine-*d*₅) δ 5.55 (d, 1H, $J_{1,2}$ = 3.1 Hz, H₁), 5.49 (d, 1H, $J_{1,2}$ = 3.1 Hz, H₁), 5.48–5.43 (m, 4H, 4 \times H₁), 4.74–4.62 (m, 6H, 6 \times H₃), 4.52–4.29 (m, 10H, H₂, H₄, 6 \times H₅, H_{6a}), 4.23–3.91 (m, 21H, 5 \times H₂, 5 \times H_{6a}, 6 \times H_{6b}, 5 \times H₄), 3.73–3.58 (m, 10H, 5 \times OCH₂), 1.75–1.58 (m, 10H, 5 \times CH₂-CH₂CH₂CH₃), 1.43–1.23 (m, 10H, 5 \times CH₂CH₃, 5 \times CH₂CH₂-CH₃), 0.90–0.82 (m, 15H, 5 \times CH₃). ¹³C-NMR (100 MHz, pyridine-*d*₅) δ 104.46, 104.28, 104.18 (C₁), 83.07, 83.92, 83.83, 83.69 (C₂), 75.59, 75.55 (C₃), 74.70, 74.62, 74.40, 74.51 (C₄), 73.09, 73.03 (C₅), 72.47, 72.44, 72.42, 72.37 (O-CH₂), 70.91, 70.86, 70.77, 70.74, 70.59, 62.04 (C₆), 30.57, 30.56 (CH₂CH₂-CH₂CH₃), 29.35, 29.31 (CH₂CH₂CH₃), 3.44 (CH₂CH₃), 14.86 (CH₃). HRMS (ESI-TOF, M - H⁻) m/z calcd for C₆₁H₁₀₉O₃₀ 1321.7004, found 1321.6957.

A similar method to that described for obtaining **7e**, was performed to give the title compound **8e** (81.10%) as a white powder. The R_f = 0.48 (dichloromethane : methanol, 8 : 1); $[\alpha]_D$ = +81.5 (*c* 0.7, CHCl₃ : methanol, 7 : 3); ¹H-NMR (400 MHz, pyridine-*d*₅) δ 5.46 (d, 1H, $J_{1,2}$ = 3.1 Hz, H₁), 5.18–5.02 (br, 2H, 2 \times OH), 4.65 (t, 1H, J = 9.14 Hz, H₃), 4.44–4.38 (m, 1H, H₅), 4.19–4.13 (m, 2H, H₄, H_{6a}), 4.11 (dd, 1H, $J_{1,2}$ = 3.10 Hz, $J_{2,3}$ = 9.70 Hz, H₂), 4.04–3.99 (m, 1H, H_{6b}), 3.72–3.66 (m, 2H, O-CH₂), 1.75–1.61 (m, 2H, CH₂CH₂CH₂CH₃), 1.44–1.27 (m, 4H, CH₂CH₃, CH₂CH₂CH₃), 0.87 (t, 1H, J = 7.2 Hz, CH₃). ¹³C-NMR (100 MHz, pyridine-*d*₅) δ 104.26 (C₁), 83.90 (C₄), 75.52 (C₃), 74.55 (C₂), 73.01 (C₅), 72.43 (O-CH₂), 70.79 (C₆), 30.55 (CH₂CH₂CH₂CH₃), 29.34 (CH₂CH₂CH₃), 23.42 (CH₂CH₃), 14.85 (CH₃). HRMS (ESI, M + Na⁺) m/z calcd for C₆₆H₁₂₀O₃₀Na 1415.7762, found: 1415.7760; HRMS (ESI, M + K⁺) m/z calcd for C₆₆H₁₂₀O₃₀K 1431.7502, found 1431.7544; HRMS (ESI, M + 2Na⁺) m/z calcd for C₆₆H₁₁₉O₃₀Na₂ 1437.7582, found 1437.7544.

2.5. Per-6-O-ethyl-2,3-di-O-benzyl- α -cyclodextrin (6a)

A similar method to that described for obtaining **6e**, was performed to give the title compound **6a** (80.50%) as a white powder. The R_f = 0.32 (cyclohexane/ethyl acetate, 5 : 1.5); $[\alpha]_D$ = +20.1 (*c* 1, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) δ 7.40–7.04 (m, 60H, Ph), 5.20, 4.89 (dd, 12H, J = 10.00 Hz, CH₂Ph), 5.04 (d, 6H, $J_{1,2}$ < 1 Hz, H₁), 4.50, 4.42 (2d, 12H, J = 10.00 Hz, CH₂Ph), 4.13 (dd, 6H, H₃), 3.63–3.56, 3.55–3.38 (m, 42H, H_{6a}, H₅, H₄, H_{6b}, H₂, O-CH₂), 1.14 (s, 18H, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ 139.46 (C, Ph), 138.41 (C, Ph), 128.06 (CH, Ph), 127.89 (CH, Ph), 127.79

(CH, Ph), 127.35 (CH, Ph), 127.12 (CH, Ph), 126.79 (CH, Ph), 98.97 (C₁), 80.99 (C₃), 79.80, 78.98 (C₂, C₄), 75.45 (CH₂Ph), 72.76 (CH₂Ph), 71.16 (O-CH₂), 69.34 (C₅), 66.56 (C₆), 15.13 (CH₃). HRMS (MALDI/TOF, M + Na⁺) m/z calcd for C₁₃₂H₁₅₆O₃₀Na 2244.0561, found 2244.0574.

2.6. Per-6-O-allyl-per-2,3-di-O-benzyl- α -cyclodextrin (6b)

A similar method to that described for obtaining **6e**, was performed to give the title compound **6b** (81.70%) as a white powder. The R_f = 0.27 (cyclohexane : ethyl acetate, 5 : 1); $[\alpha]_D$ = +36.6 (*c* 1, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) δ 7.42–7.05 (m, 10H, Ph), 5.97–5.77 (m, 1H, CH=CH₂), 5.20, 4.88 (dd, 2H, J = 11.08 Hz, CH₂Ph), 5.03 (d, 1H, $J_{1,2}$ = 2.92 Hz, H₁), 5.13–5.11 (m, 2H, CH=CH₂), 4.47, 4.41 (2d, 2H, J = 10.95 Hz, CH₂Ph), 4.17–3.43 (8H, H₃, H₄, H_{6a}, H₅, H_{6b}, O-CH₂, H₂), 1.26–0.82 (m, 2H, CH₂-CH=CH₂). ¹³C-NMR (125 MHz, CDCl₃) δ 139.44 (C, Ph), 138.37 (C, Ph), 134.87 (CH=CH₂), 128.10 (CH, Ph), 127.92 (CH, Ph), 127.83 (CH, Ph), 127.39 (CH, Ph), 127.16 (CH, Ph), 126.84 (CH, Ph), 117.85 (CH=CH₂), 99.00 (C₁), 80.91 (C₃), 79.75 (C₄), 78.91 (C₂), 75.49 (CH₂Ph), 72.74 (CH₂Ph), 72.30 (O-CH₂), 71.29 (C₅), 69.05 (C₆). HRMS (MALDI/DHB, M + Na⁺) m/z calcd for C₁₃₈H₁₅₆O₃₀Na 2316.0574, found 2316.0574.

2.7. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-propyl-(per-2,3-di-O-benzyl)- α -cyclodextrin (5c) and per-6-O-propyl-2,3-di-O-benzyl- α -cyclodextrin (6c)

A similar method to that described for obtaining **5e** was performed to give the title compound **5c** (60.40%) as a white powder. The R_f = 0.15 (cyclohexane : ethyl acetate, 5 : 1); $[\alpha]_D$ = +21.2 (*c* 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.37–7.05 (m, 60H, Ph), 5.64 (m 1H, H₁), 5.67 (m 1H, H_{1'}), 5.48, 5.42 (dd, 2H, J = 9.71 Hz, CH₂Ph), 5.23, 5.18 (dd, 2H, J = 11.05 Hz, CH₂Ph), 4.95–4.70, 4.58–4.30, 4.28–3.24 (m, 70H, H₁, CH₂Ph, H₅, H₄, H_{6a}, H₃, H₂, H_{6b}, O-CH₂), 1.60–1.26 (m, 10H, -CH₂-), 0.96–0.81 (m, 15H, -CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 139.47, 139.38, 139.36, 139.34, 139.29, 139.21, 138.71, 138.54, 138.50, 138.25, 138.16, 137.99 (C, Ph), 128.33–126.34 (CH, Ph), 98.97, 98.27, 98.16, 98.11, 98.06, 97.73 (C₁), 81.70, 81.51, 81.33, 81.20, 80.95, 80.90, 80.71, 80.64, 80.22, 79.85, 79.67, 79.18, 79.02, 78.15, 77.72, 77.20, 76.35, 76.18, 76.02, 76.00, 75.67, 74.07, 74.04, 73.86, 73.39, 73.32, 73.23, 73.18, 73.11, 72.92, 72.34, 72.29, 71.94, 71.89, 71.75, 71.39, 70.99, 70.49, 69.99, 69.60, 69.43, 60.73 (C₂, C₃, C₄, C₅, CH₂Ph, O-CH₂, C₆), 22.96, 22.85, 22.76, 22.65, 22.56 (-OCH₂CH₃), 10.64–10.38 (-CH₃). HRMS (MALDI/DHB, M + Na⁺) m/z calcd for C₁₃₅H₁₆₂O₃₀Na 2286.1045, found 2286.1043.

A similar method as that described for obtaining **6e**, was performed to give the title compound **6c** (33.73%) as a white powder. The R_f = 0.44 (cyclohexane : ethyl acetate, 5 : 1); $[\alpha]_D$ = +18.3 (*c* 1, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) δ 7.36–7.06 (m, 10H, Ph), 5.19, 4.87 (dd, 2H, J = 10.00 Hz, CH₂Ph), 5.10 (d, 1H, $J_{1,2}$ = 3.15 Hz, H₁), 4.47, 4.44 (dd, 2H, J = 10.00 Hz, CH₂Ph), 4.14 (dd, 1H, $J_{2,3}$ = 10.10 Hz, $J_{3,4}$ = 8.56 Hz, H₃), 4.03–3.88 (m, 3H, H₄, H₅, H_{6a}), 3.61–3.27 (m, 4H, H_{6b}, H₂, O-CH₂), 1.33–1.19 (m, 2H, CH₂), 0.92–0.81 (m, 3H, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ 139.43 (C, Ph), 138.38 (C, Ph), 128.06 (CH, Ph), 127.90 (CH,

Ph), 127.72 (CH, Ph), 127.32 (CH, Ph), 127.19 (CH, Ph), 126.81 (CH, Ph), 98.75 (C₁), 81.05 (C₃), 79.49, 79.02 (C₄, C₂), 75.46 (CH₂Ph), 73.21 (CH₂Ph), 72.72 (O-CH₂), 71.40 (C₅), 69.48 (C₆), 29.63, (OCH₂-CH₂), 10.54 (CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₃₈H₁₆₈O₃₀Na 2328.1473, found 2328.1513.

2.8. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-butyl-(per-2,3-di-O-benzyl)- α -cyclodextrin (5d) and per-6-O-butyl-2,3-di-O-benzyl- α -cyclodextrin (6d)

A similar method as that described for obtaining 5e, was performed to give the title compound 5d (51.88%) as a white powder. The *R_f* = 0.29 (cyclohexane : ethyl acetate, 5 : 1); [α]_D = +19.5 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.46–6.98 (m, 60H, Ph), 5.66 (d, 1H, *J*_{1,2} = 3.36 Hz, H₁), 5.62 (d, 1H, *J*_{1,2} = 3.36 Hz, H_{1'}), 5.47, 5.41 (dd, 2H, *J* = 9.86 Hz, CH₂Ph), 5.21, 5.17 (dd, 2H, *J* = 10.05 Hz, CH₂Ph), 4.94–4.64, 4.59–4.27, 4.25–3.32 (m, 70H, H₁, CH₂Ph, H₅, H₄, H_{6a}, H₃, H₂, H_{6b}, O-CH₂), 1.65–1.20 (m, 20H, -CH₂CH₂-), 0.95–0.83 (m, 15H, -CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 139.48, 139.40, 139.36, 139.33, 139.23, 138.69, 138.55, 138.51, 138.28, 138.18, 138.03 (C, Ph), 128.31–126.36 (CH, Ph), 98.90, 98.86, 98.20, 98.10, 97.83, 97.77 (C₁), 81.65, 81.55, 81.47, 81.22, 81.11, 80.95, 80.92, 80.75, 80.56, 80.17, 79.88, 79.71, 79.24, 79.12, 78.23, 77.80, 76.29, 76.14, 76.01, 75.96, 75.69, 75.64, 74.35, 74.13, 74.07, 73.30, 73.22, 73.10, 72.90, 72.36, 72.28, 71.95, 71.88, 71.78, 71.61, 71.45, 71.37, 71.33, 71.19, 71.08, 70.54, 69.92, 69.67, 69.50, 69.46, 60.94 (C₂, C₃, C₄, C₅, CH₂Ph, O-CH₂, C₆), 31.92–31.49, 29.67, 19.39–19.15 (-OCH₂-CH₂CH₂-), 14.03–13.84 (-CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₄₀H₁₇₂O₃₀Na 2356.1793, found: 2356.1826.

A similar method to that described for obtaining 6e, was performed to give the title compound 6d (35.37%) as a white powder. The *R_f* = 0.52 (cyclohexane : ethyl acetate, 5 : 1); [α]_D = +21.6 (c 1, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) δ 7.24–7.11 (m, 10H, Ph), 5.18, 4.87 (dd, 2H, *J* = 10.97 Hz, CH₂Ph), 5.12 (d, 1H, *J*_{1,2} = 3.15 Hz, H₁), 4.52, 4.45 (2d, 2H, *J* = 8.93 Hz, CH₂Ph), 4.16–4.10 (m, 1H, H₃), 4.02–3.97, 3.92–3.88, 3.56–3.44, 3.39–3.32 (m, 7H, H₄, H₅, H₂, H_{6a}, H_{6b}, O-CH₂), 1.34–1.18 (m, 4H, CH₂-CH₂), 0.96–0.78 (m, 3H, CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ 139.43 (C, Ph), 138.38 (C, Ph), 128.06 (CH, Ph), 127.90 (CH, Ph), 127.72 (CH, Ph), 127.32 (CH, Ph), 127.19 (CH, Ph), 126.81 (CH, Ph), 98.83 (C₁), 81.05 (C₃), 79.49, 79.02 (C₄, C₂), 75.46 (CH₂Ph), 73.21 (CH₂Ph), 72.72 (O-CH₂), 71.40 (C₅), 69.48 (C₆), 29.63, 22.80 (CH₂-CH₂), 10.51 (CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₄₄H₁₈₀O₃₀Na 2412.2493, found: 2412.2452.

2.9. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-pentyl-(per-2,3-di-O-benzyl)- α -cyclodextrin (5f) and per-6-O-pentyl-2,3-di-O-benzyl- α -cyclodextrin (6f)

A similar method to that described for obtaining 5e, was performed to give the title compound 5f (71.68%) as a white powder. The *R_f* = 0.32 (cyclohexane : ethyl acetate, 5 : 1); [α]_D = +18.2 (c 1, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) δ 7.51–6.86 (m, 60H, Ph), 5.67 (d, 1H, *J*_{1,2} = 2.58 Hz, H₁), 5.64 (d, 1H, *J*_{1,2} = 3.86 Hz, H_{1'}), 5.48, 5.41 (dd, 2H, *J* = 12.44 Hz, CH₂Ph), 5.21, 5.17 (dd, 2H, *J* = 10.72 Hz, CH₂Ph), 4.94–4.64, 4.59–4.27, 4.25–3.32 (m, 70H, H₁, CH₂Ph, H₅, H₄, H_{6a}, H₃, H₂, H_{6b}, O-CH₂), 1.60–

1.20 (m, 30H, -CH₂CH₂-), 0.95–0.82 (m, 15H, -CH₃). ¹³C-NMR (125 MHz, CDCl₃) δ 139.40, 139.36, 139.26, 139.16, 138.64, 138.49, 138.44, 138.22, 138.11, 137.36 (C, Ph), 128.62–126.29 (CH, Ph) 98.75, 98.03, 98.01, 97.96, 97.71, 97.66 (C₁), 81.56, 81.42, 81.20, 81.10, 81.06, 80.88, 80.67, 80.47, 80.42, 80.07, 79.92, 79.86, 79.66, 79.15, 79.10, 79.02, 78.94, 78.12, 77.68, 76.32, 76.17, 76.03, 75.97, 75.14, 74.05, 73.99, 73.29, 73.19, 73.07, 72.86, 72.32, 72.21, 71.92, 71.88, 71.82, 71.66, 71.51, 71.37, 71.28, 70.97, 70.48, 69.78, 69.58, 69.43, 60.84 (C₂, C₃, C₄, C₅, CH₂Ph, O-CH₂, C₆), 29.63, 28.13, 22.47 (-OCH₂-CH₂-CH₂-CH₂-), 14.00 (-CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₄₅H₁₈₂O₃₀Na 2426.2603, found 2426.2608.

A similar method to that described for obtaining 6e, was performed to give the title compound 6f (24.32%) as a white powder. The *R_f* = 0.56 (cyclohexane : ethyl acetate, 5 : 1); [α]_D = +16.0 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.25–7.10 (m, 10H, Ph), 5.17, 4.86 (dd, 2H, *J* = 11.01 Hz, CH₂Ph), 5.13 (d, 1H, *J*_{1,2} = 3.22 Hz, H₁), 4.52, 4.45 (2d, 2H, *J* = 12.17 Hz, CH₂Ph), 4.18–4.09 (m, 1H, H₃), 4.04–3.97 (m, 2H, H_{6a}, H₄), 3.92–3.87 (m, 1H, H₅), 3.56–3.43 (m, 3H, H_{6b}, H₂, one of O-CH₂), 3.37–3.30 (m, 1H, one of O-CH₂), 1.60–1.50 (m, 2H, OCH₂-CH₂), 1.36–1.19 (m, 4H, -CH₂-CH₂), 0.90–0.84 (m, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 139.38 (C, Ph), 138.39 (C, Ph), 128.10 (CH, Ph), 127.93 (CH, Ph), 127.70 (CH, Ph), 127.35 (CH, Ph), 127.25 (CH, Ph), 126.86 (CH, Ph), 98.35 (C₁), 81.13 (C₃), 79.05, 78.99 (C₄, C₂), 75.48 (CH₂Ph), 72.73 (CH₂Ph), 71.79 (O-CH₂), 71.34 (C₅), 69.50 (C₆), 29.37, 28.22, 22.50 (CH₂-CH₂-CH₂), 14.00 (CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₅₀H₁₉₂O₃₀Na 2496.3388, found 2496.3391.

2.10. 6^I-O-Hydroxyl-6^{II-VI}-penta-O-hexyl-(per-2,3-di-O-benzyl)- α -cyclodextrin (5g) and per-6-O-butyl-2,3-di-O-benzyl- α -cyclodextrin (6g)

A similar method to that described for obtaining 5e, was performed to give the title compound 5g (45.68%) as a white powder. The *R_f* = 0.35 (cyclohexane : ethyl acetate, 5 : 1); [α]_D = +22.2 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δ 7.40–6.97 (m, 60H, Ph), 5.67 (d, 1H, *J*_{1,2} = 4.00 Hz, H₁), 5.64 (d, 1H, *J*_{1,2} = 4.00 Hz, H_{1'}), 5.48, 5.41 (dd, 2H, *J* = 12 Hz, *J* = 8 Hz, CH₂Ph), 5.21, 5.17 (dd, 2H, *J* = 12.00 Hz, CH₂Ph), 4.95–4.70, 4.59–4.30, 4.25–3.28 (m, 70H, H₁, CH₂Ph, H₅, H₄, H_{6a}, H₃, H₂, H_{6b}, O-CH₂), 1.63–1.47, 1.36–1.20 (m, 40H, -CH₂CH₂CH₂CH₂-), 0.92–0.82 (m, 15H, -CH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 139.41, 139.30, 139.27, 139.17, 138.64, 138.49, 138.43, 138.22, 138.11, 137.96 (C, Ph), 128.27–126.29 (CH, Ph), 98.74, 98.04–97.96, 97.64 (C₁), 81.60, 81.55, 81.41, 81.19, 81.06, 80.88, 80.67, 80.42, 80.06, 79.90, 79.68, 79.14, 79.10, 78.13, 77.70, 77.18, 76.28, 76.16, 76.01, 75.93, 75.16, 74.05, 74.00, 73.29, 73.19, 73.06, 72.86, 72.37, 72.29, 72.22, 71.93, 71.88, 71.91, 71.70, 71.36, 71.30, 70.97, 70.49, 69.81, 69.60, 69.42, 60.84 (C₂, C₃, C₄, C₅, CH₂Ph, O-CH₂, C₆), 31.84–31.56, 29.81–29.31, 25.75–25.63, 22.56 (-CH₂CH₂CH₂CH₂CH₂-), 14.00 (-CH₃). HRMS (MALDI/DHB, M + Na⁺) *m/z* calcd for C₁₅₀H₁₉₂O₃₀Na 2496.3432, found 2496.3391.

A similar method to that described for obtaining 6e, was performed to give the title compound 6g (34.32%) as a white



Table 1 Optimization of regioselective substitution for compound **4** with 5-bromo-1-pentene

Entry	Reaction ratio (mol)		Yield (%)	
	4 : NaH : 5-bromo-1-pentene		5e	6e
1	1 : 12 : 10		6.08	91.28
2	1 : 12 : 12		7.00	90.00
3	1 : 12 : 14		20.00	73.80
4	1 : 12 : 16		32.00	61.30
5	1 : 12 : 18		40.00	56.78
6	1 : 12 : 20		56.28	40.90
7	1 : 12 : 30		50.24	47.05
8	1 : 14 : 24		65.81	31.94
9	1 : 14 : 18		62.93	30.07
10	1 : 16 : 12		5.00	91.00

Table 2 Yields of regioselective 6-substituted α -CDs (compound **4** with diverse RBr^a)

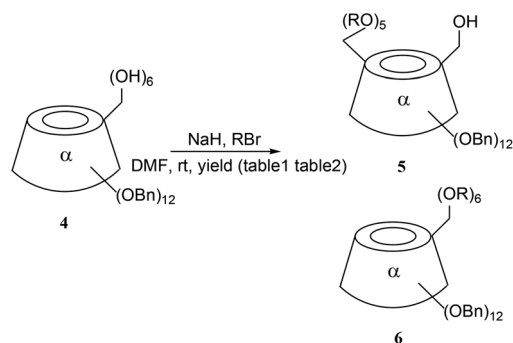
Entry	Yield (%)		
	RBr	5	6
1	$-\text{CH}_2\text{CH}_3$	0	6a 80.50
2	$-\text{CH}_2\text{CH}=\text{CH}_2$	0	6b 81.70
3	$-\text{CH}_2\text{CH}_2\text{CH}_3$	5c 60.40	6c 33.73
4	$-(\text{CH}_2)_3\text{CH}_3$	5d 51.88	6d 35.37
5	$-(\text{CH}_2)_3\text{CH}=\text{CH}_2$	5e 65.81	6e 31.94
6	$-(\text{CH}_2)_4\text{CH}_3$	5f 71.68	6f 24.32
7	$-(\text{CH}_2)_5\text{CH}_3$	5g 45.68	6g 34.32

^a Reaction ratio (mol): **4** : NaH : RBr = 1 : 14 : 24.

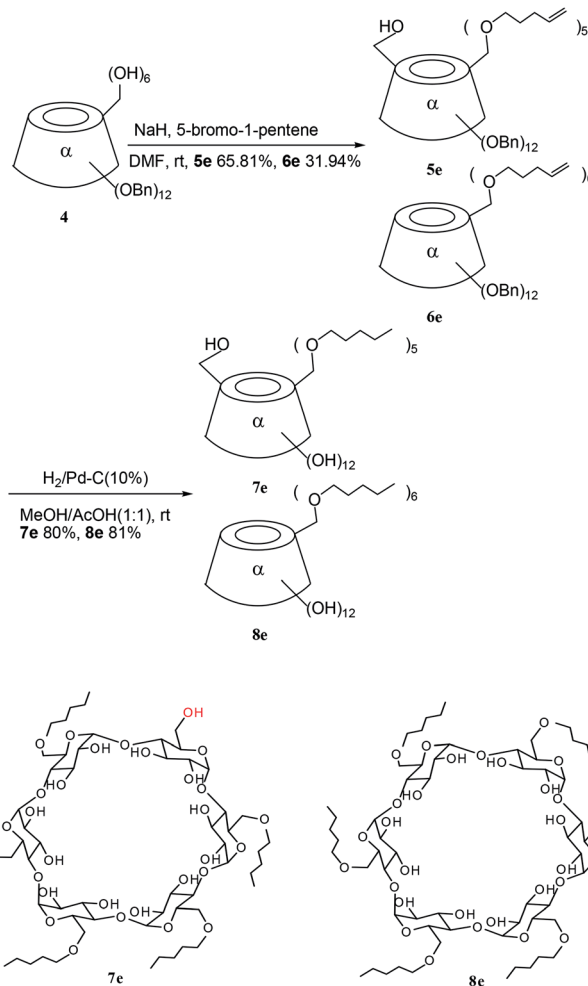
powder. The R_f = 0.64 (cyclohexane : ethyl acetate, 5 : 1); $[\alpha]_D^{25} = +30.2$ (c 1, CHCl_3); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.27–7.07 (m, 10H, Ph), 5.17, 4.86 (dd, 2H, J = 12.61 Hz, CH_2Ph), 5.15 (d, 1H, $J_{1,2}$ = 3.34 Hz, H_1), 4.48 (2d, 2H, J = 12.61 Hz, CH_2Ph), 4.13 (t, 1H, J = 9.00 Hz, H_3), 4.04–3.95 (m, 2H, H_4 , H_{6a}), 3.93–3.86 (m, 1H, H_5), 3.56–3.41 (m, 3H, H_{6b} , H_2 , one of O-CH_2), 3.37–3.28 (m, 1H, one of O-CH_2), 1.58–1.49 (m, 2H, $\text{OCH}_2\text{-CH}_2$), 1.36–1.20 (m, 6H, $-\text{CH}_2\text{-CH}_2\text{-CH}_2-$), 0.89–0.85 (m, 3H, CH_3). ^{13}C (100 MHz, CDCl_3) δ 139.40 (C, Ph), 138.41 (C, Ph), 128.10 (CH, Ph), 127.94 (CH, Ph), 127.70 (CH, Ph), 127.35 (CH, Ph), 127.25 (CH, Ph), 126.86 (CH, Ph), 98.42 (C_1), 81.15 (C_3), 79.07, 78.98 (C_4 , C_2), 75.48 (CH_2Ph), 72.74 (CH_2Ph), 71.85 (O-CH_2), 71.34 (C_5), 69.52 (C_6), 31.73, 29.68, 25.79, 22.61 ($\text{OCH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$), 14.05 (CH_3). HRMS (MALDI/DHB, $\text{M} + \text{Na}^+$) m/z calcd for $\text{C}_{156}\text{H}_{204}\text{O}_{30}\text{Na}$ 2580.4328, found 2580.4330.

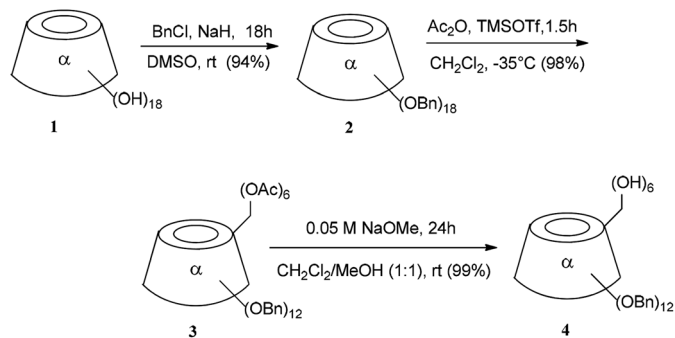
3. Results and discussion

This involved phenomenon caught in our previous research on cyclodextrins.^{8,20} This study was performed by using compound **4**, which was synthesized from native α -CD according to a method the literature, as the starting material (Scheme 3).¹⁴ In



- 6a:** R = $-\text{CH}_2\text{CH}_3$
6b: R = $-\text{CH}_2\text{CH}=\text{CH}_2$
5c, 6c: R = $-\text{CH}_2\text{CH}_2\text{CH}_3$
5d, 6d: R = $-(\text{CH}_2)_3\text{CH}_3$
5e, 6e: R = $-(\text{CH}_2)_3\text{CH}=\text{CH}_2$
5f, 6f: R = $-(\text{CH}_2)_4\text{CH}_3$
5g, 6g: R = $-(\text{CH}_2)_5\text{CH}_3$

Scheme 1 Diverse RBr induced outcomes of 6-substituted α -CDs.**Scheme 2** Reaction of pentenyl α -CD derivatives.

Scheme 3 Synthesis of α -CD derivative 4.

this nucleophilic substitution, NaH promoted the deprotonation of CD hydroxyl groups for nucleophilic agent formation, or reacts with the bromine ion of RBr. The RBr forms carbon cations for use as electrophiles.

Firstly, 5-bromo-1-pentene was chosen for alkylation on the primary face of α -CD derivative 4 because pentenyl has terminal double bond, which can then form cyclodextrin dimers and oligomers or perform click reactions, or be converted into other groups (Scheme 2). When compound 4 was treated with 5-bromo-1-pentene in the presence of NaH at a ratio of 4 : NaH : 5-bromo-1-pentene = 1 : 12 : 10, 6-hexa-*O*-pentenyl α -CD 6e was obtained as the major product (91%), and 6-hydroxyl-6-penta-*O*-pentenyl α -CD 5e was isolated as a minor product

(6%, Table 1, entry 1). When the amounts of 5-bromo-1-pentene were increased, the yield of mono hydroxyl α -CD derivative 5e increased up to 66% (Table 1, entry 8) whereas the complete alkylation of α -CD 6e decreased. However, only the amount of NaH was increased singly, that not leading to the yield of 5e improved (Table 1, entries 2 and 10). It seemed that a balance between the amount of NaH and 5-bromo-1-pentene existing. The ratio (4 : NaH : RBr = 1 : 14 : 24) was found from the experiments to be beneficial for obtaining 5e.

After accidentally discovering this phenomenon, we were very curious about whether other alkyl bromides caused the same selections. Next a variety of alkyl bromides were used, instead of 5-bromo-1-pentene, to perform a similar alkylation on the primary face of α -CD derivative 4 (Scheme 1).

When bromoethane or 3-bromopropene were used, only the complete alkylation of α -CDs 6a, 6b were found even under the conditions of 4 : NaH : RBr = 1 : 14 : 24 (Table 2, entries 1 and 2). In the other reactions involved, similar phenomena were observed as when 5-bromo-1-pentene was used. In particular when the ratio of 4 : NaH : RBr was 1 : 14 : 24, some mono hydroxyl α -CD derivatives could be obtained as major compounds, the highest yield (72%) being obtained for 5f (Table 2, entry 6).

The pentenyl α -CD derivatives 5e and 6e were hydrogenated with hydrogen catalyzed by Pd-C (10%) at 14 kPa to give 7e and 8e for further amphiphilic study (Scheme 2). The hydroxyl group existing in 5e and 7e could also be modified for use in CD applications.

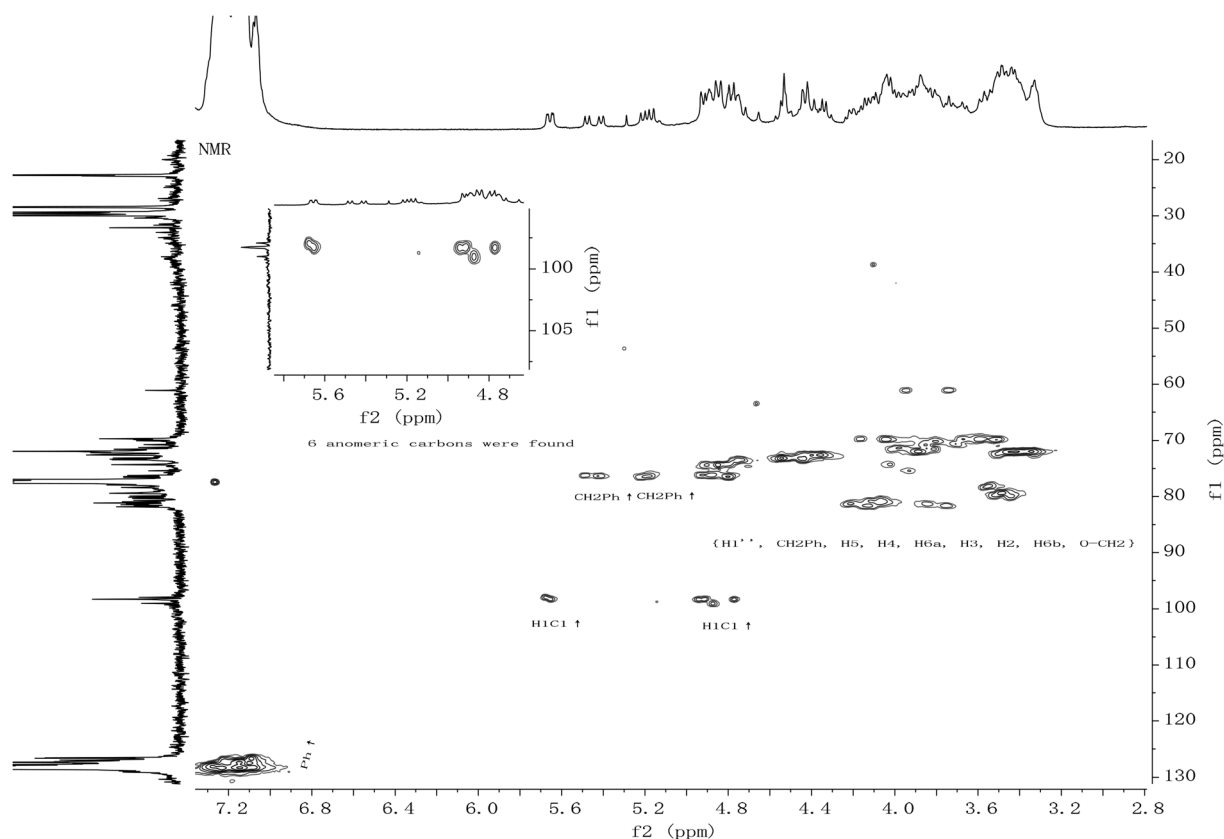


Fig. 1 The heteronuclear multiple quantum interference coherence (HMQC) of compound 5f.



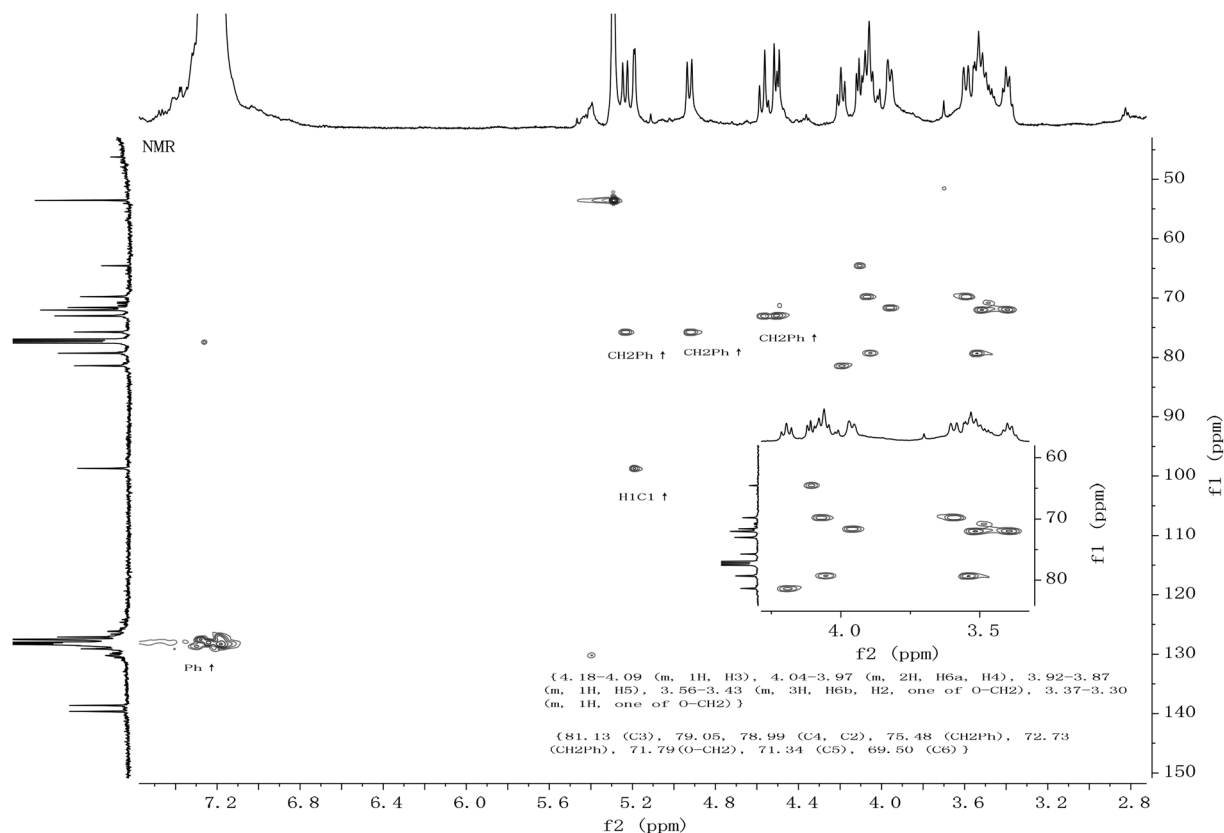


Fig. 2 The HMQC of compound 6f.

All the new synthetic compounds **5c**, **5d**, **5f**, **5g**, **6a**, **6b**, **6c**, **6d**, **6f**, **6g** and **5e**, **6e**, **7e**, **8e** were characterized by ^1H -NMR and ^{13}C -NMR, as well as HRMS (see ESI †). It can be seen from the NMR spectra that the hydroxyl on the CDDs (**5c**, **5d**, **5e**, **5f**, **5g**, **7e**) made the molecules asymmetric (Fig. 1), from their ^{13}C -NMR 6 anomeric carbons were found, whereas the 6-per alkyl CDDs (**6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g**, **8e**) were symmetric because the NMR spectra look like those of monosaccharides (Fig. 2). In a paper from 1991, Angibeaud and Utille¹⁹, assigned 79.00 to C_4 , 80.80 to C_2 . In fact, the ^1H - ^{13}C correlation spectrum indicated that C_2 should be at 79.00, and C_4 80.80 (in this case C_2 at 78.93 and C_4 at 79.56). Moreover, C_3 was not assigned at all in ref. 19.

For the mechanism, it was speculated that there were two interfering factors, the concentration of alkali in the system and the steric effects of the electrophilic reagent RBr. When the RBr amount increased, the NaH concentration decreased and the ratio of the **4** : NaH : RBr arrived at a certain value, fewer NaH in the system would lose deprotonation capacity to one of the hydroxyl groups of compound **4** leading to weakening of its nucleophilic attack. Therefore, the regioselective products accounted for a certain yield. The steric hindrance also affected the regioselective reaction. It can be seen from the short chain RBr bromoethane or 3-bromopropene that even if the ratio of **4** : NaH : RBr was adjusted no regioselective product was obtained.

4. Conclusion

In summary, we have achieved 6-hydroxyl and penta-alkyl on primary face of α -cyclodextrin in one pot. It seems that the mono 6-hydroxyl α -cyclodextrin derivatives would be difficult to obtain directly through a traditional thought. Even though the exact mechanism is still unclear, the regioselective modifications described previously minimized the reagents required, the labor, the time, and facilitated the availability of a variety of selectively modified α -CDs on the primary face which will be useful for cross-disciplinary researchers. The novel molecule **5e** has two reactive points, hydroxyl and pentenyl groups, which can be further used for research in supramolecular chemistry, biological materials, drug delivery, and so on. In our unpublished data, we are exploring the derivatization on two reactive points for further applications.

Conflicts of interest

There are no conflicts to declare.

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