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γ-Cyclodextrins possessing an azido group and a triisopropylbenzenesulfonyl group as useful synthetic and authentic intermediates for unsymmetrically functionalized derivatives

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ABSTRACT

Seven isomers of cyclomaltooctaose (γ-cyclodextrin) whose C6s were unsymmetrically disubstituted with both an azido group and an arenesulfonyloxy group were prepared and each of them was isolated by reversed phase chromatography. The assignment of the modified positions in each regioisomers was unambiguously performed by chemical correlation with the authentic compounds and chemical conversion to the 3,6-anhydro derivatives followed by high-resolution 2D-^{1}H NMR (COSY, TOCSY, and HOHAHA) analyses. The compounds are versatile synthetic and authentic intermediates to prepare sophisticated derivatives with two different functionalities at desired positions on the molecule for supramolecular chemistry.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucoses. The most common species are known as cyclomaltohexaose (α-CD), cyclomaltoheptaose (β-CD), and cyclomaltooctaose (γ-CD), respectively. The natural CDs are of interest because of their ability to include a guest molecule into their cavity. In addition, the CDs serve as scaffolds on which functional groups can be assembled through chemical modification. Actually, bifunctionalized CDs have proved to be promising candidates to perform sophisticated enzyme-like activities[1] and an exquisite guest chirality recognition.[2] On view point of expressing a desired function it must be most important to arrange the two functional groups systematically on a CD molecule. The CDs composed of six-to-eight glucose residues possess doughnut-like annular structures with wide and narrow hydrophilic ends delineated by secondary 2-OH and 3-OH and primary 6-OH groups, respectively. The 6-OHs exist in every ca. 0.5 nm on the narrow side (ca. 1 nm diameter) of CD molecule as shown in Figure 1. Arrangement of two different functional groups on the primary hydroxyl side of α-, β-, and γ-CD has five, six, and seven patterns and, therefore, generates five, six, and seven regioisomers, respectively. Six regioisomers of unsymmetrically modified β-CDs were prepared.[3] Recently, Sollogoub reported a regiospecific tandem reaction on β-CD to afford two regioisomeric (AD and AC) amino alcohol-difunctionalized derivatives.[4] In the case of γ-CD, Fujita prepared two (AB and AG) among seven regioisomers of derivatives whose C6s were bifunctionalized by a tosyloxy group and a cysteinyl group.[5a] Hamada reported the γ-CD derivatives possessing a tosyloxy group and a dansylamino group on the C6s expressed unique fluorescent chemo-sensor ability and their sensitivity and selectivity depended on the substituents positions, although the used CDs were diastereomeric mixtures unfortunately.[5b] There have been no reports on complete sets of seven γ-CD regioisomers. It seems reasonable that the seven regioisomeric γ-CDs must enable more sophisticated molecular interaction such as chiral recognition by cooperation of both the different functional moieties regiospecifically situated on the CDs. Here we will report a complete set of seven regioisomers of γ-CD derivatives possessing an azido group and a sulfonyloxy group on its primary hydroxyl side. The azido group can be converted to an amino group reductively or to a functional moiety through a triazine ring formation by click chemistry[6] and the sulfonyloxy group can be easily substituted by a nucleophile. Therefore, the isomers are expected to be useful as authentic regioisomers and synthetic intermediates for novel unsymmetrically bifunctional γ-CD derivatives on which the two substituents are systematically arranged on the nanoplane with a desired distance.

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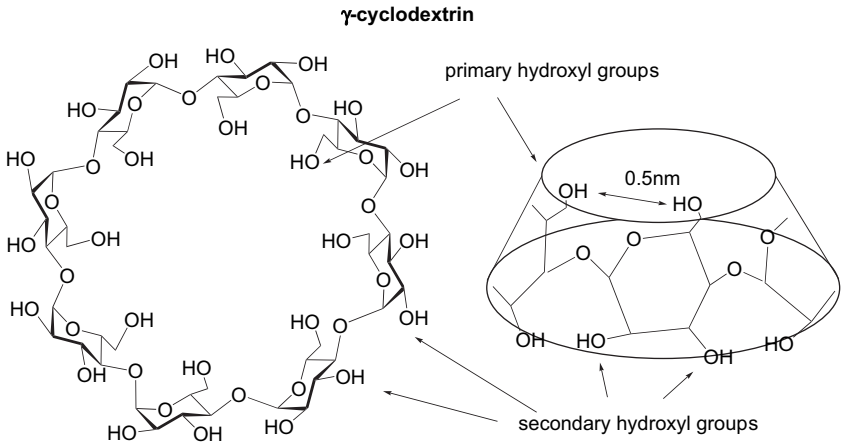
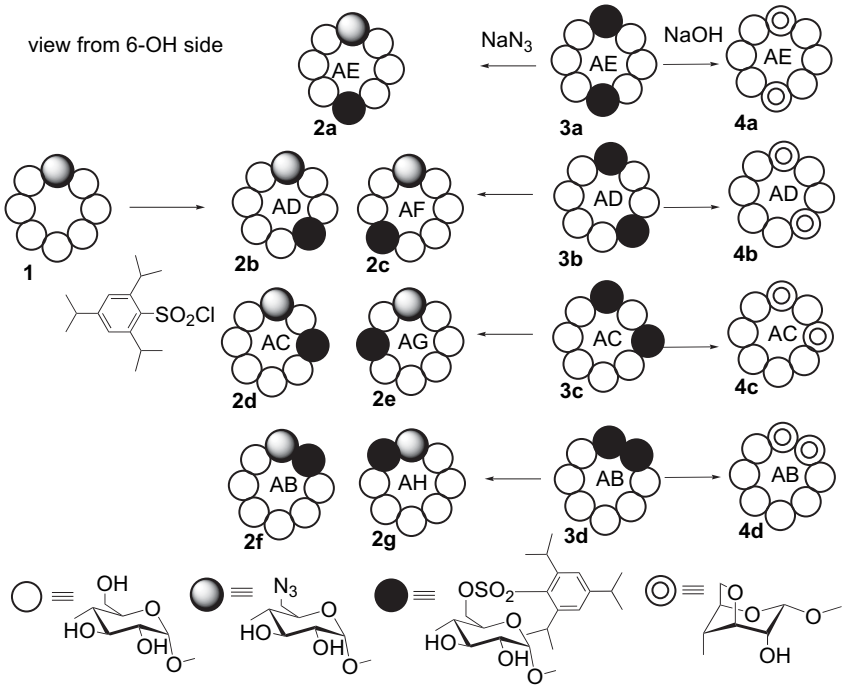


Figure 1. Structure of γ-cyclodextrin.

2. Results and discussion

Each of CD molecules, α-, β-, and γ-CD, generally affords a 6-*O*-sulfonate by reaction in pyridine with the corresponding arenesulfonyl chloride.[7] In the case of a γ-CD derivative **1** whose 6-OH is substituted with an azido group[8] additional sulfonylation of its 6-OH gives seven regioisomers (AB–AH) **2a**–**2g** (Scheme 1). It seems that the most efficient method to separate the seven isomers is reversed phase column chromatography.[9] Here we can optimize the separation of the regioisomers by changing the aryl groups as it was demonstrated in the case of polyarenesulfonylated CDs.[9] On this view point an arenesulfonyloxy group as a leaving group for nucleophilic substitution seems superior to a halo group because difference among Cl, Br, and I is too small to cause enough affinity change to column stationary phase to ensure the separation of the regioisomers from each other. Therefore, we surveyed by use of RP-HPLC on the arenesulfonyl groups to find out the one that gave the optimal separation of azido-arenesulfonyl CDs. γ-CD was reacted with sulfonyl chloride possessing mesityl, 1- and 2-naphtyl, 2,4,6-triisopropylphenyl groups and the reaction products were analyzed by RP-HPLC, demonstrating that the last aryl group enabled the optimal separation (Fig. 2). It should be noted here that a 2,4,6-triisopropylbezenenesulfonyl (Tips) group was superior to a mesitylenesulfonyl group that was used in the previous polyarenesulfonylated CDs studies.[9] In my opinion a bulkier Tips group may make each of the seven regioisomers form a unique molecular structure with unique affinity to column stationary phase, enabling good separation from each other. However the steric hindrance of the Tips group gave significant disadvantages to the reaction. The reaction proceeded very slowly and more amounts of the sulfonyl chloride (20 times that of γ-CD) and longer reaction time (two times longer than those by other sulfonyl chloride) were necessary. In order to overcome the problem we adopted zinc bromide as an additive to promote the sulfonylation.[10] In the presence of zinc bromide (2.6 times that of γ-CD) 6-azido-γ-CD **1** was reacted with Tips chloride (2.5 times) for 40 min to give the desired derivatives **2a**–**2g**. The reaction mixture was applied to low-pressure column chromatography using an ODS column to get three mixtures of



Scheme 1.

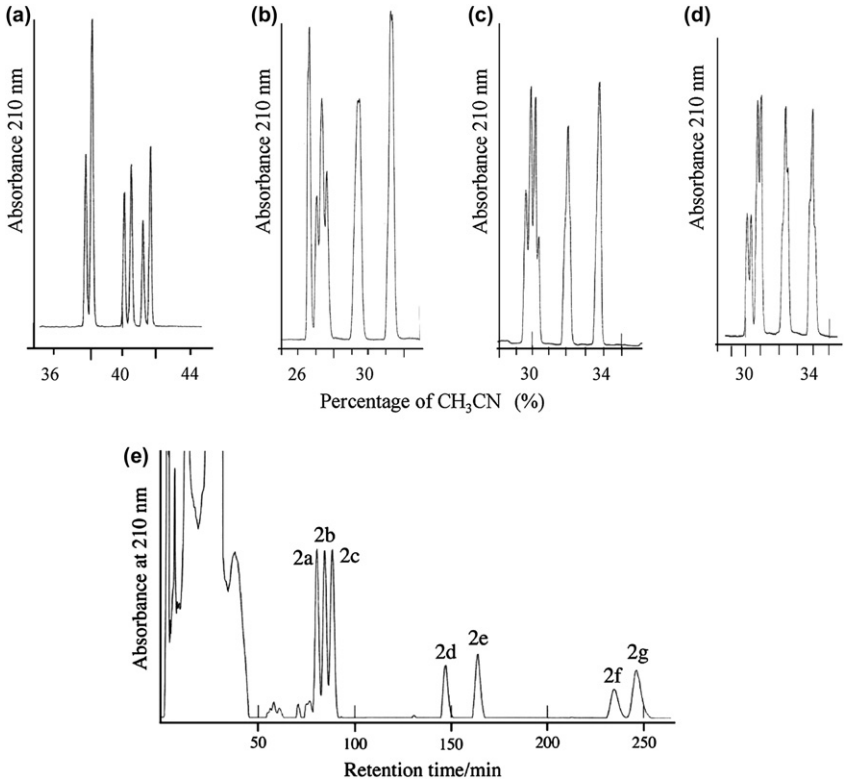
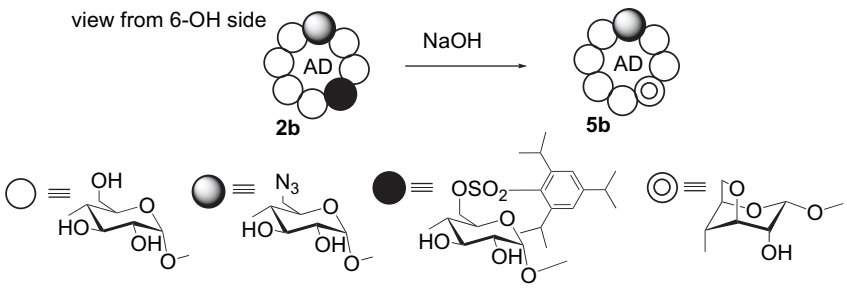


Figure 2. RP-HPLC of reaction products of γ-CD with sulfonyl chloride possessing (a) mesityl, (b) 1- and (c) 2-naphtyl, (d) and (e) 2,3,4-triisopropylphenyl groups. Conditions were as follows: column:ODS-M80 (250×4.6 mm, YMC), flow rate: 1.0 mL/min, eluent: (a) 20–50% aq MeCN (30 min); (b)–(d) 10–40% aq MeCN (30 min); (e) 24% aq MeCN. Regioisomers of azido-Tips-γ-CDs **2a**–**2g** were shown on (e).

seven isomers, namely that of **2a**–**2c**, **2d**–**2e**, and **2f**–**2g**. Each of the mixtures was applied to preparative ODS-HPLC to isolate each regioisomer. Total isolated yields of the isomers **2a**–**2g** were 3.9%, 3.8%, 3.9%, 3.7%, 4.0%, 2.2%, and 2.9%, respectively. Each of the isolated isomers gave satisfactory data to demonstrate existence of both an azido group and a Tips group on a γ-CD molecule on its ^{1}H NMR, MS, and IR spectra.

After separation/isolation, the regioisomers were subjected to regioisomeric assignment. The isomers **2a**–**2g** were firstly correlated with two-Tips-group-possessing γ-CD derivatives **3a**–**3d**. By substituting one of the two Tips groups on **3a**–**3d** with an azido group, AB isomer **3a** gives AB and AH isomers of the azido-Tips-CDs (Scheme 1). Similarly AC, AD, and AE isomers of the bis-Tips CDs give (AC and AG), (AD and AF), and AE isomers, respectively. This provides not only structure correlation between **2a**–**2g** and **3a**–**3d** but also an alternative route to give **2a**–**2g** to the synthesis from azido-CD **1** described above. So we prepared the bis-Tips γ-CD **3a**–**3d**. Palin reported that reaction of γ-CD with Tips chloride gave only a monosulfonate selectively and no disulfonates were observed.[11] It demonstrated that the di-sulfonylation on CD was difficult presumably due to steric hindrance of the bulky Tips group. However, addition of zinc bromide achieved the desired di-sulfonylation and low-pressure RP column chromatography separated four isomers **3a** (2.4%), **3b** (2.7%), **3c** (4.5%), and **3d** (2.0%), respectively, although the yields were relatively low. Each of the isolated isomers gave satisfactory data to demonstrate existence of two Tips group on a γ-CD molecule in its ^{1}H NMR and MS spectra. Structure assignment of **3a**–**3d** was done by chemical conversion of **3a**–**3d** to the known bis(3,6-anhydro) CDs **4a**–**4d** and subsequent NMR analysis. Each of the four regioisomers of **4a**–**4d** was known to show characteristic proton signals on the ^{1}H NMR spectrum enough to clarify the relative positions of the two 3,6-anhydroglucose residues on the CD molecule.[12] The obtained **4a**–**4d** were correlated with the authentic isomers and accordingly the bis-Tips CDs **3a**–**3d** were assigned as AE, AD, AC, and AB isomers, respectively (Scheme 1). In order to correlate the bis-Tips CDs **3a**–**3d** with azido-Tips CDs **2a**–**2g**, one of the Tips group on each of **3a**–**3d** was substituted with an azido group. The bis-Tips



Scheme 2.

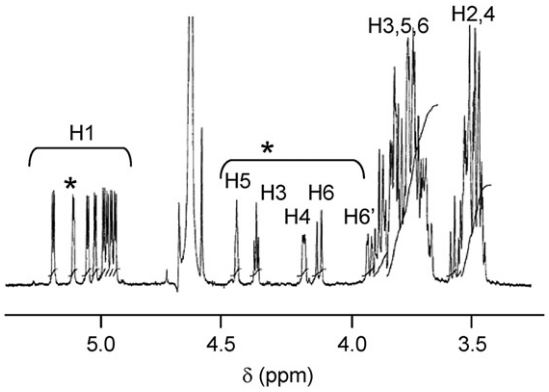


Figure 3. 1D-^{1}H NMR spectrum of azido-3,6-anhydro-γ-CD **5b**. Protons of the 3,6-anhydroglucose residue were marked with asterisk.

AE isomer **3a** gave only one azido-Tips CD isomer **2a** with the smallest retention time on RP-HPLC, which demonstrated that **2a** was the AE isomer (Scheme 1) The AD isomer **3b** was correlated with **2b** and **2c** where an azido group existed on A position on the CD and the Tips group existed on D position or vice versa. Similarly, AC isomer **3c** and AB isomer **3d** were correlated with **2d** and **2e**, and (**2f** and **2g**), respectively.

Complete structure assignment of **2a**–**2g** was done by chemical conversion to their corresponding 3,6-anhydro-CD derivatives followed by high-resolution 2D-NMR (COSY, TOCSY, and HOHAHA) analysis. Compound **2a**–**2g** themselves did not show proton signals separated enough for the sequence of the eight sugar residues to be determined. Transformation of a normal glucose ($^4C_1$ conformation) to a 3,6-anhydroglucose ($^1C_4$ conformation) on the CD ring was known to cause drastic changes on the proton signals of not only the residue itself but also other glucose residues presumably due to the distortion of CD ring, which facilitated assignment of the protons and therefore isomer determination.[9b,13] Isomer **2b** was converted with alkaline treatment to **5b** (Scheme 2) and the product showed satisfactory data to demonstrate existence of an azidoglucose and a 3,6-anhydroglucose on a γ-CD molecule in its MS and IR spectra. Similarly other isomers **5a** and **5c**–**5f** were obtained from **2a** and **2c**–**2f**. ^{1}H NMR (600 MHz) spectrometric analyses for **5a**–**5g** firstly allowed the assignment of the H1–H6 protons in each glucose residues with the aid of COSY and TOCSY experiments, where correlation of the protons started from the distinctive H1 signals around 5 ppm. Figures 3 and 4a show the 1D and TOCSY spectra of the isomer **5b**. It was easy to discriminate proton signals of the 3,6-anhydroglucose from those of sulfonylated and unmodified glucoses in each isomer since the coupling constants and chemical shifts of the 3,6-anhydroglucose residues with $^1C_4$ conformation are unique compared to those other residues with $^4C_1$ conformation.[14] The six intact glucoses with $^4C_1$ conformation in each isomer showed very similar chemical shift patters. However, the high-resolution NMR experiments (COSY and TOCSY) enabled the discrimination and assignment of almost all signals of sugar residues of each regioisomeric CD (Fig. 4a). It is especially important to identify the H1 and H4 of all residues. NOEs between H1 of one residue and H4 of another adjoining residue clarify the interresidual relationship, that is, the connecting sequence of the sugar residue. The ROESY spectrum of the isomer **5b** displayed eight distinct interresidual cross peaks between all the eight pairs of H1s and H4s as shown in Figure 4b, and suggested the existence of a $3^{IV},6^{IV}$-anhydro-6^I-azidomaltotetraose moiety. Therefore, **2b** was unambiguously assigned as the 6A-azido-6D-TipsCD isomer, which was in consistence with the results of conversion of the AD-bis-Tips CDs **3b** giving **2b** and **2c** described above. With this result in hand, the other diastereomer **2c** was determined to be AF isomer. Similarly all the isomers **2a** and **2c**–**2f** were analyzed by the NMR methods (Fig. 5) and the positions of the azidoglucose and 3,6-anhydroglucose on each of them were assigned, which did not contradict the results of conversion of bis-Tips CDs **2a**–**2d** to **1a**–**1g** described above. Therefore, the structures of all the **2a**–**2g** were unambiguously established as AE, AD, AF, AC, AG, AB, and AH, respectively.

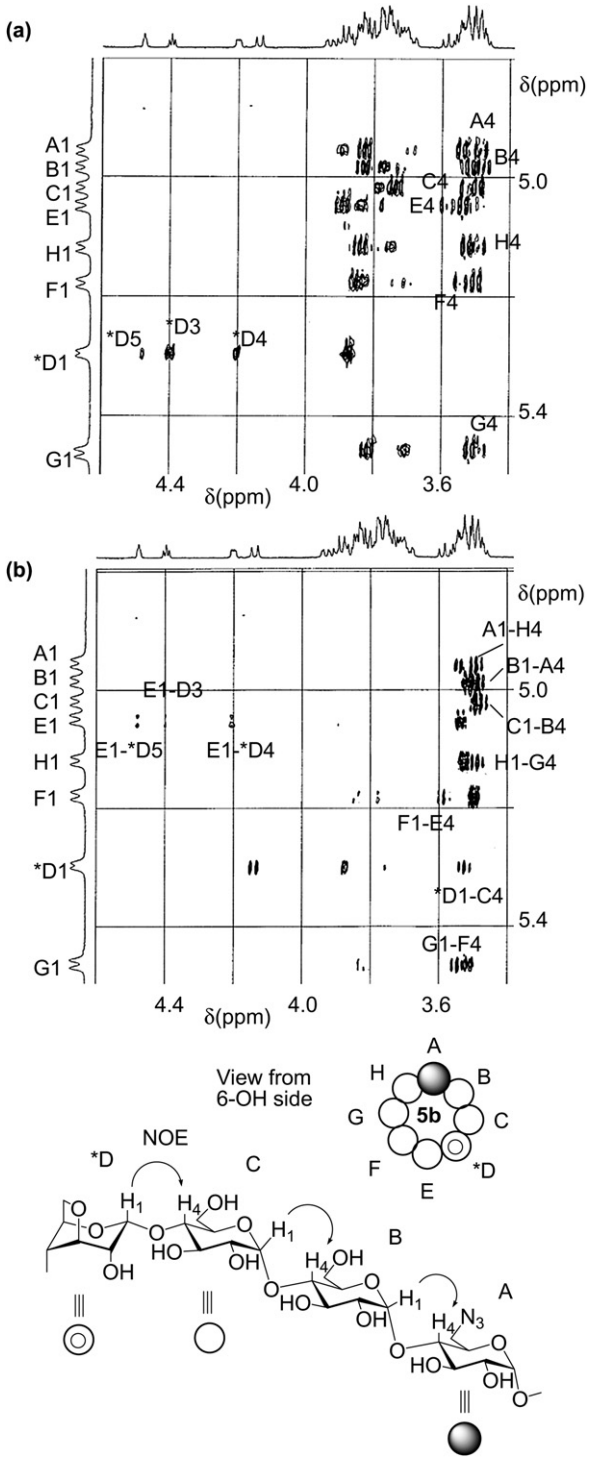


Figure 4. TOCSY (a) and ROESY (b) spectra of azido-3,6-anhydro-γ-CD **5b**. Glucose residues of **5b** were named as A–G and protons of the 3,6-anhydroglucose residue (D residue) were marked with asterisk.

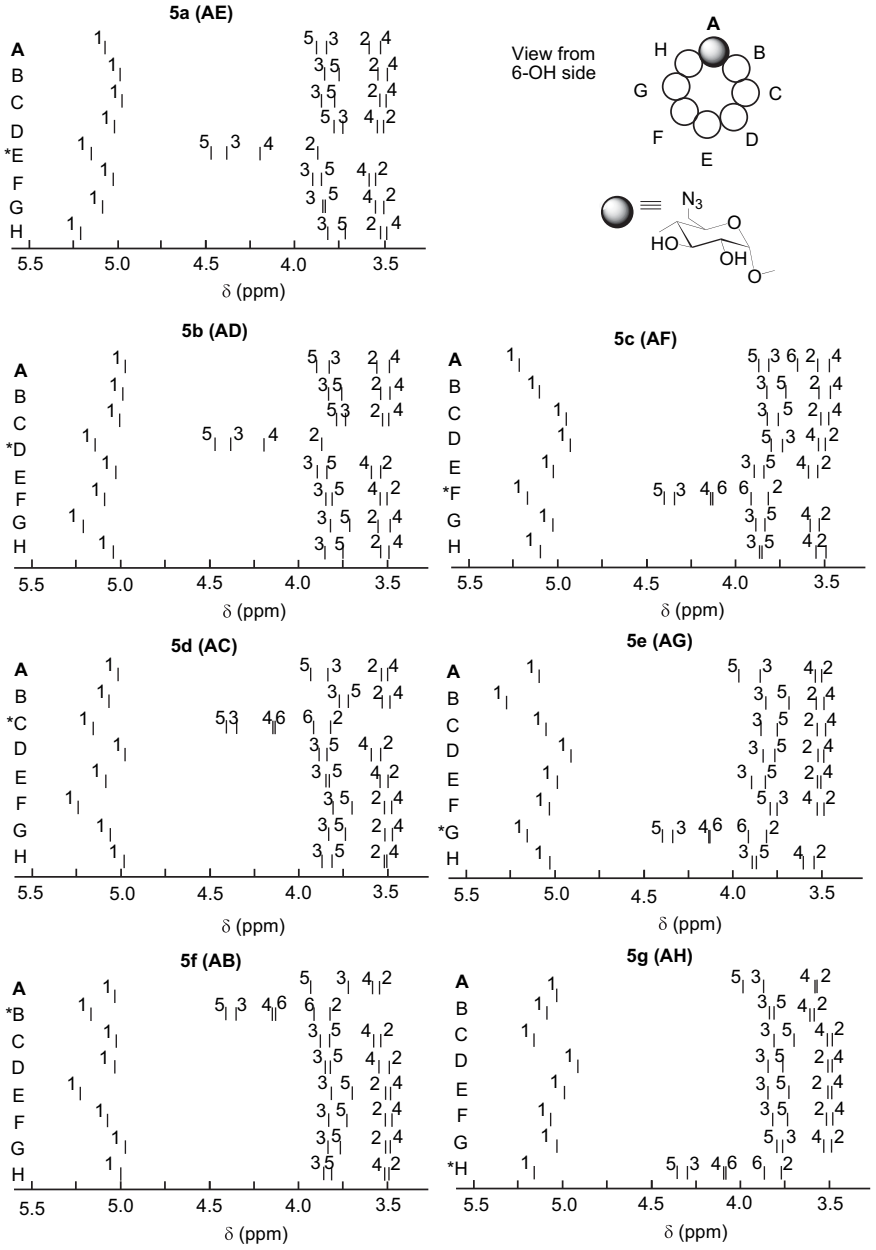


Figure 5. Proton signals of isomers **5a**–**5g**. The 3,6-anhydroglucoses were marked with asterisk.

3. Conclusion

In conclusion, a set of seven isomers of unsymmetrically C6 disubstituted γ-CD were prepared for the first time. Each of isomers was isolated using reversed phase chromatographic separation based on unique affinity of each regioisomer to the stationary phases. Low yield of AB/AH isomers **2f**/**2g** seemed similar to those seen in previous disulfonates studies.[15] It is presumably due to steric hindrance of the two sulfonyl groups. Relationship between elution order of the regioisomers **2a**–**2g** and their corresponding structures are not clear. We hypothesize that one of the Tips groups in the corresponding isomer can be self-included in the CD cavity and therefore each regioisomer forms a unique hydrophobic molecular structure with unique affinity to column stationary phase. The assignment of the modified positions in each regioisomers was unambiguously performed by chemical correlation with the authentic compounds and chemical conversion followed by high-resolution 2D-^{1}H NMR (COSY, TOCSY, and HOHAHA) analyses to observe interresidual NOEs. By use of the seven regioisomers of γ-CDs possessing an azido group and a sulfonyloxy group on its primary hydroxyl side as authentic and versatile synthetic intermediates sophisticated γ-CD derivatives with two different functionalities at desired positions are now available for supramolecular chemistry. Zwitterionic receptor molecules possessing both an NH_3^+ group and a COO^- group regiospecifically situated on γ-CD molecule for chiral recognition of amino acids are now being studied.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 (300 MHz) or a Bruker Avance 600 (600 MHz). Proton signals were assigned using COSY, TOCSY (mixing time, 120 ms), and ROESY (mixing time, 200 ms) experiments. MALDI-TOF mass measurements

were performed with a SHIMADZU AXIMA-Resonance, with 2,5-dihydroxybenzoic acid as the matrix. UV absorbance of fractions on low-pressure RP column chromatography was recorded on a Shimadzu UVmini-1240 instrument. IR spectra were recorded on a Jasco FT IR 200. TLC was run on precoated silica-gel plates (Art 5554, Merck) using 1-propanol/ethyl acetate/water (7:7:5, v/v/v) as the eluent and visualizing using UV light and/or staining with 0.1% 1,3-naphthalenediol in EtOH/water/H_2SO_4 [200:157:43 (v/v/v)]. Prepacked ODS column [Merck, LiChroprep RP-18, size C (37×440 mm)] was used for low-pressure RP column chromatography. Analytical RP-HPLC was carried out using an YMC J'sphere ODS-M80 column (4 μm; 4.6×250 mm, YMC Inc.). Preparative HPLC was performed using an YMC-Pack ODS-M80 column (4 μm; 20×250 mm, YMC Inc.) with an YMC-Guard pack ODS-M80 (5 μm; 20×50 mm, YMC Inc.). A Pharmacia Fine Chemicals Sephadex LH-20 was used for gel permeation chromatography.

4.2. Azido-Tips-CDs 2a–2f

6-Azido-γ-CD **1**[8] (576 mg, 0.44 mmol) and zinc bromide (252 mg, 1.1 mmol) were dissolved in dry pyridine (6 mL) cooled in an ice water bath and reacted with TipsCl (0.343 g, 1.10 mmol) for 40 min. After addition of water (3 mL), the reaction mixture was concentrated in vacuo and the residue was added to acetone (180 mL). The precipitate was collected by centrifugation (3000 rpm, 10 min) and dissolved in 28% aq MeCN (100 mL). The solution was subjected to low-pressure RP column chromatography (size C). After elution with 28% aq MeCN (600 mL) followed by a gradient elution from 28% aq MeCN (2.7 L) to 31% aq MeCN (2.7 L), a gradient elution from 31% aq MeCN (2.7 L) to 34% aq MeCN (2.7 L) gave mixtures of **2a**–**2c** (124 mg), **2d** and **2e** (65 mg), and **2f** and **2g** (53 mg). The mixture of **2a**–**2c** was applied to preparative HPLC using 24% aq MeCN as an eluent, which gave **2a** (26.9 mg, 3.9%), **2b** (26.0 mg, 3.8%), and **2c** (27.3 mg, 3.9%). The mixture of **2d** and **2e** gave **2d** (25.5 mg, 3.7%) and **2e** (27.6 mg, 4.0%) using 27% aq MeCN as an eluent. The isomers **2f** (15.2 mg, 2.2%) and **2g** (19.8 mg, 2.9%) were obtained, respectively, from the corresponding mixture using 27% aq MeCN. Compound **2a**: R_f 0.48; t_R 80.2 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.02–1.32 [18H, 6×CH_3], 2.92 (2H), 3.19–3.80, 3.82 (1H), 3.98 (2H), 4.18–4.31 (3H), 4.43–4.62 (6H), 4.78–4.95 [8H, C(1)H], 5.65–5.94 [16H, C(2)OH and C(3)OH], 7.26 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.3, 24.7, 25.2, 25.3, 25.7, 28.9, 30.0, 30.7, 32.5, 34.1, 34.4, 60.0, 60.5, 60.6, 60.7, 61.0, 69.9, 71.2, 72.9, 73.0, 73.1, 73.2, 73.4, 73.5, 73.6, 73.8, 80.8, 81.2, 81.5, 82.0, 83.6, 101.7, 102.0, 102.5, 102.8, 103.0, 122.2, 124.6, 129.9, 147.6, 150.9, 154.6; MS m/z 1610.5434 (M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2104 cm^{-1}. Compound **2b**: R_f 0.48; t_R 84.4 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.11–1.23 [18H, 6×CH_3], 2.94 (1H), 3.05–3.80, 3.82 (1H), 4.00 (2H), 4.19–4.30 (3H), 4.43–4.62 (7H), 4.78–4.95 [8H, C(1)H], 5.67–5.93 [16H, C(2)OH and C(3)OH], 7.29 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.3, 24.7, 25.2, 25.3, 25.7, 28.9, 30.0, 30.7, 31.6, 34.1, 34.4, 51.9, 60.1, 60.3, 60.7, 60.8, 70.0, 71.2, 73.0, 73.1, 73.2, 73.4, 73.5, 73.6, 73.7, 80.9, 81.5, 81.6, 81.9, 83.3, 101.7, 102.2, 102.5, 102.7, 103.0, 103.1, 122.2, 124.6, 129.9, 147.6, 147.9, 150.9, 154.6; MS m/z 1610.5397 (M+Na, 161.5529 calcd for $_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2104 cm^{-1}. Compound **2c**: R_f 0.48; t_R 88.4 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.08–1.30 [18H, 6×CH_3], 2.93 (1H), 3.03–3.80, 3.85 (1H), 4.00 (2H), 4.24 (2H), 4.32 (1H), 4.44 (1H), 4.49–4.61 (4H), 4.67 (1H), 4.80–4.99 [8H, C(1)H], 5.64–6.01 [16H, C(2)OH and C(3)OH], 7.28 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.3, 24.7, 25.2, 25.3, 25.7, 28.9, 29.9, 30.0, 34.1, 34.4, 51.9, 60.0, 60.5, 60.6, 60.7, 61.0, 61.1, 72.9, 73.1, 73.4, 73.5, 73.6, 73.8, 80.9, 81.0, 81.4, 81.5, 81.6, 81.9, 82.2, 83.5, 101.9, 102.4, 102.5, 102.6, 102.8, 103.0, 103.1, 122.2, 124.5, 129.9, 147.6, 150.9, 154.7; MS m/z 1610.5499 (M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2104 cm^{-1}. Compound **2d**: R_f 0.48; t_R 146.9 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.18–1.23 [18H, 6×CH_3], 2.94 (1H), 3.05–3.80, 3.80–3.90 (1H), 4.00 (2H), 4.26 (2H), 4.33 (1H), 4.51–4.62(6H), 4.82–4.96 [8H, C(1)H], 5.71–5.93 [16H, C(2)OH and C(3)OH], 7.28 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 24.7, 25.2, 25.3, 25.7, 28.9, 30.0, 34.1, 34.4, 51.8, 60.7, 60.8, 69.3, 70.0, 71.3, 73.0, 73.1, 73.2, 73.4, 73.5, 73.6, 73.7, 73.8, 80.6, 81.4, 81.7, 81.9, 83.4, 101.9, 102.1, 102.3, 102.5, 102.6, 103.0, 103.1, 122.2, 124.6, 130.0, 142.9, 147.6, 148.0, 150.9, 154.6; MS m/z 1610.5540 (M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2104 cm^{-1}. Compound **2e**: R_f 0.48; t_R 163.9 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.18–1.23 [18H, 6×CH_3], 2.94 (1H), 3.08–3.79, 3.82 (1H), 4.01 (2H), 4.27 (2H), 4.38–4.48 (2H), 4.49–4.65 (5H), 4.80–4.98 [8H, C(1)H], 5.70–6.00 [16H, C(2)OH and C(3)OH], 7.29 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 24.7, 25.2, 25.3, 25.7, 28.9, 30.0, 34.1, 34.4, 60.6, 60.7, 60.8, 61.0, 70.0, 71.3, 72.9, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6, 73.7, 73.8, 80.2, 81.4, 81.5, 81.7, 81.8, 82.0, 83.5, 101.7, 101.9, 102.4, 102.6, 102.7, 103.1, 122.2, 124.6, 129.9, 147.7, 148.0, 150.9, 154.6; MS m/z 1610.5450(M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2105 cm^{-1}. Compound **2f**: R_f 0.48; t_R 234.7 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.19–1.23 [18H, 6×CH_3], 2.95 (1H), 3.05–3.96, 3.82 (1H), 4.00 (2H), 4.18–4.45 (4H), 4.48–4.73 (6H), 4.82–5.03 [8H, C(1)H], 5.65–6.10 [16H, C(2)OH and C(3)OH], 7.30 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 24.7, 25.2, 25.3, 25.7, 28.9, 30.0, 30.7, 34.1, 34.4, 60.8, 60.9, 70.1, 71.1, 72.7, 72.9, 73.1, 73.2, 73.3, 73.4, 73.6, 73.7, 73.8, 73.9, 81.3, 81.5, 81.7, 81.9, 82.0, 83.5, 102.0, 102.2, 102.4, 102.5, 102.6, 102.7, 102.8, 103.2, 122.2, 124.6, 129.7, 147.6, 150.9, 151.1, 154.7; MS m/z 1610.5437 (M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2104 cm^{-1}. Compound **2g**: R_f 0.48; t_R 246.3 min [24% MeCN in water; flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.18–1.23 [18H, 6×CH_3], 2.94 (1H), 3.08–3.80, 3.88 (1H), 4.03 (2H), 4.08–4.16 (2H), 4.48–4.61 (6H), 4.66 (1H), 4.83–4.89 [8H, C(1)H], 5.70–5.99 [16H, C(2)OH and C(3)OH], 7.30 (2H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 24.7, 25.2, 25.7, 28.9, 30.0, 30.7, 34.1, 34.3, 60.6, 60.7, 60.8, 60.9, 69.9, 71.0, 72.9, 73.1, 73.3, 73.4, 73.6, 73.9, 81.1, 81.3, 81.6, 81.7, 81.8, 81.9, 82.0, 82.2, 82.6, 101.7, 102.4, 102.5, 102.6, 102.7, 102.8, 103.1, 122.2, 124.7, 129.9, 147.6, 147.9, 151.0, 154.6; MS m/z 1610.5474 (M+Na, 1610.5529 calcd for $C_{63}H_{101}N_3NaO_{41}S$); IR (KBr) 2105 cm^{-1}.

4.3. Di-Tips-CDs 3a–3d

γ-CD (3.86 g, 3.0 mmol) and zinc bromide (1.70 g, 7.5 mmol) were dissolved in dry pyridine (50 mL) cooled in an ice water bath and reacted with TipsCl (2.32 g, 7.43 mmol) for 90 min. After addition of water (5 mL), the reaction mixture was concentrated in vacuo and the residue was added to acetone (200 mL). The precipitate was collected by centrifugation (3000 rpm, 10 min) and dissolved in 45% aq MeCN (100 mL). The solution was subjected to low-pressure RP column chromatography (size C). After elution with 45% aq MeCN (600 mL) followed by a gradient elution from 45% aq MeCN (1.5 L) to 65% aq MeCN (1.5 L), a gradient elution from 65% aq MeCN (750 mL) to 75% aq MeCN (750 mL) gave **3a** (130 mg, 2.4%), **3b** (145 mg, 2.7%), **3c** (244 mg, 4.5%), and **3d** (110 mg, 2.0%). Compound **3a**: R_f 0.54; t_R 19.9 min [gradient, 30–70% MeCN in water (40 min); flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 0.95–1.30 (36H, 12×CH_3), 2.92 (2H), 2.95–3.75, 3.80–4.05 (6H), 4.06 (2H), 4.15–4.30 (4H), 4.40–4.70 (5H), 4.85–5.00 [8H, C(1)H], 5.60–6.05 [16H, C(2)OH and C(3)OH], 7.24 (4H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 25.1, 25.3, 30.0, 34.3, 60.0, 60.3, 60.5, 69.4, 69.8, 72.8, 73.0, 73.1, 73.4, 73.5, 73.6, 73.9, 80.8, 80.9, 81.2,

81.6, 101.7, 102.4, 102.8, 124.5, 129.7, 150.9, 154.5; MS *m*/*z* 1851.6800 (M+Na, 1851.6804 calcd for $C_{78}H_{124}NaO_{44}S_2$). Compound **3b**: R_f 0.54; t_R 21.0 min [gradient, 30–70% MeCN in water (40 min); flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.05–1.30 (36H, 12×CH_3), 2.89 (2H), 3.05–3.78, 3.86 (2H), 4.00 (4H), 4.15–4.20 (7H), 4.45–4.65 (4H), 4.80–4.95 [8H, C(1)H], 5.65–6.05 [16H, C(2)OH and C(3)OH], 7.26 (4H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.3, 25.1, 25.2, 25.3, 25.6, 30.0, 34.4, 60.0, 60.1, 60.3, 60.5, 60.7, 69.1, 69.9, 72.8, 72.9, 73.0, 73.2, 73.3, 73.5, 73.6, 73.7, 80.6, 81.0, 81.3, 81.4, 81.5, 82.0, 101.8, 102.0, 102.4, 102.5, 103.0, 103.1, 124.5, 129.8, 129.9, 150.9, 154.6; MS *m*/*z* 1851.6789 (M+Na, 1851.6804 calcd for $C_{78}H_{122}NaO_{44}S_2$), 1825.3 (M+H, calcd for $C_{78}H_{123}O_{44}S_2$). Compound **3c**: R_f 0.54; t_R 24.5 min [gradient, 30–70% MeCN in water (40 min); flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.05–1.15 (36H, 12×CH_3), 2.93 (2H), 3.05–3.90, 3.90–4.30 (10H), 4.39–4.65 (6H), 4.75–4.95 [8H, C(1)H], 5.65–6.05 [16H, C(2)OH and C(3)OH], 7.28 (4H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 24.7, 25.2, 25.3, 25.7, 34.4, 60.1, 60.6, 60.7, 69.1, 69.3, 70.0, 72.9, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6, 73.8, 80.0, 80.7, 81.5, 81.6, 81.7, 81.8, 101.4, 101.9, 102.4, 102.5, 102.9, 124.5, 124.6, 129.8, 130.0, 150.9, 151.0, 154.6, 154.6; MS *m*/*z* 1851.6795 (M+Na, 1851.6795 calcd for $C_{78}H_{122}NaO_{44}S_2$). Compound **3d**: R_f 0.54; t_R 25.4 min [gradient, 30–70% MeCN in water (40 min); flow rate, 1.0 mL/min]; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 1.00–1.20 (36H, 12×CH_3), 2.93 (2H), 3.00–3.95, 3.97 (4H), 4.05–4.45 (5H), 4.45–4.65 (5H), 4.70–4.95 [8H, C(1)H], 5.60–5.90 [16H, C(2)OH and C(3)OH], 7.27 (4H, s, aromatic H); ^{13}C NMR (150 MHz, Me_2SO-d_6) δ 24.1, 24.2, 25.1, 25.2, 25.3, 30.0, 34.3, 34.4, 60.5, 60.6, 60.7, 60.8, 68.8, 69.9, 72.7, 73.0, 73.1, 73.2, 73.4, 73.5, 73.7, 73.8, 80.8, 80.9, 81.2, 81.3, 81.4, 81.7, 81.9, 101.6, 102.1, 102.3, 102.4, 102.5, 102.6, 102.9, 124.4, 124.5, 130.1, 130.4, 150.7, 150.8, 154.5, 154.6; MS *m*/*z* 1861.6835 (M+Na, 1851.6804 calcd for $C_{78}H_{122}KO_{44}S_2$).

4.4. Conversion of di-Tips-CDs 3a–3d to bis(3,6-anhydro)-CDs 4a–4d

Compound **3a** (16.7 mg, 9.1×10^{-6} mol) in 1 M aq NaOH (1 mL) was kept at 60 °C for 2 h. After neutralized by 1 M aq HCl the reaction mixture was concentrated in vacuo. The residue was dissolved in water (0.5 mL) and applied to gel permeation column chromatography to give a bis(3,6-anhydro) derivative **4a** (9.5 mg, 90%). Each of **3b**–**3d** gave the corresponding **4b**–**4d**, respectively (yield; **4b** 76%, **4c** 82%, **4d** 91%).

4.5. Conversion of di-Tips-CDs 3a–3d to azido-Tips-CDs 2a–2g

Compound **3a** (3.5 mg, 2.0×10^{-6} mol) in 1 M aq NaOH (1 mL) reacted with sodium azide (0.14 mg, 2.2×10^{-6} mol) at 60 °C for 1 h. After the reaction mixture was concentrated in vacuo the residue was dissolved in 60% aq CH_3CN (0.4 mL) and applied to RP-HPLC analysis. Each of **3b**–**3d** was treated similarly.

4.6. Conversion of azido-Tips-CDs 2a–2g to azido-3,6-anhydro-CDs 5a–5g

Compound **2a** (16.7 mg, 1.2×10^{-5} mol) in 1 M aq NaOH (1 mL) was kept at 60 °C for 2 h. After neutralized by 1 M aq HCl the reaction mixture was concentrated in vacuo. The residue was dissolved in water (0.5 mL) and applied to gel permeation column chromatography (eluent: water) to give a azido-(3,6-anhydro) CD derivative **5a** (9.5 mg, 90%). Each of **2b**–**2g** gave the corresponding **5b**–**5g**, respectively. Compound **5a**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S13; MS *m*/*z* 1326.4045 (M+Na, 1326.4085 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2104 cm^{-1}. Compound **5b**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figures 3 and 5; MS *m*/*z* 1326.4045 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$), 1299.7 (M+H, calcd for $C_{48}H_{78}N_3O_{38}$); IR (KBr) 2104 cm^{-1}. Compound **5c**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S18; MS *m*/*z* 1326.4031 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2103 cm^{-1}. Compound **5d**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S22; MS *m*/*z* 1326.4053 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2105 cm^{-1}. Compound **5e**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S26; MS *m*/*z* 1326.4084 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2105 cm^{-1}. Compound **5f**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S30; MS *m*/*z* 1326.4088 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2104 cm^{-1}. Compound **5g**: R_f 0.20; ^{1}H NMR (600 MHz, D_2O): see Figure 5 and Figure S34; MS *m*/*z* 1326.4088 (M+Na, 1326.4083 calcd for $C_{48}H_{77}N_3NaO_{38}$); IR (KBr) 2105 cm^{-1}.

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Supplementary data

RP-HPLC chromatogram of di-Tips-CDs **3a**–**3d**, ^{13}C NMR spectral data of **2a**–**2g** and **3a**–**3d**, and ^{1}H NMR spectral data of **5a**–**5g** (**5a** and **5c**–**5g**; 1D, COSY, TOCSY, ROESY; **5b**: COSY) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.08.061.

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