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Polysulfonylated cyclodextrins. Part 13: Chemistry of cyclomaltoheptaose tetrasulfonates providing a complete 6-*O*-sulfonylated cyclomaltoheptaoses library

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Abstract—Five regioisomeric cyclomaltoheptaose (β-cyclodextrin) tetramesitylenesulfonates were prepared and each of them was isolated by a combination of reversed and ordinary phase chromatographic separations. The positions of the substituents on each regioisomer were unambiguously determined using interresidual NOEs. As a result of this study, an indexed library of sulfonylated β-cyclodextrins composed of 19 sulfonates has been established.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of D-glucose units. The most common are composed of six, seven and eight glucose units and are known as cyclomaltohexaose (α-CD), cyclomaltoheptaose (β-CD) and cyclomaltooctaose (γ-CD), respectively. The molecular cavity of a CD can include a suitable guest molecule. This CD-complexation is very useful in improving the guest's properties such as solubility, stability and absorption.[1] Therefore, CDs have been applied in the food, cosmetics and pharmaceutical fields. However, a native (unmodified) CD is not always satisfactory. For example, a native β-CD causes unacceptable kidney complications when administered by intravenous injection. Sulfoalkyl-β-CD has been successfully developed as an excellent derivative to avoid such health troubles.[2] This clearly demonstrates that sophisticated modifications can equip a CD molecule with the desired property. In addition, the chemistry of multifunctionalized CDs so far has demonstrated that the rational arrangement of two or more functional groups on a CD molecule was promising in expressing an elegant enzyme-like activity[3] and an exquisite guest chirality recognition.[4] Regiospecifically-poly arenesulfonylated CD derivatives are essential intermediates to enable rational arrangement and positioning of the functional moieties on a CD molecule. Accordingly we have been constructing an indexed library of all possible regioisomers of β-CD 6-*O*-sulfonates leading to derivatives possessing the desired number of functional moieties at the desired positions.[5] Here we will report five regioisomeric β-CD tetrasulfonates as the last among nineteen 6-*O*-sulfonates to complete the library.

2. Results and discussion

Each of the CD molecules (α-, β- and γ-CD) affords 6-*O*-sulfonate(s) by reaction in pyridine with the corresponding arene/alkanesulfonyl chloride.[6] The reaction affords a mixture of CD sulfonates as products, namely those with a certain number of sulfonyl groups and also under- and oversulfonylated derivatives. This is because there are six, seven and eight 6-hydroxy groups in the α-, β- and γ-CD molecules, respectively, and these hydroxyl groups have almost the same reactivity with the corresponding arene/alkanesulfonyl chloride. In the specific case of the preparation of tetrasulfonylated β-CD as a major product, tri- and pentasulfonylated derivatives are also generated and these should firstly be separated from each other. The next consideration is that, when more than two hydroxyl groups on a CD are sulfonylated, regioisomers are produced. In the case of tetrasulfonylated β-CD five regioisomers **1**–**5** exist (Fig. 1). The regioisomers must be separated from each other in order to obtain the necessary synthetic intermediates for attachment of four functional moieties at the desired positions (glucose residues) in the CD molecule. The most useful method for performing the two separations mentioned above has been reversed phase column chromatography.[7] A 6-deoxy-6-halo-CD derivative is an alternative to a CD sulfonate as a useful intermediate for the synthesis of modified CD derivative; in fact, per-6-iodo- and bromo CDs were often used.[8]

Keywords: Cycloheptamaltose; Cyclodextrin; Tetrasulfonate; Regioisomeric determination; Interresidual NOE.
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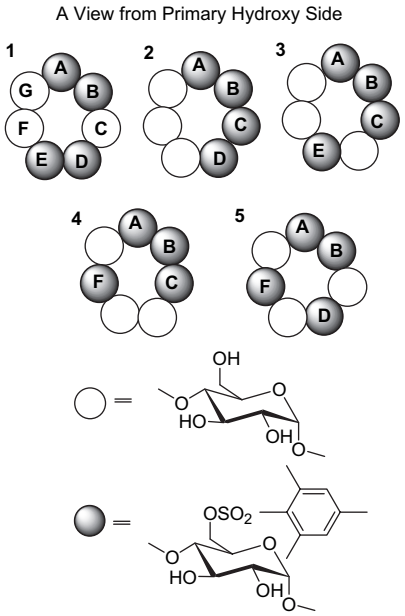

Figure 1. Structure of tetrakis(6-*O*-mesitylsulfonyl)-β-CD regioisomers.

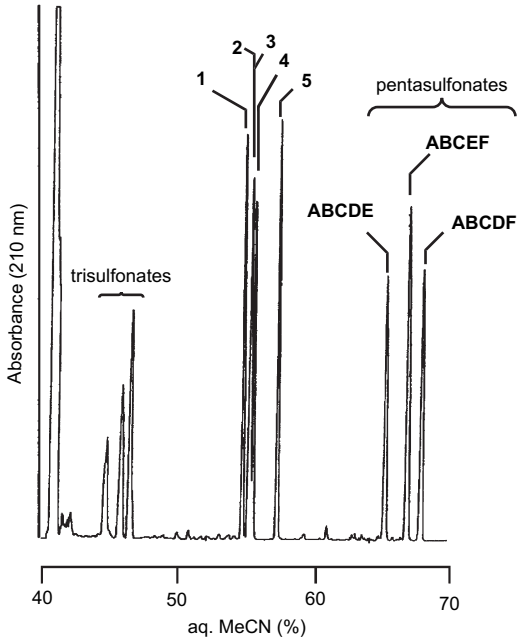

Figure 2. RP-HPLC of the mixture obtained by the reaction of β-CD with mesitylenesulfonyl chloride in pyridine. A linear gradient of MeCN was applied.

However, polyarenesulfonylated CDs seem superior to polyhalides. One of the advantages of polyarenesulfonylated CDs is that they are UV–vis detectable, greatly aiding the detection process during chromatography. The other advantage of polyarenesulfonylated CDs is the ability to optimize separation of regioisomers by changing the aryl moiety. In the case of polyhalide regioisomers the difference among Cl, Br and I is too small to cause sufficient changes in affinity to the stationary phase and to enhance the separation of regioisomers. We prepared a variety of tetrasulfonylated CDs and surveyed them by use of octadecylsilane-HPLC (ODS-HPLC) with UV detector in order to determine, which kind of arenesulfonates can be separated the most effectively. Analyses of reaction products of β-CD with sulfonyl chloride possessing tolyl, mesityl, 1- and 2-naphthyl, phenyl, *o*-, *m*- and *p*-nitrophenyl groups demonstrated that in all cases tetrasulfonates were separated from tri- and pentasulfonates. However, with respect to the separation of five regioisomers of tetrasulfonates, the most promising seemed to be the mesitylenesulfonates (Fig. 2), as we saw in previous studies.[5d,7] We hypothesize that one of the mesitylenesulfonyl groups in each CD isomer can be self-included in the CD cavity and therefore each regioisomer forms a unique 'hydrophobic' molecular structure with unique affinity to stationary phase column. However, the five regioisomers appeared as almost four peaks on their ODS-HPLC chromatogram because the two regioisomers **2** and **3** have very similar retention times. Existence of five possible isomers in the reaction mixture was ascertained by use of the other type of reversed phase column, a phenyl-modified silica gel column. However, the separation by use of the column was still not sufficient enough to isolate each isomer. As we had previously separated trimesitylenesulfonylated α-CD regioisomers with silica gel chromatography,[7] we applied this method to the tetramesitylenesulfonylate analogues in this study. While an unmodified CD is too hydrophilic to undergo ordinary phase chromatography, the three aryl groups endow the corresponding α-CD sulfonates with hydrophobic character for mobility on normal phase silica. When subjected to silica gel chromatography using water-saturated chloroform/MeOH as an eluent, we found that the mixture of tetramesitylenesulfonylated β-CDs **1**–**5** eluted in the following order: **5**, **1**, mixture of **3** and **4**, and **2**. Most importantly compounds **2** and **3**, which were not separable by reversed phase chromatography, were separated. It should be also noted that the order of elution in the ordinary phase chromatography was not exactly the reverse of the order with ODS-HPLC (chromatogram shown in Fig. 2). In particular, isomer **1** was eluted earlier than isomer **4**. This elution behaviour may be due to a unique hydrophobic cluster formed by the aromatic moieties on **1**. In an aqueous solution during a reversed phase chromatography one of the four aromatic moieties may be self-included into the CD cavity, decreasing the hydrophobicity of the molecule and so decreasing its affinity to the reversed phase column. In ordinary phase chromatography the aromatic ring is not as likely to be self-included in the CD cavity and the inherent hydrophobicity of **1** is not decreased much. Based on the results of these chromatographic experiments, a separation of **1**–**5** from the reaction mixture was established. In step 1, low-pressure column chromatography using an ODS column isolates **5** and gives a mixture of the remaining isomers **1**–**4**. In step 2, ODS-HPLC isolates pure isomers **1** and **4** and a mixture of **2** and **3**. Step 3 entails silica gel chromatography to separate **2** and **3**. The total isolated yields of isomers **1**–**5** were 5.4%, 0.4%, 1.4%, 4.4% and 9.1%, respectively. Each of the isolated isomers gave satisfactory ^{1}H NMR and MS spectral data, which demonstrated the existence of four mesitylenesulfonyl groups on a β-CD.

After the isolation of all possible regioisomers, assignment of the structure of each isomer was undertaken. The following methods have been developed in order to assign the regioisomers of CD sulfonates: additional sulfonylation,[7] conversion to thioethers and their Taka-amylolysis,[9]

3,6-anhydration followed by Taka-amylolysis,[10] 3,6-anhydration and subsequent ROESY analysis,[11] and 3,6-anhydration and correlation with structures derived from the authentic compounds.[5d] Each of these methods allowed an unambiguous structure assignment. However, all of them require further chemical conversion of the corresponding sulfonylated glucose residues to those required for regioisomer determination. For example, conversion of a sulfonylated glucose residue to a 3,6-anhydroglucose residue causes drastic changes in the ^{1}H NMR spectrum. The change is of sufficient magnititude to allow discrimination between sugar residue protons and to observe interresidual NOEs, which assist in regioisomeric structure assignment.[11] However, an alternative straightforward method for regioisomer assignment without further chemical modification would be more useful. From this point of view, we adopted high-resolution ^{1}H NMR (600 MHz) spectrometry for analyses of the tetrasulfonates **1**–**5**. This method enabled discrimination between seven sugar residues, namely four 6-*O*-mesitylenesulfonylated glucoses and three unmodified glucoses in each regioisomer. For all five sulfonate isomers **1**–**5**, firstly the H1–H6 protons in each glucose residue were assigned by COSY and TOCSY experiments. Correlation of the protons started from the distinctive H1 signals around 4.7 ppm. Figure 3a (Table 1) shows a TOCSY spectrum of the isomer **1**. It was easy to discriminate the proton signals of sulfonylated from those of unmodified glucoses in each isomer since the H1, H2 and H4 protons of the sulfonylated glucose residues resonated at higher field than those of the unmodified residues.[7] Despite protons of the four sulfonylated glucoses in each isomer appearing very close, 600 MHz high-resolution NMR experiments enabled discrimination and assignment of almost all signals of sugar residues within each regioisomeric CD. The most critical assignments were of H1 and H4 of every residue. The presence of NOE interactions between H1 of each residue and H4 of the adjoining residue clarified the interresidual relationships within each isomer, enabling the assignments of neighbouring glucose residues. ROESY experiments on isomer **1** gave a spectrum where seven distinct interresidual cross peaks between all seven pairs of H1s and H4s were observed as shown in Figure 3b. The peaks showed that the derivative contained a 6^{I},6^{II},6^{IV},6^{V}-tetrasulfonylmaltopentaose moiety. Therefore, **1** was unambiguously assigned as the ABDE-tetrasulfonylated isomer. The compound **2** also showed NOE interactions between all seven residues, clearly demonstrating the existence of a 6^{I},6^{II},6^{III},6^{IV}-tetrasulfonylmaltotetraose moiety. Accordingly, it was assigned as ABCD isomer (Fig. 4). Compound **3** also showed NOEs between all seven residues and the sequential relationship between four sulfonylated glucoses and three unmodified glucoses were easily determined, allowing the assignment of **3** as the ABCE isomer. Of the theoretical seven possible H1–H4 NOE cross peaks for isomer **4**, only five were observed. However, these were sufficient to show sequences of both 6^{I},6^{II},6^{III}-trisulfonylmaltotetraose moiety and 6^{II}-sulfonylmaltotriose moiety, allowing the isomer to be assigned the ABCF structure. In the case of **5**, a 6^{I},6^{II}-disulfonylmaltotriose moiety and also two 6^{I}-sulfonylmaltose moieties were found, suggesting that this is the ABDF isomer. These NMR experiments proved unambiguously the structures of each of the isomers. To the best of our knowledge this is the first complete regioisomer assignment of a group containing more than three-polysulfonylated CD derivatives using ^{1}H NMR only and without their further chemical conversion. Recently we studied regioisomeric determination of di-Ts β-CDs using tandem mass analyses but the assignment failed probably due to sulfonyl group migration in an ionization process.[12] Accordingly high-resolution ^{1}H NMR analysis seems the most useful for structure determination of polysulfonylated CD derivatives at present.

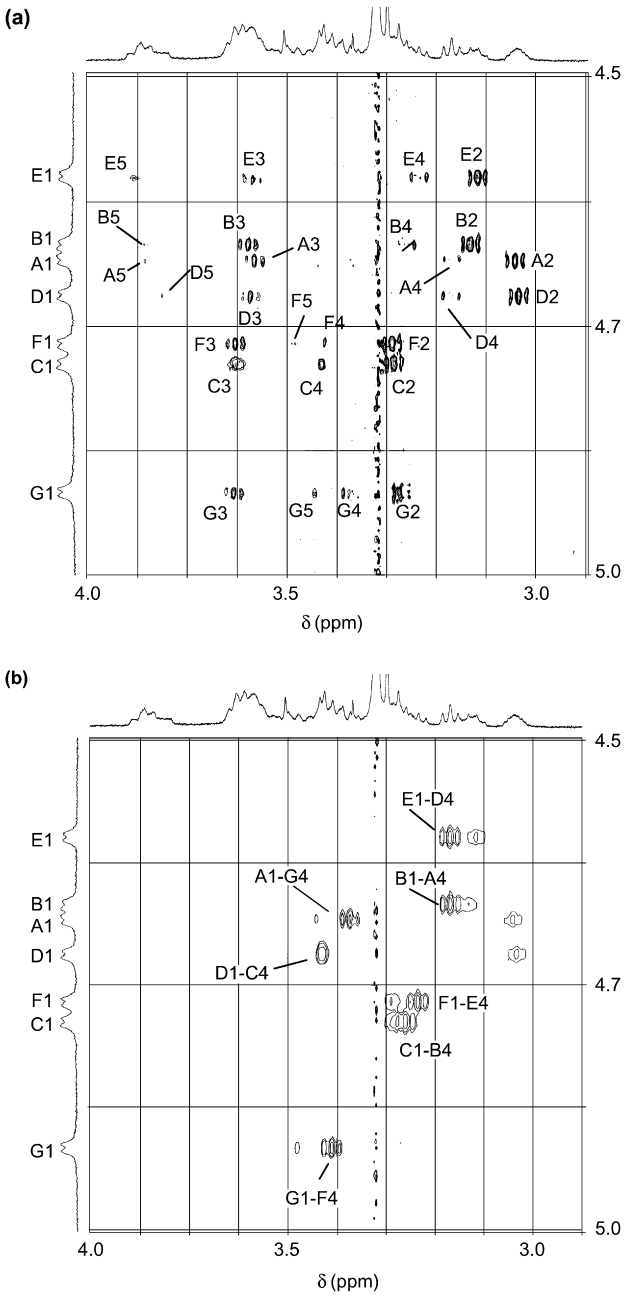

Figure 3. (a) TOCSY (mixing time 120 ms) and (b) ROESY (mixing time 200 ms) spectra of tetrasulfonate isomer **1** in D_2O. Interresidual NOEs between H1 of the glucose residue and H4 of the adjoining residue are shown in (b).

In conclusion, five regioisomers of tetramesitylenesulfonylated β-CDs were prepared and each of them was isolated using a combination of reversed and ordinary phase chromatographic separations based on the unique affinity of each

Table 1. ^{1}H NMR chemical shifts of glucose residues in tetrasulfonates **1**–**5**

Glucose residue	H1	H2	H3	H4	H5	H6	H6′
ABDE tetrasulfonate **1**							
G	4.83	3.27	3.61	3.38	3.45		
C	4.73	3.28	3.60	3.44			
F	4.71	3.29	3.60	3.42	3.49	3.61	3.61
D[a]	4.68	3.03	3.57	3.17	3.75	4.13	4.20
A[a]	4.65	3.04	3.56	3.17	3.79	4.05–4.36	
B[a]	4.64	3.13	3.58	3.24	3.78	4.05–4.36	
E[a]	4.58	3.11	3.57	3.26	3.80	4.38	4.20
ABCD tetrasulfonate **2**							
F	4.85	3.30	3.62	3.38	3.51		
G	4.83	3.28	3.61	3.47	3.60		
E	4.72	3.28	3.61	3.44	3.49	4.12	4.12
A[a]	4.64	3.34	3.56	3.16	3.78	4.02	4.25
B[a]	4.59	3.02	3.57	3.23	3.74	(4.13, 4.27) or (4.22, 4.17)[b]	
C[a]	4.58	3.15	3.58	3.26	3.74	(4.22, 4.17) or (4.13, 4.27)	
D[a]	4.55	3.16	3.59	3.23	3.82	4.15	4.30
ABCE tetrasulfonate **3**							
G	4.83	3.28	3.60	3.35	3.60		
F	4.76	3.28	3.60	3.45	3.60		
E[a]	4.74	3.16	3.60	3.21	3.82	4.12	4.12
D	4.71	3.27	3.60	3.43	3.60		
A[a]	4.64	3.01	3.54	3.16	3.71	4.08	4.08
C[a]	4.63	3.15	3.60	3.27	3.76	4.15	4.15
B[a]	4.48	2.97	3.53	3.18	3.74	4.01	4.01
ABCF tetrasulfonate **4**							
E	4.84	3.27	3.61	3.37	3.46		
G	4.77	3.26	3.58	3.42	3.46		
F[a]	4.71	3.15	3.58	3.22	3.80	4.28–4.07	
D	4.71	3.29	3.59	3.42	3.46		
A[a]	4.66	2.98	3.55	3.16	3.67	4.16	4.11
C[a]	4.59	3.13	3.58	3.28	3.80	4.28–4.07	
B[a]	4.53	3.00	3.55	3.20	3.74	4.32	4.17
ABDF tetrasulfonate **5**							
E or G	4.76	3.27	3.59	3.42	3.58		
G or E	4.75	3.27	3.59	3.42	3.58		
D[a] and F[a]	4.73	3.14	3.57	3.24	3.77	4.04–4.31	
C	4.69	3.26	3.59	3.41	3.60		
A[a]	4.65	3.00	3.57	3.17	3.76	4.04–4.31	
B[a]	4.62	3.13	3.57	3.26	3.76	4.04–4.31	

[a] A sulfonylated glucose residue.
[b] Difficult to be assigned due to overlapped signals.

regioisomer to the stationary phases. The assignment of the modified positions in each regioisomer was unambiguously achieved by use of high-resolution 2D-^{1}H NMR techniques to observe interresidual NOEs. Finally, the chemistry of β-CD 6-*O*-sulfonate derivatives can be summarized as follows. Mono-6-*O*-tosylated β-CD, an important intermediate for the synthesis of other modified CDs, has often been prepared by use of tosyl chloride in pyridine.[13] Recently

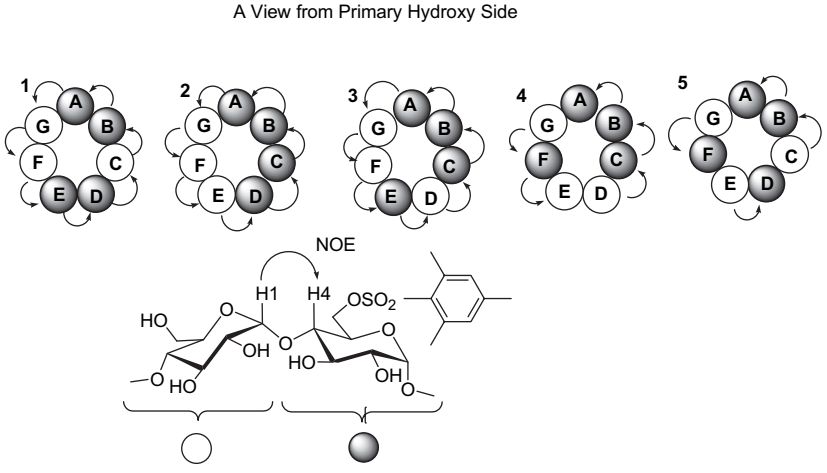

Figure 4. Observed interresidual NOEs on ROESY spectra of **1**–**5**. Each of the observed correlation between H1 of the glucose residue and H4 of the adjoining residue (H1 → H4) is shown by arrow.

an alternative procedure using tosyl anhydride has also been reported.[14] Ditosylates (three regioisomers),[9] tritosylates (five regioisomers)[5b] and pentasulfonates (mesitylenesulfonates, three regioisomers)[5d] were prepared using the corresponding sulfonyl chloride and isolated by ODS reversed phase column chromatography. A hexatosylate and a heptatosylate were also obtained.[5c] As a consequence of this tetrasulfonates study, all the β-CD 6-*O*-sulfonates (19 species from mono- to heptasulfonates) have become available as versatile synthetic intermediates. A gate to the superchemistry of sophisticated β-CD derivatives with multi-functionalities at desired positions is now opened.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded at 30 °C on a Bruker Avance 600 spectrometer operating at 600 MHz. Each of the tetrasulfonates **1**–**5** was dissolved in Me_2SO-d_6. Proton signals were assigned using COSY, TOCSY (mixing time, 120 ms) and ROESY (mixing time, 200 ms) experiments. FAB mass spectra were obtained with a Shimadzu-Kratos CONCEPT 32IH spectrometer. MALDI-TOF mass measurements were performed with Perseptive Voyager RP. 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)]. A prepacked ODS column [LiChroprep RP-18, size C (37×440 mm), Merck] was used for low-pressure RP column chromatography. Analytical RP-HPLC was carried out using a YMC-pack ODS-M80 column (4 μm; 4.6×250 mm, YMC Inc.). Preparative HPLC was performed using a YMC-Pack ODS-M80 column (4 μm; 20×250 mm, YMC Inc.) with a YMC-Guard pack Ph (5 μm; 20×50 mm, YMC Inc.).

3.2. Tetramesitylenesulfonylated β-CDs 1–5

β-CD (467 mg, 0.41 mmol) was dissolved in dry pyridine (30 mL) and reacted with mesitylenesulfonyl chloride (2.25 g, 6.18 mmol) at −10 °C for 4.2 h. After addition of water (10 mL), the reaction mixture was concentrated in vacuo and the residue was dissolved in 48% aq MeCN (600 mL) followed by neutralization with $NaHCO_3$. The solution was subjected to low-pressure RP column chromatography (applying the separation procedure described in the text) to give each of the five isomers. After elution with 48% aq MeCN (1.5 L) a gradient elution from 18% aq MeCN (1.5 L) to 58% aq MeCN (1.5 L) gave a mixture of **1**–**4** (151 mg) and pure **5** (69.9 mg, 9.1%). The mixture of **1**–**4** dissolved in 47% aq MeCN underwent preparative HPLC separation using 47% aq MeCN as an eluent, giving **1** (41.5 mg, 5.4%), **4** (33.6 mg, 4.4%) and a mixture of **2** and **3** (45.5 mg). The mixture of **2** and **3** was subjected to silica gel chromatography using a mobile phase of a lower layer of $CHCl_3$/MeOH/H_2O (7:3:1) to isolate **2** (3.1 mg, 0.4%) and **3** (10.8 mg, 1.4%). Some of the mixture was also recovered (6.9 mg). *Compound* ***1***: R_f 0.53; t_R 28.1 min [gradient, 50–60% MeCN in water (40 min); flow rate, 1.0 ml/min]; ^{1}H NMR (Me_2SO-d_6): see Table 1; MS (positive FAB) *m*/*z* 1885.5 (M+Na), 1901.5 (M+K), (negative FAB) 1861.5 (M−H), 2063.1 (M−mesitylenesulfonate). *Compound* ***2***: R_f 0.53; t_R 29.5 min [gradient, 50–60% MeCN in water (40 min); flow rate, 1.0 ml/min]; ^{1}H NMR (Me_2SO-d_6): see Table 1. *Compound* ***3***: R_f 0.53; t_R 29.9 min [gradient, 50–60% MeCN in water (40 min); flow rate, 1.0 ml/min]; ^{1}H NMR (Me_2SO-d_6): see Table 1; MS (MALDI-TOF) *m*/*z* 1887.5 (M+Na). *Compound* ***4***: R_f 0.53; t_R 30.7 min [gradient, 50–60% MeCN in water (40 min); flow rate, 1.0 ml/min]; ^{1}H NMR (Me_2SO-d_6): see Table 1; MS (MALDI-TOF) *m*/*z* 1887.5 (M+Na). *Compound* ***5***: R_f 0.53; t_R 37.2 min [gradient, 50–60% MeCN in water (40 min); flow rate, 1.0 ml/min]; ^{1}H NMR (Me_2SO-d_6): see Table 1; MS (positive FAB) *m*/*z* 1885.5 (M+Na), 1901.5 (M+K), (negative FAB) 1861.5 (M−H), 2063.1 (M−mesitylenesulfonate). Anal. Calcd for $C_{78}H_{110}O_{43}S_4\cdot 4H_2O$: C, 48.39; H, 6.14; S, 6.63. Found: C, 48.20; H, 5.81; S. 6.64.

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