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Facile preparation of mono-2-*O*-modified eicosa-*O*-methylcyclomaltoheptaoses (-β-cyclodextrins)

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Abstract

Mono-2-*O*-benzylated eicosa-*O*-methylcyclomaltoheptaose (-β-cyclodextrin) was prepared in one pot from cyclomaltoheptaose (β-cyclodextrin) in 33% isolated yield and quantitatively converted to mono-2-OH-free eicosa-*O*-methylcyclomaltoheptaose, which is the key compound for further modification. Transformation of this 2-OH group successfully gave several mono-2-*O*-modified eicosa-*O*-methylcyclomaltoheptaoses such as the acetate, the *N*,*N*-dimethylcarbamate, the *N*-*n*-butylcarbamate, the methanesulfonate, and the *S*-methyldithiocarbonate.

Keywords: Cyclomaltoheptaoses; β-Cyclodextrin, mono-2-*O*-modified; *O*-Permethylcyclodextrin; Selective modification

1. Introduction

Modification of the hydroxy groups of cyclomaltooligosaccharides (cyclodextrins, CDs) is important to alter the character of the CD as well as to create a functional material composed of CDs.[1,2] Sometimes selective transformation of only one hydroxyl group among 18 (α-), 21 (β-), and 24 (γ-CD) such groups is required to introduce a linking position for further modification. Although this transformation looks difficult, considerable effort has made it possible to some extent.[1,2]

Very recently, we have found *O*-permethylated cyclodextrins (MeCDs) can act as macrocyclic monomers for cationic ring-opening polymerization to give linear glucans.[3] In the course of further studies, we plan to employ mono-modified MeCD, which has a different functional group in place of one methoxy group at the C-2 position, as the monomer candidate. Several methods are known to modify a single hydroxy group at the C-2 position of a CD: i.e., mono-tosylation by using an inclusion phenomenon[4,5] or a tin alkoxide intermediate;[6] mono-alkylation or tosylation via selective generation of the alkoxide anion;[7,8] mono-acetalization, esterification, silylation, or tosylation to 6-*O*-full-protected CD;[9–11] mono-amination or iodination by the process of ring-scission and reformation.[12,13] We contemplated strategies to synthesize the objective C-2 mono-modified MeCD by using the above known methods. Some of them were actually examined, but it became apparent that it would be necessary to search out a new, easier method.

Selective benzylation of one of the 2-OH groups was planned, since the benzyl ether group is inert under basic conditions, which are necessary for the residual hydroxy groups to effectively undergo full methylation. Furthermore, the benzyl group is easily removed by hydrogenolysis, and the resulting OH group can be transformed into various functional groups. In this context, we noted previous reports about the preparation of the CD dimers linked at each C-2 position through a *m*-xylylene group.[14] As a result, mono-2-*O*-benzylated β-CD has been found to be effectively produced by the modified procedure. This article deals with the one-pot preparation of mono-2-*O*-benzylated eicosa-*O*-methyl-β-CD (**2**) from β-CD and its transformation to several mono-2-*O*-modified eicosa-*O*-methyl-β-CDs.

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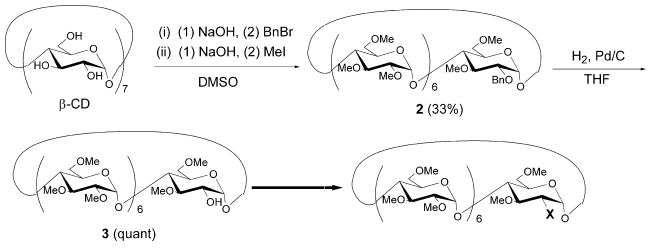
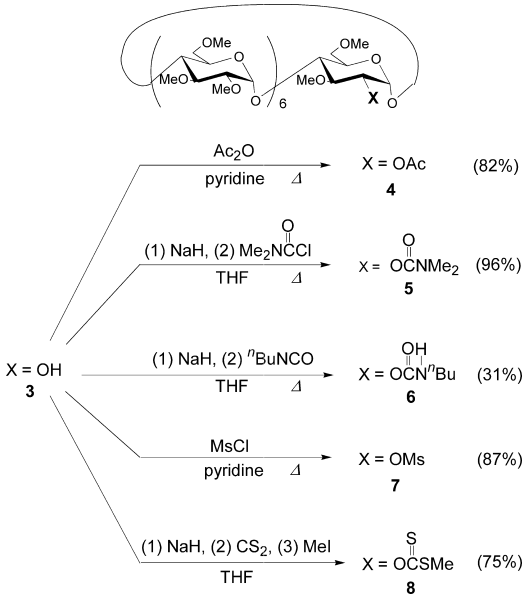
2. Results and discussion

*Preparation of mono-2-*O*-benzylated eicosa-*O*-methyl-β-CD* (**2**).—β-CD was treated with powdery NaOH (mole ratio β-CD/NaOH = 1:10) in DMSO at 55 °C[14] and subsequently with benzyl bromide (mole ratio β-CD/BnBr = 1:1) also at 55 °C. The hydroxy group at the C-2 position, which is more acidic than those at the C-3 and C-6 positions,[1] was expected to be predominantly activated and converted to the ether. Although TLC analysis (5:4:3 BuOH–EtOH–H_2O) suggested the formation of the benzylated CD, it was difficult to isolate the mono-benzylated CD. Thus, the reaction mixture was subjected to the full methylation, which could be conveniently performed in one-pot by the second addition of excess amounts of NaOH, followed by MeI (Scheme 1). As a result, **2** was successfully isolated by silica gel column chromatography in 33% yield, which is comparable to yields of previous methods for the mono-modification. It is interesting that replacing only one among 21 methyl ether groups with the benzyl ether group induces a good separation of **2** from β-MeCD (**1**) on a preparative scale. One benzyl group is enough to change the polarity of the CD molecule, which arises from the large conformational transformation due to the steric effect of the benzyl group.



Scheme 1.



Scheme 2.

*Transformation of **2** to various mono-2-*O*-modified eicosa-*O*-methyl-β-CDs.*—The benzyl ether group of **2** was easily restored to the hydroxy group in a quantitative yield by a usual manner of Pd-catalyzed hydrogenation under atmospheric pressure (Scheme 1). The mono-2-OH-free eicosa-*O*-methyl-β-CD (**3**) obtained is a key compound for synthesis of various mono-2-*O*-modified eicosa-*O*-methyl-β-CDs (Scheme 2). The hydroxy group of **3** was transformed to the acetate **4**, the *N*,*N*-dimethylcarbamate **5**, the *N*-*n*-butylcarbamate **6**, the methanesulfonate **7**, and the *S*-methyldithiocarbonate **8** in 31–96% yields. While pyridine was an effective base to prepare **4** and **7**, the use of NaH to generate the alkoxy anion was necessary for producing **5** and **6**. Steric hindrance probably reduces the reactivity of the hydroxy group, and harsher reaction conditions than usual are required. The reaction of the alkoxy anion with *n*-BuNCO to give **6** was found to stop before the complete conversion, which is not understandable, resulting in the low yield. The unreacted *n*-BuNCO was quenched with MeOH in the workup; use of H_2O in place of MeOH was found to be unfavorable because the resultant dibutyl urea contaminated **6**, probably due to inclusion complex formation between these two compounds. In the formation of **7**, heating at 50 °C for 5 days was unusually required to complete the reaction. It is noteworthy that tosylation resulted in the recovery of **3**, which is also ascribable to the steric hindrance. Reduction of the *S*-methyldithiocarbonate group of **8** was also attempted to prepare the C-2-mono-hydrodeoxygenated derivative (X = H) using *n*-Bu_3SnH, but instead gave **3**.

*Identification of mono-2-*O*-modified eicosa-*O*-methyl-β-CDs.*—The structures of **2**–**8** were identified by means of ^1H NMR and ^1H–^1H COSY analyses as well as an ESI mass spectroscopy. Fig. 1 presents the characteristic parts of the ^1H NMR spectra (in $CDCl_3$) showing the signal area of the anomeric protons of **1**–**8**. The signals have been assigned with the aid of ^1H–^1H COSY spectra, which informatively show the cross peaks between the protons at the C-1, C-2, and C-3 positions. The ESI mass spectra (MeOH) are summarized in Table 1. There are observed the molecular ion peaks with Na^+ and K^+, in some cases, along with the peak due to the H_3O^+ adducted molecule, which may be formed by the inclusion of H_2O into the CD cavity or by the chemical reaction (hydrolysis) through the ionization process. At any rate, the mass values of the observed peaks are in very good agreement with the calculated ones. The doubly charged ion peaks, which are omitted from Table 1, were also reasonably detected in each mass spectrum.

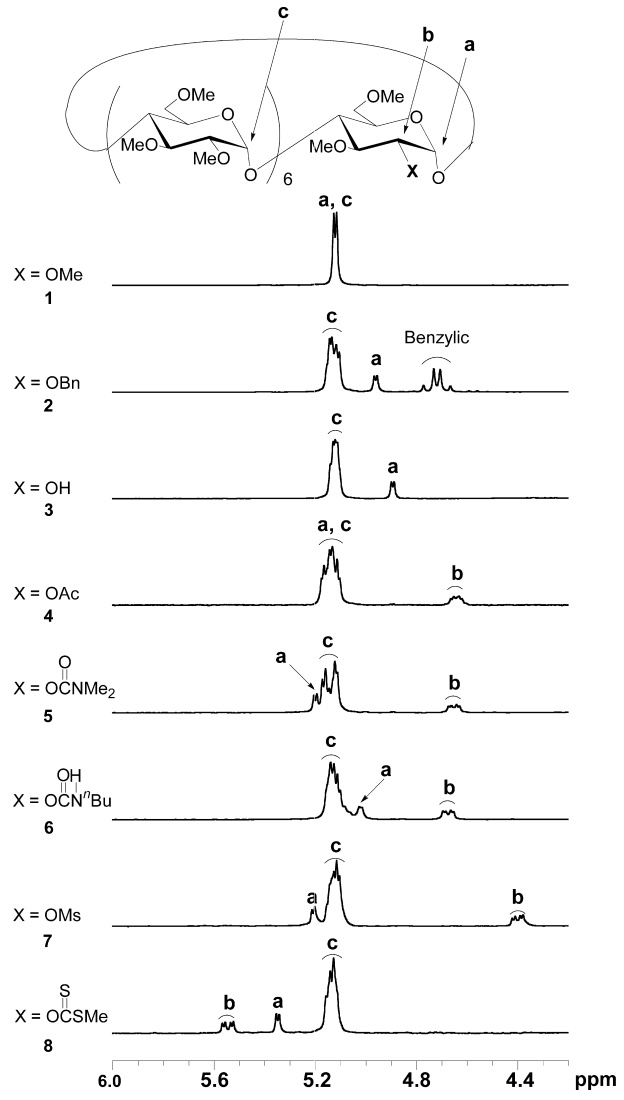


Fig. 1. Characteristic portions of the ^{1}H NMR spectra of mono-2-*O*-modified eicosa-*O*-methyl-β-cyclodextrins.

3. Experimental

General methods.—Cyclomaltoheptaose (β-Cyclodextrin, β-CD, Wako Pure Chemical Industries) was dried over P_2O_5 at 100 °C under vacuum. Dimethyl sulfoxide (DMSO) was fractionally distilled and dried over 4 Å molecular sieves. Tetrahydrofuran (THF) was dried over CaH_2 and distilled. Powdery NaOH was prepared by the careful treatment of NaH with an equimolar amount of water in dry THF.[15] Benzyl bromide and methyl iodide were purified by distillation. Other commercially available reagents were used without further purification. TLC was carried out on Silica Gel 60 F_{254} plates (E. Merck) and visualized by *p*-anisaldehyde–sulfuric acid. Column chromatography was carried out using Silica Gel 60 (spherical, neutral) (Kanto Chemical Co.). ^{1}H and ^{1}H–^{1}H COSY NMR spectra were recorded on a Bruker DPX 300 spectrometer (300 MHz for ^{1}H). Mass spectra were measured by the ESI method (10 pmol/μL in MeOH; probe voltage, 4.5 KV; CLD temp., 250 °C; positive-ion mode) on a Shimazu MS-QP8000α machine.

2^A-O-Benzyl-2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-eicosa-O-methylcyclomaltoheptaose (-β-cyclodextrin) (**2**).—In a 500-mL three-necked flask equipped with a 50-mL dropping funnel and a mechanical stirrer, β-CD (13.6 g, 12 mmol) was dissolved in dry DMSO (60 mL) by stirring at rt under a nitrogen atmosphere. Afterwards, powdered NaOH (4.8 g, 120 mmol) was added, and the mixture was stirred at 55 °C for 30 min, giving a yellowish milky-white suspension. Benzyl bromide (1.42 mL, 12 mmol) in dry DMSO (30 mL) was slowly added dropwise at 55 °C, and then the mixture was additionally stirred at 55 °C for 2 h. To the brown reaction mixture cooled to rt were again added dry DMSO (360 mL) and powdered NaOH (28.8 g, 720 mmol). Stirring at rt for 2 h

Table 1
ESI mass spectra of mono-2-*O*-modified eicosa-*O*-methyl-β-cyclodextrins

Compound X =	$[M+H_3O]^+$ (*m*/*z*)		$[M+Na]^+$ (*m*/*z*)		$[M+K]^+$ (*m*/*z*)	
	Calcd	Found (%)[a]	Calcd	Found (%)[a]	Calcd	Found (%)[a]
OMe (**1**)	1447.71	–	1451.68	1451.80 $_{(100)}$	1467.65	1467.90 $_{(40)}$
OBn (**2**)	1523.74	1524.05 $_{(16)}$	1527.71	1527.85 $_{(95)}$, 1528.85 $_{(100)}$	1543.69	1543.90 $_{(49)}$
OH (**3**)	1433.69	–	1437.66	1437.80 $_{(100)}$	1453.64	1453.80 $_{(86)}$
OAc (**4**)	1475.70	1474.90 $_{(35)}$	1479.67	1479.85 $_{(100)}$	1495.65	1495.90 $_{(50)}$
$OCONMe_2$ (**5**)	1504.73	–	1508.70	1508.95 $_{(100)}$	1524.68	1525.45 $_{(52)}$
OCONH^{n}Bu (**6**)	1532.76	–	1536.73	1537.05 $_{(100)}$	1552.71	1552.85 $_{(58)}$, 1553.90 $_{(68)}$
OMs (**7**)	1511.67	1510.65 $_{(5)}$	1515.64	1515.65 $_{(57)}$	1531.62	1531.90 $_{(100)}$
OCS_2Me (**8**)	1523.65	1523.15 $_{(6)}$	1527.62	1527.80 $_{(71)}$	1543.60	1543.80 $_{(100)}$

[a] Relative intensity of peaks is shown in the parenthesis.

was followed by the slow addition of CH_3I (30 mL, 480 mmol) under ice-cooling. The reaction mixture was stirred overnight at rt. The milky-white suspension obtained was separated into five portions, each of which was poured into ice-cooled water (700 mL) and then extracted with EtOAc (1 L). Five organic portions were combined, concentrated to the volume of 1 L under reduced pressure, and washed with water (3×1 L). The organic layer was dried with $MgSO_4$ and concentrated to give a pale-yellow amorphous solid (17.6 g). Purification by silica gel column chromatography (4:3 acetone–hexane) gave **2** (5.9 g, 3.9 mmol, 33% yield) (R_f 0.50), together with **1** (1.7 g, 1.2 mmol, 10% yield) (R_f 0.40). **2**: R_f 0.57 (2:1 acetone–hexane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 7.42–7.21 (m, 5 H, Ph), 5.15–5.10 (m, 6 H, H-1^{B-G}), 4.96 (d, 1 H, J 3.9 Hz, H-1^A), 4.75 (d, 1 H, J 12.3 Hz, CH_2Ph), 4.68 (d, 1 H, J 12.3 Hz, CH_2Ph).

2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Eicosa-O-*methylcyclomaltoheptaose (-β-cyclodextrin)* (**3**).—In a 100-mL flask containing **2** (1.6 g, 1.06 mmol) under a nitrogen atmosphere were added dry THF (10 mL) and 10-wt% Pd/C (113 mg). Hydrogen gas was introduced, and the mixture was stirred at rt for 3 days; quantitative consumption of **2** was confirmed by TLC analysis. Afterwards, Pd/C was filtered off, and the filtrate was concentrated to dryness under vacuum. Mono-hydroxy derivative **3** (1.58 g) was quantitatively obtained in almost pure form and was used without further purification; R_f 0.46 (2:1 acetone–hexane), 0.33 (1:2 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.14–5.10 (m, 6 H, H-1^{A-F}), 4.89 (d, 1 H, J 3.3 Hz, H-1^G).

2^A - O - *Acetyl* - *2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G* - *eicosa* - O - *methylcyclomaltoheptaose (-β-cyclodextrin)* (**4**).—In a 20-mL flask, **3** (567 mg, 0.4 mmol) was treated with dry pyridine (5 mL) and Ac_2O (5 mL) at 60 °C for 8 h under a nitrogen atmosphere; TLC analysis showed the quantitative conversion of **3**. Afterwards, the reaction mixture was concentrated to dryness under reduced pressure. The addition of EtOAc (50 mL) was followed by successive washes with 1 M aq HCl (3×20 mL) and water (20 mL). The organic layer was dried with $MgSO_4$ and then concentrated under vacuum. The residue (539 mg) was dissolved in refluxing hexane (8 mL), and the precipitate generated by cooling was filtered and dried under vacuum at 90 °C for 1 day to give **4** (476 mg, 0.33 mmol, 82% yield); R_f 0.52 (2:1 acetone–hexane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.17–5.10 (m, 7 H, H-1), 4.64 (dd, 1 H, J 3.6, 9.6 Hz, H-2^A), 2.15 (s, 3 H, OCOCH_3).

2^A - O - *(*N,N - *Dimetylamino)carbonyl* - *2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G* - *eicosa*-O-*methylcyclomaltoheptaose (-β-cyclodextrin)* (**5**).—In a 20-mL flask, NaH (60% dispersion in mineral oil, 80 mg, 2 mmol), washed with dry THF (3×2 mL) was suspended in dry THF (10 mL) under a nitrogen atmosphere. The THF (4 mL) solution of **3** (567 mg, 0.4 mmol) was added dropwise along with vigorous evolution of hydrogen gas. Stirring at rt for 30 min gave a milky-white solution, to which *N*,*N*-dimethylcarbamoyl chloride (0.18 mL, 2 mmol) was slowly added. The reaction mixture was stirred at rt overnight and at 50 °C for 6 h; TLC analysis was not informative in monitoring the reaction, as it showed one spot throughout. MeOH (5 mL) and water (10 mL) were successively added, and the solution was extracted with EtOAc (2×15 mL). The organic layer was dried with $MgSO_4$ and then concentrated under vacuum. The residue (580 mg), whose ^{1}H NMR spectra revealed the quantitative conversion of **3**, was dissolved in refluxing hexane (15 mL), and the precipitate generated by cooling was dried under vacuum at 90 °C for 1 day to give **5** (568 mg, 0.38 mmol, 96% yield); R_f 0.46 (2:1 acetone–hexane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.20 (d, 1 H, J 3.6 Hz, H-1^A), 5.17–5.11 (m, 6 H, H-1^{B-G}), 4.65 (dd, 1 H, J 3.6, 9.9 Hz, H-2^A), 3.01 (s, 3 H, NCH_3), 2.92 (s, 3 H, NCH_3).

2^A - O - *(*N - *Butylamino)carbonyl* - *2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G* - *eicosa* - O-*methylcyclomaltoheptaose (-β-cyclodextrin)* (**6**).—Using the same method as for preparation of **5**, **3** (567 mg, 0.4 mmol) was reacted with NaH (2 mmol). Afterwards, to the milky-white solution was slowly added *n*-butyl isocyanate (0.23 mL, 2 mmol). The reaction mixture was stirred at rt overnight and at 50 °C for 3 days; TLC analysis showed that the reaction stopped before the complete consumption of **3**. MeOH (5 mL) and water (10 mL) were successively added, and the solution was extracted with EtOAc (2×15 mL). The organic layer was washed with water (3×10 mL), dried with $MgSO_4$, and concentrated under vacuum. The resultant brown syrup was subjected to silica gel column chromatography (1:2 acetone–dichloromethane) to isolate **6**, which was dried under vacuum at 90 °C for 1 day (188 mg, 0.12 mmol, 31% yield); R_f 0.56 (2:1 acetone–hexane), 0.47 (1:2 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.15–5.06 (m, 6 H, H-1^{B-G}), 5.02 (d, 1 H, J 3.9 Hz, H-1^A), 4.68 (dd, 1 H, J 3.9, 9.3 Hz, H-2^A), 3.20–3.10 (m, 2 H, NCH_2), 1.51–1.46 (m, 2 H, $CH_2CH_2CH_2$), 1.38–1.31 (m, 2 H, CH_2CH_3), 0.96–0.84 (m, 3 H, CH_3).

2^A - O - *Methanesulfonyl-2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G* - *eicosa* - O - *methylcyclomaltoheptaose (-β-cyclodextrin)* (**7**).—To **3** (567 mg, 0.4 mmol) dissolved in dry pyridine (5 mL) in a 20-mL flask, methanesulfonyl chloride (96 μL, 1.2 mmol) was slowly added under nitrogen. The reaction mixture was stirred at rt for 5 h and then at 50 °C for 5 days; the reaction was monitored by TLC analysis to show the quantitative conversion of **3**. Water (15 mL) was added,

followed by the extraction with CH_2Cl_2 (30 mL). The organic layer was successively washed with 1 M aq HCl (2×15 mL), satd aq $NaHCO_3$ (15 mL), and water (15 mL). The resultant solution was dried with $MgSO_4$, and concentrated to dryness under vacuum. The residue was found to be almost pure **7** (523 mg, 0.35 mmol, 87% yield), which was characterized without further purification; R_f 0.58 (2:1 acetone–hexane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.20 (d, 1 H, J 3.9 Hz, H-1^A), 5.15–5.10 (m, 6 H, H-1$^{B\text{-}G}$), 4.40 (dd, 1 H, J 3.9, 9.3 Hz, H-2^A), 3.12 (s, 3 H, SCH_3).

2^A-O-(S-Methyldithio)carbonyl-2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-eicosa-O-methylcyclomaltoheptaose (-β-cyclodextrin) (**8**).—The following is a modified procedure from the literature.[16] In a 20-mL flask, NaH (60% dispersion in mineral oil, 16 mg, 0.4 mmol,) washed with dry THF (3×1 mL) was suspended in dry THF (8 mL) under a nitrogen atmosphere. The addition of **3** (284 mg, 0.2 mmol) and a catalytic amount of imidazole was followed by stirring at rt for 30 min. To the resultant green-gray mixture was slowly added CS_2 (36 μL, 0.6 mmol). The reaction mixture was stirred for 1.5 h, giving a yellow suspension, before the slow addition of CH_3I (22 μL, 0.35 mmol). After 30 min at rt, HOAc (1 mL) was added, and the reaction mixture was concentrated under vacuum; TLC analysis revealed the disappearance of **3**. The residue was dissolved in EtOAc (25 mL), washed with satd aq $NaHCO_3$ (3×15 mL), and dried with $MgSO_4$. The crude product (266 mg) obtained by evaporation was dissolved in refluxing hexane (5 mL) with acetone (0.2 mL). The precipitate generated by cooling was filtered and dried at 100 °C for 1 day to give **8** (223 mg, 0.15 mmol, 75% yield); R_f 0.55 (2:1 acetone–hexane); ^{1}H NMR ($CDCl_3$, characteristic signals): δ 5.54 (dd, 1 H, J 3.9, 9.7 Hz, H-2^A), 5.34 (d, 1 H, J 3.9 Hz, H-1^A), 5.15–5.11 (m, 6 H, H-1$^{B\text{-}G}$), 2.59 (s, 3 H, SCH_3).

4. Summary

Mono-2-*O*-modified eicosa-*O*-methyl-β-CDs were easily prepared via mono-benzylation of β-CD and subsequent debenzylation. Mono-2-*O*-benzylated CD is a useful starting compound for various mono-2-*O*-modified CDs other than the methylated derivatives demonstrated herein.

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