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Improved access to 2-*O*-monobenzyl ethers of β-cyclodextrin as precursors of catalysts for organophosphoryl esters hydrolysis

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Abstract—A comparative study of reaction conditions was performed for the synthesis of a 2-*O*-monobenzyl ether of cyclomaltoheptaose (β-CD). Optimal conditions involved sodium ethoxide in Me_2SO and benzyl bromide. The methodology was extended to the preparation of various 2^I-*O*-iodobenzyl and 2^I-*O*-carboxymethylbenzyl derivatives of β-CD including a 3-carboxymethyl-4-iodobenzyl derivative of interest as precursor of an enzyme mimic to degrade the organophosphoryl ester diethyl 4-nitrophenyl phosphate (paraoxon).

Keywords: β-Cyclodextrin monosubstitution; Benzyl ethers; Enzyme mimics; Catalysts; Organophosphoryl esters

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Functionalized cyclodextrins (cyclomalto-oligosaccharides, CDs) have been often synthesized as enzyme mimics.[1] Recently, functionalized cyclomaltoheptaose (β-CD) derivatives bearing the 2-iodosobenzoic acid functionality were developed as artificial enzymes to scavange and hydrolyze neurotoxic organophosphorus (OP) molecules.[2] This catalytic group is known to react as an anionic nucleophile active against various OPs,[3] showing potential to detoxify OP agents. An improved activity against diethyl 4-nitrophenyl phosphate (paraoxon) was achieved using 2^I-*O*-(3-carboxy-4-iodoso)benzyl-cyclomaltoheptaose **2**.[2] This compound was obtained by oxidation of 2^I-*O*-(3-carboxymethyl-4-iodo)benzyl-cyclomaltoheptaose **1** (Scheme 1).

The synthesis of **1** was initially based on a strategy developed by Rong and D'Souza[4] for CDs C-2 functionalization using sodium hydride in *N*,*N*-dimethylformamide, which led predominantly to the expected 2-O-substituted β-CD derivatives but in an admixture with several isomers. With the base/solvent system sodium hydroxide in dimethyl sulfoxide, monosubstitution at O-2 was achieved but with a low 16% yield.[2] In order to obtain larger amounts of **2** for kinetic and detoxification studies, it was necessary to improve the synthesis of **1**. In the present study, we investigated various approaches for the monosubstitution by benzyl groups at O-2, using several base/solvent systems (Scheme 2, Table 1) and differently substituted benzyl halides (Scheme 3, Table 2).

In a first approach, two aprotic dipolar solvents and five bases were tested (Table 1). Depending on the

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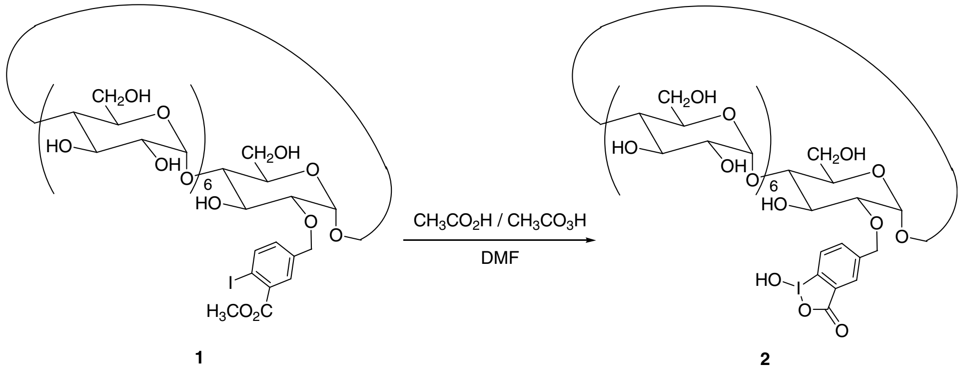
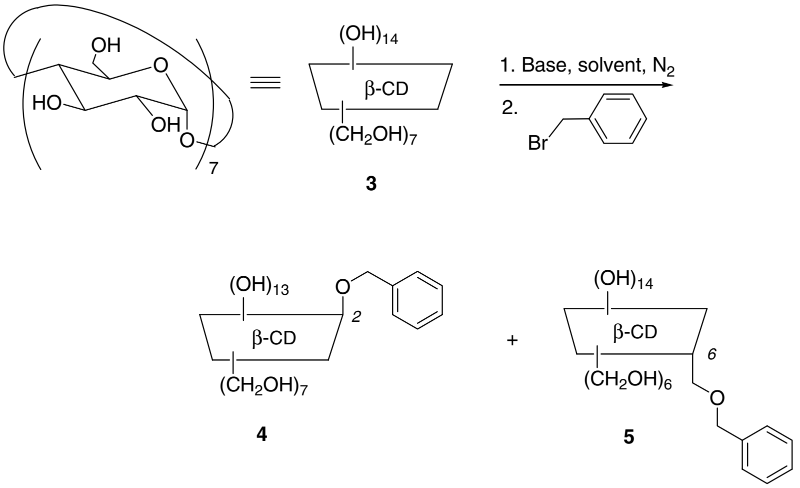


Scheme 1.



Scheme 2.

Table 1. Efficiency of β-CD substitution under various conditions of base and solvent

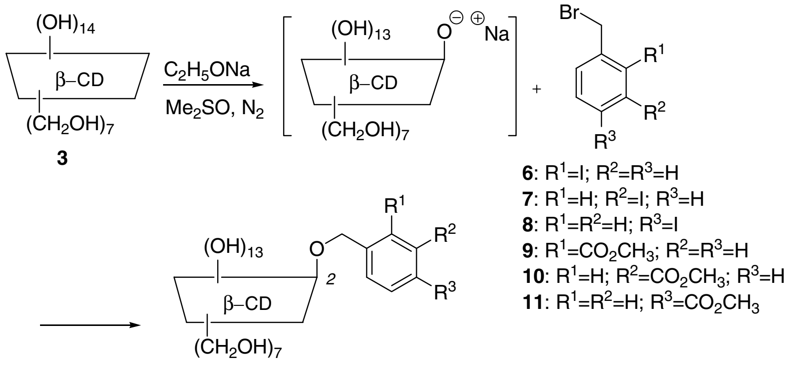
Solvent		Base				
		NaH	NaOH	C_2H_5ONa	$NaNH_2$	LDA
DMF	Isolated compounds	**4** + **5** (Mixture)	No substitution	**4**	**4** + **5** (Mixture)	**4** + **5** (Mixture)
	Global yield (%)	5.5	0	11	10	24
Me_2SO	Isolated compounds	**4**	**4**	**4**	**4**	**4**
	Global yield (%)	14	17	23	18	30

conditions, 2-monosubstituted β-CD **4** or a mixture of 2- and 6-monosubstitued β-CD **4** and **5** were obtained.

The efficiency of the nucleophilic substitution was dependent on the nature of the solvent. Higher substitution yields were obtained with Me_2SO (Table 1) as compared to DMF, which is probably related to the solvent polarity values (μ_D 7.2, Me_2SO; μ_D 6.4, DMF).

The solvent also affected the regioselectivity of the substitution reaction as this had already been observed.[5] Experiments carried out in Me_2SO led only to the corresponding 2^I-*O*-substituted β-CD **4**, which was not always the case with DMF. The nature of the base had also a dramatic influence on the yield and regioselectivity of the benzylation reaction. The best conditions, which led to isolate only 2^I-*O*-benzylated derivatives were obtained with 1 equiv of sodium ethoxide, whatever the solvent used (DMF or Me_2SO). In DMF, the three other tested bases (sodium hydride, sodium amide, and lithium diisopropylamide) led to a mixture of 2- and 6-monosubstituted compounds. No substitution was observed in DMF with sodium hydroxide.

Bases such as sodium hydroxide or sodium ethoxide have a pK_a (~15.5–16) higher than the pK_a (~12) of sec-



6: R^1=I; R^2=R^3=H
7: R^1=H; R^2=I; R^3=H
8: R^1=R^2=H; R^3=I
9: R^1=CO_2CH_3; R^2=R^3=H
10: R^1=H; R^2=CO_2CH_3; R^3=H
11: R^1=R^2=H; R^3=CO_2CH_3

12: R^1=I; R^2=R^3=H
13: R^1=H; R^2=I; R^3=H
14: R^1=R^2=H; R^3=I
15: R^1=CO_2CH_3; R^2=R^3=H
16: R^1=H; R^2=CO_2CH_3; R^3=H
17: R^1=R^2=H; R^3=CO_2CH_3

Scheme 3.

Table 2. Influence of benzyl bromide substituents on the substitution rates

Electrophilic benzylic reagent	Total substitution yield (%)	Relative percentage of 2-monosubstitution	Relative percentage of disubstitution
6 (*ortho*-Iodo)	23	83 (Compound **12**)	17
7 (*meta*-Iodo)	16	100 (Compound **13**)	0
8 (*para*-Iodo)	36	89 (Compound **14**)	11
9 (*ortho*-Ester)	18	100 (Compound **15**)	0
10 (*meta*-Ester)	18	83 (Compound **16**)	17
11 (*para*-Ester)	29	69 (Compound **17**)	31

ondary alcohols at C-2 of β-CD. Therefore, they should allow to deprotonate these alcohol groups more selectively in the presence of stoichiometric amounts of base. The other bases (sodium hydride, sodium amide, and lithium diisopropylamide) with a pK_a ~35–40 resulted in a lack of discrimination between hydroxy groups. The sodium ethoxide reactant was prepared by metal dissolution in ethanol. Consequently, DMF or Me_2SO contain about 10% of protic solvent, which could improve the formation of cationic species from benzyl bromide during synthesis. The choice of lithium diisopropylamide in Me_2SO could have been thought as the best, because the yields were in that case the highest (30%). Unfortunately, this base/solvent system was not suitable for the reactions with substituted benzyl bromides. The presence of a carboxymethyl group decreased the substitution efficiency. For example, reaction carried out with methyl 4-(bromomethyl)benzoate, using lithium diisopropylamide in Me_2SO, led to the expected substitution only in 9% yield. Sodium ethoxide was then chosen because this base led to univocal substitution at O-2 of β-CD in both solvents, and because this base was compatible with the presence of an ester function.

For the synthesis of iodosobenzoic acid-type catalysts such as **2**, iodo- and carboxymethyl substituents had to be present on the nucleus. In order to study the influence of these substituents on the O-benzylation reaction, the reactivity of monosubstituted benzyl bromides with either an iodo or a carboxymethyl substituent at positions 2, 3, and 4 were studied (Scheme 3 and Table 2).

The β-CD derivatives **12**–**14** were prepared using halogenobenzylic compounds **6**–**8**, respectively, and sodium ethoxide in Me_2SO as base/solvent system (Scheme 3). Results are summarized in Table 2. When benzyl bromide was substituted in *meta*-position (compound **7**) by an iodine atom, the 2-monobenzylated β-CD derivative (compound **13**) was the only compound isolated. In the case of the *ortho*- and *para*-substituted benzyl bromides **6** and **8**, the electron donor effect of the iodine atom increased the reactivity and explained also the formation of disubstituted β-CD derivatives as by-products. The monosubstitution yield was higher in the case of *ortho*- and *para*-iodosubstituted benzyl halides **6** and **8** (respectively, 23% and 36%) than for the *meta*-substituted derivative **7** (16%). This difference is also in agreement with an electron donor effect of the iodine atom. The role of steric hindrance was revealed by the better yield obtained when an iodine atom was in *para*-position (36%) as compared to the *ortho*-position (23%).

In order to study the influence of the presence of a carboxymethyl group on the benzyl substituent, β-CD derivatives **15**–**17** were obtained from halogenobenzylic compounds **9**–**11** substituted by a carboxymethyl group in *ortho*-, *meta*-, or *para*-positions, respectively (Scheme 3). The base/solvent system was sodium ethoxide in Me_2SO. Results proved that the position of the substituents on the ring influenced significantly the substitution degree (Table 2). Thus, comparison of yields obtained when the carboxymethyl group was in *ortho*- or *para*-positions (i.e., with similar electronic effects) showed that when the steric hindrance increased, the total substitution rate decreased (18% in the case of **9** *ortho*-substituted vs 29% in the case of **11** *para*-substituted). So far as disubstitution was concerned, the role of steric hindrance was quite significant because when steric hindrance decreased, the disubstitution yield increased (0%, 17%, and 31%, respectively, for **9**, **10**, and **11**).

The fact that benzylation yields for bromides substituted in *ortho*- and *meta*-positions were identical was in agreement with the expected concomitant influence of both electronic effects and steric hindrance. Considering only electronic effects, the yield should have been lower in *meta*-position than in *ortho*-position, but the steric hindrance playing a role in an opposite direction, the results were finally equivalent.

The nature of the reactive halogen atom in the benzylating reagent played also an important role in the reaction. Thus, replacement of benzyl bromide by benzyl chloride led to 2-substituted β-CD with a very low yield (3%). This is not surprising because bromide is a better leaving group than chloride. Even when benzyl chloride was substituted by an iodine atom at position 2, which usually increased the substitution rate, the yield was only slightly increased, but remained low (7%).

Addition of 1, 2, or 3 equiv of benzyl bromide reagent with β -CD led to the 2-*O*-monosubstituted β-CD **4** with close yields in all cases (respectively, 23%, 25%, and 23%). Not surprisingly the use of 2 or 3 equiv of benzylating reagent favored the disubstitution.

These univocal conditions of base and solvent (i.e., 1 equiv sodium ethoxide in Me_2SO) were implemented for the synthesis of compound **1**, the precursor of the most active catalyst **2**. The monosubstitution yield at O-2 of β-CD was improved (∼23%) as compared with the method previously reported[2] (16% yield). These conditions were also efficient (23.5% yield) to prepare **1** on a larger scale (>1 g).

In conclusion, this study allowed to improve the monosubstitution at O-2 of β-CD by benzyl groups. The best results were obtained with the base/solvent system sodium ethoxide in Me_2SO. This improved process will be useful for the synthesis of new substituted cyclodextrin derivatives of interest as catalysts active against OPs.

1. Experimental

1.1. General methods

Melting points are uncorrected. Optical rotations were determined at room temperature with a Perkin–Elmer polarimeter (241-MC) in 0.1 dm-cell at 589 nm for solns in water. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer working at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR). Chemical shifts are reported in δ parts per million downfield from tetramethylsilane. ESIMS experiments were performed on a MICROMASS Quattro 2 equipment (Altrincham, G.B.). Solns were introduced through a Z-spray source, which was continuously fed (5 μL min^{-1}) with a soln (1 mg/mL) of the studied compound, which was diluted in 50:50:0.1 MeCN–water–formic acid. This soln was delivered by a syringe pump HARVARD APPARATUS type 22A. The temperature of the source was set at 80 °C. The electrospray probe (capillary) voltage was optimized in the range 2.5–4 kV for positive or negative ion electrospray. The sample cone was set within the range 40–160 V. The microanalytical results showed a maximum deviation of 0.4% from the theoretical value. Water of crystallization was deduced from microanalytical data and corroborated by ^1H NMR spectroscopy.

2-Iodobenzyl bromide **6**,[6] methyl 2-(bromomethyl)-benzoate **9**,[7] and methyl 2-iodo-5-(bromomethyl)benzoate[3e] (used for the semi-preparative synthesis of **1**) were prepared according to published procedures and showed satisfying purity data (elemental analysis).

1.2. General procedure for substitution of β-CD

To a soln of β-CD (1 g, 0.88 mmol) previously dried for 48 h under diminished pressure at 120 °C in 40 mL of the appropriate solvent was added 0.88 mmol of base. In the case of EtONa, the base was prepared by dissolving 200 mg of Na in 50 mL of EtOH and 5 mL of this soln was used. The soln was stirred under N_2 for 14 h. A soln of 0.88 mmol of the electrophile reagent in 5 mL of solvent was then added dropwise to the reaction medium. The mixture was stirred for additional 9 h. Acetone (500 mL) was added and the crude product precipitated. After filtration, the solid residue was chromatographed on silica gel (12:7:4, EtOAc–isopropanol–water).

1.2.1. 2^I-*O*-Benzyl-cyclomaltoheptaose (4). Reaction of β-CD (1 g, 0.88 mmol) with benzyl bromide (150 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa led to **5** (250 mg, 23%, pale yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +30 (*c* 1.00, water). NMR-spectra were in agreement with the published data.[8]

1.2.2. 2^{I}-*O*-(2-Iodo)benzyl-cyclomaltoheptaose (12). Reaction of β-CD (1 g, 0.88 mmol) with **6** (260 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as a base led to **12** (220 mg, 19%, pale yellow solid); mp: 240–247 °C [dec]; $[\alpha]_D^{20}$ +67 (*c* 1.00, water); ^1H NMR (Me_2SO-d_6): δ 7.84 (d, 1 H, *J* 7.5 Hz, H–Ar), 7.58 (d, 1H, *J* 7.5 Hz, H–Ar), 7.42 (t, 1H, *J* 7.5 Hz, H–Ar), 7.06 (t, 1H, *J* 7.5 Hz, H–Ar), 6.09 (br s, 13H, OH-2 and 3), 4.82 (br s, 14H, H-1, OH-6), 3.63–3.31 (m, 98H, 54 from H_2O); ^{13}C NMR (Me_2SO-d_6) 140.12, 138.92, 129.72, 129.34, 128.45, 102.03, 100.12, 98.44, 81.65, 80.51, 77.03, 73.22, 72.94, 72.52, 72.12, 71.91, 60.03, 54.99. ESIMS: *m*/*z* 1373 $[M+Na]^+$. Anal. Calcd for $C_{49}H_{75}O_{35}I$, $14H_2O$: C, 36.71; H, 6.48. Found: C, 37.05; H, 6.86.

1.2.3. 2^{I}-*O*-(3-Iodo)benzyl-cyclomaltoheptaose (13). Reaction of β-CD (1 g, 0.88 mmol) with **7** (260 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as a base led to **13** (190 mg, 16%, pale yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +69 (*c* 1.05, water); ^1H NMR (Me_2SO-d_6): δ 7.78 (s, 1H, H–Ar), 7.66 (d, 1H, *J* 7.5 Hz, H–Ar), 7.42 (t, 1H, *J* 7.5 Hz, H–Ar), 7.17 (t, 1H, *J* 7.5 Hz, H–Ar), 5.98 (br s, 13H, OH-2 and 3), 4.83 (br s, 7H, H-1), 4.54 (m, 7H, OH-6), 3.62–3.40 (m, 168H, 124 from H_2O); ^{13}C NMR (Me_2SO-d_6) 140.73, 136.51, 130.69, 127.39, 102.00, 100.17, 94.97, 81.63, 79.84, 79.39, 73.19, 72.47, 72.29, 72.11, 71.87, 59.99, 48.68. ESIMS: *m*/*z* 1417 $[M-2H+3Na]^+$, 1395 $[M-H+2Na]^+$, 1373 $[M+Na]^+$. Anal. Calcd for $C_{49}H_{75}O_{35}I$, $27H_2O$: C, 32.03; H, 7.08. Found: C, 32.07; H, 7.30.

1.2.4. 2^{I}-*O*-(4-Iodo)benzyl-cyclomaltoheptaose (14). Reaction of β-CD (1 g, 0.88 mmol) with **8** (260 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as base led to **14** (380 mg, 32%, pale yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +48 (*c* 0.50, water); ^1H NMR (Me_2SO-d_6): δ 7.71 (d, 2H, *J* 8.3 Hz, H–Ar), 7.20 (d, 2H, *J* 8.3 Hz, H–Ar), 6.04 (br s, 13H, OH-2 and 3), 4.75 (br s, 7H, H-1), 4.71 (br s, 7H, OH-6), 3.31–3.62 (m, 80H, 36 from H_2O); ^{13}C NMR (Me_2SO-d_6) 137.77, 137.15, 130.35, 101.87, 100.07, 93.68, 82.18, 81.74, 79.56, 73.13, 72.48, 72.08, 59.97, 56.07. ESIMS: *m*/*z* 1395 $[M-H+2Na]^+$, 1373 $[M+Na]^+$. Anal. Calcd for $C_{49}H_{75}O_{35}I$, $18H_2O$: C, 35.13; H, 6.68. Found: C, 34.75; H, 6.32.

1.2.5. 2^{I}-*O*-(2-Carboxymethyl)benzyl-cyclomaltoheptaose (15). Reaction of β-CD (1 g, 0.88 mmol) with **9** (200 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as base led to **15** (200 mg, 18%, pale yellow solid); mp: 215 °C [dec]; $[\alpha]_D^{20}$ +62 (*c* 0.95, H_2O); ^1H NMR (Me_2SO-d_6): δ 7.84 (d, 1H, *J* 7.5 Hz, H–Ar), 7.75 (d, 1H, *J* 7.5 Hz, H–Ar), 7.61 (t, 1H, *J* 7.5 Hz, H–Ar), 7.42 (t, 1H, *J* 7.5 Hz, H–Ar), 6.09 (br s, 13H, OH-2 and 3), 4.82 (br s, 7H, H-1), 4.63 (m, 7H, OH-6), 3.83 (s, 3H, OCH_3), 3.63–3.45 (m, 136H, 92 from H_2O); ^{13}C NMR (Me_2SO-d_6) 167.00, 139.45, 132.47, 130.08, 128.71, 128.48, 127.66, 102.00, 100.04, 81.59, 80.48, 73.18, 72.50, 72.10, 71.08, 69.85, 59.98, 52.24. ESIMS: *m*/*z* 1305 $[M+Na]^+$. Anal. Calcd for $C_{51}H_{78}O_{37}$, $24H_2O$: C, 35.71; H, 7.40. Found: C, 35.81; H, 7.12.

1.2.6. 2^{I}-*O*-(3-Carboxymethyl)benzyl-cyclomaltoheptaose (16). Reaction of β-CD (1 g, 0.88 mmol) with **10** (200 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as base led to **16** (170 mg, 15%, pale yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +83 (*c* 1.00, water); ^1H NMR (Me_2SO-d_6): δ 8.00 (s, 1H, H–Ar), 7.90 (d, 1H, *J* 7.5 Hz, H–Ar), 7.70 (d, 1H, *J* 7.5 Hz, H–Ar), 7.53 (t, 1H, *J* 7.5 Hz, H–Ar), 6.24 (br s, 13H, OH-2 and 3), 4.82 (br s, 7H, H-1), 4.58 (br s, 7H, OH-6), 3.86 (s, 3H, OCH_3), 3.63–3.31 (m, 100H, 56 from H_2O); ^{13}C NMR (Me_2SO-d_6) 166.26, 138.79, 133.00, 129.76, 128.74, 128.67, 102.07, 100.23, 81.67, 79.74, 79.28, 73.24, 72.51, 72.16, 71.85, 60.04, 52.29. ESIMS: *m*/*z* 1371 $[M-3H+4Na]^+$, 1349 $[M-2H+3Na]^+$, 1327 $[M-H+2Na]^+$, 1305 $[M+Na]^+$. Anal. Calcd for $C_{51}H_{78}O_{37}$, $9H_2O$: C, 42.38; H, 6.69. Found: C, 42.31; H, 6.90.

1.2.7. 2^{I}-*O*-(4-Carboxymethyl)benzyl-cyclomaltoheptaose (17). Reaction of β-CD (1 g, 0.88 mmol) with **11** (200 mg, 0.88 mmol, 1 equiv) in Me_2SO using EtONa as base led to **17** (230 mg, 20%, pale yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +43 (*c* 0.95, water); ^1H NMR (Me_2SO-d_6): δ 7.95 (d, 2H, *J* 7.9 Hz, H–Ar), 7.55 (d, 2H, *J* 7.9 Hz, H–Ar), 6.28 (br s, 13H, OH-2 and 3), 4.82 (br s, 7H, H-1), 4.64 (br s, 7H, OH-6), 3.86 (s, 3H, OCH_3), 3.63–3.31 (m, 78H, 34 from H_2O); ^{13}C NMR (Me_2SO-d_6) 166.18, 143.66, 129.27, 128.92, 127.98, 102.03, 100.13, 81.67, 79.91, 79.28, 73.22, 72.79, 72.51, 72.13, 71.79, 69.25, 60.03, 52.20. ESIMS: *m*/*z* 1327 $[M-H+2Na]^+$, 1305 $[M+Na]^+$. Anal. Calcd for $C_{51}H_{78}O_{37}$, $11H_2O$: C, 41.35; H, 6.80. Found: C, 41.62; H, 7.13.

1.3. Semi-preparative synthesis of 2^{I}-*O*-(3-carboxymethyl-4-iodo)benzyl-cyclomaltoheptaose (1)

To a soln of β-CD previously dried for 48 h under diminished pressure at 120 °C (4 g, 3.52 mmol) in 160 mL of Me_2SO was added 3.52 mmol of EtONa (the base was prepared by dissolving 200 mg of Na in 50 mL of EtOH and 16 mL of this soln were used). The soln was stirred under N_2 for 14 h. A soln of 3.52 mmol (1.25 g) of methyl 2-iodo-5-(bromomethyl)benzoate[3e] in 20 mL of Me_2SO was then added dropwise to the reaction medium. The mixture was stirred for nine additional hours. Acetone (2 L) was added and the crude product precipitated. After filtration, the solid residue was chromatographed on silica gel (12:7:4, EtOAc–isopropanol–water) yielding **1** (1.15 g, 23.5%, yellow solid); mp >260 °C; $[\alpha]_D^{20}$ +107 (*c* 1.05, water), ESIMS and NMR-spectra were in agreement with the published data.[2]

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