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Note

A simple synthesis of hexakis(6-*O*-carboxymethyl-2,3-di-*O*-methyl)cyclomaltohexaose and heptakis(6-*O*-carboxymethyl-2,3-di-*O*-methyl)cyclomaltoheptaose

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Abstract

Hexakis(2,3-di-*O*-methyl)cyclomaltohexaose **1a** and heptakis(2,3-di-*O*-methyl)cyclomaltoheptaose **1b** were reacted with ethyl diazoacetate to give hexakis(6-*O*-ethoxycarbonylmethyl-2,3-di-*O*-methyl)cyclomaltohexaose **2a** and heptakis(6-*O*-ethoxycarbonylmethyl-2,3-di-*O*-methyl)cyclomaltoheptaose **2b**. Subsequent alkaline hydrolysis of **2a,b** gave the title compounds. © 1997 Elsevier Science Ltd.

Keywords: Carboxymethylation; α-Cyclodextrin; β-Cyclodextrin

In the course of supramolecular self-assembly studies, we needed selectively modified α- and β-cyclodextrins having the primary hydroxyl groups persubstituted with amino and carboxylic moieties. An examination of the literature reveals that great efforts have been devoted to the synthesis of pure hexakis(6-amino-6-deoxy)cyclomaltohexaose, heptakis(6-amino-6-deoxy)cyclomaltoheptaose, and their per(2,3-di-*O*-methyl) analogues [1–3]. On the other hand, very little is known about the corresponding cyclodextrins that would carry carboxylic groups attached to the primary rim [1].

It was reported [4,5] that oxidation of β-cyclodextrin, with either nitrogen dioxide or oxygen on platinum catalyst in carbon tetrachloride, gave heptakis(5-carboxy-5-dehydroxymethyl)cyclomaltoheptaose. However, no evidence establishing structural identity as well as chemical homogeneity of the product was provided.

Carboxymethyl ethers of β-cyclodextrin were obtained as mixtures from the reaction of the parent cyclodextrin with sodium chloroacetate in different media [6]. Using ^{13}C NMR spectra, Pitha and coworkers [7] investigated the distribution of substituents in the reaction of β-cyclodextrin with sodium chloroacetate in aqueous sodium hydroxide solution and found that the selectivity of the alkylation into

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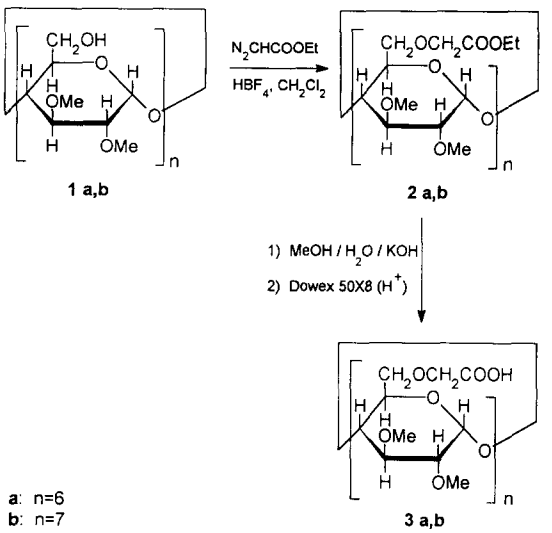
the 2-, 3-, and 6-position was highly dependent on the concentration of sodium hydroxide. Moreover, the average degree of substitution of primary hydroxyls never exceeded 0.264.

We chose hexakis(2,3-di-*O*-methyl)cyclomaltohexaose **1a** [8] and heptakis(2,3-di-*O*-methyl)cyclomaltoheptaose **1b** [9] as the starting substrates so that only primary hydroxyl groups were available for the alkylation reaction. A model reaction of **1b** with a large excess of either sodium chloroacetate or sodium bromoacetate in dimethylformamide in the presence of sodium hydride gave a mixture that proved difficult to separate. Using the more lipophilic benzyl 2-bromoacetate as the alkylating agent [10], an improved separation of the products was achieved. The course of the reaction could be conveniently monitored by TLC and individual spots of partially alkylated products were detected. However, the final steps were too sluggish compared to side reactions so that only partially carboxymethylated cyclodextrins could be obtained, even when a large excess of benzyl bromoacetate was employed. Change of the reaction conditions (solvent, ratio of reagents, temperature) gave no substantial improvement.

The above-mentioned results suggest that the customary method of carbohydrate carboxymethylation fails if pure and defined per(carboxymethylated) cyclodextrins are required.

Seeking an alternative method, we employed ethyl diazoacetate [11] as the alkylating reagent [12] in the carboxymethylation reaction (Scheme 1). It turned out that carboxymethylation of all seven primary hydroxyl groups of **1b** could be attained. The reaction was carried out with an excess (~ 50%) of ethyl diazoacetate in dry, alcohol-free dichloromethane employing boron trifluoride etherate as catalyst (2–5 mol% with respect to **1b**). The desired per(carboxymethylated) product was detected within 0.5 h. The reaction was stopped after 24 h and pure **2b** was



Scheme 1.

Table 1
^{1}H and ^{13}C NMR data for compounds **2a,b** and **3a,b**

Compd	Solv	^{1}H NMR									
		H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	H-6a ($J_{5,6b}$)	H-6b ($J_{6a,6b}$)	O–CH_2– (J_{gem})	–CH_2CH_3 (J_{vic})	2 × OCH_3 COOH
2a	$CDCl_3$	5.09 (3.4)	3.19 (10.0)	3.53 (8.8)	3.66 (9.5)	3.80 (3.9)	4.04 (1.7)	3.89 (10.5)	4.22; 4.16 (16.4)	4.17; 1.26 (7.1)	3.64; 3.49
2b	$CDCl_3$	5.17 (3.5)	3.19 (9.6)	3.50 (8.8)	3.65 (9.5)	3.84 (4.1)	3.95 (n.d.) [a]	3.85 (10.8)	4.17; 4.12 (16.3)	4.17; 1.26 (7.1)	3.65; 3.50
3a	Me_2SO	5.03 (3.6)	3.01 (9.5)	3.34 (8.9)	3.57 (9.5)	3.76 (4.0)	3.82 (2.0)	3.69 (11.0)	4.00 (2 H)	–	3.49; 3.37 12.49
3b	Me_2SO	5.14 (3.6)	3.05 (9.6)	3.32 (8.8)	3.56 (9.6)	3.71 (4.0)	3.86 (2.0)	3.65 (11.0)	4.00 (2 H)	–	3.50; 3.39 12.52
		^{13}C NMR									
		C-1	C-2 [b]	C-3 [b]	C-4 [b]	C-5	C-6	O–CH_2–	CO–O–	–CH_2CH_3	2 × OCH_3
2a	$CDCl_3$	100.80	82.35	82.00	81.14	71.17	68.62	70.21	170.22	60.52; 14.17	61.83; 57.73
2b	$CDCl_3$	99.13	82.01	81.69	80.55	70.97	68.60	70.38	170.19	60.52; 14.18	61.52; 58.47
3a	Me_2SO	98.99	81.83	81.66	81.33	70.87	68.16	70.04	171.87	–	61.24; 57.44
3b	Me_2SO	97.89	81.72	81.55	79.38	70.84	68.28	70.03	171.45	–	60.62; 57.90

[a] n.d. = not determined.
[b] Assignments of C-2, C-3, and C-4 signals may be interchanged.

obtained in 45% yield after flash chromatography. Use of an ethereal solution of tetrafluoroboric acid as the catalyst (2 mol% with respect to **1b**) increased the yield to 65%. With **1a**, the reaction required 30 h to be complete and gave 61% of pure **2a**. Further modifications of the reaction conditions gave no improvement. Both longer reaction time and higher concentration of tetrafluoroboric acid led to an increase of the amount of side products. Monitoring by TLC showed that the slowest step of the reaction is the substitution of the last hydroxyl group, suggesting operation of steric hindrance. This hypothesis was supported by an experiment in which **1a** was reacted with the less sterically demanding methyl diazoacetate [11]. The reaction proceeded faster and was quenched after 7 h to give about 60% of the corresponding methyl esters. Owing to an inconvenient manipulation [11] with methyl diazoacetate, the reaction was not further pursued.

A quantitative hydrolysis of the esters **2a,b** was achieved using a three-fold excess of potassium hydroxide in a mixture of methanol–water at ambient temperature.

The structures of compounds **2a,b** and **3a,b** were confirmed by ^{1}H and ^{13}C NMR spectroscopy (see Table 1). NMR spectra of free acids **3a,b** at 20 °C showed a line-broadening effect which was partly reduced at a higher temperature (50 °C).

1. Experimental

General methods.—NMR spectra were measured on a Varian UNITY-500 instrument at 499.84 MHz (^{1}H) or 125.70 MHz (^{13}C). Spectra of esters were run at 20 °C in $CDCl_3$ and referenced to Me_2Si (^{1}H) or the solvent peak (77.0 ppm for ^{13}C). Spectra of free acids were run at 20 and 50 °C in Me_2SO-d_6 using the solvent peak for referencing (2.5 ppm for ^{1}H or 39.7 ppm for ^{13}C NMR spectra). The structural assignment of proton signals was derived from 2D-COSY spectra. 'Attached proton test' pulse sequence [13] was used for distinguishing CH_3, CH_2, CH, and quaternary carbon signals. FABMS spectra were recorded with a ZAB-EQ VG analytical instrument using a diethyl disulfide matrix. Thin-layer chromatography (TLC) was performed with precoated Silica Gel $60F_{254}$ plates (E. Merck) which were developed by spraying with 5% H_2SO_4 in EtOH and heating. The starting compounds **1a,b** [8,9] were recrystalized from dichloroethane–diisopropylether and thoroughly dried prior to use.

Heptakis(6-O-ethoxycarbonylmethyl-2,3-di-O-methyl)cyclomaltoheptaose (**2b**).—Heptakis(2,3-di-*O*-methyl)cyclomaltoheptaose **1b** (0.25 g, 0.188 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and ethyl diazoacetate (0.225 g, 1.97 mmol) was added under nitrogen atmosphere. After a soln of HBF_4 (3.6 μL of 54% ethereal soln dissolved in 0.1 mL of CH_2Cl_2; 26.3 μmol) was added, bubbles of N_2 were observed. The course of the reaction was monitored by TLC (19:3:2:1 EtOAc–acetone–EtOH–H_2O). The reaction mixture was kept at room temperature for 24 h and then 2% aq $NaHCO_3$ (2 mL) was added with stirring. After 5 min, the mixture was diluted with CH_2Cl_2 (10 mL), the organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was dried in high vacuum at room temperature for 30 min and subjected to flash chromatography (gradient elution from $CHCl_3$ to 25:1 $CHCl_3$–MeOH) to give pure **2b** (0.24 g, 66%) as a white foam; TLC (19:3:2:1 EtOAc–acetone–EtOH–H_2O): R_f 0.51; $[\alpha]_D$ +109° (*c* 0.48, $CHCl_3$); ^{1}H and ^{13}C NMR (see Table 1); FABMS: *m/z* 1956 for $[M + Na]^+$. Anal. Calcd for $C_{84}H_{140}O_{49}$: C, 52.35; H, 7.41. Found: C, 52.17; H, 7.30.

Heptakis(6-O-carboxymethyl-2,3-di-O-methyl)cyclomaltoheptaose (**3b**).—Compound **2b** (0.34g, 0.1758 mmol) was dissolved in MeOH (5 mL). Then, KOH (3.7 mL of 1 N aq soln; 3.7 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvents were partially evaporated, water (5 mL) was added, and the soln was applied to a column of Dowex 50-X8 (H^+, 6 mL). The column was eluted with water to neutral reaction of the eluate. Evaporation of the eluate gave **3b** (0.298 g, 97%) as a white foam after extensive drying over P_2O_5 in high vacuum: $[\alpha]_D$ +118° (*c* 0.48, water); ^{1}H and ^{13}C NMR (see Table 1); FABMS: *m/z* 1760 for $[M + Na]^+$. Anal. Calcd for $C_{70}H_{112}O_{49}$: C, 48.39; H, 6.50. Found: C, 48.02; H, 6.61.

Hexakis(6-O-ethoxycarbonylmethyl-2,3-di-O-methyl)cyclomaltohexaose (**2a**).—Compound **2a** was prepared from **1a** (0.218 g, 0.2 mmol) in the same way as described for **2b**. After 30 h and a usual work-up of the reaction mixture, **2a** (0.202 g, 61%) was obtained; TLC (19:3:1:2 EtOAc–acetone–EtOH–H_2O): R_f 0.50; $[\alpha]_D$ +120° (*c* 0.50, $CHCl_3$); ^{1}H and ^{13}C NMR (see Table 1); FABMS: *m/z* 1680 for $[M + Na]^+$. Anal. Calcd for $C_{72}H_{120}O_{42}$: C, 52.17; H, 7.30. Found: C, 52.48; H, 7.33.

Hexakis(6-O-carboxymethyl-2,3-di-O-methyl)cyclomaltohexaose (**3a**).—Hydrolysis of **2a** (0.114 g, 68.8 μmol) in the same way as described

for the preparation of **3b** gave **3a** (0.97 g, 96%); $[\alpha]_D$ +104° (*c* 0.53, water); ^1H and ^{13}C NMR (see Table 1); FABMS: *m/z* 1512 for $[M + Na]^+$. Anal. Calcd for $C_{60}H_{96}O_{42}$: C, 48.39; H, 6.50. Found: C, 48.30; H, 6.51.

Acknowledgements

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