Carbohydrate Research, 192 (1989) 366–369
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

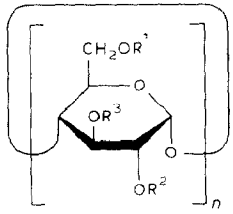
Synthesis of heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose and octakis(6-*O*-*tert*-butyldimethylsilyl)cyclomalto-octaose

PÉTER FÜGEDI
Institute of Biochemistry, L. Kossuth University, P.O. Box 55, H-4010 Debrecen (Hungary)

(Received February 1st, 1989; accepted for publication, March 21st, 1989)

The regioselective protection of all the primary hydroxyl groups of cyclomalto-oligosaccharides (cyclodextrins, CDs) is difficult[1] because of steric interactions that develop with increasing degree of substitution. Methods which are useful for monosaccharides fail[2] to give fully 6-substituted CDs as was found, for example, with tritylation[3–5]. Fully 6-substituted derivatives, obtainable by direct reaction of CDs, include only the 6-deoxy-6-halogeno and the 6-sulfonate derivatives[2], which are useful for further nucleophilic displacement reactions, but are less valuable as 6-*O*-protected derivatives.

tert-Butyldimethylsilylation of cyclomaltoheptaose (βCD, **1**) proceeds[6] regioselectively to give heptakis(6-*O*-*tert*-butyldimethylsilyl)-βCD (**2**). Selective mono-6-substitution with the same protecting group has been used in a synthesis[7] of 6-*O*-α-D-glucopyranosyl-βCD. *tert*-Butyldimethylsilylation of cyclomaltohexaose (αCD) using different conditions has been described[8]. The details of the regioselective 6-*O*-*tert*-butyldimethylsilylation of βCD (**1**) and γCD (**3**) are now reported.



	R^1	R^2	R^3	n
1	H	H	H	7
2	Bu^tMe_2Si	H	H	7
3	H	H	H	8
4	Bu^tMe_2Si	H	H	8
5	Bu^tMe_2Si	Bu^tMe_2Si	H	7
6	Bu^tMe_2Si	Ac	Ac	7
7	Bu^tMe_2Si	Ac	Ac	8

0008-6215/89/$ 03.50 © 1989 Elsevier Science Publishers B.V.

Treatment of βCD (**1**) with 7.7 equiv. of *tert*-butyldimethylsilyl chloride in pyridine gave 83% of heptakis(6-*O*-*tert*-butyldimethylsilyl)-βCD (**2**) after column chromatography. The seven-fold symmetry of **2** was proved by the ^{13}C-n.m.r. spectra which showed only one set of signals. Similar treatment of γCD (**3**) afforded 82% of octakis(6-*O*-*tert*-butyldimethylsilyl)-γCD (**4**).

tert-Butyldimethylsilylation is generally performed with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide[9]. The use of pyridine as the solvent and the base resulted in good regioselectivity towards the primary hydroxyl groups for some simple carbohydrate derivatives[10].

The silylation reaction in pyridine was more selective towards the primary hydroxyl groups than that with imidazole in *N,N*-dimethylformamide. When **1** was treated with 21 equiv. of *tert*-butyldimethylsilyl chloride in pyridine at room temperature for 24 h, the major product was **2** (61%). The corresponding reaction using imidazole in *N,N*-dimethylformamide showed a greater tendency for further silylation. After 24 h, **2** was not present and, from the mixture which contained only less polar compounds, 5% of heptakis(2,6-di-*O*-*tert*-butyldimethylsilyl)-βCD[11] (**5**) was isolated. A higher yield (66%) of **5** was obtained by performing the reaction at 90°. It is known that, under these conditions, *tert*-butyldimethylsilylation takes place both at O-6 and O-2 of CD derivatives[11–13].

Addition of acetic anhydride to the crude silylation mixture in pyridine allowed the preparation of the symmetrical 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl derivatives (**6** and **7**) of βCD and γCD, in yields of 73% and 75%, respectively, without the need to isolate **2** and **4**. Compounds **6** and **7** were also obtained by acetylation of pure **2** and **4**.

The symmetrically 6-substituted derivatives **2** and **4** have potential for the preparation of 6- and 2,3-substituted derivatives of βCD and γCD.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined with a Kofler apparatus. Optical rotations were measured with a Perkin–Elmer 241 polarimeter for solutions in chloroform. N.m.r. spectra were recorded with a Bruker WP 200 SY spectrometer; chemical shifts are given relative to that of internal Me_4Si for solutions in $CDCl_3$. Reactions were monitored by t.l.c. on Kieselgel 60 F_{254} (Merck) with detection by charring with sulfuric acid. Kieselgel G was used for short-column chromatography and Kieselgel 60 (0.063–0.2 mm) for conventional column chromatography. CDs were dried *in vacuo* over P_4O_{10} at 80° prior to use.

Heptakis(6-O-tert-butyldimethylsilyl)cyclomaltoheptaose (**2**). — To a stirred solution of dry βCD (2.270 g) in dry pyridine (30 mL) at 0° was added dropwise a solution of *tert*-butyldimethylsilyl chloride (2.321 g) in dry pyridine (20 mL). The mixture was kept at 0° for 3 h and then at room temperature overnight. Water was added, and the precipitate was collected and washed with water. Column

chromatography (dichloromethane–methanol–water, 80:19:1) afforded **2** (3.23 g, 83.5%), which was recrystallized from methanol; m.p. 314–318° (dec.), $[\alpha]_D$ +105° (*c* 0.7), R_F 0.5 (butanone–1-butanol–water, 7:1:1). ^{13}C-N.m.r. data: δ 102.1 (C-1), 81.8 (C-4), 73.7, 73.4, 72.6 (C-2,3,5), 61.7 (C-6), 25.9 (CMe_3), 18.3 (CMe_3), −5.1 and −5.2 ($SiMe_2$).

Anal. Calc. for $C_{84}H_{168}O_{35}Si_7$: C, 52.15; H, 8.75. Found: C, 52.23; H, 8.81.

Octakis(6-O-tert-butyldimethylsilyl)cyclomalto-octaose (**4**). — γCD (2.594 g) was treated with *tert*-butyldimethylsilyl chloride (2.652 g) as described for **2**. Column chromatography gave **4** (3.630 g, 82.1%), m.p. 268–270° (dec.) (from chloroform–methanol), $[\alpha]_D$ +116.5° (*c* 1), R_F 0.5 (butanone–1-butanol–water, 7:1:1). ^{13}C-N.m.r. data: δ 102.4 (C-1), 82.2 (C-4), 74.0, 73.0, 72.8 (C-2,3,5), 61.9 (C-6), 25.9 (CMe_3), 18.3 (CMe_3), −5.0 and −5.2 ($SiMe_2$).

Anal. Calc. for $C_{96}H_{192}O_{40}Si_8$: C, 52.15; H, 8.75. Found: C, 52.33; H, 8.87.

Heptakis(2,6-di-O-tert-butyldimethylsilyl)cyclomaltoheptaose (**5**). — To a mixture of βCD (1.135 g) and imidazole (2.859 g) in dry *N,N*-dimethylformamide (30 mL) was added *tert*-butyldimethylsilyl chloride (3.156 g), and the mixture was heated at 90° under argon for 24 h and then concentrated. A solution of the residue in dichloromethane was washed with M sulfuric acid, aqueous sodium hydrogencarbonate, and water, and then concentrated. Column chromatography (dichloromethane) of the residue gave **5**[11] (1.808 g, 66.1%), m.p. 289–291° (from chloroform–methanol), $[\alpha]_D$ +58° (*c* 0.5), R_F 0.3 (dichloromethane). ^{13}C-N.m.r. data: δ 102.6 (C-1), 82.1 (C-4), 74.9, 72.1, 71.9 (C-2,3,5), 62.0 (C-6), 26.3 and 25.9 (2 CMe_3), 18.9 and 18.3 (2 CMe_3), −4.5, −4.6, −5.0, and −5.2 (2 $SiMe_2$).

Anal. Calc. for $C_{126}H_{266}O_{35}Si_{14}$: C, 55.34; H, 9.80. Found: C, 55.11; H, 9.97.

Reaction of **1** *with excess of* tert-*butyldimethylsilyl chloride*. — (*a*) *In pyridine*. βCD (1.135 g) was treated with *tert*-butyldimethylsilyl chloride (3.165 g) in pyridine (30 mL) at room temperature for 24 h. T.l.c. (butanone–1-butanol–water, 7:1:1) indicated the presence of **2** and some less-polar compounds. After processing and column chromatography, as described above, **2** (1.180 g, 61.0%) was isolated.

(*b*) *In* N,N-*dimethylformamide*. A mixture of βCD (1.135 g), imidazole (2.859 g), and *tert*-butyldimethylsilyl chloride (3.165 g) was stirred in *N,N*-dimethylformamide (30 mL) at room temperature for 24 h. T.l.c. in butanone–1-butanol–water (7:1:1) showed that **2** was absent, whereas in dichloromethane–ethyl acetate (9:1) the presence of **5** together with compounds having chromatographic mobilities between those of **2** and **5** were detected. Processing, as described for **5**, gave **5** (0.146 g, 5.3%).

Heptakis(2,3-di-O-acetyl-6-O-tert-butyldimethylsilyl)cyclomaltoheptaose (**6**). — (*a*) βCD (2.270 g) was silylated as described above for **2**. After 1 day, acetic anhydride (10 mL) was added, and the mixture was kept at 60° for 1 day. Water was added, followed by dichloromethane, and the organic layer was washed with M sulfuric acid, aqueous sodium hydrogencarbonate, and water, and then concentrated. Short-column chromatography (hexane–acetone, 3:1) of the residue gave amorphous **6** (3.684 g, 73.0%), $[\alpha]_D$ +83° (*c* 1), R_F 0.3 (hexane–acetone, 7:3).

^{13}C-N.m.r. data: δ 96.5 (C-1), 75.2 (C-4), 71.8, 71.5, 71.2 (C-2,3,5), 61.8 (C-6), 25.8 (CMe_3), 20.8 and 20.7 (2 OOC*Me*), 18.2 (CMe_3), −5.1 and −5.3 ($SiMe_2$).

Anal. Calc. for $C_{112}H_{196}O_{49}Si_7$: C, 53.31; H, 7.83. Found: C, 53.51; H, 8.00.

(*b*) To a solution of **2** (0.967 g) in pyridine (10 mL) was added acetic anhydride (3.3 mL) and the mixture was heated at 60° for 1 day. The residue obtained after work-up was purified by column chromatography (hexane–acetone, 3:1) to give **6** (1.150 g, 91.2%).

*Octakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomalto-octaose* (**7**). — (*a*) Acetic anhydride (15 mL) was added to the silylation reaction mixture of **3** (2.594 g) after 1 day, and the mixture was kept at 60° for 1 day. Short-column chromatography of the processed mixture gave amorphous **7** (4.341 g, 75.3%), $[\alpha]_D$ +94° (*c* 0.7), R_F 0.3 (hexane–acetone, 7:3). ^{13}C-N.m.r. data: δ 95.6 (C-1), 74.0 (C-4), 72.1, 71.6, 71.0 (C-2,3,5), 61.9 (C-6), 25.9 (CMe_3), 20.8 and 20.5 (2 OOC*Me*), 18.3 (CMe_3), −5.1 and −5.3 ($SiMe_2$).

Anal. Calc. for $C_{128}H_{224}O_{56}Si_8$: C, 53.31; H, 7.83. Found: C, 53.47; H, 7.96.

(*b*) Compound **4** (0.553 g) was acetylated as described for **6**. Column chromatography (hexane–acetone, 3:1) gave amorphous **7** (0.631 g, 87.5%).

REFERENCES

1 J. Boger, R. J. Corcoran, and J.-M. Lehn, *Helv. Chim. Acta*, 61 (1978) 2190–2218.
2 A. P. Croft and R. A. Bartsch, *Tetrahedron*, 39 (1983) 1417–1474.
3 F. Cramer, G. Mackensen, and K. Sensse, *Chem. Ber.*, 102 (1969) 494–508.
4 R. Bergeron, Y. Machida, and K. Bloch, *J. Biol. Chem.*, 250 (1975) 1223–1230.
5 J. Boger, D. G. Brenner, and J. R. Knowles, *J. Am. Chem. Soc.*, 101 (1979) 7630–7631.
6 A. Liptàk, P. Fügedi, Z. Szurmai, J. Imre, P. Nánási, and J. Szejtli, in J. Szejtli (Ed), *Advances in Inclusion Science, Proc. Int. Symp. Cyclodextrins, 1st*, Akadémiai Kiadó, Budapest, 1982, pp. 275–287.
7 P. Fügedi, P. Nánási, and J. Szejtli, *Carbohydr. Res.*, 175 (1988) 173–181.
8 K. Takeo, K. Uemura, and H. Mitoh, *J. Carbohydr. Chem.*, 7 (1988) 293–308.
9 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94 (1972) 6190–6191.
10 F. Franke and R. D. Guthrie, *Aust. J. Chem.*, 30 (1977) 639–647.
11 R. L. Wife, D. E. Reed, D. P. Leworthy, D. M. Barnett, P. D. Regan, and H. C. Volger, ref. 6, pp. 301–325.
12 T. J. Michalski, A. Kendler, and M. L. Bender, *J. Incl. Phenom.*, 1 (1983) 125–128.
13 I. Tabushi, T. Nabeshima, K. Fujita, A. Matsunaga, and T. Imoto, *J. Org. Chem.*, 50 (1985) 2638–2643.