Carbohydrate Research, 200 (1990) 481–485
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A convenient preparation of per-2,6-di-*O*-methylcyclomalto-oligosaccharides

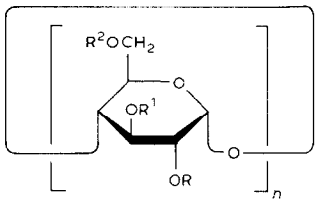
Kenichi Takeo
Department of Agricultural Chemistry, Kyoto Prefectural University, Shimogamo, Kyoto 606 (Japan)

(Received May 6th, 1989; accepted for publication, July 22nd, 1989)

The synthesis of per-2,6-di-*O*-methyl derivatives of cyclomalto-hexaose (**1**), -heptaose (**2**), and -octaose (**3**) has been studied extensively[1–5]. Hexakis(2,6-di-*O*-methyl)cyclomaltohexaose (**4**) and heptakis(2,6-di-*O*-methyl)heptaose (**5**) were obtained[1] by partial methylation of **1** and **2**, respectively, with dimethyl sulfate and barium oxide in methyl sulfoxide[6], but both were shown[2] to contain small proportions of products having a higher degree of substitution[2]. Pure **4**[3] (72%) and **5**[4] (78%) were claimed to be formed by methylation of **1** and **2** with dimethyl sulfate, barium oxide, and barium hydroxide in *N*,*N*-dimethylformamide and methyl sulfoxide[6], followed by fractionation of the products either by column chromatography[3] or by recrystallisation[4]. Methylation of **3** under conditions[3,4] similar to those used for the preparation of **4** and **5** was reported to give octakis (2,6-di-*O*-methyl)cyclomalto-octaose (**6**), but the details of the isolation and the physical constants were not reported[5]. However, Koizumi *et al.*[7] (by t.l.c. and h.p.l.c.) and Spencer *et al.*[8] (by n.m.r. spectroscopy) showed that **5**, isolated by the procedures of Boger *et al.*[3] and Szejtli *et al.*[4], was a mixture of **5** and hexakis(2,6-di-*O*-methyl)mono(2,3,6-tri-*O*-methyl)cyclomaltoheptaose (**7**). Pure **5** was isolated by preparative h.p.l.c.[7] and by a sequence involving benzoylation of a mixture of **5** and **7**, column chromatography of the product to give heptakis(3-*O*-benzoyl-2,6-di-*O*-methyl)cyclomaltoheptaose (**8**, 40%), and *O*-debenzoylation[8]. Alternatively, pure **4** and **5** were synthesised[9] in yields of 14 and 19% from **1** and **2**, respectively, by unambiguous six-step routes *via* the 6-*O*-*tert*-butyldimethylsilyl derivatives **9** and **10**. Recently, Tanimoto *et al.*[10] found (by h.p.l.c.) **4** and **6** prepared by the method of Boger *et al.*[3] to be contaminated, and isolated pure **4** and **6** by preparative h.p.l.c. We now report an efficient selective methylation of **1**–**3** and a convenient isolation of pure **4**–**6** without recourse to preparative h.p.l.c.

Selective methylation of **1** with 18 mol of methyl iodide in *N*,*N*-dimethylformamide in the presence of barium oxide and barium hydroxide[6] for 3 h at room temperature (conditions comparable to those employed[9] for partial methylation of **9** and **10**), followed by crystallisation[3] of the product, gave a mixture, column chromatography of which afforded 13% of **4**. The low isolated yield was due to the elution of a significant

0008-6215/90/$ 03.50



	n	R	R¹	R²		n	R	R¹	R²
1	6	H	H	H	8	7	Me	Bz	Me
2	7	H	H	H	9	6	H	H	X
3	8	H	H	H	10	7	H	H	X
4	6	Me	H	Me	11	6	Me	Bzl	Me
5	7	Me	H	Me	12	7	Me	Bzl	Me
6	8	Me	H	Me	13	8	Me	Bzl	Me

X = *tert*-butyldimethylsilyl

proportion of **4** in admixture with another major product having a slightly higher mobility.

When the above crystalline mixture was benzylated with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide[11], t.l.c. gave a clear separation of the products and column chromatography gave hexakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomaltohexaose (**11**, 30%) which, on catalytic hydrogenolysis (Pd–C), provided **4** (92%). Likewise, methylation of **2** with methyl iodide (21 mol)–barium oxide–barium hydroxide in *N*,*N*-dimethylformamide for 4 h at room temperature, followed by crystallisation of the product, benzylation, and column chromatography, gave heptakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomaltoheptaose (**12**, 43%), which was hydrogenolysed to give **5** (93%). Similar methylation of **3** with methyl iodide (24 mol) gave a mixture of at least ten components (t.l.c.). The fractions containing the three major products with similar mobilities were isolated by column chromatography and benzylated. Column chromatography then gave octakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomalto-octaose (**13**, 9%). Hydrogenolysis of **13** furnished **6** (92%).

The structures of **4**–**6** were confirmed by hydrolysis, followed by reduction with sodium borohydride, and acetylation, which gave 1,3,4,5-tetra-*O*-acetyl-2,6-di-*O*-methyl-D-glucitol as the sole product (g.l.c.). H.p.l.c.[10] of **4**–**6** showed a single peak for each compound.

Tanimoto *et al.*[10] found that the reaction mixtures obtained by methylation of **1**–**3**, as described above, contained **4**–**6**, respectively, as well as the by-products, in proportions essentially identical to those of the products prepared by the method of Boger *et al.*[3]. However, the methylation procedure described here involves a reaction time (3–5 h), which is much shorter than that (2–4 days) of the previous methods[1–4]. The isolation of **4**–**6** *via* **11**–**13**, respectively, may be preferable to the previous procedure[8], since the benzylation was complete within 1 h and, in subsequent column chromatography, **11**–**13** were each eluted before the by-products.

EXPERIMENTAL

General methods. — Unless stated otherwise, these were the same as described previously[9]. N.m.r. spectra (^{1}H 270 MHz, ^{13}C 67.8 MHz) were recorded with a Jeol JNM-GX 270 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) or D_2O (^{1}H, external Me_4Si; ^{13}C, internal methanol, δ_{MeOH} *vs* δ_{Me_4Si} 49.80). H.p.l.c. was kindly performed by Dr. T. Tanimoto[10].

Hexakis (2,6-di-O-methyl)cyclomaltohexaose (**4**). — (*a*) Methyl iodide (2.88 mL, 46.3 mmol) was added at 5° to a stirred solution of **1** (2.5 g, 2.6 mmol) in *N*,*N*-dimethylformamide (75 mL) containing barium oxide (3.75 g) and barium hydroxide octahydrate (1.9 g). The mixture was stirred for 3 h at room temperature, and the inorganic material was collected on a layer of Celite and washed with chloroform. The combined filtrate and washings were concentrated and a solution of the residue in chloroform was washed successively with brine, aq. sodium thiosulfate, and brine, dried, and concentrated. The residue was crystallised from chloroform–hexane[3] to give a product (2.35 g) which was shown by t.l.c. (19:1 chloroform–methanol) to contain two major [R_F 0.48 and 0.42 (**4**)] and four minor components (R_F 0.53, 0.28, 0.23, and 0.14). Column chromatography (99:1→49:1 chloroform–methanol, stepwise) of the mixture gave **4** (0.38 g, 13%), m.p. 301–307° (dec.) (from methanol), $[\alpha]_D^{24}$ +119° (*c* 1.2, chloroform), $[\alpha]_D^{24}$ +153° (*c* 1.2, water); lit.[9] m.p. 301–306° (dec.), $[\alpha]_D^{20}$ +118° (chloroform), $[\alpha]_D^{18}$ +152.5° (water). The ^{13}C-n.m.r. spectrum was identical with that described previously[9].

(*b*) A solution of the crystalline mixture (2.5 g) obtained in (*a*) in *N*,*N*-dimethylformamide (25 mL) was stirred with sodium hydride (0.95 g; 50% mineral oil) for 30 min at room temperature, then cooled to 0°. Benzyl bromide (2.2 mL) was added dropwise and the mixture was stirred for 1 h at room temperature. Methanol was added to decompose the excess of sodium hydride, most of the solvent was evaporated, and a solution of the residue in dichloromethane was washed with water, dried, and concentrated. Column chromatography (2:1→1:1→2:3 benzene–ethyl acetate, stepwise) of the syrupy residue afforded hexakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomaltohexaose (**11**) as an amorphous powder (1.31 g, 30%), $[\alpha]_D^{24}$ +99.5° (*c* 1.3, chloroform), R_F 0.5 (t.l.c., 2:1 ethyl acetate–benzene). N.m.r. data ($CDCl_3$): ^{1}H, δ 7.44–6.93 (m, 30 H, 6 Ph), 5.16 (d, 6 H, $J_{1,2}$ 3.35 Hz, H-1), 5.13 and 4.48 (2 d, each 6 H, $J \sim 10.7$ Hz, 6 PhCH_2), 5.14 and 4.79 (2 d, each 18 H, 12 OMe); ^{13}C, δ 139.58 (aromatic C-1), 99.65 (C-1), 82.26, 81.64, 80.13, and 75.76 (C-2,3,4, PhCH_2), 71.59 (C-6), 71.40 (C-5), and 59.00 and 58.76 (OMe).

A solution of **11** (1.04 g) in 2:1 methanol–acetic acid (15 mL) was hydrogenated in the presence of 10% Pd–C (0.3 g) at atmospheric pressure for 2 h at room temperature then filtered through a layer of Celite, which was washed with methanol. The combined filtrate and washings were concentrated and the residue was eluted (49:1 chloroform–methanol) from a short column to yield **4** (0.65 g, 92%), m.p. 301–307° (from methanol), $[\alpha]_D^{24}$ +153° (*c* 1.1, water).

Heptakis(2,6-di-O-methyl)cyclomaltoheptaose (**5**). — A mixture of **2** (2.0 g, 1.8 mmol), barium oxide (3.0 g), and barium hydroxide octahydrate (1.5 g) in *N*,*N*-

dimethylformamide (60 mL) was treated with methyl iodide (2.3 mL, 36.9 mmol). The mixture was stirred for 4 h at room temperature and then processed as described for the preparation of **4**. Crystallisation of the residue from chloroform–hexane gave a product (1.86 g) which was shown by t.l.c. (19:1 chloroform–methanol) to be composed of major (R_F 0.40) and minor (R_F 0.16) components. Treatment of the solid (1.86 g) in *N,N*-dimethylformamide (20 mL) with sodium hydride (0.75 g; 50% mineral oil) and benzyl bromide (1.73 mL), followed by column chromatography of the product, as described for the preparation of **11**, afforded heptakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomaltoheptaose (**12**) as an amorphous powder (1.49 g, 43%), $[\alpha]_D^{24}$ +71° (*c* 1.2, chloroform), R_F 0.39 (t.l.c., 2:1 ethyl acetate–benzene). N.m.r. data ($CDCl_3$): ^1H, δ 7.42–6.93 (m, 30 H, 7 Ph), 5.28 (d, 7 H, $J_{1,2}$ 3.66 Hz, H-1), 5.12 and 4.82 (2 d, each 7 H, $J \sim 10.5$ Hz, 7 PhCH_2), and 3.41 and 3.29 (2 s, each 21 H, 14 OMe); ^{13}C, δ 139.39 (aromatic C-1), 98.45 (C-1), 81.86, 80.79, 79.39, and 75.56 (C-2,3,4, PhCH_2), 71.51 (C-6), 71.11 (C-5), and 59.08 and 59.00 (OMe).

Hydrogenolysis of **12** (1.36 g), followed by column chromatography of the product, as described for **11**, afforded **5** (0.86 g, 93%), m.p. 299–305° (dec.) (from methanol), $[\alpha]_D^{24}$ +121° (*c* 1.1, chloroform), $[\alpha]_D^{24}$ +155.5° (*c* 1.1, water); lit.[9] m.p. 300–305° (dec.), $[\alpha]_D^{24}$ +122° (chloroform), $[\alpha]_D^{23}$ +156° (water). The ^{13}C-n.m.r. spectrum was identical with that described previously[9].

Octakis(2,6-di-O-methyl)cyclomalto-octaose (**6**). — The product obtained by treatment of a mixture of **3** (3.0 g, 2.3 mmol), barium oxide (4.5 g), and barium hydroxide octahydrate (2.3 g) in *N,N*-dimethylformamide (90 mL) with methyl iodide (3.46 mL, 55.6 mmol) for 5 h at room temperature, as described previously, was subjected to column chromatography (99:1→49:1 chloroform–methanol, stepwise). The appropriate fractions containing (t.l.c., 19:1 chloroform–methanol) three major products (R_F 0.43, 0.41, and 0.38) were collected and concentrated to dryness. Benzylation of the residue (1.24 g), followed by column chromatography of the product, as described for the preparation of **11**, gave octakis(3-*O*-benzyl-2,6-di-*O*-methyl)cyclomalto-octaose (**13**; 0.47 g, 9%), m.p. 83–88° (from methanol), $[\alpha]_D^{24}$ +87° (*c* 1.1, chloroform), R_F 0.28 (t.l.c., 2:1 ethyl acetate–benzene). N.m.r. data ($CDCl_3$): ^1H, δ 7.41–7.18 (m, 40 H, 8 Ph), 5.335 (d, 8 H, $J_{1,2}$ 3.66 Hz, H-1), 5.135 and 4.79 (2 d, each 8 H, *J* 10.4 Hz, 8 PhCH_2), and 3.41 and 3.33 (2 s, each 24 H, 16 OMe); ^{13}C, δ 139.21 (aromatic C-1), 98.26 (C-1), 81.98, 80.98, 78.78, 75.80 (C-2,3,4, PhCH_2), 71.38 (C-6), 71.19 (C-5), and 59.18 and 59.04 (OMe).

Hydrogenolysis of **13** (0.39 g), followed by column chromatography of the product, as described above, gave **6** (0.24 g, 92%), m.p. 260–264° (dec.) (from ethanol), $[\alpha]_D^{24}$ +127° (*c* 1, chloroform), $[\alpha]_D^{24}$ +179.5° (*c* 1.3, water); lit.[10] m.p. 260–264° (dec.), $[\alpha]_D^{25}$ +180° (water). N.m.r. data (D_2O): ^1H, δ 5.365 (d, 8 H, $J_{1,2}$ 2.44 Hz, H-1), 3.99–3.90 (m, 16 H, H-3,5), 3.71 (bs, 16 H, H-6), 3.61 (t, 8 H, $J_{4,5}$ 9.5 Hz, H-4), 3.54 and 3.38 (2 s, each 24 H, 16 OMe), and 3.32 (dd, 8 H, $J_{2,3}$ 9.92 Hz, H-2); ^{13}C, δ 98.47 (C-1), 82.37 (C-2), 79.36 (C-4), 73.00 and 70.63 (C-3,5), 71.65 (C-6), and 60.12 and 59.35 (OMe).

ACKNOWLEDGMENTS

Drs. T. Tanimoto and K. Koizumi of Mukogawa Women's University are thanked for the h.p.l.c. analyses, Dr. Y. Nitta of the University of Osaka Prefecture for recording the n.m.r. spectra, and Sanraku Inc. for a supply of cyclomalto-oligosaccharides.

REFERENCES

1 B. Casu, M. Reggiani, G. G. Gallo, and A. Vigevani, *Tetrahedron*, 24 (1968) 803–821.
2 B. Casu, M. Reggiani, and G. R. Sanderson, *Carbohydr. Res.*, 76 (1979) 59–66.
3 J. Boger, R. J. Corcoran, and J.-M. Lehn, *Helv. Chim. Acta*, 61 (1978) 2190–2218.
4 J. Szejtli, A. Lipták, I. Jodál, P. Fügedi, P. Nánási, and A. Neszmélyi, *Staerke*, 32 (1980) 165–169.
5 J. Pitha, *Life Sci.*, 29 (1981) 307–311.
6 R. Kuhn and H. Trischmann, *Chem. Ber.*, 96 (1963) 284–287.
7 K. Koizumi, Y. Kubota, T. Utamura, and S. Horiyama, *J. Chromatogr.*, 368 (1986) 329–337.
8 C. M. Spencer, J. F. Stoddart, and R. Zarzycki, *J. Chem. Soc., Perkin Trans. 2*, (1987) 1323–1336.
9 K. Takeo, H. Mitoh, and K. Uemura, *Carbohydr. Res.*, 187 (1989) 203–221.
10 T. Tanimoto and K. Koizumi, personal communications.
11 J. S. Brimacombe, *Methods Carbohydr. Chem.*, 6 (1972) 376–378.