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Carbohydrate Research 262 (1994) 271–282

CARBOHYDRATE
RESEARCH

Selective pivaloylation and diphenylacetylation of cyclomalto-oligosaccharides

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Received 26 January 1994; accepted in revised form 19 April 1994

Abstract

Regioselective acylation of cyclomalto-oligosaccharides was achieved using pivaloyl and diphenylacetyl chlorides. The reaction of cyclomaltohexaose (**1**) with pivaloyl chloride gave the hexakis(2,6-di-*O*-pivaloyl) derivative **19** in 66% yield. Similar reaction with cyclomaltoheptaose (**2**) led to the octakis($2^{I},6^{I},6^{II},6^{III},6^{IV},6^{V},6^{VI},6^{VII}$-*O*-pivaloyl) **26** and the **17** heptakis(6-*O*-pivaloyl) derivatives in 34 and 26% yields, respectively. The octakis(6-*O*-pivaloyl) derivative **18** was the only compound isolated (72%) in the reaction of pivaloyl chloride with cyclomalto-octaose (**3**). Diphenylacetylation of **1–3** gave the symmetrical (**20–22**) and the non-symmetrical (**27–29**) per(6-*O*-diphenylacetyl) esters as major and minor products, respectively.

Key words: Cyclomalto-oligosaccharides; Selective acylation; Pivaloylation; Diphenylacetylation; Cyclodextrin acylation

1. Introduction

The chemistry of cyclomalto-oligosaccharides has been widely investigated during the last decade [1]. Selective chemical modification of the hydroxyl groups of these compounds is a major area of interest which is not exempt from problems. Thus, the regioselective and complete modification of all the primary hydroxyl groups by standard procedures is difficult to achieve because of the statistical

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SSDI 0008-6215(94)00132-Y

problems and the geometry of the cyclodextrin molecules [1h,2]. In spite of these difficulties, recent advances have been made in the direct selective replacement of OH-6 by azido [2], bromo [3], iodo [3b,c], and phenylthio [3c] groups. On the other hand, selective protection of all the primary hydroxyl groups of cyclodextrins has been achieved efficiently by using *tert*-butylchlorodimethylsilane [4] and chlorodimethylthexylsilane [[5].

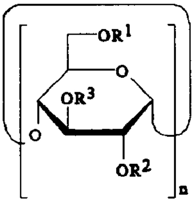
In continuation of our work in the field of cyclodextrin chemistry [3c,6], we are presently interested in the synthesis of cyclodextrin derivatives with sulfate groups specifically located at primary or secondary hydroxyl groups. However, protecting groups other than silyl groups are needed to attain this objective in a protection–sulfation–deprotection strategy. Considering that mono- and di-saccharides can be selectively acylated using bulky diphenylacetyl chloride [7], we have examined the reactions of cyclomalto-hexaose (**1**), -heptaose (**2**), and -octaose (**3**) with this acid chloride and with pivaloyl chloride.

2. Results and discussion

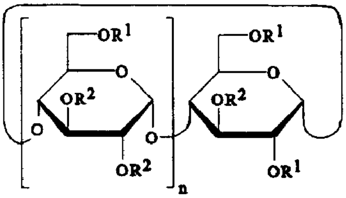
The selective reaction of **1–3** with pivaloyl chloride was first investigated. The reactions were performed at −15°C in pyridine but, in all cases, complex mixtures were detected by TLC. In order to identify the desired compounds **16–18** and then to carry out a feasible monitoring of the acylations, we first decided to synthesize these compounds by an alternative route. Per(2,3-di-*O*-acetyl) derivatives **10–12** were obtained [4] by a sequence of silylation–acetylation–desilylation of **1–3** (**1** → **4** → **7** → **10**, **2** → **5** → **8** → **11**, and **3** → **6** → **9** → **12**, respectively). The reaction of **10–12** with an excess of pivaloyl chloride in dry pyridine gave the per(6-*O*-pivaloyl) derivatives **13–15** in high yield (75–84%). Selective per(2,3-*O*-deacetylation) of these compounds was carried out using guanidine [8] in ethanol–dichloromethane. Compounds **16–18** were obtained under these conditions in high yields (> 92%).

With the per(6-*O*-pivaloyl) derivatives **16–18** in our hands, the selective pivaloylation of **1–3** was then investigated. In the reaction of **1**, the formation of compound **16** was detected by TLC. However, this was not at any time the major product of the reaction. Therefore, the reaction was continued until a major spot was observed. After purification by column chromatography of the mixture, the hexakis(2,6-di-*O*-pivaloyl) derivative **19** was isolated in 66% yield. When the reaction was performed with **2**, two major products were observed in TLC. The faster-moving component was characterized as the octapivaloate **26** (34%), while the slower-moving one was the symmetrical derivative **17** (26%). The selective pivaloylation of **3** led to the per(6-*O*-pivaloyl) derivative **18** in 72% yield.

The selective reactions of **1–3** with diphenylacetyl chloride were performed in dry pyridine, initially at −25°C for 3 h and then at room temperature. In all cases, a mixture of the corresponding per(6-*O*-diphenylacetyl) derivatives **20–22** and the non-symmetrical compounds **27–29** were obtained as major and minor products, respectively.



	n	R¹	R²	R³
1	6	H	H	H
2	7	H	H	H
3	8	H	H	H
4	6	TBDMS	H	H
5	7	TBDMS	H	H
6	8	TBDMS	H	H
7	6	TBDMS	Ac	Ac
8	7	TBDMS	Ac	Ac
9	8	TBDMS	Ac	Ac
10	6	H	Ac	Ac
11	7	H	Ac	Ac
12	8	H	Ac	Ac
13	6	Piv	Ac	Ac
14	7	Piv	Ac	Ac
15	8	Piv	Ac	Ac
16	6	Piv	H	H
17	7	Piv	H	H
18	8	Piv	H	H
19	6	Piv	Piv	H
20	6	DPA	H	H
21	7	DPA	H	H
22	8	DPA	H	H
23	6	DPA	Ac	Ac
24	7	DPA	Ac	Ac
25	8	DPA	Ac	Ac



	n	R¹	R²
26	6	Piv	H
27	5	DPA	H
28	6	DPA	H
29	7	DPA	H
30	6	Piv	Ac
31	5	DPA	Ac
32	6	DPA	Ac
33	7	DPA	Ac

Piv = $COBu^t$ DPA = Ph_2CHCO

The structures of **13–22** and **26–29** were established on the basis of their elemental analyses, FABMS, and spectroscopic data (^{1}H and ^{13}C NMR), together with those of the acetylated derivatives **23–25** and **30–33** obtained from **20–22** and **26–29**, respectively, by conventional acetylation. Tables 1–3 shows the ^{1}H and ^{13}C NMR data for compounds **13–25**.

Compounds **13–25** gave ^{1}H NMR spectra with only one set of signals for H-1–H-6, as required by the six-, seven-, and eight-fold symmetries of uniformly hexa-, hepta-, and octa-substituted derivatives of **1–3**. In compounds **20–25**, the presence of the diphenylacetyl group at O-6 caused an upfield chemical shift of ~ 0.4–0.5 and ~ 0.2 ppm for protons H-1,4 and H-2,3,5, respectively, as compared with the corresponding chemical shifts of the 6-*O*-pivaloyl derivatives **13–19** (see Table 1).

In compounds **26–29**, the FABMS spectra demonstrated the presence of an additional acyl group relative to the per(6-*O*-acyl) derivatives **16** and **20–22**. The position of attachment of this acyl group was expected to be at O-2 of one glucose moiety owing to the higher reactivity of the OH-2 relative to OH-3 [9]. This expectation is in agreement with the C-1′ resonances in compounds **26–28** which are shifted upfield (2.00–4.00 ppm) as compared with the symmetrical derivatives **16–18** and **20–22**, reflecting the acylation of a β-carbon [10] (see Table 3 and Experimental). In addition, the ^{1}H NMR spectra of **26–28** showed no signals for H-3 at δ 5.00–5.40 ppm, as observed in the ^{1}H NMR spectra of the acylated derivatives **13–15** and **23–25**. Furthemore, a double doublet at δ 4.80 ppm for H-2′ in the ^{1}H NMR spectrum of compound **26** is similar to that of the symmetrical acylated derivatives **13–15** and **19** (see Table 1 and Experimental).

In summary, both pivaloyl and diphenylacetyl chlorides are good reagents for regioselective acylation of **1–3**. In particular, diphenylacetyl chloride was shown to be a convenient acylating reagent to obtain selectively per(6-*O*-acylated) derivatives of **1–3**. The regioselectivity of these reactions increases with the size of the cyclomalto-oligosaccharides (**3** > **2** > **1**), as can be deduced from the yields of these reactions.

3. Experimental

General methods.—TLC was performed on precoated plates of Silica Gel 60 F_{254} (E. Merck) with detection by UV light, and the spots were visualized with a spray containing 5% H_2SO_4 in EtOH followed by heating. Organic solutions were dried over Na_2SO_4. Column chromatography was performed on Silica Gel 60 (70–230 and 230–400 mesh, E. Merck). Melting points, determined with an electrothermal apparatus, are uncorrected. Optical rotations were measured at room temperature in $CHCl_3$. Infrared data were obtained with a Perkin–Elmer IR 983 spectrometer; only bands of spectral structural significance are listed. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300, 500, and 600 MHz (Bruker instruments). FABMS spectra data were obtained with a Kratos Ms-80-RFA instrument.

Table 1
^{1}H NMR data for **13**–**25**

Compound	Chemical shifts (δ)							
	H-1	H-2	H-4	H-3	H-5	H-6	H-6′	Others
13 [a]	5.02d	4.70dd	3.87dd	5.46dd	4.10m	4.41dd	4.30dd	2.04, 2.03 (s, Ac), 1.19 (s, Me$_3$C)
14 [a]	5.05d	4.72dd	3.75dd	5.33dd	4.10bd	4.49bd	4.20dd	2.07, 2.04 (s, Ac), 1.20 (s, Me$_3$C)
15 [a]	5.09d	4.69dd	3.70dd	5.30dd	4.03m	4.47dd	4.21dd	2.06, 2.03 (s, Ac), 1.19 (s, Me$_3$C)
16 [b]	4.79d	3.33m	3.46dd	3.79dt	3.92m	4.22bd	4.08dd	5.51 (d, *J* 7.2 Hz, OH-2), 5.42 (d, *J* 2.9 Hz, OH-3), 1.10 (s, Me$_3$C)
17 [b]	4.79d	← 3.45–3.30m →		3.63dt	3.84m	4.21bd	4.02dd	5.83 (d, *J* 6.8 Hz, OH-2), 5.74 (d, *J* 2.3 Hz, OH-3), 1.10 (s, Me$_3$C)
18 [b]	4.81d	← 3.40–3.36m →		3.60dt	3.77m	4.19bd	4.02dd	5.86 (m, OH-2,3), 1.10 (s, Me$_3$C)
19 [a]	4.99d	4.83dd	4.13t	3.61dd	3.97bd	4.35bd	4.15dd	3.00 (bs, OH), 1.19, 1.15 (s, Me$_3$C)
20 [b]	4.28d	3.08m	3.15t	3.62dt	3.82bd	← 4.27–4.14m →		7.30 –7.15 (m, *Ph*$_2$CH),5.43 (d, *J* 7.1 Hz,OH-2), 5.29 (s, Ph$_2$C*H*), 5.28 (d, *J*, 3.4 Hz, OH-3)
21 [b]	4.24d	← 3.10–3.05m →		3.45t	3.69bd	4.27bd	4.15bd	7.30–7.15 (m, *Ph*$_2$CH), 5.75–5.55 (bs, OH-2,3), 5.27 (s, Ph$_2$C*H*)
22 [b]	4.31d	← 3.10–3.03m →		3.43bt	3.64bd	4.30m	4.11dd	7.30–7.15 (m, *Ph*$_2$CH), 5.70 (bs, OH-2,3), 5.24 (s, Ph$_2$C*H*)
23 [a]	4.60d	4.47dd	3.38dd	5.23dd	3.88bd	4.38dd	4.31dd	7.40–7.10 (m, *Ph*$_2$CH), 5.10 (s, Ph$_2$C*H*), 1.97, 1.99 (s, Ac)
24 [a]	4.67d	4.50dd	3.28dd	5.10dd	3.91bd	4.60bd	4.25dd	7.35–7.15 (m, *Ph*$_2$CH), 5.15 (s, Ph$_2$C*H*), 2.03, 2.00 (s, Ac)
25 [a]	4.73d	4.44dd	3.25t	5.12dd	3.77bd	4.48bd	3.75dd	7.45–7.15 (m, *Ph*$_2$CH), 5.06 (s, Ph$_2$C*H*), 2.00 (s, Ac)

[a] CDCl$_3$.
[b] Me$_2$SO-d_6.

Per(2,3-di-O-acetyl-6-O-pivaloyl)cyclomalto-oligosaccharides (**13–15**).—To each of a solution of the per(2,3-di-*O*-acetyl) derivatives **10–12** [4] in dry pyridine was added pivaloyl chloride. The mixture was kept at room temperature for 72 h, poured into ice–water (100 mL), and extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with 5% HCl (2 × 100 mL), aq $NaHCO_3$ (2 × 100 mL), and water (100 mL), then dried and concentrated. The crude product was purified by passage through a column of SiO_2. The following amounts and conditions were used:

Compound (g)	Me_3CCOCl (mL)	Py (mL)	Product (g, %)
10 (0.37)	1.5	10	**13** (0.42, 83.6)
11 (0.75)	3.0	15	**14** (0.75, 75.0)
12 (0.31)	1.5	10	**15** (0.33, 80.0)

Hexakis(2,3-di-O-acetyl-6-O-pivaloyl)cyclomaltohexaose (**13**).—Purified by column chromatography (5 : 1 EtOAc–hexane), the product had: mp 133–136°C; $[\alpha]_D$ + 99° (*c* 1, $CHCl_3$); v_{max} 1744 cm^{-1}. FABMS: m/z 2004 $[M + Na]^+$. Anal. Calcd for $C_{90}H_{132}O_{48} \cdot 2H_2O$: C, 53.56; H, 6.79. Found: C, 53.69; H, 6.69.

Heptakis(2,3-di-O-acetyl-6-O-pivaloyl)cyclomaltoheptaose (**14**).—Purified by column chromatography (Et_2O → EtOAc), the product had: mp 153–157°C (from ether–hexane); $[\alpha]_D$ +98° (*c* 1, $CHCl_3$); v_{max} 1753 cm^{-1}. Anal. Calcd for $C_{105}H_{154}O_{56} \cdot H_2O$: C, 54.11; H, 6.75. Found: C, 54.17; H, 6.65.

Octakis(2,3-di-O-acetyl-6-O-pivaloyl)cyclomalto-octaose (**15**).—Purified by column chromatography (1 : 1 EtOAc–hexane), the product had: mp 158–161°C; $[\alpha]_D$

Table 2
Coupling constants for **13–25**

Compound	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
13 [a]	3.5	10.2	8.5	~ 8.4	2.6	2.0	12.8
14 [a]	3.7	10.2	8.4	~ 9.0	3.0	[c]	12.7
15 [a]	3.8	9.7	8.4	~ 9.0	3.0	1.5	12.8
16 [b]	3.4	~ 9.0	~ 9.0	~ 9.0	3.5	[c]	12.1
17 [b]	3.5	~ 9.0	~ 9.0	[c]	3.3	[c]	12.2
18 [b]	3.8	~ 9.3	~ 9.3	[c]	2.7	[c]	11.5
19 [a]	3.4	10.4	~ 9.0	~ 9.0	3.0	[c]	12.0
20 [b]	3.4	~ 9.1	~ 9.1	~ 9.0	[c]	[c]	[c]
21 [b]	3.4	~ 9.2	~ 9.2	~ 9.8	[c]	[c]	11.5
22 [b]	3.9	~ 9.0	~ 9.0	9.3	3.3	[c]	12.5
23 [a]	3.4	10.1	8.6	~ 9.0	2.0	1.4	12.5
24 [a]	3.8	9.7	8.2	9.3	2.6	[c]	12.5
25 [a]	3.8	9.9	~ 9.0	~ 9.0	2.5	[c]	12.1

[a] $CDCl_3$.
[b] Me_2SO-d_6.
[c] Accurate data would not be obtained from the spectrum.

Table 3
^{13}C NMR data for **13–25**

Compound	Chemical shifts (δ)						
	C-1	C-2	C-3	C-5	C-4	C-6	Others
13[a]	96.8	← 71.4, 71.1, 70.1 →			76.3	62.5	177.7 (Me$_3$C*C*O), 170.7, 169.4 (Me*C*O), 39.0 (Me$_3$*C*), 27.3 (*Me*$_3$C), 20.9, 20.7 (*Me*CO)
14[a]	96.8	71.0	71.0	69.9	76.5	62.2	177.4 (Me$_3$C*C*O), 170.8, 169.4 (Me*C*O), 39.0 (Me$_3$*C*), 27.3 (*Me*$_3$C), 20.9, 20.8 (*Me*CO)
15[a]	96.5	← 70.9, 70.4, 70.2 →			76.0	62.3	177.4 (Me$_3$C*C*O), 170.7, 169.4 (Me*C*O), 38.9 (Me$_3$*C*), 27.2 (*Me*$_3$C), 20.8, 20.7 (*Me*CO)
16[b]	101.9	← 72.8, 71.6, 69.1 →			82.1	62.8	176.8 (Me$_3$C*C*O), 38.1 (Me$_3$*C*), 26.7 (*Me*$_3$C)
17[b]	102.1	← 72.7, 72.0, 69.0 →			81.6	62.7	176.8 (Me$_3$C*C*O), 38.1 (Me$_3$*C*), 26.7 (*Me*$_3$C)
18[b]	102.2	← 72.5, 72.3, 69.1 →			81.4	62.6	176.8 (Me$_3$C*C*O), 38.1 (Me$_3$*C*), 26.6 (*Me*$_3$C)
19[a]	99.4	← 72.6, 70.8, 69.8 →			82.2	62.5	178.0, 177.5 (Me$_3$C*C*O), 39.1, 38.8 (Me$_3$*C*), 27.2, 27.0 (*Me*$_3$C)
20[b,c]	101.7	← 72.6, 71.3, 68.5 →			81.6	63.5	171.4 (CO), 55.5 (Ph$_2$*C*H)
21[b,c]	101.9	← 72.5, 71.7, 68.6 →			81.2	63.3	171.4 (CO), 55.6 (Ph$_2$*C*H)
22[b,c]	101.8	← 72.3, 71.9, 68.8 →			80.9	63.2	171.3 (CO), 55.7 (Ph$_2$*C*H)
23[a,c]	96.5	← 71.0, 70.5, 70.0 →			75.8	62.7	171.6, 170.4, 169.3 (CO), 57.2 (Ph$_2$*C*H), 20.8 (*Me*CO)
24[a,c]	96.9	← 70.7, 70.2, 70.0 →			76.2	62.3	171.4, 170.4, 169.3 (CO), 57.0 (Ph$_2$*C*H), 20.7 (*Me*CO)
25[a,c]	96.4	← 70.5, 70.2, 70.2 →			75.6	62.2	171.3, 170.4, 169.3 (CO), 57.1 (Ph$_2$*C*H), 20.8 (*Me*CO)

[a] CDCl$_3$.
[b] Me$_2$SO-d_6.
[c] All diphenylacetyl derivatives showed several signals for *Ph*$_2$CH in the range δ 139.0–126.5.

+110° (c 1, $CHCl_3$); ν_{max} 1741 cm^{-1}. Anal. Calcd for $C_{120}H_{176}O_{64}$: C, 54.54; H, 6.71. Found: C, 54.91; H, 6.89.

Per-6(O-pivaloyl)cyclomalto-oligosaccharides (**16–18**).—To each of a solution of the 2,3-di-*O*-acetyl-6-*O*-pivaloyl derivatives **13–15** in 9:1 $CHCl_3$–EtOH was added a solution of guanidine [2.5 equiv obtained from the treatment of guanidine hydrochloride with Amberlite IRA-400 (OH^-) resin] in EtOH. The reaction was monitored by TLC (30:5:4 EtOAc–EtOH–H_2O). Brine (50 mL) was added when the reaction was complete. The solution was extracted with CH_2Cl_2 (2 × 50 mL), and the organic phase was dried and concentrated. The following amounts and conditions were used:

Compound (g)	EtOH–CH_2Cl_2 (mL)	Reaction time (h)	Product (g, %)
13 (0.35)	30	0.5	**16** (0.27, ~ 100)
14 (0.65)	65	1.0	**17** (0.49, 92.0)
15 (0.32)	20	0.5	**18** (0.23, 97.0)

Hexakis(6-O-pivaloyl)cyclomaltohexaose (**16**).—Purified by column chromatography (5:1 $CHCl_3$–MeOH), the product had: mp 204–207°C; $[\alpha]_D$ +106° (c 1, $CHCl_3$); ν_{max} 3394, 1732 cm^{-1}. Anal. Calcd for $C_{66}H_{108}O_{36} \cdot 3H_2O$: C, 51.74; H, 7.51. Found: C, 51.76; H, 7.34.

Heptakis(6-O-pivaloyl)cyclomaltoheptaose (**17**).—Purified by column chromatography (5:1 $CHCl_3$–MeOH), the product had: mp 238–240°C; $[\alpha]_D$ +103° (c 1, $CHCl_3$); ν_{max} 3378, 1731 cm^{-1}. FABMS: m/z 1746 $[M+Na]^+$. Anal. Calcd for $C_{77}H_{126}O_{42} \cdot H_2O$: C, 53.10; H, 7.41. Found: C, 52.96; H, 7.68.

Octakis(6-O-pivaloyl)cyclomalto-octaose (**18**).—Purified by column chromatography (5:1 $CHCl_3$–MeOH), the product had: mp 245–247°C; $[\alpha]_D$ +93° (c 1, $CHCl_3$); ν_{max} 3350, 1732 cm^{-1}. FABMS: m/z 1993 $[M+Na]^+$. Anal. Calcd for $C_{88}H_{144}O_{48}$: C, 53.76; H, 7.37. Found: C, 53.26; H, 7.13.

Selective pivaloylation of **1–3**.—To each of a solution of **1–3** in dry pyridine at −15°C was added dropwise pivaloyl chloride. The mixture was kept at this temperature and monitored by TLC (30:5:4 EtOAc–EtOH–H_2O) until the highest concentration of compounds **17–19**, respectively, was observed. The mixture was poured into ice-water, extracted with $CHCl_3$, and the extract was dried and concentrated to give a crude product that was purified by column chromatography. The following amounts and conditions were used:

Compound (g)	Pyridine (mL)	Me_3CCOCl (mL)	Reaction time (h)	Product (g, %)
1 (0.25)	20	0.30	24	**19** (0.35, 66.0)
2 (0.56)	15	0.90	7	**17** (0.23, 26.0), **26** (0.30, 34.0)
3 (0.20)	8	0.30	6	**18** (0.22, 72.0)

Hexakis(2,6-di-O-pivaloyl)cyclomaltohexaose (**19**).—Purified by column chromatography (5:1 EtOAc–hexane), the product had: mp 158–161°C; $[\alpha]_D$ +87° (c

1, $CHCl_3$); υ_{max} 3515, 1734 cm^{-1}. FABMS: *m/z* 2004 $[M+Na]^+$, 1981 $[M]^+$. Anal. Calcd for $C_{96}H_{156}O_{42}$: C, 58.17; H, 7.93. Found: C, 57.90; H, 7.58.

Heptakis(6-O-pivaloyl)cyclomaltoheptaose (**17**) *and octakis(2^I,6^I,6^{II},6^{III},6^{IV},6^V, 6^{VI},6^{VII}-O-pivaloyl)cyclomaltoheptaose* (**26**).—Column chromatography (15:1 → 5:1, $CHCl_3$–MeOH) of the crude product gave, first, **26**; mp 230–232°C; $[\alpha]_D$ +125° (*c* 1, $CHCl_3$); υ_{max} 3370, 1733 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.15 (d, *J* 3.0 Hz, H-1′), 4.97 (d, *J* ~ 2.7 Hz, H-1), 4.94 (d, *J* 3.0 Hz, H-1), 4.92 (d, *J* 3.2 Hz, H-1), 4.80 (dd, *J* 10.5 and 3.0 Hz, H-2′), 3.50 (pseudo t, *J* ~ 8.5 Hz, H-4′). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 102.15, 101.95, 101.90, 101.48 (6 C-1), 97.83 (C-1′), 82.94, 82.42, 82.00 (6 C-4), 79.62 (C-4′), 63.00, 62.47, 62.37, 62.04, 61.82 (7 C-6). FABMS: *m/z* 1830 $[M+Na]^+$. Anal. Calcd for $C_{82}H_{136}O_{43} \cdot 3H_2O$: C, 52.89; H, 7.58. Found: C, 52.75; H,7.44.

Eluted second was **17**.

Octakis(6-O-pivaloyl)cyclomalto-octaose (**18**).—This was isolated by column chromatography of the crude product using 7:1 $CHCl_3$–MeOH.

Selective acylation of **1–3** *with diphenylacetyl chloride.*—To each of a solution of **1–3** in dry pyridine at −15°C was added a solution of diphenylacetyl chloride in pyridine dropwise during 3 h. The mixture was allowed to warm to room temperature and the progress of the reaction was monitored by TLC (30:5:4 EtOAc–EtOH–H_2O). The mixture was poured into ice-water and the resulting solid was filtered, dried, and purified by column chromatography. The following amounts and conditions were used:

Compound–Py (g, mL)	$Ph_2CHCOCl$–Py (g, mL)	Reaction time (h)	Product (g, %)
1 (0.30, 10.0)	0.64, 15.0	24	**20** (0.45, 68.0), **27** (0.08, 12.0)
2 (1.00, 40.0)	2.15, 30.0	30	**21** (1.61, 73.2), **28** (0.43, 22.0)
3 (0.20, 10.0)	0.70, 20.0	24	**22** (0.35, 77.0), **29** (0.08, 18.0)

Hexakis(6-O-diphenylacetyl)cyclomaltohexaose (**20**) *and heptakis(2^I,6^I,6^{II},6^{III}, 6^{IV},6^V,6^{VI}-O-diphenylacetyl)cyclomaltohexaose* (**27**).—Column chromatography (9:1 $CHCl_3$–MeOH) of the crude product gave, first, **27**; mp 140–143°C; $[\alpha]_D$ +122° (*c* 1, $CHCl_3$); υ_{max} 3358, 1736 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.22, 5.21, 5.19, 5.15 (4 s, 7 Ph_2CH). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 102.17, 101.21, 101.11, 100.88 (5 C-1), 99.11 (C-1′), 81.59, 81.35, 81.20 (C-4), 63.35, 63.18, 62.99 (6 C-6), 56.88 (6 Ph_2CH), 55.38 (Ph_2CH-C-2′). FABMS: *m/z* 2355 $[M+Na]^+$. Anal. Calcd for $C_{134}H_{130}O_{37} \cdot 2H_2O$: C, 67.94; H, 5.71. Found: C, 68.06; H, 5.65.

Eluted second was **20**; mp 149–151°C; $[\alpha]_D$ +120° (*c* 1, $CHCl_3$); υ_{max} 1749 cm^{-1}. FABMS: *m/z* 2160 $[M+Na-H]^+$. Anal. Calcd for $C_{120}H_{120}O_{36} \cdot 3H_2O$: C, 65.73; H, 5.80. Found: C, 65.87; H, 5.71.

Heptakis(6-O-diphenylacetyl)cyclomaltohexaose (**21**) *and octakis(2^I,6^I,6^{II},6^{III},

6^{IV},6^{V},6^{VI},6^{VII}-O-diphenylacetyl)cyclomaltoheptaose (**28**).—Column chromatography (12:1 $CHCl_3$–MeOH) of the crude product gave, first, **28**; mp 142–146°C; $[\alpha]_D$ +130° (*c* 1, $CHCl_3$); υ_{max} 3340, 1735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.22, 5.20, 5.18, 5.17, 5.16, 5.12 (6 s, 8 Ph_2CH). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 102.56, 101.39, 101.28 (6 C-1), 99.70 (C-1′), 82.11, 81.97, 81.87, 81.62, 81.38, 81.19 (7 C-4), 63.09, 62.88 (7 C-6), 56.95 (7 Ph_2CH), 55.24 (Ph_2CH C-2′). FABMS: *m/z* 2710 $[M+Na]^+$. Anal. Calcd for $C_{154}H_{150}O_{43}$: C, 68.78; H, 5.73. Found: C, 68.50; H, 5.80.

Eluted second was **21**; mp 155–160°C; $[\alpha]_D$ +122° (*c* 1, $CHCl_3$); υ_{max} 3402, 1735 cm^{-1}. FABMS: *m/z* 2517 $[M+Na]^+$. Anal. Calcd for $C_{140}H_{140}O_{42} \cdot 5H_2O$: C, 65.06; H, 5.85. Found: C, 64.89; H,5.70.

Octakis(6-O-diphenylacetyl)cyclomalto-octaose (**22**) *and nonakis(2^{I},6^{I},6^{II},6^{III}, 6^{IV},6^{V},6^{VI},6^{VII},6^{VIII}-O-diphenylacetyl)cyclomalto-octaose* (**29**).—Column chromatography (9:1 $CHCl_3$–MeOH) of the crude product gave, first, **29**; mp 165–168°C; $[\alpha]_D$ +107° (*c* 1, $CHCl_3$); υ_{max} 3330, 1733 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.18, 5.16, 5.15, 5.14, 5.11 (5 s, 9 Ph_2CH). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 101.96 (C-1), 82.02, 81.28 (C-4), 56.96 (8 Ph_2CH), 55.28 (Ph_2CH). FABMS: *m/z* 3066 $[M+Na]^+$. Anal. Calcd for $C_{174}H_{170}O_{49} \cdot 2H_2O$: C, 67.81; H, 5.70. Found: C, 67.59; H, 5.62.

Eluted second was **22**; mp 176–179°C; $[\alpha]_D$ +111° (*c* 1, $CHCl_3$); υ_{max} 3402, 1735 cm^{-1}. FABMS: *m/z* 2872 $[M+Na]^+$. Anal. Calcd for $C_{160}H_{160}O_{48} \cdot 5H_2O$: C, 65.32; H, 5.83. Found: C, 65.11; H, 5.75.

Acetylation of **20–22** *and* **26–29**.—Conventional acetylation of compounds **20–22** and **26–29** with Ac_2O–pyridine in the presence of a catalytic amount of dimethylaminopyridine at room temperature during 30 h gave a crude product that was purified by column chromatography (2:1 EtOAc–hexane).

Hexakis(2,3-di-O-acetyl-6-O-diphenylacetyl)cyclomaltohexaose (**23**).—Isolated in > 95% yield; mp 105–107°C; $[\alpha]_D$ +55° (*c* 1, $CHCl_3$); υ_{max} 1749 cm^{-1}. Anal. Calcd for $C_{144}H_{144}O_{48} \cdot 2H_2O$: C, 64.55; H, 5.57. Found: C, 64.65; H, 5.49.

Heptakis(2,3-di-O-acetyl-6-O-diphenylacetyl)cyclomaltoheptaose (**24**).—Isolated in 84% yield; mp 92–94°C; $[\alpha]_D$ +51° (*c* 1, $CHCl_3$); υ_{max} 1749 cm^{-1}. FABMS: *m/z* 3106 $[M+Na]^+$. Anal. Calcd for $C_{168}H_{168}O_{56}$: C, 65.43; H, 5.50. Found: C, 65.64; H, 5.45.

Octakis(2,3-di-O-acetyl-6-O-diphenylacetyl)cyclomalto-octaose (**25**).—Isolated in > 95% yield; mp 121–123°C; $[\alpha]_D$ +65° (*c* 1, $CHCl_3$); υ_{max} 1749 cm^{-1}. FABMS: *m/z* 3545 $[M+Na-H]^+$. Anal. Calcd for $C_{192}H_{192}O_{64}$: C, 65.43; H, 5.50. Found: C, 65.13; H, 5.68.

Tridecakis(3^{I},2^{II},3^{II},2^{III},3^{III},2^{IV},3^{IV},2^{V},3^{V},2^{VI},3^{VI},2^{VII},3^{VII}-O-acetyl)-octakis(2^{I}, 6^{I},6^{II},6^{III},6^{IV},6^{V},6^{VI},6^{VII}-O-pivaloyl)cyclomaltoheptaose (**30**).—Isolated in 80% yield; mp 144–147°C; $[\alpha]_D$ +90° (*c* 1, $CHCl_3$); υ_{max} 1741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.47 (t, *J* 10.3 Hz, H-3), 5.45 (t, *J* 9.0 Hz, H-3), 5.40 (t, *J* 10.0 Hz, 3 H-3), 5.35 (t, *J* 8.3 Hz, H-3), 5.32 (t, *J* 8.4 Hz, H-3), 5.14 (d, *J* 3.8, 2 H-1), 5.12 (d, *J* 4.1 Hz, H-1), 5.11 (d, *J* 3.2 Hz, H-1), 5.09 (d, *J* 3.6 Hz, H-1), 5.07 (d, *J* 3.8 Hz, H-1), 5.05 (d, *J* 3.4 Hz, H-1), 4.83–4.76 (m, 5 H-2), 4.71 (dd, *J* 9.7 and 3.5 Hz, H-2), 4.64 (dd, *J* 10.4 and 3.2 Hz, H-2), 1.28–1.22 (8 s, 8 Me_3C).

^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 96.94, 96.80, 96.73, 96.57, 95.52 (C-1), 76.74, 76.39, 76.18, 75.16 (7 C-4), 62.37, 62.17, 62.00 (7 C-6). Anal. Calcd for $C_{108}H_{160}O_{56}$: C, 55.08; H, 6.85. Found: C, 55.39; H, 7.04.

Dodecakis($3^{I},2^{II},3^{II},2^{III},3^{III},2^{IV},3^{IV},2^{V},3^{V},2^{VI},3^{VI}$*-O-acetyl)-heptakis*($2^{I},6^{I},6^{II},6^{III},6^{IV},6^{V},6^{VI}$*-O-diphenylacetyl)cyclomaltohexaose* (**31**).—Isolated in 40% yield; mp 96–98°C; $[\alpha]_D$ +54° (*c* 1, $CHCl_3$); v_{max} 1750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.35–5.22 (m, 6 H-3), 5.16, 5.16, 5.15, 5.14, 5.05, 4.96 (7 s, 7 Ph_2CH), 4.74 (d, *J* 2.8 Hz, H-1), 4.69 (d, *J* 3.2 Hz, H-1), 4.64 (d, *J* 3.1 Hz, H-1), 4.62 (d, *J* 3.1 Hz, H-1), 4.59 (d, *J* 2.9 Hz, 2 H-1). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 96.77, 96.38 (C-1), 76.16, 75.84, 75.70, 75.55, 75.44 (6 C-4), 62.68, 62.50 (6 C-6), 57.04 (6 Ph_2CH), 56.14 (Ph_2CH C-2'). Anal. Calcd for $C_{156}H_{152}O_{48} \cdot 2H_2O$: C, 66.17; H, 5.55. Found: C, 66.15; H, 5.89.

Tridecakis($3^{I},2^{II},3^{II},2^{III},3^{III},2^{IV},3^{IV},2^{V},3^{V},2^{VI},3^{VI},2^{VII},3^{VII}$*-O-acetyl)-octakis*($2^{I},6^{I},6^{II},6^{III},6^{IV},6^{V},6^{VI},6^{VII}$*-O-diphenylacetyl)cyclomaltoheptaose* (**32**).—Isolated in 80% yield; mp 126–131°C; $[\alpha]_D$ +59° (*c* 1, $CHCl_3$); v_{max} 1742 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) (selected signals): δ 5.18, 5.17, 5.16, 5.02, 5.00 (5 s, 8 Ph_2CH), 5.15–5.03 (m, 7 H-3). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 96.94, 96.84, 96.70, 96.51 (7 C-1), 76.41, 76.34, 76.20, 76.11, 75.99, 75.87 (7 C-4), 62.33, 62.25, 62.18, 62.08 (7 C-6), 56.98 (7 Ph_2CH), 56.18 (Ph_2CH C-2'). Anal. Calcd for $C_{180}H_{176}O_{56}$: C, 66.81; H, 5.49. Found: C, 66.95; H, 5.75.

Tetradecakis($3^{I},2^{II},3^{II},2^{III},3^{III},2^{IV},3^{IV},2^{V},3^{V},2^{VI},3^{VI},2^{VII},3^{VII},2^{VIII},3^{VIII}$*-O-acetyl)-nonakis*($2^{I},6^{I},6^{II},6^{III},6^{IV},6^{V},6^{VI},6^{VII},6^{VIII}$*-O-diphenylacetyl)cyclomalto-octaose* (**33**).—Isolated in 40% yield; mp 112–114°C; $[\alpha]_D$ +61° (*c* 1, $CHCl_3$); v_{max} 1742 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (selected signals): δ 5.20–5.08 (m, 8 H-3), 5.17, 5.15, 5.14, 5.13, 5.12, 5.04, 4.98 (7 s, 8 Ph_2CH), 4.78 (d, *J* 3.4 Hz, H-1), 4.76 (d, *J* 3.5 Hz, H-1), 4.75 (d, *J* 3.1 Hz, H-1), 4.62 (d, *J* 3.2 Hz, H-1). ^{13}C NMR (125.76 MHz, $CDCl_3$) (selected signals): δ 96.35 (C-1), 75.45 (C-4), 62.14 (8 C-6), 57.00, 56.55, 56.20 (9 Ph_2CH). FABMS: *m/z* 3545 ($M^+ + Na - H$). Anal. Calcd for $C_{204}H_{200}O_{64}$: C, 66.66; H, 5.48. Found: C, 66.46; H, 5.55.

Acknowledgments

We thank the Comisión Asesora de Investigación Científica y Técnica for financial support (no. PB92/0936), Dr. J. Vega-Pérez (Universidad de Sevilla), Professor K. Bock, and Mr. B.O. Petersen (Carlsberg Laboratory, Copenhagen) for the recording of several mass and 500- and 600-MHz NMR spectra, respectively.

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