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1,6-ANHYDRO-β-MALTOTRIOSE: PREPARATION FROM PULLULAN, AND REGIOSELECTIVE PARTIAL-PROTECTION REACTIONS

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ABSTRACT

1,6-Anhydro-β-maltotriose (**4**) was prepared from the microbial polysaccharide pullulan in 33% overall yield by a combination of enzymic degradation and subsequent chemical treatments. Reaction of **4** with α,α-dimethoxytoluene and with 2,2-dimethoxypropane, respectively, in the presence of an acidic catalyst afforded the 4″,6″-*O*-benzylidene and 4″,6″-*O*-isopropylidene derivatives in good yields. Employement of an excess of α,α-dimethoxytoluene resulted in the 3′,2″:4″,6″-di-*O*-benzylidene derivative in 62% yield; it is characterized by having an eight-membered interglycosidic acetal ring. A few partially benzylated derivatives were prepared from these cyclic acetals as intermediates. Discrimination among three sets of hydroxyl pairs, namely, 2:3, 2′:3′, and 2″:3″, of the 4″,6″-*O*-benzylidene-6′-*O*-trityl derivative was achieved by treatment with one equimolar proportion of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, which selectively reacts with the 2′:3′ hydroxyl pair, leaving the diaxial (2:3) and one of the diequatorial (2″:3″) hydroxyl pairs unaffected.

INTRODUCTION

Success in the regioselective protections of such disaccharides as maltose and cellobiose[1], which are readily accessible by enzymic degradation of starch and cellulose, has prompted us to employ these disaccharides as key starting-materials for the synthesis of biologically active compounds[2]. Discrimination of a pair of D-glucopyranose moieties comprising these disaccharides was a common and essential problem to be first overcome. 1,6-Anhydro derivatives of the disaccharides are useful compounds for such discrimination, because their constituent monosaccharide residues have reversed conformations; *i.e.*, one is $^4C_1$(D), and the other, $^1C_4$(D). Thus, we developed efficient procedures for the synthesis[3] and further selective protections of 1,6-anhydro disaccharides[1].

Our attention has now been directed towards a trisaccharide, maltotriose. First described is the synthesis of 1,6-anhydro-β-maltotriose (**4**) from a microbial

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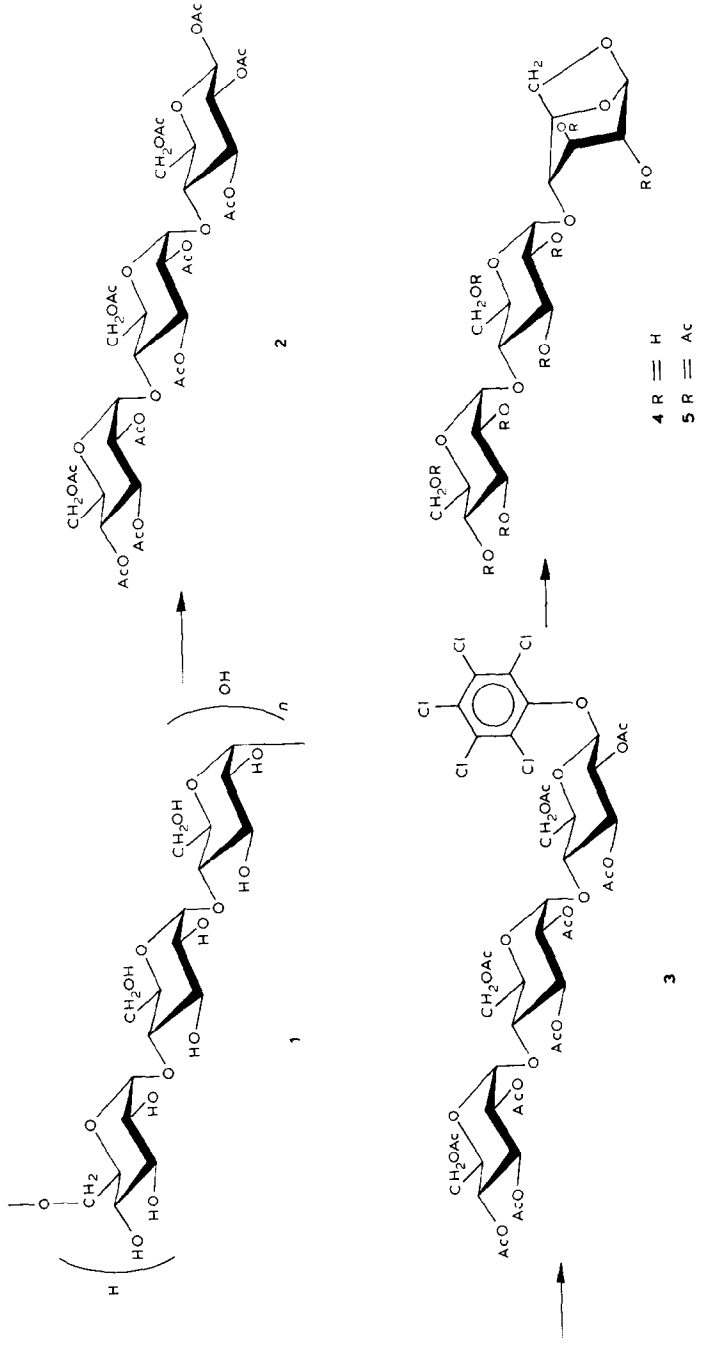
polysaccharide, pullulan, by a combination of enzymic degradation and subsequent chemical treatments. Regioselective modifications of **4** seem much more difficult than that of the disaccharide homolog , as **4** contains two D-glucopyranose moieties having the $^4C_1$(D) conformation. We examined the chemical behavior of **4** in such reactions as cyclic acetal and cyclic silyl ether formation, finding several novel types of protections, which are also described here.

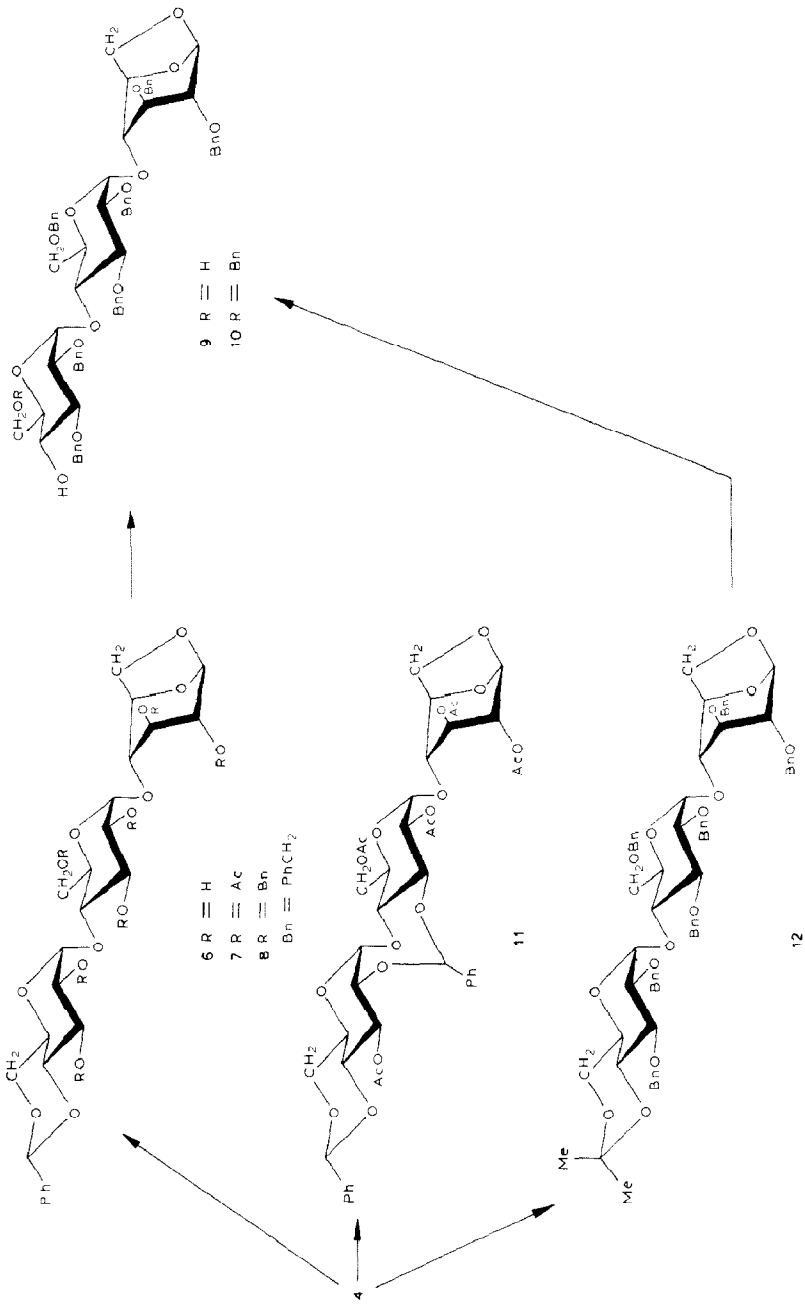
A part of the experimental results was applied to the preparation of an enzyme inhibitor named "dihydroacarbose", which has been preliminarily communicated[4].

RESULTS AND DISCUSSION

Pentachlorophenyl β-glycosides were the key intermediates in our modified preparation of 1,6-anhydro disaccharides, and they were expected to play a similar role for the preparation of the corresponding trisaccharide derivative. Crystalline pentachlorophenyl 2,3,6,2′,3′,6′,2″,3″,4″,6″-deca-*O*-acetyl-β-maltotrioside (**3**) was obtained in 53% overall yield by a series of enzymic and chemical treatments of pullulan (**1**), without purifying any intermediates. Thus, **1** was treated with a catalytic amount of pullulanase, endo-(1→6)-α-D-glucosidase (EC 3.2.1.41), and the resulting products were isolated after acetylation. The crude hendecaacetate (**2**) was converted by means of HBr in acetic acid into a glycosyl bromide which underwent glycosidation on treatment with sodium pentachlorophenoxide, to give crystalline **3**. Similarly to our previous experiments with disaccharides[3], treatment with aqueous potassium hydroxide converted **3** into 1,6-anhydro-β-maltotriose (**4**), which was isolated as the corresponding nonaacetate (**5**) in 63% yield. The physical constants observed for **5** were identical with those reported by Takeo *et al.*[5], and its ^{1}H-n.m.r. spectrum (see Tables I and II) was consistent with the expected structure. In order to generate **4** (ref. 5), **5** underwent Zemplén deacetylation with sodium methoxide.

Cyclic acetals constitute one of the most useful of derivatives available for *O*-protection with high regioselectively in carbohydrate chemistry[6]. Evans benzylidenation[7] by an acetal exchange reaction is known to give kinetically controlled products. Thus, treatment of **4** with α,α-dimethoxytoluene (1.2 mol. equiv.) in *N,N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid at 60° under diminished pressure gave the 4″,6″-*O*-benzylidene derivative (**6**), which was isolated as the heptaacetate (**7**) in 76% yield. In addition to **7**, a small proportion of less-polar product (**11**) was isolated from the reaction mixture. Compound **11** was obtainable as the major product (62% yield), when **4** was treated with an excess of the dimethyl acetal in the same manner and the product acetylated. It was identified as 2,3,2′,6′,3″-penta-*O*-acetyl-1,6-anhydro-3′,2″:4″,6″-di-*O*-benzylidene-β-maltotriose. The 400-MHz, ^{1}H-n.m.r. spectrum of **11** (Tables I and II) revealed two 1-proton-singlet signals, at δ 5.39 and 5.93, assignable to the methine protons of the two benzylidene groups, as well as five 3-proton singlets assignable to *O*-acetyl groups. The positions of the acetals were determined on the


1
2
3
4 R = H
5 R = Ac


6 R = H
7 R = Ac
8 R = Bn
Bn = PhCH2
9 R = H
10 R = Bn
11
12
4

basis of the results of decoupling experiments. The doublet of doublets at δ 4.89 and the triplet at δ 5.45 were assigned to H-2′ and H-3″, respectively, and the resonances at such low field indicates that the hydroxyl groups on these positions are acetylated, whereas the signals due to H-3′ and H-2″ appear at higher field (δ 4.55 and ~3.5, respectively), suggesting that an acetal group is present at these positions. Although formation of interglycosidic isopropylidene acetals of disaccharides had been reported[8], the regioselectivities are low and the yields are poor. On the other hand, **11** is the first compound containing a versatile interglycosidic benzylidene acetal that might undergo further useful modifications, such as reductive or oxidation ring-opening reactions of acetals[9].

The 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group has been used successfully in our laboratory for discrimination between pairs of D-glucopyranosyl residues of 1,6-anhydro disaccharides[1]. Application of this type of protection to the 1,6-anhydro trisaccharide was quite interesting. Treatment of **6** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine gave a complex mixture, probably because a highly reactive primary hydroxyl group was present at the 6′-position. After the 6′-hydroxyl group of **6** had been selectively protected by a trityl group, the resulting hexaol **13** was treated with the silylating agent (1.2 mol. equiv.). The reaction mixture was subsequently acetylated for purification and characterization of the products. Three silylated products, **15, 16,** and **14**, were isolated from the mixture by chromatography on a column of silica gel in yields of 60, 8, and 5%, respectively. In addition to these compounds, the hexaacetate **17** was isolated in 15% yield.

Structure elucidation of these products was achieved mainly on the basis of ^{1}H-n.m.r. analyses as described in the following. The spectra of **14, 15**, and **16** were recorded for solutions in benzene-d_6 (see Tables I and II). In the spectrum of **15**, H-2′ and H-3′ resonate at higher field (δ 3.80 and 4.66) than H-2, H-3, H-2″, and H-3″, indicating that the silyl group attaches to the 2′- and 3′-hydroxyl groups. Several protons on the $^4C_1$(D) glucopyranosyl residues could not however, be assigned with certainty due to overlapping signals. The structure of **15** was further confirmed by converting it into the corresponding 6′-*O*-acetyl derivative. Thus, **15** was successively treated with *p*-toluenesulfonic acid in chloroform–methanol at room temperature and with acetic anhydride in pyridine, to give the pentaacetate (**18**). The ^{1}H-n.m.r. spectrum of **18** contains signals of H-6′ at δ 4.58 and ~4.3, in contrast to those of H-6″ at δ ~4.3 and 3.92. All protons on the $^4C_1$(D) glucopyranosyl group at the nonreducing end were assigned by decoupling experiments. The signals attributable to H-2″ and H-3″ at lower field (δ 5.09 and 5.42) support the conclusion that *O*-acetyl groups are situated at these positions. By analogy with **15**, the minor products, **14** and **16**, were identified as the corresponding 2,3- and 2″,3″-cyclic silyl ethers, respectively. The fact that silylation of **13** (and subsequent acetylation) gave the 2′,3′-cyclic silyl ether **15** as the major product indicates that the 2′,3′- and 2″,3″-hydroxyl pairs can be well discriminated through this silylation

TABLE I

^{1}H-N.M.R. DATA FOR 1,6-ANHYDRO-β-MALTOTRIOSE DERIVATIVES[a]

Hydrogen atom	*Chemical shift (δ) and multiplicity*										
	5[b]	**7**[c]	**8**[d]	**9**	**10**[e]	**11**[f]	**14**[g]	**15**[h]	**16**[i]	**17**[j]	**18**[k]
H-1	5.50s	5.50s	5.48s	5.49s	5.47s	5.49s	5.14s	5.12s	5.15s	5.52s	5.46s
H-2	4.60s	4.59s	3.6m[l]	3.8m[l]	3.6m[l]	4.61s	3.3m[l]	4.84s	4.82s	4.59s	4.61s
H-3	4.83s	4.83t	3.6m[l]	3.8m[l]	3.6m[l]	4.86t	3.80s	5.58s	5.55s	4.81s	4.86s
H-4	3.84s	3.48s	3.39d	3.39s	3.38d	3.5m[l]	3.62s	3.42s	3.55s	3.53s	3.49s
H-5	4.78d	4.47d	4.71d	4.74d	4.74d	4.82d	4.87d	4.94d	5.07d	4.94d	4.76d
H-6a	3.81dd	3.98d	3.89d	3.88d	3.87d	3.98d	4.32t	3.64d	3.6m[l]	3.95d	3.99d
H-6b	4.0m[l]	3.81dd	3.6m[l]	3.8m[l]	3.6m[l]	3.81dd	3.77d	3.58t	3.6m[l]	3.67dd	3.80m[l]
H-1′	5.18d	5.17d	5.01d	4.99d	5.00d	5.28d	5.48d	5.22d	5.52d	5.26d	4.98d
H-2′	4.71dd	4.73dd	3.6m[l]	3.8m[l]	3.6m[l]	4.89dd	4.95dd	3.80dd	5.04dd	4.80dd	3.69dd
H-3′	5.57dd	5.58dd	4.18t	4.18t	4.17t	4.55dd	5.66t	4.66t	5.69t	5.3m	4.3m[l]
H-4′	4.0m[l]	4.01t	3.99t	3.97t	3.97t	3.69t	3.3m[l]	3.9m[l]	3.19t	3.45m[l]	3.78t
H-5′	4.40dt	4.40dt	4.1m	4.1m[l]	4.1m	4.4m[l]	3.3m[l]	3.3m[l]	3.4m	3.85bd	4.3m[l]
H-6′a	4.51dd	4.58dd	3.8m[l]	3.8m[l]	3.78dd	4.4m[l]	3.88d	4.00d	4.70d	3.45m[l]	4.58dd
H-6′b	4.25dd	4.3m[l]	3.6m[l]	3.8m[l]	3.6m[l]	4.4m[l]	3.3m[l]	3.3m[l]	3.6m[l]	3.45m[l]	4.3m[l]
H-1″	5.42d	5.37d	5.71d	5.63d	5.66d	5.44d	5.51d	6.22d	5.31d	5.21d	5.89d
H-2″	4.88dd	4.91dd	3.49dd	3.37dd	3.42dd	3.5m[l]	5.05dd	5.32dd	4.01dd	4.72dd	5.09dd
H-3″	5.37t	5.47t	3.6m[l]	3.8m[l]	3.37t	5.45t	5.93t	5.49t	4.33t	5.58t	5.42t
H-4″	5.08t	3.63t	3.6m[l]	3.48t	3.6m[l]	3.42t	3.3m[l]	3.3m[l]	3.30t	3.74t	3.66t
H-5″	4.0m[l]	3.90dt	3.8m[l]	4.1m[l]	3.6m[l]	3.90dt	3.57dt	3.70dt	3.7m	4.38bt	3.84m
H-6″a	4.22dd	4.3m[l]	4.15dd	3.8m[l]	3.6m[l]	4.26dd	4.33t	3.9m[l]	3.85d	3.64d	4.3m[l]
H-6″b	4.05dd	3.74t	4.04d	3.8m[l]	3.6m[l]	3.56t	3.85dd	3.3m[l]	3.6m[l]	3.24t	3.92dd

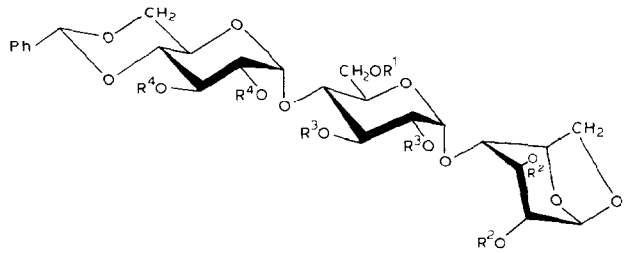
[a] ^{1}H-N.m.r. spectra were measured for solutions in $CDCl_3$, unless otherwise noted, using tetramethylsilane as the internal standard. [b] CH_3CO: 2.00, 2.01, 2.03, 2.04, 2.05, 2.12, 2.14, and 2.21. [c] CH_3CO: 2.02, 2.04, 2.05, 2.06, 2.10, 2.11, and 2.22. PhC*H*: 5.49. [d] PhC*H*: 5.52s. [e] O*H*: 2.41d. [f] CH_3CO: 2.03, 2.09, 2.10, 2.13, and 2.25. PhC*H*: 5.39s and 5.93s. [g] In C_6D_6. CH_3CO: 1.63, 1.83, 1.85, and 1.98. PhC*H*: 5.57s. [h] In C_6D_6. CH_3CO: 1.53, 1.71, 1.76, and 1.89. PhC*H*: 5.16s. [i] In C_6D_6. CH_3CO: 1.50, 1.66, 1.90, and 1.95. PhC*H*: 5.16s. [j] CH_3CO: 1.99, 2.04, 2.05, 2.06, 2.08, and 2.21. PhC*H*: 5.39. [k] CH_3CO: 2.01, 2.04, 2.10, 2.11, and 2.12. PhC*H*: 5.64. [l] Not analyzed, due to overlapping signals.

TABLE II

^1H–^1H COUPLING CONSTANTS OF 1,6-ANHYDRO-β-MALTOTRIOSE DERIVATIVES

Coupling	*J-values (Hz)*										
	5	**7**	**8**	**9**	**10**	**11**	**14**	**15**	**16**	**17**	**18**
$J_{1,2}$	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5
$J_{2,3}$	<1.5	1.5	[a]	[a]	2.7	1.5	<1.5	<1.5	<1.5	<1.5	<1.5
$J_{3,4}$	<1.5	1.5	[a]	<1.5	<1.5	1.5	<1.5	<1.5	<1.5	<1.5	<1.5
$J_{4,5}$	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5	<1.5
$J_{5,6a}$	5.5	5.5	5.4	<1.5	<1.5	<1.5	7.3	<1.5	<1.5	<1.5	<1.5
$J_{5,6b}$	[a]	<1.5	<1.5	5.6	5.6	5.9	<1.5	6.9	5.8	6.1	5.6
$J_{6a,6b}$	7.6	7.6	6.8	7.1	7.1	7.8	7.3	7.3	[a]	7.6	7.6
$J_{1',2'}$	3.7	3.6	3.7	3.7	3.7	3.6	3.9	3.7	4.0	4.2	3.9
$J_{2',3'}$	10.0	10.2	8.5	9.0	9.2	10.5	10.0	8.8	10.1	10.2	9.0
$J_{3',4'}$	9.1	9.1	8.5	9.3	9.2	9.0	10.0	8.6	10.1	[a]	9.3
$J_{4',5'}$	9.8	9.3	9.5	9.3	9.4	9.0	[a]	[a]	10.2	9.4	9.3
$J_{5',6'a}$	3.2	2.9	[a]	[a]	4.9	[a]	[a]	<1.5	<1.5	<2	2.2
$J_{5',6'b}$	3.2	2.9	[a]	[a]	[a]	[a]	1.5	[a]	[a]	<2	[a]
$J_{6'a,6'b}$	12.3	10.0	[a]	[a]	10.5	[a]	8.5	9.5	7.6	[a]	11.7
$J_{1'',2''}$	3.9	4.2	4.0	3.6	3.7	4.1	4.4	3.9	3.7	3.9	3.8
$J_{2'',3''}$	9.5	10.2	9.5	9.8	9.7	9.8	10.2	9.9	9.5	9.5	10.0
$J_{3'',4''}$	9.5	10.0	[a]	8.6	9.7	9.8	10.2	9.8	9.2	9.3	9.4
$J_{4'',5''}$	9.5	10.0	[a]	8.6	9.4	9.8	9.3	9.0	9.5	9.3	9.4
$J_{5'',6''a}$	3.7	4.9	4.9	[a]	[a]	4.9	9.5	9.0	<1.5	<2	[a]
$J_{5'',6''b}$	2.4	10.0	<1.5	[a]	[a]	9.8	5.4	4.0	[a]	8.1	8.3
$J_{6''a,6''b}$	12.1	10.2	10.8	[a]	[a]	10.3	9.6	[a]	8.5	8.1	9.3

[a]Not analyzed, due to overlapping of signals.



	R^1	R^2	R^3	R^4
13	Tr	H	H	H
14	Tr	TIPS	Ac	Ac
15	Tr	Ac	TIPS	Ac
16	Tr	Ac	Ac	TIPS
17	Tr	Ac	Ac	Ac
18	Ac	Ac	TIPS	Ac

TIPS = $(Me_2CH)_2Si\overset{|}{O}\overset{|}{Si}(CHMe_2)_2$

Tr = Ph_3C

reaction, although both pairs are situated in D-glucopyranosyl residues having the same $^4C_1$(D) conformation. Furthermore, this means that silylation would be very useful for discrimination of the three D-glucopyranosyl residues of **4**, because the silylating agent selectively reacts with the middle residue, leaving the terminal $^4C_1$(D) and $^1C_4$(D) glucose residues unaffected.

A few partially benzylated derivatives were prepared from **4** by utilizing its cyclic acetals as intermediates. The 4″,6″-*O*-benzylidene derivative **7** was successively treated with sodium methoxide in methanol and with benzyl bromide–sodium hydride in DMF to give the hepta-*O*-benzyl derivative (**8**). *O*-Debenzylidenation of **8** with aqueous trifluoroacetic acid afforded the corresponding 4″,6″-diol (**9**) in good yield. As an alternative route to **9**, compound **4** was successively treated in DMF with 2,2-dimethoxypropane–*p*-toluenesulfonic acid and with benzyl bromide–sodium hydride, giving the 4″,6″-*O*-isopropylidene derivative **12**. Removal of the *O*-isopropylidene group of **12** with 80% aqueous acetic acid afforded **9** in 60% overall yield from **4**. For regioselective protection at the 6″-hydroxyl group, **9** was subjected to tributyltin alkoxide-mediated benzylation[10]. Thus, treatment of **9** with bis(tributyltin) oxide in toluene under reflux, followed by treatment with benzyl bromide–tetraethylammonium bromide at 80°, afforded **10** in 58% yield. These partially benzylated derivatives were used[4] as the building blocks for the synthesis of "dihydroacarbose".

EXPERIMENTAL

General methods. — Melting points were determined with a Yamato micro melting-point apparatus, and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241MC polarimeter. I.r. spectra were recorded with a Shimadzu IR-27 spectrophotometer, for potassium bromide disks or on KRS (thallium bromide–iodide) for thin films. ^{1}H-N.m.r. spectra were recorded at 400 MHz or 500 MHz with JEOL JNM-GX 400 or JEOL JNM-GX 500 spectrometers, using tetramethylsilane as the internal standard. Reactions were monitored by t.l.c. on precoated plates of silica gel $60F_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). Column chromatography was performed on silica gel 60 (70–230 mesh; E. Merck, Darmstadt, Germany). Preparative thin-layer chromatography was performed with a plate precoated with silica gel $60F_{254}$ (layer thickness, 2 mm; E. Merck, Darmstadt, Germany). Solvent extracts were dried with anhydrous sodium sulfate unless otherwise specified, and solutions were evaporated under diminished pressure below 40°. Pullulan (PI-20, a food-additive grade) and pullulanase (2000 units/g) were purchased from Hayashibara Co. Ltd.

1,2,3,6,2′,3′,6′,2″,3″,4″,6″-Hendeca-O-acetyl-β-maltotriose (**2**). — To a viscous solution of pullulan (**1**; 200 g) in water (2 L) was added pullulanase (2 g, 4000 units), and the mixture was stirred for 3 d at room temperature. T.l.c. with 2:2:1 2-propanol–ethyl acetate–water then revealed the disappearance of **1** (R_F 0) and the presence of a major product (R_F 0.25) together with several faint spots. The

mixture was heated for 30 min at 90°, and cooled. After addition of a 20% aqueous solution of sulfosalicyclic acid (10 mL), the mixture was stirred for 2 h at room temperature and filtered through a Celite pad. The filtration was made neutral with aqueous sodium hydrogencarbonate and evaporated to a syrup, the remaining water being removed by co-evaporation several times with toluene–ethanol. A mixture of the residual syrup and anhydrous sodium acetate (50 g) was heated at 130°, and acetic anhydride (600 mL) was added in portions to the mixture. The mixture was heated under reflux for 3 h, poured into ice–water (1 L), stirred for 5 h at room temperature, and extracted several times with chloroform. The extracts were combined, successively washed with 2M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried (anhydrous magnesium sulfate), and evaporated, to give thick syrupy **2** (312 g, 75%) which was pure enough for the next step; t.l.c. (1:1 chloroform–ethyl acetate) showed a major spot (R_F 0.42) together with faint spots (R_F 0.5 and 0.22). Crystallization from ethanol gave an analytical sample; m.p. 133–134.5°, $[\alpha]_D^{20}$ +83° (*c* 0.43, chloroform) {lit.[11] m.p. 134–136°, $[\alpha]_D^{25}$ +89.5° (*c* 2.9, chloroform)}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.74 (d, 1 H, *J* 8.2 Hz, H-1), 5.41 (d, 1 H, *J* 4.0 Hz, H-1″), 5.40 (dd, 1 H, *J* 8.2 and 10.4 Hz, H-3), 5.36 (t, 1 H, *J* 10.1 Hz, H-3′), 5.30 (t, 1 H, *J* 9.9 Hz, H-3″), 5.27 (d, 1 H, *J* 4.3 Hz, H-1′), 5.07 (t, 1 H, *J* 10.1 Hz, H-4″), 4.97 (t, 1 H, *J* 8.2 Hz, H-2), 4.85 (dd, 1 H, *J* 4.0 and 10.0 Hz, H-2″), 4.74 (dd, 1 H, *J* 4.3 and 10.2 Hz, H-2′), 2.17, 2.16, 2.11, 2.10, 2.06, 2.04, 2.03, 2.02, 2.01 (9 s, 9 × 3 H, 9 CH_3CO), and 1.98 (s, 6 H, 2 CH_3CO).

Pentachlorophenyl 2,3,6,2′,3′,6′,2″,3″,4″,6″-deca-O-acetyl-β-maltotrioside (**3**). — To an ice-cold solution of syrupy **2** (310 g, 0.32 mol) in acetic acid (800 mL) was added dropwise a 25% solution of hydrogen bromide in acetic acid (200 mL), and the mixture was stirred for 3 h at 15–20°; R_F 0.45 (t.l.c. with 1:1 chloroform–ethyl acetate). The resulting solution was poured into ice–water, and extracted with chloroform (3 × 500 mL). The extracts were combined, successively washed with cold water (five times), aqueous sodium hydrogencarbonate (twice), and brine, dried (anhydrous magnesium sulfate), and evaporated to dryness. The residual syrup was dissolved in acetone (1.5 L), sodium pentachlorophenoxide (200 g) was added, and the mixture was heated under reflux overnight, cooled, and evaporated under diminished pressure. The residue was dissolved in chloroform–water, and the aqueous layer was separated and extracted with chloroform. The organic layers were combined, successively washed with brine, M sodium hydroxide, and brine, dried, and evaporated. The residual syrup was chromatographed on a column of silica gel (1500 g) with 4:1 chloroform–ethyl acetate as the eluant, giving **3** (242 g, 69%); m.p. 109–112° (from ethanol), $[\alpha]_D^{23}$ +114° (*c* 0.63, chloroform); ν_{max}^{film} 1735 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): δ 5.41 (d, 1 H, *J* 4.0 Hz, H-1″), 5.40 (dd, 1 H, *J* 8.2 and 7.3 Hz, H-3′), 5.36 (t, 1 H, *J* 9.2 Hz, H-3), 5.34 (t, 1 H, *J* 9.9 Hz, H-3″), 5.31 (d, 1 H, *J* 4.0 Hz, H-1′), 5.07 (t, 1 H, *J* 9.9 Hz, H-4″), 4.85 (dd, 1 H, *J* 4.3 and 10.5 Hz, H-2″), 4.74 (dd, 1 H, *J* 4.0 and 10.3 Hz, H-2′), 4.47 (d, 1 H, *J* 11.9 Hz, H-6′a), 4.29 (dd, 1 H, *J* 3.9 and 12.0 Hz, H-6a), 4.23 (dd, 1 H, *J* 3.4 and 12.5 Hz, H-6″a), 4.13 (d, 1 H, *J* 11.9 Hz, H-6′b), 4.09 (dd, 1 H, *J* 2.4 and

12.5 Hz, H-6″b), 4.06 (t, 1 H, *J* 9.5 Hz, H-4), 3.67 (dt, 1 H, *J* 3.9, 3.9, and 12.0 Hz, H-5), 2.16, 2.12, 2.10, 2.08, 2.04, 2.03, 2.02, 2.00 (8 s, 8 × 3 H, 8 CH_3CO), and 1.95 (s, 6 H, 2 CH_3CO).

Anal. Calc. for $C_{42}H_{51}Cl_5O_{26}$: C, 45.05; H, 4.38; Cl, 15.11. Found: C, 44.86; H, 4.36; Cl, 15.02.

2,3,2′,3′,6′,2″,3″,4″,6″-Nona-O-acetyl-1,6-anhydro-β-maltotriose (**5**). — Compound **3** (242 g, 211 mmol) was added in portions to 4M aqueous potassium hydroxide (1 L) at 90–100°, and the suspension was heated under reflux overnight, cooled, made neutral with 3M sulfuric acid, and filtered through a Celite pad. The solvent was evaporated and co-evaporated with toluene–ethanol several times. To a mixture of the residue and anhydrous sodium acetate (80 g) was added acetic anhydride (500 mL) in portions; the mixture was heated under reflux for 3 h, cooled, poured into ice–water, and extracted twice with chloroform. The extracts were combined, successively washed with aqueous sodium hydrogencarbonate and brine, dried, evaporated to a syrup, and crystallized from ethanol, to afford **5** (112 g, 63%); m.p. 159–161°, $[\alpha]_D^{23}$ +89° (*c* 0.46, chloroform); {lit.[5] m.p. 156.5–157°, $[\alpha]_D^{15}$ +82.4° (*c* 1.5, chloroform)}; ν_{max}^{film} 1730 cm^{-1} (C=O); for ^{1}H-n.m.r. data, see Tables I and II.

2,3,2′,3′,6′,2″,3″-Hepta-O-acetyl-1,6-anhydro-4″,6″-O-benzylidene-β-maltotriose (**7**). — A solution of 1,6-anhydro-β-maltotriose (**4**; 23 g, 47.5 mmol; prepared from **5** according to the literature[5]), α,α-dimethoxytoluene (9 mL, 60 mmol), and *p*-toluenesulfonic acid (200 mg) in DMF (500 mL) was evacuated for 3 h in a rotary evaporator at 60–70°. T.l.c. (4:1 chloroform–methanol) then showed a major spot (R_F 0.14) and a faint spot (R_F 0.62). After cooling in an ice–bath, pyridine (300 mL) was added to the solution, and then acetic anhydride (50 mL) was added dropwise with stirring. The mixture was stirred overnight at room temperature, poured into ice–water, and extracted with chloroform. The extract was successively washed with M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and evaporated to dryness. The residual syrup was chromatographed on silica gel with 4:1 benzene–ethyl acetate as the eluant, to give **11** (2.7 g, 6%), which was identical with the sample described next. Further elution with 3:1 benzene–ethyl acetate gave **7** (31.3 g, 76%) as a colorless syrup; $[\alpha]_D^{23}$ +55° (*c* 0.29, chloroform); for ^{1}H-n.m.r. data see Tables I and II.

Anal. Calc. for $C_{39}H_{48}O_{22}$: C, 53.92; H, 5.57. Found: C, 54.29; H, 5.59.

2,3,2′,6′,3″-Penta-O-acetyl-1,6-anhydro-3′,2″:4″,6″-di-O-benzylidene-β-maltotriose (**11**). — A solution of **4** (2.3 g, 4.8 mmol), α,α-dimethoxytoluene (3.6 mL, 18 mmol), and *p*-toluenesulfonic acid monohydrate (150 mg) in DMF (200 mL) was evacuated for 3 h in a rotary evaporator at 60–70°. T.l.c. (4:1 chloroform–methanol) then revealed spots having R_F 0.14, 0.62, 0.73, 0.75, and 0.94. After cooling to room temperature, water (0.5 mL) was added to the mixture, and the solution was stirred for 10 min at room temperature; t.l.c. with the same solvent system showed a major spot (R_F 0.62) and several minor ones. To the resulting solution were successively added pyridine (100 mL) and acetic anhydride (20 mL)

with stirring at 0°. The mixture was stirred overnight at room temperature, poured into ice–water, stirred for 5 h, and extracted with chloroform (2 × 200 mL). The extracts were combined, successively washed with M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and evaporated. The residual syrup was chromatographed on a column of silica gel with 4:1 benzene–ethyl acetate as the eluant, to afford **11** as a white solid (2.6 g, 62%); $[\alpha]_D^{23}$ +19° (*c* 0.24, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{42}H_{48}O_{20}$ 0.7 H_2O: C, 56.97; H, 5.62. Found: C, 56.90; H, 5.49.

Further elution of the column with 3:1 benzene–ethyl acetate gave **7** (0.82 g, 20%).

*1,6-Anhydro-2,3,2',3',6',2'',3''-hepta-*O*-benzyl-4'',6''-*O*-benzylidene-β-maltotriose* (**8**). — To a solution of **7** (24.4 g, 28 mmol) in anhydrous methanol (300 mL) was added 28% methanolic sodium methoxide (1 mL), and the mixture was stirred for 5 h at room temperature, and evaporated, and the residual syrup dissolved in DMF (300 mL). To the ice-cold solution was added 60% sodium hydride oil dispersion (16 g, 670 mmol) in portions, and the mixture was stirred for 1 h at the same temperature. Benzyl bromide (90 mL) was added dropwise to the suspension, and the mixture was stirred overnight at room temperature, cooled in an ice bath, and methanol (50 mL) and water (50 mL) were successively added dropwise. The mixture was stirred for 3 h at room temperature, and diluted with diethyl ether and water. The organic layer was washed with brine, dried (anhydrous potassium carbonate), and evaporated. The residual syrup was chromatographed on a column of silica gel with 19:1 benzene–diethyl ether as the eluant, to afford **8** (22.8 g, 67%) as a colorless syrup; $[\alpha]_D^{23}$ +18° (*c* 0.28, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{74}H_{76}O_{15}$: C, 73.73; H, 6.34. Found: C, 73.69; H, 6.36.

*1,6-Anhydro-2,3,2',3',6',2'',3''-hepta-*O*-benzyl-4'',6''-*O*-isopropylidene-β-maltotriose* (**12**). — A mixture of **4** (2.45 g, 5 mmol), *p*-toluenesulfonic acid monohydrate (300 mg), 2,2-dimethoxypropane (5 mL), and DMF (50 mL) was stirred overnight at room temperature. After addition of water (20 mL), the solution was stirred for 5 min at room temperature, and the acid neutralized with Amberlite IRA-411 (OH^-) resin. The resin was fitered off and washed with water. The filtrate and washings were combined and evaporated. To an ice-cold solution of the residue in DMF (150 mL) was added, in portions, 60% sodium hydride oil dispersion (5.5 g), and the suspension was stirred for 1 h at room temperature. Benzyl bromide (40 mL) was added dropwise to the suspension at 0°, and the mixture was stirred for 16 h at room temperature. After addition of methanol (8 mL), the mixture was stirred for 3 h at room temperature, poured into ice–water, and extracted with chloroform. The extract was washed with brine, dried (anhydrous potassium carbonate) and evaporated. The residual syrup was chromatographed on a column of silica gel with 10:1 toluene–ethyl acetate as the eluant, to give syrupy **12** (3.68 g, 64%); $[\alpha]_D^{23}$ +30° (*c* 0.11, chloroform).

Anal. Calc. for $C_{70}H_{76}O_{15}$: C, 72.65; H, 6.62. Found: C, 72.69; H, 6.57.

1,6-Anhydro-2,3,2',3',6',2'',3''-hepta-O-benzyl-β-maltotriose (**9**). — *From* **8**. To an ice-cold solution of **8** (0.60 g, 0.5 mmol) in oxolane (1 mL) was added 90% aqueous trifluoroacetic acid (5 mL), and the mixture was stirred for 10 min at 0°. The reaction was quenched by addition of pyridine (10 mL), and the mixture diluted with water (100 mL), and extracted with chloroform (2 × 50 mL). The extracts were combined, successively washed with water, M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and evaporated. The residue was chromatographed on a column of silica gel with 2:1 toluene–ethyl acetate as the eluant, giving **9** (454 mg, 81%); $[\alpha]_D^{23}$ +25° (*c* 0.83, chloroform); ν_{max}^{film} 3500 cm^{-1} (OH); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{67}H_{72}O_{15}\cdot H_2O$: C, 71.45; H, 6.53. Found: C, 71.50; H, 6.45.

From **12**. To a solution of **12** (2.0 g, 1.7 mmol) in acetic acid (25 mL) was added water (5 mL); the mixture was stirred at overnight room temperature, poured into aqueous saturated sodium hydrogencarbonate, and extracted with chloroform (2 × 100 mL). The extracts were combined, successively washed with aqueous sodium hydrogencarbonate and brine, dried, and evaporated to dryness. The residue was chromatographed as already described, to give **9** (1.83 g, 94%).

1,6-Anhydro-2,3,2',3',6',2'',3'',6''-octa-O-benzyl-β-maltotriose (**10**). — A solution of **9** (1.13 g, 1 mmol) and bis(tributyltin) oxide (520 mg, 0.85 mmol) in toluene (40 mL) was heated for 4 h under reflux, with azeotropic removal of water. Tetraethylammonium bromide (160 mg) and benzyl bromide (510 mg, 3 mmol) were added, and the mixture was heated with stirring, under an argon atmosphere, overnight at 80°. The same amounts of tetraethylammonium bromide and benzyl bromide were added to the mixture, and the mixture was further stirred for 7 h at 80°, cooled, and diluted with ethyl acetate (200 mL). The organic layer was separated, successively washed with aqueous sodium hydrogencarbonate and brine, dried (anhydrous magnesium sulfate), and evaporated. The residual syrup was chromatographed on a column of silica gel with 9:1 benzene–ethyl acetate as the eluant, to give **10** (0.70 g, 58%); $[\alpha]_D^{23}$ +28° (*c* 0.84, chloroform); ν_{max}^{film} 3400 cm^{-1} (OH); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{74}H_{78}O_{15}$: C, 73.61; H, 6.51. Found: C, 73.46; H, 6.49.

1,6-Anhydro-4'',6''-O-benzylidene-6'-O-trityl-β-maltotriose (**13**). — To a solution of **7** (1.74 g, 2 mmol) in methanol (40 mL) was added 28% methanolic sodium methoxide (0.1 mL), and the mixture was stirred for 5 h at room temperature, made neutral with Dowex 50W X-8 (H^+) ion-exchange resin, and evaporated. The trace of solvent remaining was removed by co-evaporation with pyridine (20 mL), and trityl chloride (620 mg) was added to a solution of the residue in pyridine (20 mL). The mixture was stirred for 3 d at room temperature, and then evaporated to a syrup, which was chromatographed on a column of silica gel with 9:1 chloroform–methanol as the eluant, to give **13** (0.88 g, 54%); $[\alpha]_D^{24}$ +68° (*c* 0.23, methanol).

Anal. Calc. for $C_{44}H_{48}O_{15}\cdot 1.2\ H_2O$: C, 63.03; H, 6.06. Found: C, 62.86; H, 5.77.

2',3',2'',3''-Tetra-O-acetyl-1,6-anhydro-4'',6''-O-benzylidene-2,3- (**14**), *2,3,2'',-*

3″-tetra-O-acetyl-1,6-anhydro-4″,6″-O-benzylidene-2′,3′- (**15**), *and 2,3,2′,3′-tetra-O-acetyl-1,6-anhydro-4″,6″-O-benzylidene-2″,3″-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-6′-O-trityl-β-maltotriose* (**16**). — To an ice-cold solution of **13** (0.41 g, 0.5 mmol) in pyridine (20 mL) was added dropwise 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.18 mL, 0.57 mmol), and the mixture was stirred overnight at 0°. T.l.c. (1:1 benzene–ethyl acetate) then revealed the disappearance of **13** (R_F 0) and the presence of a component having R_F 0.80, together with several faint spots. Acetic anhydride (1 mL) was added dropwise at 0°, and the mixture was stirred overnight at room temperature. T.l.c. (4:1 benzene–ethyl acetate) then showed four spots (R_F 0.57, 0.51, 0.38, and 0.09). The solution was poured into ice–water, stirred for 4 h, and extracted with chloroform (2 × 100 mL). The extracts were combined, successively washed with M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and evaporated. The residual syrup was applied to a column of silica gel and eluted with 24:1 benzene–ethyl acetate, giving **14** (30 mg, 5%); $[\alpha]_D^{24}$ +43° (*c* 0.26, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{64}H_{82}O_{20}Si_2$: C, 62.62; H, 6.73. Found: C, 62.58; H, 6.74.

Elution (with the same solvent) next gave amorphous **15** (366 mg, 60%); $[\alpha]_D^{24}$ +43° (*c* 0.34, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{64}H_{82}O_{20}Si_2$: C, 62.62; H, 6.73. Found: C, 62.62; H, 6.72.

Elution with 9:1 benzene–ethyl acetate afforded **16** (50 mg, 8%); $[\alpha]_D^{24}$ +42° (*c* 0.40, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{64}H_{82}O_{20}Si_2$: C, 62.62; H, 6.73. Found: C, 62.62; H, 6.70.

Further elution with 4:1 benzene–ethyl acetate gave amorphous 2,3,2′,3′,2″,3″-hexa-*O*-acetyl-1,6-anhydro-4″,6″-*O*-benzylidene-6′-*O*-trityl-β-maltotriose (**17**, 80 mg, 15%); $[\alpha]_D^{25}$ +51° (*c* 0.29, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{56}H_{60}O_{21}$: C, 62.92; H, 5.66. Found: C, 62.85; H, 5.73.

2,3,2′,3′,6′,2″,3″-Hepta-O-acetyl-1,6-anhydro-4″,6″-O-benzylidene-2′,3′-(tetraisopropyldisiloxan-1,3-diyl)-β-maltotriose (**18**). — A mixture of **15** (20 mg, 0.16 mmol) and *p*-toluenesulfonic acid monohydrate (1 mg) in 1:1 chloroform–methanol (2 mL) was stirred for 6 h at room temperature. The reaction was quenched by addition of pyridine (2 mL), and the solution was evaporated to a syrup. Pyridine (2 mL) and acetic anhydride (0.5 mL) were added to the residue, and the mixture was stirred overnight at room temperature, poured into ice–water, stirred for 3 h, and extracted with chloroform. The extract was successively washed with M hydrochloric acid, aqueous sodium hydrogencarbonate, and brine, dried, and evaporated. The product was purified by preparative t.l.c. with 4:1 benzene–ethyl acetate, to give unchanged **15** (6 mg, 30%) and **18** (9 mg, 55%); $[\alpha]_D^{24}$ +44° (*c* 0.34, chloroform); for ^{1}H-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{47}H_{70}O_{21}Si_2$: C, 54.96; H, 6.87. Found: C, 54.91; H, 6.87.

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