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Synthesis of [6″-^{3}H]-, (6″-^{2}H)- and (2-^{2}H)-maltotriose

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Abstract

To prepare labeled precursors for biosynthetic studies, methods for the specific introduction of tritium and deuterium into the reducing and the terminal glucose unit of maltotriose were developed. Thus [6″-^{3}H]- and (6″-^{2}H)-maltotriose (**17**) and (**18**) were prepared via selective methoxytritylation, deprotection and subsequent modified Pfitzner–Moffatt oxidation, followed by reduction with sodium borotritiide or sodium borodeuteride, respectively. A simple two step procedure utilizing the Lobry de Bruyn/van Ekenstein transformation gave (2-^{2}H)maltotriose (**20**).

Keywords: Maltotriose; Isotope-labeled; Synthesis

1. Introduction

Previous preparations of isotope-labeled maltotriose and homologs reported in the literature have been used to study substrate complexes of maltose-binding proteins and the specificities of amylases. Thus, [1-^{3}H]maltotriose has been prepared by an exchange reaction with tritium gas [1,2], and the transfer of D-[UL-^{14}C]glucose to the reducing end of oligosaccharides has been achieved by enzymatic procedures [3,4]. Because of the low enrichment it produces, the first method is unsuitable for the preparation of the corresponding deuterated compound, whereas the second gives only very low yields due to the formation of complex product mixtures which require tedious, low yielding chromatographic workup procedures.

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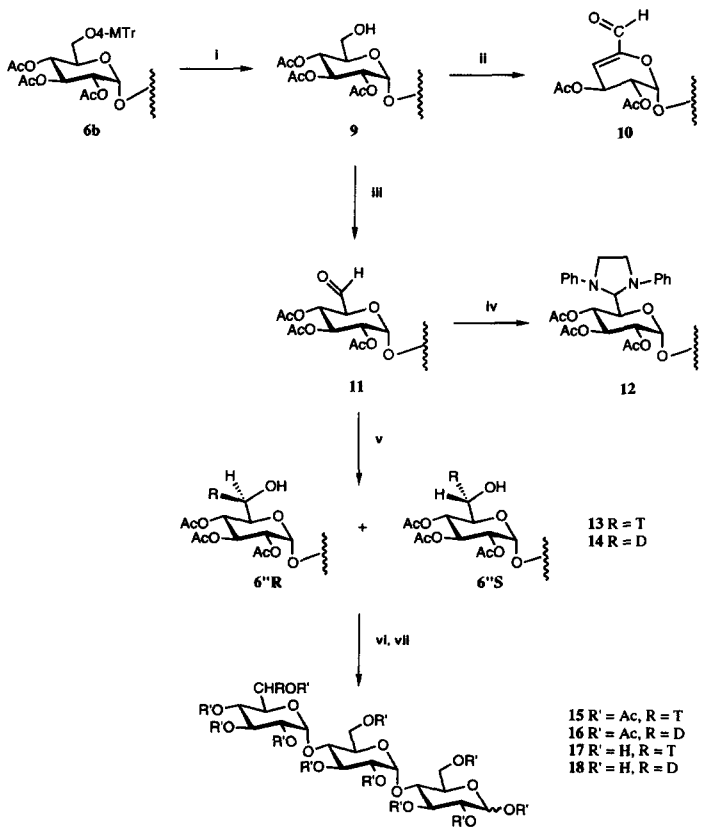
Our goal was to develop simple preparative routes for the specific introduction of tritium or deuterium at both the reducing and the non-reducing end of maltotriose. These specifically labeled substrates were required for biosynthetic studies.

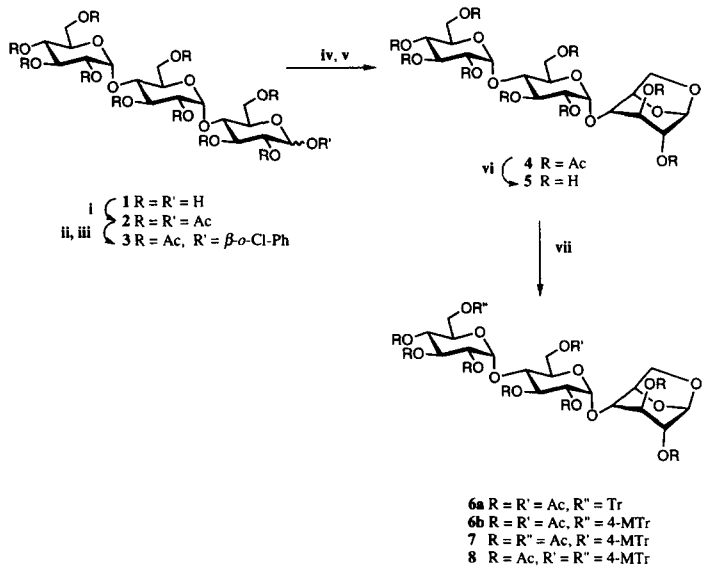
2. Results and discussion

Our overall strategy for the synthesis of [6″-^{3}H]- (**17**) and (6″-^{2}H)-maltotriose (**18**) is summarized in Scheme 1. The preparation of the suitably protected starting material **6b** is shown in Scheme 2.

1,6-Anhydro-β-maltotriose (**5**), the first key intermediate, has been prepared previously using slightly different routes [5,6]. In our hands the approach of Takeo et al. [5] using the *o*-chlorophenyl glycoside **3** was superior with regard to feasibility and yield. Tritylation or methoxytritylation followed by acetylation gave crystalline **6a** or **6b** in



Scheme 1. (i) Amberlite IR-120 (H^+), RT; or 80% aq HOAc, RT. (ii) Me_2SO, $(CO)_2Cl_2$, Et_3N. (iii) Me_2SO, benzene, DIPCD, pyridine, TFA. (iv) *N*,*N*′-diphenylethane-1,2-diamine. (v) $NaBT_4$ in H_2O, MeOH; or $NaBD_4$ in dry MeOH. (vi) $AcOH/Ac_2O/H_2SO_4$ (30:70:1), RT. (vii) NaOMe, MeOH.



Scheme 2. (i) Ac_2O, pyridine. (ii) HBr, AcOH. (iii) HO–*o*-Cl–Ph, acetone, aq KOH. (iv) aq KOH. (v) Ac_2O, NaOAc. (vi) NaOMe, MeOH. (vii) TrCl, pyridine, DMAP; or 4-MTrCl, pyridine, DMAP.

moderate yields (Scheme 2). The physical constants observed for **6a** were identical with those reported by Takeo et al. [7], and its ^1H and ^{13}C NMR spectra (see Tables 1–3) were consistent with the expected structure. In addition to the 6″-methoxytrityl ether **6b**, its 6′-isomer **7** and the diether **8** were also isolated and characterized. Compound **6b** turned out to be an excellent substrate for the deprotection to the 6″-hydroxy compound **9**. Both the conventional detritylation procedure using 80% aqueous acetic acid [7,8] and treatment with Amberlite IR-120 (H^+-form) in methanol at room temperature yielded **9** quantitatively (Scheme 1). The latter method is more selective; in another instance selective demethoxytritylation in the presence of a boc-protected amine could be achieved [9]. The proton signals for H-6″a and H-6″b of **9** showed characteristic ddd-multiplicities (Tables 1 and 2) due to the coupling with the proton of the unprotected hydroxy group.

Oxidations of the primary hydroxyl groups of carbohydrates are often accompanied by α,β-elimination reactions, especially if the potential leaving group located in the β-position is an acetate [10–12]. Thus, Swern oxidation [13] (dimethyl sulfoxide/oxalyl chloride/triethylamine) of **9** afforded the unsaturated aldehyde **10** in quantitative yield (Scheme 1).

A Moffatt reagent formulation, however, using *N,N′*-diisopropylcarbodiimide (DIPCD) with dimethyl sulfoxide/pyridinium trifluoroacetate gave the desired aldehyde **11** in 65% yield. This method had been successfully applied by Singh et al. [14] to generate methyl dialdopyranosides of monosaccharides. Since aldehydo forms of carbohydrates are extensively hydrated [15], compound **11** could only be isolated as a mixture of the aldehyde and the corresponding hydrate. Both were identified by the ^{13}C NMR signals of their C-6″ carbons at 194.9 and 94.5 ppm, respectively. To obtain a homogeneous

Table 1
^{1}H NMR data for 1,6-anhydro-β-maltotriose derivatives [a]

Hydrogen atom	Chemical shift (δ) and multiplicity							
	4 [c]	**6a** [d]	**6b** [e]	**7** [f]	**8** [g]	**9** [h]	**10** [i]	**12** [j]
H-1	5.47s	5.48s	5.46s	5.50s	5.47s	5.50s	5.47s	5.43s
H-2	4.57s	4.58	4.57s	4.58s	4.57s	4.62s	4.57s	4.54s
H-3	4.81s	4.84s	4.82s	4.81s	4.82s	4.86s	4.79s	4.73s
H-4	3.44s	3.47s	3.46s	3.53s	3.46s	3.49s	3.44s	3.38s
H-5	4.74d	4.74d	4.72d	4.93d	4.84d	4.78d	4.72	4.61d
H-6a	3.77dd	3.80dd	3.77dd	3.72dd	3.62dd	3.83dd	3.77dd	m [b]
H-6b	3.97d	3.98d	3.97d	3.96d	3.90d	4.02d	3.96d	3.92d
H-1′	5.16d	5.18d	5.15d	5.27d	5.23d	5.19d	5.18d	5.33d
H-2′	4.68dd	4.78dd	4.75dd	4.72dd	4.77dd	4.75dd	4.67dd	4.17dd
H-3′	5.54t	5.60t	5.57t	5.57t	5.58t	5.58t	5.61t	5.46t
H-4′	3.97t	4.03t	4.03t	3.77t	3.89t	4.04t	4.15t	m [b]
H-5′	4.36dt	4.35dt	4.34dt	4.37m	4.31m	4.41dt	4.23dt	4.02dt
H-6a′	4.48dd	4.48dd	4.45dd	3.49dd	3.45dd	4.54dd	4.27dd	m [b]
H-6b′	4.23dd	4.20dd	4.16dd	3.28dd	3.22m [b]	4.23dd	3.83dd	3.91dd
H-1″	5.39d	5.49d	5.45d	5.29d	5.38d	5.44s	5.87d	5.08d
H-2″	4.86dd	4.97dd	4.95dd	4.78dd	4.90dd	4.87dd	5.77dd	4.74dd
H-3″	5.34t	5.33t	5.28m [b]	5.16t	5.21t	5.43t	4.95dd	5.28dd
H-4″	5.05t	5.27t	5.28m [b]	4.88t	5.06t	4.98t	5.63d	5.07t
H-5″	3.98m [b]	3.93dt	3.89dt	3.41m	3.22m [b]	3.80dt	–	4.33dd
H-6a″	4.17dd	3.29dd	3.24dd	3.58dd	3.05dd	3.58ddd	9.16s	5.53d
H-6b″	4.03dd	3.03dd	2.98dd	3.86dd	2.52dd	3.66ddd	–	–

[a] ^{1}H NMR spectra were measured for solutions in $CDCl_3$, using tetramethylsilane as the internal standard.
[b] Not analyzed due to overlapping signals.
[c] 2.19, 2.14, 2.11, 2.07, 2.06, 2.04, 2.03, 2.00, 1.99 (s, 3 H each, –OAc).
[d] 7.5–7.2 (m, 15 H, –Ph); 2.22, 2.12, 2.08, 2.07, 2.06, 1.99, 1.84, 1.73 (s, 3 H each, –OAc).
[e] 7.45–7.15 (m, 12 H, –Ph, –PhOMe–*2,6*); 6.82 (d, 2 H, –PhOMe–*3,5*), 3.78 (s, 3 H, –OMe); 2.17, 2.08, 2.05, 2.04, 2.03, 1.98, 1.80, 1.69 (s, 3 H each, –OAc).
[f] 7.35–7.0 (m, 12 H, –Ph, –PhOMe–*2,6*); 6.59 (d, 2 H, –PhOMe–*3,5*); 3.67 (s, 3 H, –OMe); 2.18, 2.03, 2.025, 2.015, 2×1.96, 1.93, 1.73 (s, 3 H each, –OAc).
[g] 7.35–7.0 (m, 24 H, –Ph, –PhOMe–*2,6*); 6.81, 6.59 (d, 4 H, –PhOMe–*3,5*); 3.78, 3.67 (s, 3 H each, –OMe); 2.18, 2.035, 2×2.03, 2.02, 1.95, 1.70 (s, 3 H each, –OAc).
[h] 2.19, 2.12, 2.10, 2.08, 2.02, 2.01, 1.99, 1.98 (s, 3 H each, –OAc).
[i] 2.18, 2.09, 2.07, 2.06, 2.03, 2.02, 2.00 (s, 3 H each, –OAc).
[j] 7.28–7.13 and 6.82–6.67 (m, 10 H, –Ph); 3.83–3.42 (m, 7 H, –N*CH*$_2$*CH*$_2$N–, H-4′, H-6′a, H-6a); 2.12, 2.07, 2.03, 2.025, 2.02, 2.01, 1.93, 1.57 (s, 3 H each, –OAc).

Table 2
$^1H-^1H$ spin-coupling constants of 1,6 anhydro-β-maltotriose derivatives

Coupling	J-values (Hz)							
	4	**6a**	**6b**	**7**	**8**	**9**	**10**	**12**
$J_{1,2}$	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5
$J_{2,3}$	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5
$J_{3,4}$	< 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
$J_{5,6a}$	5.8	5.9	5.9	5.8	5.8	5.9	5.9	5.6
$J_{5,6b}$	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5	< 1.5
$J_{6a,6b}$	7.5	7.5	7.6	7.5	7.5	7.6	7.5	7.8
$J_{1',2'}$	3.7	3.7	3.6	3.8	3.7	3.7	3.6	3.7
$J_{2',3'}$	10.2	10.3	10.3	10.2	10.0	10.2	10.3	10.3
$J_{3',4'}$	9.4	9.5	9.1	9.2	9.1	9.2	9.2	9.3
$J_{4',5'}$	9.9	10.0	9.8	9.9	9.9	9.9	9.7	9.7
$J_{5',6a'}$	2.4	2.6	2.4	< 1.5	< 1.5	2.4	1.9	5.8
$J_{5',6b'}$	3.5	3.5	3.3	7.6	6.3	3.7	3.5	3.5
$J_{6a',6b'}$	12.2	12.3	12.3	9.6	10.0	12.3	11.8	12.1
$J_{1'',2''}$	4.0	4.1	3.9	4.1	4.1	3.7	2.4	3.7
$J_{2'',3''}$	10.6	10.1	10.2	10.6	10.4	10.5	9.2	10.6
$J_{3'',4''}$	10.2	9.6	9.5	9.8	9.8	10.0	2.9	9.0
$J_{4'',5''}$	9.8	9.5	9.5	9.8	9.8	9.9	–	10.2
$J_{5'',6a''}$	3.9	1.4	1.5	1.9	< 1.5	4.0	–	< 1.5
$J_{5'',6b''}$	2.2	3.5	3.3	3.8	2.9	2.1	–	–
$J_{6'',6b''}$	12.3	10.5	10.5	12.4	10.3	12.6	–	–
$J_{6a'',OH}$	–	–	–	–	–	5.9	–	–
$J_{6b'',OH}$	–	–	–	–	–	8.1	–	–

compound for characterization purposes, a small sample of **11** was derivatized in high yield to the imidazolidine **12**.

Sodium borotriride reduction of **11** in water/methanol gave a 64:36 (*R*:*S*) mixture of the diastereomers of **13**. The *R*,*S*-assignments were obtained by applying the rule that ^3J values of H6(*S*) in D-glucose derivatives are less than those of H6(*R*) [14,16,17].

The final steps, cleavage of the anhydro-bridge and deacetylation, were carried out according to literature procedures [18], affording (*R*,*S*)-[6″-^{3}H]maltotriose (**17**) in an overall yield of 7% (based on **5**).

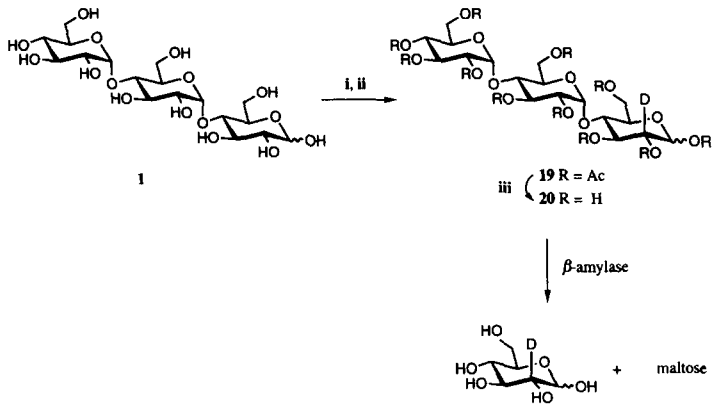
Due to partial deacetylation during sodium borodeuteride reduction of **11**, the crude reaction product **14** was directly converted to the peracetylated derivative **16**, which was characterized by ^{1}H, ^{2}H and ^{13}C NMR. The ^{1}H NMR spectrum of **16** showed the H-6″a (δ 4.20 ppm) and H-6″b (δ 4.02 ppm) signals as doublets with 0.03–0.01 ppm upfield shifts due to the deuterium isotope effect [19]. The intensities of both signals indicate a 55:45 (*R*:*S*) mixture of the diastereomers. The ^{2}H NMR spectrum of **16** measured at room temperature gave a broad signal at 4.15 ppm, which sharpened upon raising the temperature to 65 °C, but the signals of the two diastereomers could still not be resolved. The structure of the deacetylated compound **18** was confirmed by NMR analysis and by electrospray mass spectrometry.

Table 3
^{13}C NMR data for 1,6-anhydro-β-maltotriose derivatives [a]

Carbon atom	Chemical shift (δ)								
	5 [b]	**4** [c]	**6a** [d]	**6b** [e]	**7** [f]	**8** [g]	**9** [h]	**10** [i]	**12** [j]
C-1	102.7	99.1	99.1	99.1	99.0	99.0	99.1	99.1	99.1
C-2	71.2	68.6	68.5	68.5	68.9	68.8	68.5	68.6	69.1
C-3	71.3	70.4	70.4	70.5	70.2	70.2	70.3	70.3	70.6
C-4	77.4	76.7	76.6	76.7	76.3	76.2	76.6	76.8	76.7
C-5	76.9	74.3	74.2	74.3	74.5	74.4	74.2	74.3	74.6
C-6	66.8	65.0	65.0	65.0	65.2	65.1	64.9	65.0	65.4
C-1′	99.3	96.8	97.0	96.9	96.7	96.7	96.8	97.1	97.0
C-2′	72.9	71.2	71.1	71.1	71.3	71.3	71.1	71.0	71.0
C-3′	74.9	72.2	72.2	72.3	73.3	72.7	72.3	71.9	71.7
C-4′	78.5	72.7	72.5	72.5	72.4	72.45	72.3	71.4	74.5
C-5′	72.5	68.4	68.5	68.5	70.0	70.1	68.35	68.2	68.8
C-6′	62.1	62.8	62.7	62.7	63.8	63.3	62.7	61.8	63.0
C-1″	101.3	95.7	95.9	95.8	95.4	95.4	95.7	117.6	95.4
C-2″	73.4	69.9	70.3	70.3	69.8	70.1	70.1	65.4	70.2
C-3″	74.5	69.3	68.2	68.2	69.3	67.8	68.8	68.9	70.0
C-4″	71.0	68.0	69.9	69.9	67.6	70.1	68.7	95.7	70.3
C-5″	74.3	68.5	69.8	69.7	68.1	69.3	70.7	148.3	72.2
C-6″	62.1	61.4	60.8	60.8	61.4	60.6	61.0	184.9	74.3

[a] ^{13}C NMR spectra were measured for solutions in $CDCl_3$, unless otherwise noted.
[b] D_2O.
[c] 170.55–169.3 (9 $COCH_3$); 20.9–20.5 (9 $COCH_3$).
[d] 170.7–168.9 (8 $COCH_3$); 143.6, 143.5, 143.4 (Ph-*1*); 128.7 (6 Ph-*2*); 127.8 (6 Ph-*3*); 127.05 (3 Ph-*4*); 86.5 (CPh_3); 21.0–20.4 (8 $COCH_3$).
[e] 170.65–168.9 (8 $COCH_3$); 158.5 (PhOMe-*4*); 143.97, 143.96 (Ph-*1*); 135.1 (PhOMe-*1*); 130.3 (2 PhOMe-*2*); 128.5, 128.4 (4 Ph-*2*); 128.2, 127.8 (4 Ph-*3*); 126.9 (2 Ph-*4*); 113.1 (2 PhOMe-*3*); 86.2 (CPh_2PhOMe); 55.2 (OCH_3), 21.4–20.4 (8 $COCH_3$).
[f] 170.5–169.4 (8 $COCH_3$); 158.6 (PhOMe-*4*); 144.2, 144.1 (Ph-*1*); 135.0 (PhOMe-*1*); 130.35 (2 PhOMe-*2*); 128.4, 128.2 (4 Ph-*2*); 127.9 (4 Ph-*3*); 127.1 (2 Ph-*4*); 113.2 (2 PhOMe-*3*); 86.8 (CPh_2PhOMe); 55.15 (OCH_3); 20.9–20.6 (8 $COCH_3$).
[g] 170.6–168.7 (7 $COCH_3$), 158.4 (2 PhOMe-*4*); 144.05–143.7 (4 Ph-*1*); 135.4, 135.0 (PhOMe-*1*); 130.2, 130.1 (4 PhOMe-*2*); 128.5–128.2 (8 Ph-*2*); 127.8–127.6 (8 Ph-*3*); 127.1 126.9 (4 Ph-*4*); 113.0, 112.95 (4 PhOMe-*3*); 86.6 (2 CPh_2PhOMe); 55.2, 55.05 (OCH_3); 21.05–20.4 (7 $COCH_3$).
[h] 170.8–169.3 (8 $COCH_3$); 20.9–20.6 (8 $COCH_3$).
[i] 170.9–169.35 (7 $COCH_3$); 20.9–20.5 (7 $COCH_3$).
[j] 170.6–169.0 (8 $COCH_3$); 149.7 (Ph-*1*); 129.7, 119.6, 117.9, 115.2, 112.8 (Ph-*2*, *-3*, *-4*); 48.5, 47.1 (N–CH_2–CH_2–N); 21.5–20.5 (8 $COCH_3$).

A well-established route for the introduction of deuterium at the anomeric center of mono- and di-saccharides is the reduction of the corresponding 1,5-lactone with sodium borodeuteride, either in water at pH 3–4 [20] or in water–pyridine mixtures [21]. Both methods gave unsatisfactory results with the maltotriono-1,5-lactone, which was obtained by heating maltotrionic acid in methoxyethanol [22]. However, incorporation of deuterium at C-2 of maltotriose could be achieved with high specificity by taking advantage of a Lobry de Bruyn/van Ekenstein-type rearrangement [23] (Scheme 3). Prompted by the preparative application for the synthesis of β-D-(2-^{2}H)arabinose



Scheme 3. (i) NaOD, D_2O. (ii) Ac_2O, pyridine. (iii) NaOMe, MeOH.

reported by Lemieux and Stevens [24], we lyophilized maltotriose several times from D_2O, and then treated it with 2% sodium deuteroxide in D_2O for 20–40 h at room temperature. Although a substantial amount of the starting material was degraded to glucose and maltose derivatives, as judged after peracetylation, no trisaccharides containing mannose or fructose at the reducing end could be detected. This result was unexpected, since similar transformations of glucose in calcium hydroxide solutions led to mixtures of glucose, fructose and mannose. Thus, the isolation of peracetylated (2-^{2}H)maltotriose **19** was easily achieved by chromatography and crystallisation in 14% yield. The enrichment of deuterium at C-2 was higher than 95%, as evident from the ^{1}H NMR integration of the remaining H-2 signals of the anomeric mixture of **19** at 4.94 and 4.93 ppm. The ^{2}H NMR spectrum, on the other hand, revealed that less than 5% of the anomeric protons had been exchanged for deuterium. The ^{13}C NMR signals of C-2 were undetectable for both compounds **19** and the unprotected **20**, since their already low intensities were further reduced by splitting due to the coupling with deuterium.

β-Amylase digestion [25] (Scheme 3), which specifically cleaves the maltose unit from the non-reducing end, and subsequent gel chromatography gave rise to labeled glucose from the reducing end, NMR analysis of which confirmed the incorporation pattern measured before. The ratio of the intensities of the deuterium at C-2 were determined to be 47:53 (α:β anomer). On the other hand, virtually no deuterium could be detected in the maltose fraction from the enzymatic hydrolysis.

The two procedures reported here permit the preparation of not only specifically deuterated and tritiated maltotriose samples in good yield and high enrichment, but also the correspondingly labeled lower and higher homologs, maltose, maltotetrose, etc.

3. Experimental

General methods.—Melting points were determined with a Mel-Temp micro melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco

DIP-370 polarimeter. ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 or AF 500 spectrometers. Chemical shifts (δ) for solutions in $CDCl_3$ are expressed in ppm downfield of the internal standard, tetramethylsilane, whereas those for D_2O solutions are calibrated to the HDO signal (δ 4.68 ppm). ^{13}C signal assignments were made by ^1H–^{13}C-correlated spectra. Reactions were monitored by TLC on precoated plates of Silica Gel $60F_{254}$ (E. Merck). Detection was accomplished by UV light, where applicable, and by charring with 10% H_2SO_4 in ethanol. Flash chromatography was performed on silica gel (J.T. Baker). Solutions were concentrated under reduced pressure below 45 °C. β-Amylase (from sweet potato, ~ 900 units/mg) was purchased from Sigma.

2,3,2′,3′,6′,2″,3″,4″,6″-Nona-O-acetyl-1,6-anhydro-β-maltotriose (**4**).—**4** was prepared from **3** (5.50 g, 5.3 mmol) according to a literature procedure [5]. Yield: 2.20 g (49%); mp 158–160 °C; $[\alpha]_D^{20}$ +92° (*c* 1, $CHCl_3$); [ref. [6]: mp 159–161 °C; $[\alpha]_D^{23}$ +89° (*c* 0.46, $CHCl_3$)]. For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

1,6-Anhydro-β-maltotriose (**5**).—To a solution of **4** (2.20 g, 2.6 mmol) in dry methanol (30 mL) was added a 0.1 M solution of $NaOCH_3$ in methanol (8 mL). The mixture was stirred for 1 h at room temperature, neutralized with Amberlite IR-120 (H^+-form), filtered and evaporated to give **5** (1.22 g, 97%); mp 254–255 °C; $[\alpha]_D^{20}$ +123° (*c* 1, H_2O); [ref. [5]: mp 254–254.5 °C (from methanol); $[\alpha]_D^{15}$ +130.2° (*c* 1.1, H_2O)]; ^1H NMR (D_2O): δ 5.38 (s, 1 H, H-1), 5.32 (d, 1 H, $J_{1'',2''}$ 4.1 Hz, H-1″), 5.04 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.69 (d, 1 H, $J_{5,6a}$ 5.8 Hz, H-5), 4.05 (dd, 1 H, $J_{6a,6b}$ 7.6 Hz, H-6b), 3.97 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{3',4'}$ 8.9 Hz, H-3′), 3.82 (ddd, 1 H, $J_{4',5'}$ 9.7, $J_{5',6a'}$ 2.1, $J_{5',6b'}$ 2.7 Hz, H-5′), 3.8–3.6 (m, 5 H, H-6a,-6a′,-6b′,-6a″,-6b″), 3.74 (s, 1 H, H-3), 3.63 (ddd, 1 H, $J_{4'',5''}$ 9.8, $J_{5'',6a''}$ 2.2, $J_{5'',6b''}$ 2.6 Hz, H-5″), 3.62 (s, 1 H, H-4), 3.60 (dd, 1 H, $J_{2',3'}$ 9.8, $J_{3',4'}$ 9.2 Hz, H-3″), 3.58 (dd, 1 H, H-4′), 3.50 (dd, 1 H, H-2′), 3.49 (dd, 1 H, H-2″), 3.48 (s, 1 H, H-2), 3.33 (dd, 1 H, H-4″). For ^{13}C NMR data, see Table 3.

2,3,2′,3′,6′,2″,3″,4″-Octa-O-acetyl-6″-O-triphenylmethyl-1,6-anhydro-β-maltotriose (**6a**).—To a solution of **5** (200 mg, 0.41 mmol) in dry pyridine (3 mL) containing DMAP (10 mg) was added trityl chloride (115 mg, 0.41 mmol) at 0 °C. The mixture was stirred at room temperature. Additional portions of trityl chloride (1.05 mmol total) were added (after 3 days, 57 mg; 5 days, 57 mg; 10 days, 115 mg; and after 14 days, 65 mg). The reaction was quenched after 16 days by adding acetic anhydride (1 mL). The resulting mixture was stirred at room temperature overnight, poured into ice-water, and extracted with ethyl acetate. The extracts were washed with brine and water, dried ($MgSO_4$), and concentrated. The residue was applied to a silica gel column. Elution with 3:2 ethyl acetate–toluene and subsequent crystallisation from ethanol gave pure **6a** (130 mg, 30%); mp 234 °C; $[\alpha]_D^{20}$ +56° (*c* 0.5, $CHCl_3$); [ref. [7]: mp 233–234 °C; $[\alpha]_D^{15}$ +97.5° (*c* 1.5, $CHCl_3$)]. For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

Methoxytritylation of 1,6-anhydro-β-maltotriose (**5**).—To a solution of **5** (400 mg, 0.82 mmol) in dry pyridine (6 mL) containing DMAP (20 mg) was added 4-methoxy-triphenylmethyl chloride (304 mg, 0.82 mmol) at 0 °C. The mixture was stirred at room temperature. Additional portions of 4-methoxy-triphenylmethyl chloride (0.81 mmol total) were added (after 1 day, 150 mg; and 2 days, 150 mg). The reaction was quenched after 4 days by acetylation as described before. Flash chromatography with 1:3 ethyl

acetate–toluene and subsequent crystallisation gave pure 2,3,2′,3′,2″,3″,4″-hepta-*O*-acetyl-6′,6″-di-*O*-(4-methoxy-triphenylmethyl)-1,6-anhydro-β-maltotriose (**8**) (165 mg, 30%); mp 130–132 °C; $[\alpha]_D^{20}$ +29° (*c* 0.49, $CHCl_3$). For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3. Further elution of the column gave 2,3,2′,3′,2″,3″,4″,6″-octa-*O*-acetyl-6′-*O*-(4-methoxy-triphenylmethyl)-1,6-anhydro-β-maltotriose (**7**) (10 mg, 2%); mp 117–120 °C (ethanol); $[\alpha]_D^{20}$ +20.6° (*c* 0.4, $CHCl_3$). For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3. Finally 2,3,2′,3′,6′,2″,3″,4″-octa-*O*-acetyl-6″-*O*-(4-methoxy-triphenylmethyl)-1,6-anhydro-β-maltotriose (**6b**) (110 mg, 25%) was eluted; mp 189–190 °C (ethanol); $[\alpha]_D^{20}$ +71° (*c* 0.75, $CHCl_3$). For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

2,3,2′,3′,6′,2″,3″,4″-Octa-O-*acetyl-1,6-anhydro-β-maltotriose* (**9**).—**6a** (120 mg, 0.113 mmol) or **6b** (110 mg, 0.101 mmol), respectively, were dissolved in dry methanol (7 mL), and Amberlite IR-120 (H^+-form) (10 mg) was added. From **6a**: after stirring for 12 h at 45 °C the reaction was almost complete according to TLC (ethyl acetate), yielding **9** (75 mg, 81%) after chromatography; mp 195–197 °C (ethanol); $[\alpha]_D^{20}$ +95° (*c* 1, $CHCl_3$); [ref. [7]: mp 196–196.5 °C; $[\alpha]_D^{15}$ +82.7° (*c* 1.0, $CHCl_3$)]. From **6b**: after stirring for 5 h at room temperature the reaction was complete according to TLC (ethyl acetate), yielding **9** (79 mg, 95%) after chromatography; mp 195–197 °C (ethanol); $[\alpha]_D^{20}$ +98° (*c* 1, $CHCl_3$). For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

O-*(2″,3″-Di*-O-*acetyl-4″-deoxy-6″-aldehydo-β*-L-*threo-hex-4″-endodialdo-1″,5″-pyranosyl)-(1 → 4)*-O-*(2′,3′,6′-tri*-O-*acetyl-α*-D-*glucopyranosyl)-(1 → 4)-2,3-di*-O-*acetyl-1,6-anhydro-β*-D-*glucose* (**10**).—Dimethyl sulfoxide (80 μL, 1.15 mmol) was added to a stirred solution of oxalyl chloride (75 μL, 0.85 mmol) in methylene chloride (1 mL) under argon, and cooled in a dry ice–chloroform bath at −50 to −60 °C. The mixture was stirred for 10 min and a solution of **9** (30 mg, 0.04 mmol) in methylene chloride (1.4 mL) was added within 5 min; stirring was continued for an additional 15 min. Triethylamine (320 μL, 2.3 mmol) was added and the mixture was stirred for 10 min and then allowed to warm to room temperature. Water (240 μL) was added and the mixture was diluted with methylene chloride. The organic layer was washed with ice cold 0.5 M HCl and 5% $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield **10** (27 mg, 97%); mp 104–107 °C (ethanol); $[\alpha]_D^{20}$ +143° (*c* 1.21, $CHCl_3$). For ^1H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

2,3,2′,3′,6′,2″,3″4″-Octa-O-*acetyl-1,6-anhydro-β-maltotrio-hexo-dialdoside-(1″-5″)* (**11**).—To a solution of **9** (39 mg, 0.047 mmol) in dry dimethyl sulfoxide (400 μL) and dry benzene (800 μL) was added *N,N′*-diisopropylcarbodiimide (25 μL, 0.16 mmol), dry pyridine (4.4 μL, 0.056 mmol), and trifluoroacetic acid (2.3 μL, 0.03 mmol). The reaction mixture was stirred overnight at room temperature, cooled to 0 °C, and a solution of oxalic acid (20.4 mg, 0.16 mmol) in methanol (600 μL) was added to destroy DIPCD. After 30 min the solution was diluted with ice water and extracted twice with ethyl acetate. The combined organic phases were washed with water twice, dried over $MgSO_4$, concentrated and chromatographed with ethyl acetate. TLC (ethyl acetate) showed two partly resolved spots (R_f 0.4–0.5), corresponding to the aldehyde and its hydrated form. Both compounds were also evident in the ^{13}C NMR spectrum. Yield: 19.2 mg (65%) (based on 0.04 mmol of starting material **9**, 0.006 mmol were used for

the preparation of **12**); ^{1}H NMR ($CDCl_3$): δ 9.48 (s, 1 H, H-6″ of aldehyde), 5.48 (s, 1 H, H-1), 5.16 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 5.06 (dd, 1 H, $J_{3',4'} = J_{4',5'} = 10.1$ Hz, H-4″), 4.82 (s, 1 H, H-3), 4.57 (s, 1 H, H-2), 4.49 (dd, 1 H, H-6a′), 4.38 (m, 1 H, H-5′), 4.23 (m, 1 H, H-6b′), 3.46 (s, 1 H, H-4); ^{13}C NMR ($CDCl_3$): δ 194.9 (C-6″, aldehyde), 99.1 (C-1), 96.8 (C-1′), 95.4 (C-1″), 94.5 (C-6″, hydrated aldehyde).

O-[2″,3″,4″-Tri-O-acetyl-5-C-(1,3-diphenyl-2-imidaylidinyl)-α-D-xylopyranosyl]-(1 → 4)-2,3,2′,3′,6′-penta-O-acetyl-1,6-anhydro-β-maltose (**12**).—An aliquot (235 μl) of the above reaction mixture containing **11** (4.9 mg, 0.006 mmol) was quenched with oxalic acid, and *N,N′*-diphenylethane-1,2-diamine (2.6 mg, 0.012 mmol) was added. The mixture was stored at room temperature for 2 days, diluted with ice water and extracted twice with ethyl acetate. The organic layer was washed with satd $NaHCO_3$, dried over $MgSO_4$ and evaporated to dryness. Chromatography with 3:2 ethyl acetate–toluene gave **12** (4.6 mg, 71%); $[\alpha]_D^{20}$ +7° (*c* 0.25, $CHCl_3$). For ^{1}H NMR data, see Tables 1 and 2; for ^{13}C NMR data, see Table 3.

(6″-R,S)-[6″-^{3}H]-2,3,2′,3′,6′,2″,3″,4″-Octa-O-acetyl-1,6-anhydro-β-maltotriose (**13**). —To a solution of **11** (5.7 mg, 0.007 mmol) in methanol (150 μL) at 0 °C was added sodium borotritiide (0.3 mg, 0.007 mmol, 2.5 mCi) dissolved in water (150 μL). The mixture was stirred for 2 h at 0 °C and for 20 min at room temperature. A solution (5%) of $NaHCO_3$ was added and the mixture was extracted 3 times with chloroform. The combined extracts were dried over $MgSO_4$ and concentrated to yield **13** (5.1 mg, 89%). Radiochemical yield: 0.2 mCi (8%). ^{3}H NMR ($CDCl_3$): δ 4.17 (^{3}H-6″*S*, 0.64) and 4.03 (^{3}H-6″*R*, 0.36).

(6″-R,S)-[6″-^{3}H]-per-O-acetyl-maltotriose (**15**).—Compound **13** (5.1 mg, 0.006 mmol) was dissolved in 30:70:1 (v/v) acetic acid/acetic anhydride/concd sulfuric acid (700 μL). The mixture was stirred for 3 h at room temperature, added to ice-cold satd $NaHCO_3$, stirred overnight, and extracted with chloroform. The extract was successively washed with satd $NaHCO_3$ and brine, and evaporated to give **15** (3.5 mg, 58%); ^{3}H NMR ($CDCl_3$): δ 4.07 (^{3}H-6″*S*, 0.64) and 3.87 (^{3}H-6″*R*, 0.36).

(6″-R,S)-(6″-^{2}H)-per-O-acetyl-maltotriose (**16**).—To a suspension of **11** (22 mg, 0.027 mmol) in MeOD (500 μL) was added a solution of sodium borodeuteride (1.1 mg, 0.027 mmol) in D_2O (70 μL) and the mixture was stirred at room temperature for 2 h. The solution was diluted with 5% $NaHCO_3$ and extracted with chloroform, dried over $MgSO_4$ and evaporated to give **14**. The crude product was treated with 30:70:1 (v/v) acetic acid/acetic anhydride/concd sulfuric acid (450 μL) and stirred at room temperature for 3 h. The solution was diluted with satd $NaHCO_3$ and extracted with chloroform, dried over $MgSO_4$ and concentrated. Chromatography of the residue with 1:1 toluene–ethyl acetate gave **16** (20 mg, 78%), as a 65:35 α:β mixture. ^{2}H NMR ($CHCl_3$): δ 4.15 (broad s, ^{2}H-6″a and ^{2}H-6″b); ^{1}H NMR ($CDCl_3$): δ 6.22 (d, $J_{1,2}$ 3.6 Hz, H-1α), 5.72 (d, $J_{1,2}$ 8.2 Hz, H-1β), 5.49 (t, 1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 9.1 Hz, H-3), 5.40 (d, 1 H, $J_{1'',2''}$ 4.0 Hz, H-1″), 5.39 (t, 1 H, $J_{3',4'}$ 9.1 Hz, H-3′), 5.34 (t, 1 H, $J_{2'',3''}$ 10.3, $J_{3'',4''}$ 10.4 Hz, H-3″), 5.28 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1′), 5.05 (t, 1 H, $J_{4'',5''}$ 10.2 Hz, H-4″), 4.93 (dd, 1 H, H-2), 4.82 (dd, 1 H, H-2″), 4.73 (dd, 1 H, $J_{2',3'}$ 10.4 Hz, H-2′), 4.45 (dd, 1 H, $J_{5',6'}$ 2.0, $J_{6'a,6'b}$ 11.3 Hz, H-6′a), 4.43 (dd, 1 H, $J_{5,6a}$ 2.6, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.25 (dd, 1 H, $J_{5,6b}$ 3.5 Hz, H-6b), 4.20 (d, 0.55 H, $J_{5'',6''a}$ 3.5 Hz, H-6″a), 4.14 (dd, 1 H, $J_{5',6'b}$ 2.6 Hz, H-6′b), 4.10 (dt, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 4.02 (d, 0.45 H, $J_{5'',6''b}$ 2.3 Hz, H-6″b),

3.98 (t, 1 H, H-4), 3.97–3.92 (m, 2 H, H-4',-5'), 3.89 (dd, 1 H, H-5''), 2.2–2.0 (11 s, each 3 H, 11 Ac). ^{13}C NMR ($CDCl_3$): δ 170.6–169.4 ($COCH_3$), 96.0 (C-1'), 95.6 (C-1''), 91.4 (C-1β), 88.9 (C-1α), 73.5 (C-4), 72.3 (C-4'), 72.1 (C-3), 71.8 (C-3'), 70.5 (C-2'), 70.2 (C-5), 70.1 (C-2''), 69.7 (C-2), 69.4 (C-3''), 69.1 (C-5'), 68.4 (C-5''), 67.9 (C-4''), 62.6 (C-6), 62.2 (C-6'), 21.0–20.4 ($COCH_3$).

(6''-R,S)-[6''-^{3}H]Maltotriose (**17**).—To a solution of **15** (3.5 mg, 0.004 mmol) in dry methanol (200 μL) was added a 0.1 M solution of NaOMe in dry methanol (50 μL). The mixture was stirred for 1 h at room temperature, diluted with methanol, and neutralized with Amberlite IR-120 (H^+-form). The resin was removed by filtration and the filtrate was concentrated. After gel permeation chromatography on Sephadex G-15 (2 cm i.d. × 37 cm), pure [6''-^{3}H]maltotriose **17** was obtained (1.6 mg, 76%). Radiochemical yield: 0.085 mCi (43%) (based on **13**); ^{3}H NMR (D_2O): δ 3.71 (^{3}H-6''*R*, 0.36) and 3.63 (^{3}H-6''*S*, 0.64).

(6''-R,S)-(6''-^{2}H)Maltotriose (**18**).—To a solution of **16** (20 mg, 0.021 mmol) in dry methanol (500 μL) was added a 0.1 M solution of NaOMe in dry methanol (500 μL). The mixture was stirred for 1 h at room temperature, diluted with methanol and neutralized with Amberlite IR-120 (H^+-form). The resin was removed by filtration and the filtrate was concentrated. Chromatography of the residue on Sephadex G-15 (2 cm i.d. × 37 cm) gave **18** (9 mg, 85%) as a 40:60 α:β mixture. ^{2}H NMR (H_2O): δ 3.62 (broad s, ^{2}H-6''a and ^{2}H-6''b); ^{1}H NMR (D_2O): δ 5.29 (d, 2 H, $J_{1',2'} = J_{1'',2''} = 3.8$ Hz, H-1', -1''), 5.12 (d, $J_{1\alpha,2}$ 3.8 Hz, H-1α), 4.45 (d, $J_{1\beta,2}$ 7.9 Hz, H-1β), 3.31 (t, 1 H, $J_{3,4} = J_{4'',5} = 10$ Hz, H-4''), 3.17 (t, 1 H, $J_{1,2} = J_{2,3} = 8.5$ Hz, H-2); ^{13}C NMR (D_2O): δ 101.0, 100.7 (C-1', -1''), 97.0 (C-1β), 93.1 (C-1α), 75.2 (C-2), 70.6 (C-4''); ES-MS: *m/z* 528 (M + Na).

Per-O-acetyl-(2-^{2}H)maltotriose (**19**).—Maltotriose hydrate (2.0 g, 4.0 mmol) was repeatedly dissolved in D_2O and lyophilized to dryness. The residue was dissolved in D_2O (38 mL) and a 40% (w/v) solution of NaOD in D_2O (2 mL) was added. The reaction mixture was kept at room temperature and was directly monitored every 5 h by ^{1}H NMR. After almost complete conversion of the H-1 doublets at 5.12 and 4.52 ppm to singlets the reaction was quenched by neutralization with concd CH_3COOD. Following lyophilization, the residue was repeatedly dissolved in water and lyophilized to dryness. To the mixture of the residue and anhydrous NaOAc (0.7 g) was added acetic anhydride (12 mL) in portions. The mixture was heated under reflux for 40 min, cooled, poured into ice-water, and extracted twice with chloroform. The extract was washed with satd $NaHCO_3$ solution, dried over $MgSO_4$, evaporated to a syrup, and chromatographed on silica gel with 3:1 chloroform–ethyl acetate. The fraction containing the product was concentrated and crystallized from ethanol to give **19** (1.04 g, 14%) as a 40:60 α:β mixture; $[\alpha]_D^{20}$ +88° (*c* 1, $CHCl_3$); ^{2}H NMR ($CHCl_3$): δ 4.93 (broad s, ^{2}H-2); ^{1}H NMR ($CDCl_3$): δ 6.22 (s, H-1α), 5.74 (s, H-1β), 5.50 (d, $J_{3\alpha,4}$ 9.0 Hz, H-3α), 5.4 – 5.2 (m, 4 H, H-1', -3', -1'', -3''), 5.20 (d, $J_{3\beta,4}$ 9.0 Hz, H-3β), 5.05 (t, 1 H, $J_{4'',5''}$ 9.7, $J_{3'',4''}$ 9.2 Hz, H-4''), 4.95 (m, > 0.05 H, H-2), 4.84 (dd, 1 H, H-2''), 4.73 (m, 1 H, H-2'), 4.44 (m, 2 H, H-6a, -6'a), 4.3 – 3.8 (m, 9 H, H-6b, -6b', -6a'', -6b'', -4, -4', -5, -5', -5''), 2.3–1.9 (11 s, each 3 H, 11 Ac); ^{13}C NMR ($CDCl_3$): δ 170.5–168.7 ($COCH_3$), 95.9 (C-1'α), 95.8 (C-1'β), 95.6 (C-1''β), 95.5 (C-1''α), 91.1 (C-1β), 88.7 (C-1α), 74.9 (C-3β), 73.4 (C-4β), 73.25 (C-4α), 72.8 (C-5β), 72.5 (C-4'β), 72.3 (C-4'α), 72.0

(C-3α), 71.7 (C-3'α), 71.6 (C-3'β), 70.41 (C-2'α), 70.35 (C-2'β), 70.05 (C-5α), 70.0 (C-2''), 69.3 (C-3''), 69.0 (C-5'), 68.4 (C-5''), 67.8 (C-4''), 62.6 (C-6'β), 62.5 (C-6'α), 62.2 (C-6β), 62.1 (C-6α), 61.3 (C-6''), 21.6–20.3 ($COCH_3$).

(2-^{2}H)Maltotriose (**20**).—To a solution of **19** (520 mg, 0.54 mmol) in dry methanol (10 mL) was added a solution of 0.1 M sodium methoxide in methanol (2.5 mL). The solution was stirred for 2 h, neutralized with Amberlite IR-120 (H^+-form), concentrated and chromatographed over Sephadex G-15 (4.5 cm i.d. × 67 cm) to give **20** (263 mg, 97%) as a 40:60 α:β mixture; $[\alpha]_D^{20}$ +150° (*c* 1, H_2O); ^{2}H NMR (H_2O): δ 3.41 (s, ^{2}H-2α) and 3.12 (s, ^{2}H-2β); ^{1}H NMR (D_2O): δ 5.28 (d, 2 H, $J_{1',2'} = J_{1'',2''} = 4$ Hz, H-1', -1''), 5.12 (s, H-1α), 4.54 (s, H-1β), 3.32 (t, 1 H, $J_{4'',5''}$ 9.7, $J_{3'',4''}$ 9.2 Hz, H-4''); ^{13}C NMR (D_2O): δ 101.0 (C-1''), 100.75 (C-1'α), 100.65 (C-1'β), 97.0 (C-1β), 93.1 (C-1α), 78.3 (C-4α), 78.1 (C-4β), 78.0 (C-4'), 77.3 (C-3β), 75.7 (C-5β), 74.55 (C-3'), 74.4 (C-3α), 74.1 (C-3''), 73.9 (C-2''), 73.0 (C-5''), 72.8 (C-2'α), 72.7 (C-2'β), 72.4 (C-5'), 71.1 (C-5α), 70.5 (C-4'') 61.9 (C-6α), 61.7 (C-6β, -6', -6'').

β-Amylase digestion of **20**.—Compound **20** (15 mg, 0.029 mmol) was dissolved in sodium acetate buffer (0.04 M, 10 mL, pH 4.9). After addition of β-amylase (1100 units, from sweet potato), the reaction mixture was incubated for 24 h at 37 °C. TLC analysis (2:1:1 *n*-butanol/water/acetic acid) showed complete digestion to glucose and maltose. These fragments were separated by gel chromatography (Sephadex G-15) and analyzed by ^{2}H NMR. Whereas the maltose fraction showed no incorporation of deuterium, the ^{2}H NMR spectrum of the glucose fraction gave: (H_2O) δ 5.12 (^{2}H-1α, < 5%), 4.54 (^{2}H-1β, < 5%), 3.42 (s, ^{2}H-2α, 45%) and 3.13 (s, ^{2}H-2β, 50%).

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