Carbohydrate Research, 63 (1978) 283–287

Note

Syntheses of benzyl and methyl 6′-*O*-trityl-β-maltoside hexaacetates having a trideuterioacetoxyl group at C-4′: an unambiguous n.m.r. signal-assignment of the 4′-acetoxyl group*

KYOKO KOIZUMI AND TOSHIKO UTAMURA

Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 4-16 Edagawa, Nishinomiya, Hyogo (Japan)

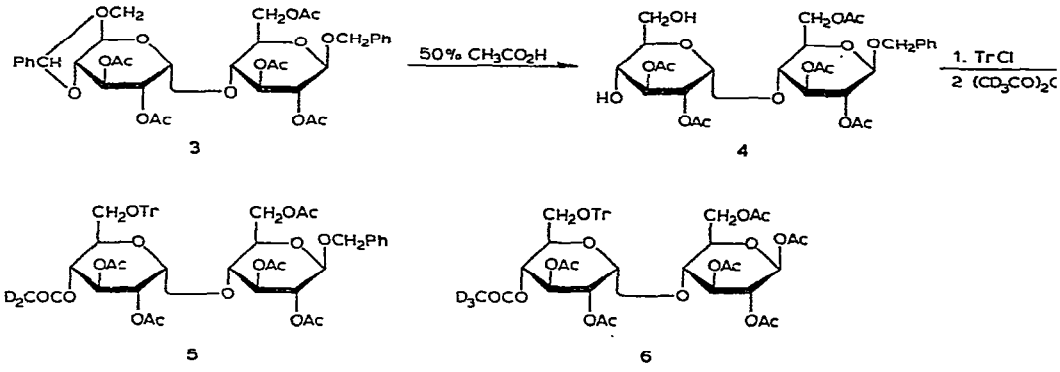
(Received June 23rd, 1977; accepted for publication in revised form, August 30th, 1977)

Tritylation of the primary hydroxyl group of maltose and subsequent acetylation has yielded[1] six different derivatives, each isolated crystalline after chromatography. The ^{1}H-n.m.r. spectrum of the 6′-trityl ether (**1**), and also that of the 6,6′-ditrityl ether (**2**), showed one of the acetyl resonances at abnormally high field (δ 1.71). This high-field resonance was assumed, without confirmation, to be due to the acetoxyl group at C-4′. Durette *et al.*[2] observed an analogous phenomenon in the ^{1}H-n.m.r. spectrum of methyl 3-*O*-mesyl-6′-*O*-trityl-β-maltoside pentaacetate and they tentatively assigned the high-field resonance to a proximate acetoxyl group, namely that at C-4′, the methyl group of which must lie within the shielding cone of one of the benzene rings of the 6′-trityloxy group.

The method of specific spectral-assignments for acetoxyl group resonances by the use of trideuterioacetyl analogs was pioneered by Horton and Lauterbach[3].

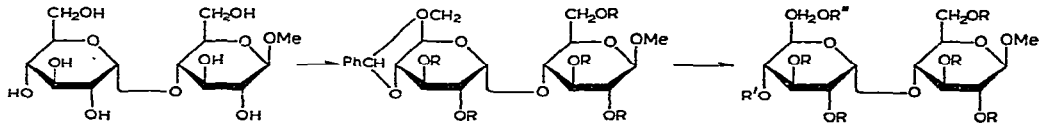
Debenzylidenation of the known benzyl 2,3,6,2′,3′-penta-*O*-acetyl-4′,6′-*O*-benzylidene-β-maltoside[4] (**3**) with 50% acetic acid[5], followed by tritylation and subsequent deuterioacetylation, afforded benzyl 2,3,6,2′,3′-penta-*O*-acetyl-4′-*O*-trideuterioacetyl-6′-*O*-trityl-β-maltoside (**5**) in 66.3% overall yield without the need for chromatography at any stage. Attempted debenzylation of **5** by using Raney nickel[6] or palladium[7] as catalyst, and subsequent acetylation to **6** was unsuccessful. Refluxing benzyl hepta-*O*-acetyl-β-maltoside in ethanol with Raney nickel (W-2) gave the debenzylated compound in high yield, whereas debenzylation of benzyl hexa-*O*-acetyl-6′-*O*-trityl-β-maltoside did not occur at all under the same conditions. Furthermore, using benzyl 4′,6′-*O*-benzylidene-β-maltoside[2] as starting material, catalytic debenzylation[4,6] before debenzylidenation was attempted, but this also ended in failure.

*Presented at the 95th Meeting of the Pharmaceutical Society of Japan, Nishinomiya, Japan, April 1975.



3 4 5 6

Accordingly, we chose to protect the 1-hydroxyl group by a methyl group instead of the benzyl group, as the 1-methoxyl group in peracetylated methyl maltoside seemed to have only slight effects on the chemical shifts of the acetoxyl groups in the same maltose molecule. To confirm this concept, methyl 2,3,6,2′,3′,4′-hexa-*O*-acetyl-6′-*O*-trityl-β-maltoside (**7**) and methyl 2,3,2′,3′,4′-penta-*O*-acetyl-6,6′-di-*O*-trityl-β-maltoside (**8**) were synthesized and their ^{1}H-n.m.r. spectra were compared with those of 6′-*O*-trityl-β-maltose heptaacetate (**1β**) and 6,6′-di-*O*-trityl-β-maltose hexaacetate (**2β**), respectively. Trityl ethers of methyl β-maltoside (**7** and **8**) have been obtained by Durette *et al.*[2], but, the structure assigned to the monoether **7** was based only on the ^{1}H-n.m.r. spectral parameters and upon the known greater reactivity of the 6′-hydroxyl group, and had not been confirmed by authentic synthesis. The diether **8** has not been crystallized.



Methyl β-maltoside

9 R = H
10 R = Ac

7 R = R′ = Ac, R″ = Tr
11 R = Ac, R′ = R″ = H
12 R = Ac, R′ = COCD3, R″ = Tr

In an unambiguous synthesis of **7**, methyl β-maltoside[8] was converted into the 4′,6′-*O*-benzylidene acetal (**9**), which was acetylated to yield compound **10**. Treatment with 50% acetic acid removed the benzylidene group to give compound **11**, which upon tritylation followed by acetylation, gave compound **7**.

The ditrityl ether **8** was synthesized from methyl β-maltoside by direct tritylation with 3 equivalents of chlorotriphenylmethane and subsequent acetylation, and was isolated as a syrup after column chromatography. The syrup was then purified by preparative t.l.c. and crystallized from acetone–ethanol.

The analog of **7**, having a trideuterioacetoxyl group at C-4′ (**12**), was prepared

TABLE I

CHEMICAL SHIFTS OF ACETYL-METHYL SIGNALS IN THE ^{1}H-N.M.R. SPECTRA OF PERACETYLATED MALTOSE DERIVATIVES IN CHLOROFORM-*d* AT 60 MHz

Peracetylated derivative	*Acetyl-methyl signals δ (p.p.m.)*[a]		
	1-OAc	*Other acetoxyl groups*	*4′-OAc*
6′-*O*-Trityl-β-maltose (**1β**)	2.07	2.07, 2.0. 2.03, 1.99, 1.86[b]	1.71
6,6′-Di-*O*-trityl-β-maltose (**2β**)	2.12	2.07, 2.04, 2.04, 1.95	1.69
Methyl 6′-*O*-trityl-β-maltoside (**7**)[c]		2.07, 2.07, 2.03, 1.99, 1.86	1.71
Methyl 6,6′-di-*O*-trityl-β-maltoside (**8**)		2.07, 2.04, 2.04, 1.95	1.69
Methyl 4′-*O*-trideuterioacetyl-6′-*O*-trityl-β-maltoside (**12**)		2.07, 2.07, 2.03, 1.99, 1.86	
Benzyl 4′-*O*-trideuterioacetyl-6′-*O*-trityl-β-maltoside (**5**)		2.05, 2.04, 1.99, 1.98, 1.87	

[a]Each signal corresponds to one acetyl group (three protons). [b]This signal was assigned[1] to 6-OAc. [c]The chemical shifts (τ values) at 220 MHz in ref. 2 are: 7.93, 7.96, 8.01, 8.17, and 8.31.

from compound **10** by essentially the same route as that to compound **7**, except that acetic anhydride-d_6 was used for acetylation.

The chemical shifts of acetyl-methyl signals in the ^{1}H-n.m.r. spectra of **1β**, **2β**, **7**, **8**, and **12** (additionally, **5**) are shown in Table I. Comparison of acetoxyl resonances of **1β** and **2β** with those of **7** and **8**, respectively, confirmed that the 1-methoxyl group of peracetylated methyl maltoside does not affect the chemical shift of any acetoxyl group of the same maltose molecule. The spectrum of **12** is identical in all respects with that of **7**, except that one three-proton singlet (δ 1.71) disappears in the latter, and this signal can thus be assigned unambiguously to the 4′-acetoxyl signal. In the spectrum of **5**, which has a trideuterioacetoxyl group at C-4′ and a trityloxy group at C-6′, no acetyl resonance at abnormally high field was observed.

EXPERIMENTAL

General methods. — Melting points were measured with a Yamato melting point apparatus MP-21 and are uncorrected. Optical rotations were determined with a Jasco DIP-SL automatic polarimeter. N.m.r. spectra were recorded with solutions in chloroform-*d* on a Varian A-60A spectrometer, with tetramethylsilane as the internal standard. T.l.c. and preparative t.l.c. were performed with Silica Gel G (E. Merck, Darmstadt, Germany). Column chromatography was performed on a Lobar, prepacked column of Silica gel 60 size C (E. Merck, Darmstadt, Germany). Solvents were removed below 40° under diminished pressure.

*Benzyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**4**). — Benzyl 2,3,6,4′,6′-penta-*O*-acetyl-4′,6′-*O*-benzylidene-β-maltoside (2 g) was dissolved in 100 ml of 50% aqueous acetic acid and heated for 10 min at 100°. The solvents were evaporated off, and the last trace of acetic acid was

removed by repeated evaporation of ethanol from the residue. Recrystallization from benzene gave pure **4**; yield 1.53 g, m.p. 154–155°, $[\alpha]_D^{21}$ +17.0° (*c* 2.0, chloroform).

Anal. Calc. for $C_{29}H_{38}O_{16}$: C, 54.20; H, 5.96. Found: C, 54.24; H, 5.98.

*Benzyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4-*O*-trideuterioacetyl-6-*O*-trityl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**5**). — To a solution of **4** (1 g) in dry pyridine (25 ml) was added chlorotriphenylmethane (0.65 g, 1.5 mol equivalents) and the mixture was stirred for 56 h at 35–40°. After cooling to 20°, the mixture was acetylated for 72 h with 1 ml of acetic anhydride-d_6. The product was poured into ice–water and the resulting precipitate was crystallized from ethanol; yield 0.96 g, m.p. 171.4–171.6°, $[\alpha]_D^{21}$ +59.6° (*c* 2.18, chloroform).

Anal. Calc. for $C_{50}H_{51}D_3O_{17}$: C, 64.79; H, 5.87. Found: C, 64.42; H, 5.84.

*Methyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**7**). — Methyl β-maltoside (4.3 g) was dissolved in 110 ml of dry pyridine, 3.3 g (1 mol equivalent) of chlorotriphenylmethane was added, and the solution was stirred for 64 h at 45°. A further 15 ml of dry pyridine was added, the flask was cooled to 0°, and 20 ml of acetic anhydride was added. After the stoppered flask had been kept for 48 h at room temperature, the solution was poured into ice–water and stirred mechanically. The resulting precipitate was collected, air dried, and crystallized from ethanol; yield 2.15 g, m.p. 171.8–172.2°, $[\alpha]_D^{27}$ +83.5° (*c* 2.0, chloroform). [lit.[2] m.p. 165–168°, $[\alpha]_D$ +88° (*c* 2, chloroform)].

Anal. Calc. for $C_{44}H_{50}O_{17}$: C, 62.11; H, 5.92. Found: C, 62.07; H, 5.96.

This compound was shown to be identical (m.p., $[\alpha]_D$, t.l.c., and n.m.r.) with compound **7** prepared by an unambiguous route, as described later.

*Methyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-*D*-glucopyranosyl)-6-*O*-trityl-β-*D*-glucopyranoside* (**8**). — Methyl β-maltoside (4 g) was tritylated with a 1:3 molar ratio of reagent and subsequently acetylated according to the procedure described for the preparation of **7** to yield 16.7 g of a mixture. The mixture was fractionated on a column of silica gel with 7:2 benzene–ethyl acetate. The fractions containing **8** were collected and concentrated to a syrup that was purified by preparative t.l.c. on silica gel plates and crystallized from acetone–ethanol. The yield of pure, crystalline **8** was 73 mg, m.p. 122.5–123.5°, $[\alpha]_D^{22}$ +52° (*c* 1.0, chloroform) [lit.[2] $[\alpha]_D$ +55° (*c* 1, chloroform)].

Anal. Calc. for $C_{61}H_{62}O_{16}$: C, 69.70; H, 5.95. Found: C, 69.39; H, 5.86.

*Methyl 4-*O*-(4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**9**) *and its peracetate* (**10**). — A mixture of well dried methyl β-maltoside (2.7 g), freshly fused and powdered zinc chloride (4 g), and freshly distilled benzaldehyde (40 ml) was shaken for 22 h at room temperature. The mixture was poured into ice–water (50 ml). The excess of benzaldehyde was removed by repeated extraction with petroleum ether and the organic layers were discarded. The aqueous layer was neutralized with aqueous sodium carbonate, filtered, and the residue was washed with hot methanol. The combined filtrate and washings were evaporated and the residue was extracted with warm acetone (10 × 30 ml). Removal of acetone from

the combined extracts gave an amorphous powder that was purified by column chromatography to obtain **9** (a chromatographically pure, amorphous powder); yield 1.95 g, $[\alpha]_D^{24}$ +52.0° (*c* 2.0, methanol).

Acetylation of **9** (500 mg) gave the peracetate **10**, which was recrystallized from ethanol; yield 605 mg, m.p. 195–196°, $[\alpha]_D^{22}$ +22.7° (*c* 1.5, chloroform).

Anal. Calc. for $C_{30}H_{38}O_{16}$: C, 55.04; H, 5.85. Found: C, 54.84; H, 5.94.

Methyl 2,3,6-tri-O-acetyl-4-O-(2,3-di-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**11**). — A solution of **10** (200 mg) in 50% aqueous acetic acid (40 ml) was heated for 10 min on a boiling water-bath. The mixture was treated as described for the preparation of **4**. Recrystallization from ethanol gave pure **11**; yield 173 mg, m.p. 147–148°, $[\alpha]_D^{22}$ +45.8° (*c* 1.2, chloroform).

Anal. Calc. for $C_{23}H_{34}O_{16}$: C, 48.76; H, 6.05. Found: C, 48.96, H, 6.22.

Methyl 2,3,6-tri-O-acetyl-4-(2,3-di-O-acetyl-4-O-trideuterioacetyl-6-O-trityl-α-D-glucopyranosyl)-β-D-glucopyranoside (**12**). — To a solution of **11** (173 mg) in dry pyridine (5 ml) was added chlorotriphenylmethane (128 mg) and the mixture was maintained for 48 h at 40°. A further 3 ml of dry pyridine was added and the flask was cooled to 0°. Acetic anhydride-d_6 (2 ml) was added to the cooled solution and the solution was kept for 30 h at 20°, and then poured into ice–water. The precipitate was filtered off and crystallized from ethanol to give **12**; yield 77 mg, m.p. 169.5–170.2°, $[\alpha]_D^{22}$ +82.0° (*c* 1.0, chloroform).

Anal. Calc. for $C_{44}H_{47}D_3O_{17}$: C, 61.89; H, 5.55. Found: C, 61.53; H, 5.78.

In a similar manner, treatment of **11** with chlorotriphenylmethane in pyridine and subsequent acetylation with acetic anhydride gave **7**, m.p. and mixed m.p. 171.8–172.2°, $[\alpha]_D^{27}$ +83.5° (*c* 2.0, chloroform).

REFERENCES

1 K. KOIZUMI AND T. UTAMURA, *Carbohydr. Res.*, 33 (1974) 127–134.
2 P. L. DURETTE, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin Trans. 1*, (1974) 97–101.
3 D. HORTON AND J. H. LAUTERBACH, *J. Org. Chem.*, 34 (1969) 86–92; D. HORTON AND J. H. LAUTERBACH, *Carbohydr. Res.*, 43 (1975) 9–33.
4 A. KLEMER, *Chem. Ber.*, 92 (1959) 218–226.
5 S. TAKANASHI, Y. HIRASAKA, AND M. KAWADA, *J. Am. Chem. Soc.*, 84 (1962) 3029; R. W. JEANLOZ AND H. M. FLOWERS, *ibid.*, 84 (1962) 3030; Y. MATSUSHIMA AND J. PARK, *J. Org. Chem.*, 27 (1962) 3581–3583; N. YAMAOKA, T. FUJITA, M. KUSAKA, AND K. ASO, *Nippon Nogei Kagaku Kaishi*, 38 (1964) 5–9; R. KHAN, *Carbohydr. Res.*, 32 (1974) 375–379.
6 G. W. KENNER, C. W. TAYLOR, AND A. R. TODD, *J. Chem. Soc.*, (1949) 1620–1624.
7 N. K. RICHTMYER, *J. Am. Chem. Soc.*, 56 (1934) 1633–1637; R. L. SUNDBERG, C. M. MCCLOSKEY, D. E. REES, AND G. H. COLEMAN, *ibid.*, 67 (1945) 1080–1084; E. E. COMBS, C. M. MCCLOSKEY, R. L. SUNDBERG, AND G. H. COLEMAN, *ibid.*, 71 (1949) 276–278; C. E. BALLOU AND H. O. L. FISCHER, *ibid.*, 77 (1955) 3329–3331; R. R. KING AND C. T. BISHOP, *Can. J. Chem.*, 52 (1974) 3913–3917.
8 P. L. DURETTE, L. HOUGH, AND A. C. RICHARDSON, *Carbohydr. Res.*, 31 (1973) 114–119.