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A convenient large-scale synthesis of methyl α-maltoside: a simple model for amylose

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Abstract

Methyl 4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranoside (methyl α-maltoside), a model compound for amylose, has been synthesized in four steps and 63% overall yield from relatively inexpensive D-(+)-maltose. © 1998 Elsevier Science Ltd. All rights reserved

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1. Introduction

Methyl 4-*O*-methyl-α-D-glucopyranoside has long been used as a model compound for the key polysaccharide amylose [1] in a variety of studies [2] and whilst it possesses the necessary structural features in the correct stereochemical arrangement, a considerable drawback is that the ether linkage is much more resistant to hydrolysis than the unit linkages in the natural product. A more complex, and consequently a more representative model, should contain at least one glucose-glucose linkage and also be protected at the terminal anomeric position since in the natural compound the majority of glucose units are protected at this position by other glucose units. The simplest compound to meet these criteria is methyl 4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranoside (methyl α-maltoside) **5α** for which four syntheses have appeared hitherto in the literature. Of these, two routes use methyl α-D-glucopyranoside as the starting material for enzymatic transformations performed respectively by *Dextrin glycotransferase* in conjunction with amylopectin [3], and an unidentified pentylase enzyme isolated from *Bacillus macerans* with cyclohexaamylose [4]. An eight-step convergent synthetic route has also been used to construct **5α**, albeit in 31% overall yield (with no yield being given for two individual steps) [5]. Finally, Dick et al. [6] have also reported the synthesis of **5α** by a slightly shorter route based on D-(+)-maltose, but it is marred by repeated acetylation/de-acetylation steps and the necessity for both selective removal of admixed β-anomer by oxidation with chromic acid and large-scale chromatography. Herein we describe a much more efficient and practical route for the large-scale synthesis of **5α** from D-(+)-maltose **1**. This is accomplished in a straightforward manner as shown in Scheme 1 without recourse to the use of either an enzymatic step or the need for column chromatography.

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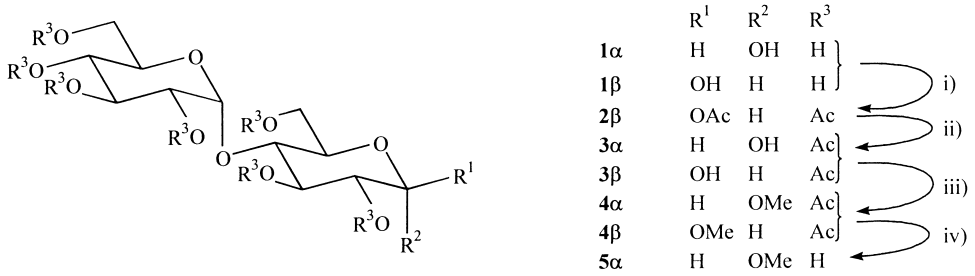

Scheme 1. Reagents and conditions: (i) 10.6 eq. pyridine/10.6 eq. acetic anhydride/0.02 eq. *N*,*N*-dimethylaminopyridine/CH_2Cl_2/31 h/0 °C→room temperature; (ii) $NH_{3(sat)}$/MeOH:THF (3:7)/100 min/room temperature; (iii) 1.2 eq. Ag_2O/1.2 eq. MeI/MeCN/60 min/ca. 80 °C: or alternatively, 2.0 eq. Ag_2O/2.0 eq. MeI/MeCN/72 h/room temperature; (iv) 3.5 eq. NaOH/MeOH/10 min/room temperature.

2. Results and Discussion

The first step involving peracetylation of a rigorously dried sample of maltose **1** was achieved by reaction with an excess of freshly distilled acetic anhydride in the presence of *N*,*N*-dimethylaminopyridine [7]. Next, the resulting β-maltose octaacetate **2**β was subjected to selective anomeric deacetylation under conditions which are equally effective on milligram and hundred gram scale [8]. Thus, **2**β was stirred at low temperature in a mixed solvent (3 parts MeOH:7 parts THF) saturated with ammonia [9]. After ca. 100 min, the resulting anomeric mixture of aldoses **3** was crystallised selectively, or alternatively used without further purification in the subsequent methylation step accomplished [10] via a modification of the traditional Purdie approach. In the absence of light, methyl iodide was added to a rapidly stirred suspension of **3** (either as an anomeric mixture or anomerically pure form) and silver (I) oxide in acetonitrile. Upon heating in a Soveril-joint ampoule for 60 min, an anomeric mixture of **4** (ca. 8:1 $\alpha:\beta$ (by ^{1}H NMR spectroscopy) was obtained in 81% yield. If on the other hand, the reaction mixture was allowed to stir at ambient temperature in a sealed tube for three days and isolated from light, the α-anomer of **4** was obtained exclusively in 83% yield, presumably as a consequence of the thermodynamic equilibrium in favour of **3**α. In the last step, complete anomeric deprotection of **4**α was achieved quantitatively by stirring in methanol with wet sodium hydroxide to furnish **5**α in 63% overall yield and complete stereochemical integrity. An added benefit of this shorter route was the efficiency of all of the individual steps irrespective of whether the reactions were carried out on a small (ca. 100 mg) or large (ca. 100 g) scale.

3. Experimental

Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates and visualised by dipping the plate into a solution of concentrated sulfuric acid in ethanol (5:95). ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker AC-250 spectrometer operating at 250 and 62.9 MHz, respectively. All other physical data including optical rotations which were measured on an Optical Activity AA 1000 polarimeter at 589 nm (the sodium D-line) using a 1 dm cell, unless quoted, were in accord with previously reported data.

Maltose octaacetate (**2**β).—To a rapidly stirring suspension of a rigorously dried sample of **1** (19.10 g, 56 mmol) in dichloromethane (150 mL) and pyridine (47.8 mL, 591 mmol) was added *N*,*N*-dimethylaminopyridine (0.14 , 1.1 mmol) under argon at 0 °C. After 30 min, freshly distilled acetic anhydride (55.8 mL, 591 mmol) was added slowly to the reaction mixture and when TLC (ethyl acetate:cyclohexane 4:1) had indicated the formation of one major fraction and no remaining starting material, it was quenched by addition of hydrochloric acid (2 M, 200 mL). After separation and extraction with dichloromethane (3×25 mL), the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (200 mL), then saturated aqueous sodium chloride (200 mL) and dried over magnesium sulfate before evaporation in vacuo to give an amorphous colourless solid, $[\alpha]_D^{20} + 65°$($c = 1$, ethanol), lit. [11]. + 64 °(34.84 g, 92%) of sufficient purity to use without further purification in subsequent steps. ^{1}H NMR ($CDCl_3$): δ_H 5.68 (d, 1H, $J_{1,2}$ 8.0, H-1), 5.30 (d, 1H, $J_{;1',2'}$ 4.0, H-1′), 5.28–5.20 (cm, 2H, H-3, H-3′), 5.01 (t, 1H, $J_{3',4'}$, $^J{}_{4',5'}$,10.0, H-4′), 4.91 (dd, 1H, $J_{2,3}$ 9.0, H-2), 4.80 (dd, 1H, $J_{2',3'}$, 10.0, H-2′), 4.37 (dd, 1H, $J_{5,6a}$ 2.0 $J_{5,6b}$ 5.0, H-6a), 4.24–4.13

(cm, 2H, H-6b, H-6a,), 4.03–3.95 (cm, 2H, H-4, H-6b,), 3.90–3.85 (cm, 1H, H-5,), 3.81–3.75 (cm, 1H, H-5), 2.07–1.93 (cm, 8×$COCH_3$), ^{13}C NMR ($CDCl_3$): δ_C 170.3–168.5 (8×$COCH_3$), 95.5, (CH), 91.0, (CH), 75.0 (CH), 72.8 (CH), 72.3 (CH), 70.7, (CH), 69.8 (CH), 69.1 (CH), 68.4 (CH), 67.8 (CH), 62.3 (CH_2), 61.2 (CH_2), 20.8–20.2 (8×$COCH_3$).

Maltose 2,3,6,2′,3′,4′,5′-heptaacetate (**3**α *and* **3**β).—β-Maltose octaacetate **2**β, 20.00 g, 29.5 mmol) was added at −78 °C to a mixed solvent (methanol:tetrahydrofuran 3:7, 450 mL) through which ammonia had been bubbled vigorously over a 25 min period. After stirring for 10 min, the reaction was allowed to warm to room temperature. When TLC (ethyl acetate:cyclohexane 4:1) had indicated the complete consumption of the starting material and the formation of a single, more polar fraction, the solvent and excess ammonia were removed by evaporation in vacuo to yield a pale yellow syrup which solidified on standing to a glass. Although not essential, this glass may be recrystallised slowly from ethanol:water (9:1) to provide **3**α solely, or as an anomeric mixture of **3**α and **3**β from *iso*-propanol to yield an amorphous solid (15.61 g, 82%). α-form ^{1}H NMR ($CDCl_3$): δ_H 5.52 (dd, 1H, $J_{2,3}$ 9.0, $J_{3,4}$ 10.0, H-3), 5.37 (d, 1H, $J_{1',2'}$, 4.0, H-1′), 5.30 (d, 1H, $J_{1,2}$ 4.0, H-1), 5.22 (t, 1H, $J_{2',3'}$, 9.0, $J_{3',4'}$, 9.0, H-3′), 5.00 (dd, 1H, $J_{4',5'}$, 10.0, H-4′), 4.70 (dd, 2H, $J_{2,3}$ 10.0, H-2, H-2,), 4.43 (dd, 1H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 13.0, H-6a), 4.26-4.14 (cm, 3H, H-5, H-6a, H-6b), 3.99, (dd, 1H, $J_{5',6a'}$, 3.5, $J_{6a',6b'}$, 12.0, H-6a′), 3.99–3.89 (cm, 2H, H-4, H-5′), 2.08–1.94 (21H, 7×CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.5–169.3 (7×*C*OCH_3), 95.3 (CH), 89.7 (CH), 72.5 (CH), 72.1 (CH), 71.4 (CH), 69.8 (CH), 69.2 (CH), 68.2 (CH), 67.8 (CH), 67.4 (CH), 62.6 (CH_2), 61.2 (CH_2), 20.7–20.3 (7×CO*C*H_3). β-form ^{1}H NMR ($CDCl_3$): δ_H 5.37 (d, 1H, $J_{1',2'}$ 4.0, H-1′), 5.30 (t, 1H, J2,3 9.0, $J_{3,4}$ 9.0, H-3), 5.22 (t, 1H, $J_{2',3'}$ 9.0, $J_{3',4'}$ 9.0, H-3′), 5.00 (dd, 1H, $J_{4',5'}$ 10.0, H-4′), 4.81 (dd, 1H, H-2′), 4.72–4.65 (cm, 2H, H-1, H-2), 4.43 (dd, 1H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 13.0, H-6a), 4.26–4.14 (cm, 2H, H-6b′, H-6a′), 3.99 (dd, 1H, $J_{5',6a'}$ 3.5, $J_{6a',6b'}$ 12.5, H-6a′), 3.99–3.89 (cm, 2H, H-5′, H-4), 3.75–3.66 (cm, 1H, H-5), 2.08-1.95 (21H, 7×*C*OCH_3). ^{13}C NMR ($CDCl_3$): δ_C 170.5–169.3 (7×$COCH_3$), 95.3 (CH), 94.6 (CH), 74.8 (CH), 73.5 (CH), 72.5 (CH), 69.8 (CH), 69.2 (CH), 68.2 (CH), 67.8 (CH), 67.4 (CH), 62.6 (CH_2), 61.2 (CH_2), 20.7–20.3 (7×CO*C*H_3).

Methyl α/β-D-*heptaacetyl-maltoside* (**4**α *and* **4**β).—To a Soveril-joint ampoule containing aldose **3** (1.01 g, 1.6 mmol) suspended in acetonitrile (7 mL) was added silver oxide (0.44 g, 1.9 mmol) and the mixture was stirred for 5 min. with the vessel protected from light. After this time, iodomethane (0.15 mL, 1.9 mmol, freshly filtered through a plug of neutral aluminium oxide) was added, the vessel sealed and immersed in an oil bath at ca. 90 °C for 90 min. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a plug of celite and evaporated in vacuo to give a faintly yellow crystalline foam which was recrystallised from ethanol as a colourless amorphous solid (0.86 g, 81%, α : β 8:1 by ^{1}H NMR spectroscopy). α-form ^{1}H NMR ($CDCl_3$): δ_H 5.35 (d, 1H, $J_{1,2}$ 4.0, H-1), 5.30–5.11 (cm, 2H, H-3, H-3′), 4.99 (t, 1H, $J_{3',4'}$ 10.0, $J_{4',5'}$ 10.0, H-4′), 4.82 (d, 1H, $J_{1',2'}$ 4.0, H-1′), 4.75 (dd, 1H, $J_{2,3}$ 9.0, H-2), 4.41 (cm, 1H, H-2′), 4.30–4.16 (cm, 3H, H-5, H-6a′, H6b′), 4.01–3.75 (cm, 3H, H-4, H-6a′, H-6b′), 3.66–3.57 (cm, 1H, H-5′), 3.43 (s, 3H, OCH_3), 2.09–1.94 (cm, 21H, 7×$COCH_3$). ^{13}C NMR ($CDCl_3$): δ_C 170.3–169.2 (7×*C*OCH_3), 100.9 (CH), 95.3 (CH), 75.2 (CH), 72.5 (CH), 71.9 (2×CH), 69.8 (CH), 69.1 (CH), 68.3 (CH), 67.8 (CH), 62.6 (CH*2*), 61.3 (CH*2*), 56.8 (OCH_3), 20.7–20.4 (7×$COCH_3$).

Methyl α-D-*heptaacetyl-maltoside* (**4**α).—To an anomeric mixture of aldose **3** (1.01 g, 1.6 mmol) suspended in acetonitrile (7 mL) in the dark, was added silver oxide (0.77 g, 3.3 mmol) with stirring. After 15 min, iodomethane (0.21 mL, 3.3 mmol, freshly filtered through a plug of neutral aluminium oxide) was added and the mixture left to stir over a 72 h period. Afterwards, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a plug of celite, and evaporated in vacuo to a crystalline foam which was recrystallised from *iso*-propanol to yield **4**α (vide supra) as colourless needles (0.86 g, 83%).

Methyl α-D-*maltoside* (**5**α).—To a rapidly stirred solution of **4**α (4.53 g, 7.0 mmol) in methanol (25 mL) was added freshly ground sodium hydroxide (0.98 g, 24.4 mmol). After 10 min, TLC (ethyl acetate) showed complete consumption of starting material and the presence of only one very polar fraction. The reaction mixture was neutralised by the addition of Dowex MR-3 ion exchange resin, and evaporated in vacuo to a crystalline foam $[\alpha]_D^{20}$ + 176 °(c = 1, water), lit. + 174 ° [6] (2.48 g, 100%). 1H NMR (D_2O): δ_H 5.20 (d, 1H, $J_{1,2}$ 4.0, H-1), 4.29 (d, 1H, $J_{1',2'}$ 8.0, H-1′), 4.10–3.22 (cm, 12H, ring protons), 3.46 (s, 3H, OCH_3); ^{13}C NMR (CD_3OD): δ_C 101.4 (CH), 100.1 (CH), 78.5 (CH), 74.8 (CH), 74.0 (CH), 73.6 (CH), 72.7 (CH), 72.0

(CH), 71.3 (CH), 70.0 (CH), 61.8 (CH_2), 61.6 (CH_2), 55.6 (OCH_3).

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