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SYNTHESIS OF METHYL 2-*O*-α-D-MANNOPYRANOSYL-α-D-TALOPYRANOSIDE AND METHYL 2-*O*-α-D-TALOPYRANOSYL-α-D-TALOPYRANOSIDE*

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ABSTRACT

Treatment of methyl 3-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**1**) with *tert*-butyldiphenylsilyl chloride in *N,N*-dimethylformamide afforded methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**2**). Oxidation of **2** with pyridinium chlorochromate, followed by reduction of the carbonyl group, and subsequent *O*-deacetylation afforded methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-α-D-mannopyranosyl-α-D-talopyranoside (**5**). Cleavage of the *tert*-butyldiphenylsilyl group of **5** with tetrabutylammonium fluoride in oxolane, followed by hydrogenolysis, gave methyl 2-*O*-α-D-mannopyranosyl-α-D-talopyranoside (**7**). *O*-Deacetylation of **1** gave methyl 3-*O*-benzyl-2-*O*-α-D-mannopyranosyl-α-D-mannopyranoside (**8**). Treatment of **8** with *tert*-butyldiphenylsilyl chloride afforded a 6,6′-disilyl derivative, which was converted into a 2′,3′-*O*-isopropylidene derivative, and then further oxidized with pyridinium chlorochromate. The resulting diketone was reduced and removal of the protecting groups gave methyl 2-*O*-α-D-talopyranosyl-α-D-talopyranoside (**15**). The structures of both **7** and **15** were established by ^{13}C-n.m.r. spectroscopy.

INTRODUCTION

Previous papers[2,3] from this laboratory described the synthesis and use of some methyl mannobiosides in an on-going program for the study of lysosomal-enzyme targeting. Thus far, of all the mannobiosides examined as substrates for the enzyme UDP-GlcNAc lysosomal enzyme *N*-acetyl-α-D-glucosamine-1-phosphotransferase (GlcNAc-*P*-transferase), the disaccharide methyl 2-*O*-α-D-manno-

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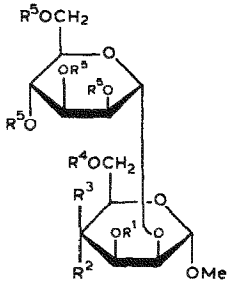

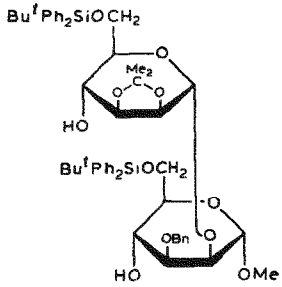

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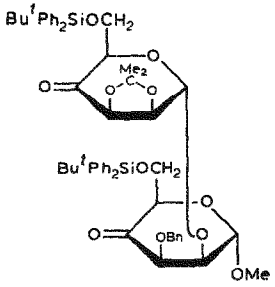
	R^1	R^2	R^3	R^4	R^5	R^6
1	Bn	OH	H	H	Ac	Ac
2	Bn	OH	H	Bu^tPh_2Si	Ac	Ac
3	Bn	O		Bu^tPh_2Si	Ac	Ac
4	Bn	H	OH	Bu^tPh_2Si	Ac	Ac
5	Bn	H	OH	Bu^tPh_2Si	H	H
6	Bn	H	OH	H	H	H
7	H	H	OH	H	H	H
8	Bn	OH	H	H	H	H
9	Bn	OH	H	Bu^tPh_2Si	H	Bu^tPh_2Si



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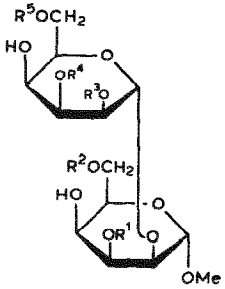

12 R^1 = Bn; R^2 = R^5 = Bu^tPh_2Si; R^3, R^4 = CMe_2
13 R^1 = Bn; R^2 = R^5 = H; R^3, R^4 = CMe_2
14 R^1 = Bn; R^2 = R^3 = R^4 = R^5 = H
15 R^1 = R^2 = R^3 = R^4 = R^5 = H

pyranosyl-α-D-mannopyranoside proved to be the best acceptor for phosphorylation[2].

In an effort to study the substrate specificity of this enzyme, we also described the synthesis of methyl 2-*O*- and 3-*O*-α-D-talopyranosyl-α-D-mannopyranoside[4], and, in furtherance of these studies, we now describe the synthesis of methyl 2-*O*-α-D-mannopyranosyl-α-D-talopyranoside and methyl 2-*O*-α-D-talopyranosyl-α-D-

talopyranoside. The use of such modified compounds in the study of the substrate specificity of GlcNAc-*P*-transferase is intended to examine the effect of changing the configuration, at either C-4, or C-4′, or both, of the mannobioside on the enzyme activity. It is also possible that such compounds may act as inhibitors for this enzyme.

RESULTS AND DISCUSSION

Treatment of methyl 3-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside[5] (**1**) with *tert*-butyldiphenylsilyl chloride in *N,N*-dimethylformamide, in the presence of imidazole, afforded in 80% yield the 6-*O*-*tert*-butyldiphenylsilyl derivative **2** as an amorphous solid, the ^{1}H-n.m.r. spectrum of which contained signals in support of the structure expected. Oxidation of **2** with pyridinium chlorochromate in dichloromethane, in the presence of molecular sieves type 3Å, followed by reduction of the resulting intermediate ketone **3** with sodium borohydride in aqueous ethanol, gave methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-talopyranoside (**4**), which was isolated in poor yield (~35%) because of extensive *O*-deacetylation, after column-chromatographic purification. Alternatively, the crude product mixture (containing **4**), obtained by reduction of **3**, was directly *O*-deacetylated in methanolic sodium methoxide to give, in excellent yield (~92%), methyl 3-*O*-ben-

TABLE I

PROPOSED 25.2 MHz ^{13}C-N.M.R. CHEMICAL SHIFTS (δ) FOR DISACCHARIDES **7** AND **15**[a], METHYL α-D-MANNOPYRANOSIDE[b], METHYL α-D-TALOPYRANOSIDE[b], AND METHYL 2-*O*-α-D-MANNOPYRANOSYL-α-D-MANNOPYRANOSIDE[c]

Atom	*Compound*				
	α-D-*ManpOMe*	α-D-*TalpOMe*	α-D-*Manp*-(1→2)-α-D-*ManpOMe*	**7**	**15**
C-1	101.9	102.2	100.1	100.80	100.80
C-2	71.2	70.7	79.3	78.38	78.62
C-3	71.8	66.2	70.8	66.52	66.12
C-4	68.0	70.3	67.8	70.09	69.94
C-5	73.7	72.1	73.4	72.18	72.08
C-6	62.1	62.3	61.9	62.39	62.40
C-1′			103.0	103.71	104.52
C-2′			71.7	70.84	70.79
C-3′			71.7	71.33	66.47
C-4′			67.8	67.86	70.58
C-5′			74.1	74.58	73.42
C-6′			61.8	62.14	62.80
OMe	55.9	55.6	55.7	55.90	55.90

[a]In D_2O at 25°, with Me_4Si as the external standard. [b]Ref. 6, [c]Ref. 7.

zyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-α-D-mannopyranosyl-α-D-talopyranoside (**5**). Cleavage of the *tert*-butyldiphenylsilyl group of **5** with fluoride ion gave, in high yield, the 3-*O*-benzyl derivative **6** as the dihydrate. Catalytic hydrogenolysis of the benzyl group of **6** in ethanol–glacial acetic acid, in the presence of 10% palladium-on-carbon, furnished, in ~88% yield, methyl 2-*O*-α-D-mannopyranosyl-α-D-talopyranoside (**7**) as the monohydrate, the ^{13}C-n.m.r. spectrum of which was consistent with the structure assigned (see Table I).

O-Deacetylation of compound **1** in methanolic sodium methoxide afforded the disaccharide derivative **8**, which, on treatment with *tert*-butyldiphenylsilyl chloride, as described for **1** (to give **2**), gave in ~81% yield, the amorphous 6,6′-di-*O*-*tert*-butyldiphenylsilyl derivative **9**. The overall structure of **9** was clearly evidenced by its ^{1}H-n.m.r. spectrum. Acetalation of **9** with 2,2-dimethoxypropane in acetone, in the presence of *p*-toluenesulfonic acid, gave the 2′,3′-*O*-isopropylidene derivative **10**. Oxidation of **10** with pyridinium chlorochromate produced the 4,4′-diulose **11**, which, on reduction with sodium borohydride as described for **3** (to give **4**), afforded in 87.5% yield the α-D-talopyranosyl derivative **12**. Sequential removal of the protecting groups of **12** furnished the title disaccharide **15**, by way of intermediates **13** and **14**, respectively. The ^{13}C-n.m.r. spectrum of **15** was also in conformity with the structure assigned (see Table I).

EXPERIMENTAL

General methods. — These methods were the same as those previously employed[2], except that the following solvent systems (v/v) were used for chromatography: (*A*) 49:1 chloroform–acetone, (*B*) 6:1 chloroform–methanol, (*C*) 9:1 chloroform–methanol, and (*D*) 4:1 chloroform–methanol. The silica gel used for column chromatography was Baker Analyzed (60–200 mesh).

*Methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside* (**2**). — To a cold (0°, bath) and stirred solution of methyl 3-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**1**; 4.5 g) and imidazole (1.25 g) in anhydrous *N*,*N*-dimethylformamide (75 mL) was added *tert*-butyldiphenylsilyl chloride (2.25 mL), and stirring was continued for 1 h at ~0°. The mixture was then poured into ice–water and extracted with chloroform. The chloroform solution was successively washed with water, saturated aqueous $NaHCO_3$, and water, dried, and evaporated to dryness. The residue was applied to a column of silica gel and eluted with solvent *A*. On evaporation, the fractions corresponding to the product afforded **2** (5 g, 80%), amorphous, $[\alpha]_D^{23}$ +27.8° (*c* 0.9, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.10 (s, 9 H, CMe_3), 1.95–2.10 (cluster of s, 12 H, OAc), 3.33 (s, 3 H, OMe), and 7.23–7.80 (m, 15 H, arom.).

Anal. Calc. for $C_{44}H_{56}O_{15}Si$: C, 61.97; H, 6.57. Found: C, 61.70; H, 6.66.

*Methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-talopyranoside* (**4**) *and methyl 3-*O*-benzyl-6-*O*-tert-butyl-*

diphenylsilyl-2-O-α-D-mannopyranosyl-α-D-talopyranoside (**5**). — A mixture of **2** (3.8 g), molecular sieves type 3A (7 g), and pyridinium chlorochromate (3 g) in dichloromethane (120 mL) was stirred overnight at room temperature. Examination of the mixture by t.l.c. (solvent *A*) showed the disappearance of **2** and the presence of a single product, faster-migrating than **2**. The mixture was diluted with ether (300 mL), the solids filtered off (a bed of silica gel), and the solution evaporated to dryness to give the 4-ulose **3** (~4 g) as a syrup, which was dissolved in 95% aqueous ethanol (40 mL). The solution was cooled (0°; bath), treated with $NaBH_4$ (1.2 g), and stirred for 1 h. After neutralization with 50% aqueous acetic acid, the solution was evaporated under diminished pressure, and the residue dissolved in chloroform. The solution was repeatedly washed with water till neutral, dried, and evaporated. T.l.c. (solvent *A*) showed the disappearance of **3** and the presence of a product, marginally slower-migrating than **3**; some slower-migrating compounds (probably due to *O*-deacetylation) were also revealed in t.l.c. The crude mixture (containing **4**; see later) was dissolved in methanol (50 mL), treated with methanolic M sodium methoxide (10 mL), and stirred for 4 h at room temperature, whereupon t.l.c. (solvent *B*) revealed the presence of a single, slower-migrating product. The base was neutralized by the addition of a few drops of glacial acetic acid, methanol and acetic acid were removed under diminished pressure, and the residue applied to a short column of silica gel. On elution with solvent *C*, evaporation of the fractions containing **5** afforded an amorphous, white powder (2.8 g, 92%), $[\alpha]_D^{23}$ +47.6° (*c* 1.4, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.00 (s, 9 H, CMe_3), 3.20 (s, 3 H, OMe), and 7.23–7.73 (m, 15 H, arom.).

Anal. Calc. for $C_{36}H_{48}O_{11}Si \cdot H_2O$: C, 61.53; H, 7.12. Found: C, 61.59; H, 7.14.

In another experiment, compound **2** (0.85 g) was oxidized with pyridinium chlorochromate and then reduced with $NaBH_4$ as just described. The crude product was subjected to column chromatography on silica gel with solvent *A* as the eluent to give the tetraacetate **4** (0.3 g, 35%), amorphous, $[\alpha]_D^{23}$ +47.3° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.17 (s, 9 H, CMe_3), 1.93–2.10 (cluster of s, 12 H, 4 OAc), 3.30 (s, 3 H, OMe), and 7.23–7.73 (m, 15 H, arom.).

Anal. Calc. for $C_{44}H_{56}O_{15}Si$: C, 61.97; H, 6.57. Found: C, 61.69; H, 6.64.

Methyl 3-O-benzyl-2-O-α-D-mannopyranosyl-α-D-talopyranoside (**6**). — A stirred solution of **5** (2 g) in anhydrous oxolane (30 mL) was treated with a molar solution of tetrabutylammonium fluoride in oxolane (3.5 mL), and the stirring was continued for 4 h at room temperature. The mixture was evaporated to dryness and the residue purified in a column of silica gel with solvent *B* as the eluent to give **6** (1.2 g, 92%), amorphous solid, $[\alpha]_D^{23}$ +75.0° (*c* 1.2, methanol).

Anal. Calc. for $C_{20}H_{30}O_{11} \cdot H_2O$: C, 49.79; H, 7.05. Found: C, 49.84; H, 6.95.

Methyl 2-O-α-D-mannopyranosyl-α-D-talopyranoside (**7**). — A mixture of **6** (1.0 g) and 10% Pd–C (0.3 g) in 3:1 ethanol–glacial acetic acid (40 mL) was shaken under H_2 at ~345 kPa for 16 h at room temperature. The suspension was filtered through a bed of Celite, the solid was thoroughly washed with ethanol, and the

filtrate and washings were combined and evaporated under reduced pressure. The residue was applied to a column of silica gel. Elution with 13:6:1 (v/v) chloroform–methanol–water and evaporation of the fractions corresponding to **7** afforded 0.7 g (88%), amorphous, $[\alpha]_D^{23}$ +85.2° (*c* 1.7, methanol); ^{13}C-n.m.r., see Table I.

Anal. Calc. for $C_{13}H_{24}O_{11} \cdot H_2O$: C, 41.71; H, 6.95. Found: C, 41.58; H, 6.71.

Methyl 3-O-benzyl-2-O-α-D-mannopyranosyl-α-D-mannopyranoside (**8**). — A solution of **1** (5 g) in 0.1M sodium methoxide in methanol (110 mL) was stirred for 4 h at room temperature. The base was neutralized by the addition of glacial acetic acid, and the solution evaporated to dryness under diminished pressure. The residue was purified in a column of silica gel with solvent *D* as the eluent to yield **8** (3.5 g, 96%), amorphous, $[\alpha]_D^{23}$ +48.2° (*c* 1.1, methanol).

Anal. Calc. for $C_{20}H_{30}O_{11}$: C, 53.81; H, 6.58. Found: C, 53.72; H, 6.58.

Methyl 3-O-benzyl-6-O-tert-butyldiphenylsilyl-2-O-(6-O-tert-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**9**). — To a cold (0°, bath), stirred solution of **8** (3 g) in anhydrous *N,N*-dimethylformamide (30 mL) containing imidazole (2.2 g) was added *tert*-butyldiphenylsilyl chloride (4.1 mL), and the stirring continued for 1 h at ~0°. After processing as described for **1** (to give **2**), followed by column-chromatographic purification with solvent *C* as the eluent, compound **9** (5 g, 81%) was obtained as an amorphous white solid, $[\alpha]_D^{23}$ +18.1° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): 1.05 (s, 18 H, 2 CMe_3), 3.15 (s, 3 H, OMe), and 7.23–7.73 (m, 25 H, arom.).

Anal. Calc. for $C_{52}H_{66}O_{17}Si_2 \cdot 1.5\ H_2O$: C, 65.75; H, 7.27. Found: C, 65.79; H, 7.14.

Methyl 3-O-benzyl-6-O-tert-butyldiphenylsilyl-2-O-(2,3-O-isopropylidene-6-O-tert-butyldiphenylsilyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**10**). — To a solution of **9** (4 g) in dry acetone (50 mL) were added 2,2-dimethoxypropane (50 mL) and *p*-toluenesulfonic acid monohydrate (0.6 g). The mixture was stirred for 1 h at room temperature, made neutral by the addition of triethylamine, and evaporated. The residue was dissolved in chloroform, the solution washed with water, dried, and concentrated. The concentrate was applied to a column of silica gel and eluted with chloroform to give amorphous **10** (3.7 g, 89%), $[\alpha]_D^{23}$ +4.8° (*c* 0.7, chloroform); ^{1}H-n.m.r. ($CDCl_3$): 1.10 (s, 18 H, 2 CMe_3), 1.33 and 1.47 (s, 2 × 3 H, CMe_2), 3.13 (s, 3 H, OMe), and 7.27–7.73 (m, 25 H, arom.).

Anal. Calc. for $C_{55}H_{70}O_{11}Si_2$: C, 68.61; H, 7.28. Found: C, 68.45; H, 7.15.

Methyl 3-O-benzyl-6-O-tert-butyldiphenylsilyl-2-O-(6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranosyl)-α-D-talopyranoside (**12**). — Treatment of **10** (2.4 g) in dichloromethane with pyridinium chlorochromate (8.4 g), under conditions analogous to those described for **2** (to give **3**), afforded the 4,4′-diketone intermediate **11**, ν_{max}^{film} 1740 (C=O) cm^{-1}, which was directly reduced with $NaBH_4$ in aqueous ethanol exactly as described for **3** (to give **4**). The resulting crude mixture afforded, after column-chromatographic purification with 1:1 chloroform–hexane as the eluent, amorphous **12** (2.1 g, 87%), $[\alpha]_D^{23}$ +25.7° (*c* 0.7, chloroform);

^{1}H-n.m.r. ($CDCl_3$): δ 1.10 (s, 18 H, 2 CMe_3), 1.33 and 1.53 (s, 2 × 3 H, CMe_2), 3.10 (s, 3 H, OMe), 7.20–7.66 (m, 25 H, arom.).

Anal. Calc. for $C_{55}H_{70}O_{11}Si_2$: C, 68.61; H, 7.28. Found: C, 68.40; H, 7.42.

Methyl 3-O-benzyl-2-O-(2,3-O-isopropylidene-α-D-talopyranosyl)-α-D-talopyranoside (**13**). — Treatment of a solution of **12** (2 g) in oxolane (40 mL) with M tetrabutylammonium fluoride in oxolane (4.4 mL), as described for **5** (to give **6**), yielded amorphous **12** (1 g, 99%), $[\alpha]_D^{23}$ +60.5° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.33 and 1.50 (s, 2 × 3 H, CMe_2), 3.30 (s, 3 H, OMe), and 7.23 (s, 5 H, arom.).

Anal. Calc. for $C_{23}H_{35}O_{11}$: C, 56.79; H, 6.99. Found: C, 56.43; H, 7.13.

Methyl 2-O-α-D-talopyranosyl-α-D-talopyranoside (**15**). — Compound **13** (0.9 g) was dissolved in 60% aqueous acetic acid (35 mL) and the solution heated for 1 h at ~60°. Acetic acid was evaporated under diminished pressure, the last traces being removed by co-evaporation with several added portions of toluene. The residue was purified in a column of silica gel with solvent *B* as the eluent to give **14** (0.8 g, 97%), amorphous, $[\alpha]_D^{23}$ +87.2° (*c* 1.4, methanol).

Compound **14** (0.75 g) was hydrogenolyzed in 3:1 (v/v) ethanol–acetic acid as described for **6** (to give **7**), to afford **15** (0.5 g, 83%), amorphous, $[\alpha]_D^{23}$ +98.4° (*c* 1.5, methanol); ^{13}C-n.m.r., see Table I.

Anal. Calc. for $C_{13}H_{24}O_{11} \cdot H_2O$: C, 42.73; H, 6.84. Found: C, 42.55; H, 6.77.

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