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Synthesis and utilization of saccharide intermediates

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ABSTRACT

A new method has been developed for preparation of partially pivaloylated saccharides in one step from readily available starting materials. These intermediates were used in the synthesis of disaccharides and a glucosteroid.

INTRODUCTION

The synthesis of organic compounds containing carbohydrate subunits is attracting increasing attention in view of their important role in living systems. These include glycosteroids, glycolipids, and glycoproteins which fulfil critical functions in regulation, inhibition, recognition, etc. Selective protection methodology has been developed in order to enable reactions on such polyhydroxy compounds as carbohydrates at selected positions[1]. The most common protective groups are esters of acetic and benzoic acid, benzyl and methyl ethers, and ketals. It had been demonstrated by Küster and Dyong[2] that any mono-unprotected glucose can be prepared in several steps using allyl and benzyl ethers as protective groups. In coupling reactions, the use of such groups can lead to unsatisfactory results, either because the deprotection step is not mild enough and such side reactions as elimination or ortho ester formation can predominate, or else because mixtures of α and β anomers are formed. This type of problem confronted us when trying to connect glucose to sterically hindered alcohol groups in such steroids as testosterone via a corresponding imidate. Kunz and Harreus[3] have reported that unwanted formation of ortho esters can be suppressed by replacing an acetyl protecting group with pivaloyl. It was therefore important to develop a simple and efficient route for selective pivaloylation in protection of saccharides, and to study its scope and limitations. In this work, we describe two aspects: (*1*) direct pivaloylation of saccharides as a synthetically useful method for preparation of

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partially protected units, and (*2*) use of such partially protected saccharides as starting materials for synthesis of other carbohydrates or of structures containing carbohydrates as subunits.

RESULTS AND DISCUSSION

The first model which we studied was D-glucose. Tomić-Kulenović and Keglević reported in 1980[4] that methyl α-D-glucopyranoside reacts with pivaloyl chloride to give three main products: methyl 2,3,6-tri-, methyl 2,4,6-tri-, and methyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside in 1.2:1:1.5 ratios. It was mentioned that the choice of solvent used in the esterification can influence the relative ratio of the esters: from 1.2:1 in ether to 1:1.5 in pyridine for the two triesters. We have found that when chloroform was used in this reaction the tri- and tetra-ester components were formed in 1.9:1.1:1 ratios, respectively. In the esterification of D-glucose, we found that chloroform was superior as solvent to diethyl and *tert*-butyl methyl ether, tetrahydrofuran, and methylene chloride. The use of such bases as triethylamine, 2,2,6,6-tetramethylpiperidine, and 2,6-lutidine required higher temperatures, and no improvement in selectivity relative to pyridine was evident. The pivaloylation of glucose, using pyridine as a base in chloroform, was followed by TLC and quenched when tetra-esters were formed in maximum amount relative to tri- and penta-esters. After conducting the reaction at 35°C for 7.5 h, it was possible to isolate by flash chromatography an 84% total yield of an esterified glucose mixture having the following composition *: 1,2,3,4,6-penta-*O*-pivaloyl-β-D-glucopyranose (**1**, 14%), 1,2,4,6-tetra-*O*-pivaloyl-β-D-glucopyranose (**2**, 27%), 1,2,3,6-tetra-*O*-pivaloyl-β-D-glucopyranose (**3**, 39%), and tri-esters (3%) having 1,3,6-tri-*O*-pivaloyl-β-D-glucopyranose as the main component. The structures of these were assigned using 2D ^{1}H and ^{13}C NMR spectroscopy; the results are described in Tables I and II. While this work was in progress, Tomić and co-workers[6] published results similar to ours although more emphasis was given to the sequence of esterification, while our aim was an optimised yield of selectively protected saccharides. At this point, it is interesting to note that with chloroform as solvent the formation of glucose unesterified at position 2 could not be detected, whereas with pyridine as solvent it was formed[6] in considerable yield (22%). Further, we found that attempting to accelerate the reaction by raising the temperature from 35 to 80°C had relatively little effect. Reaction time was found to be the major factor in the esterification of the last remaining unprotected hydroxyl group. One possible explanation could be that, in order for the reagent to penetrate between two bulky ester groups, one specific rotamer existing in low concentration must be involved. In summary, although the yield was not impres-

* In our preliminary communication[5], we mistakenly stated that the ratio of **2**:**3** was 1:2.7.

sive, we were able to prepare the mono-unprotected glucoses **2** and **3** on a gram-scale within one day.

D-Mannose was studied next using the same reaction conditions. Monitoring by TLC and quenching after 23 h gave mono-unprotected mannose in 64% isolated yield. Chromatographic separation gave two pentapivalates: 1,2,3,4,6-penta-*O*-pivaloyl-α-D-mannopyranose (**4**) and 1,2,3,4,6-penta-*O*-pivaloyl-β-D-mannopyranose (**5**) in a 1:2.7 ratio in 27% yield, whereas the mono-unprotected 1,3,4,6-tetra-*O*-pivaloyl-β-D-mannopyranose (**6**) could be isolated in 59% yield. Furthermore, the α anomer of **6** (5%) was isolated and also 1,3,6-tri-*O*-pivaloyl-β-D-mannopyranose (**7**, 8%). The overall chromatographed yield of esterified mannose under these conditions was close to being quantitative. The fact that partially esterified products (**6** and **7**) belong to the β-D-mannose family suggests that once the starting material is mono-esterified in its α-form the remaining hydroxyl groups are esterified much faster than in the case of hydroxyl groups in mannose having a monopivaloyl ester in the β configuration. The sequence of esterification in β-D-mannose was found to be $6 \sim 1 > 3 > 4 > 2$.

D-Galactose, esterified as described above, clearly reacted faster than glucose or mannose; after two hours, tetrapivaloylation had reached the maximum according to TLC. The mixture was separated to give two pentapivaloyl-galactoses: 1,2,3,4,6-penta-*O*-pivaloyl-α-D-galactopyranose (**8**) and 1,2,3,4,6-penta-*O*-pivaloyl-β-D-galactopyranose (**9**) in a 13:1 (by NMR) ratio and in 14% yield. The main product isolated (58%) was 1,2,3,6-tetra-*O*-pivaloyl-β-D-galactopyranose (**10**), whereas 1,3,6-tri-*O*-pivaloyl-β-D-galactopyranose (**11**) was obtained in 16% yield. The total yield of isolated galactose esters was 88%. In this sugar too, it was apparent that once a hydroxyl group in the α-series is esterified the remaining groups react faster than in the β-series. This assumption can be made since all isolated partially esterified intermediates belong to the β-series.

Our next step was to extend the scope of this approach to disaccharides. Some disaccharides had already been studied extensively and the sequence of reactivity determined using both benzoyl and pivaloyl chlorides. Selective pivaloylation of sucrose had been studied by Richardson and co-workers[7] who found that under suitable conditions it is possible to obtain 2,3,6,1′,3′,4′,6′-hepta-*O*-pivaloylsucrose in 52% yield. Recently the same group published their results on pivaloylation of trehalose[8], where the mono-unprotected sugar at position 4 could be isolated in 61% yield. The order of reactivity was found to be $6 \sim 6' > 2 \sim 2' > 3 \sim 3' > 4 \sim 4'$. On benzoylation of such disaccharides as lactose[9] and cellobiose[10], mixtures of partially esterified saccharides were obtained, but it was clear that position 3 is relatively inactive and $6' > 6$ very active. We applied our conditions to maltose and found that it is possible to quench the reaction at a composition of 70% of maltose with two unprotected hydroxyl groups at positions 3 and 4′: 1,2,6-tri-*O*-pivaloyl-4-*O*-(2,3,6-tri-*O*-pivaloyl-α-D-glucopyranosyl)-β-D-glucopyranose (1,2,6,2′,3′,6′-hexa-*O*-pivaloyl-β-maltose, **12**), 11% of 1,2,6,3′,6′-penta-*O*-pivaloyl-β-maltose (**13**), and 5% of 1,6,2′,3′,6′-penta-*O*-pivaloyl-β-maltose. It appears that in this disaccharide

the sequence of pivaloylation is $6 \sim 6' \sim 1 > 2$ or $2' > 3' > 2'$ or $2 > 4 > 3$. The overall yield of isolated esterified derivatives of maltose was 92%. Applying the same conditions to lactose and cellobiose gave complex mixtures of partially esterified compounds, and therefore it can be concluded that here selectivity is poor and the reaction of little practical significance. It has been reported[11] that, under reflux for five days, lactose can be converted into the corresponding octapivalate.

We then investigated whether the partially esterified saccharides could be used as intermediates in the synthesis of other carbohydrate derivatives. It was found that glucose intermediates **2** and **3** could be acetylated to give **14** and **15** in > 90% isolated yield under mild conditions; similarly, **6**, **10**, and **12** were acetylated to give **16**, **17**, and **18**. Best results were achieved using 1:1 acetic anhydride–pyridine overnight at room temperature. It was clear that the bulky pivaloyl groups which hinder reaction of an extra pivaloyl chloride molecule with the last free hydroxyl group are ineffective in blocking its acetylation.

Encouraged by the fact that these intermediates can be further acetylated, we investigated their use as starting materials for synthesis of di- and tri-saccharides. To this end, the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl imidate **19** was prepared as described by Urban et al.[12], and coupling reactions were carried out in CH_2Cl_2 at room temperature. In our hands, BF_3 etherate led to better yields than $ZnBr_2$ as used in the original procedure[12]. The reaction of **19** with **2** gave 1,2,4,6-tetra-*O*-pivaloyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (**20**) (laminaribiose ester) in 72% yield, and with **3** gave 1,2,3,6-tetra-*O*-pivaloyl-4-*O*-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (**21**) (cellobiose ester) isolated in 84% yield. Removal of ester protecting groups in saccharides under mild basic hydrolysis is well documented in the literature[13] and worked well in our case. These results demonstrate that our selective pivaloylation–glucose imidate coupling route is a short and efficient one for synthesis of such disaccharides as laminaribiose and cellobiose, and this three-step synthesis shows promise as an attractive alternative to other methods for disaccharide preparation. The coupling of imidate **19** with the mono-unprotected mannose **6** and galactose **10**, having a free hydroxy group in an axial configuration, gave the corresponding expected disaccharides **22** and **23**, but in only 23 and 49% yield, respectively.

We then investigated whether glucose unprotected at position 4 surrounded by pivaloyl groups could be used in coupling reactions at position 1. Removal of the protecting group from C-1 of **3** was carried out in moderate yield by hydrazine acetate, to give **24**. The corresponding imidate **25** was coupled with testosterone in the presence of BF_3, to give **26** in good yield. Evidently, reaction with the secondary alcohol group on the steroid can compete successfully with coupling between two molecules of glucose. We thus demonstrated that glucose can be coupled via the imidate to testosterone having a potential site for further reaction at the unprotected 4-hydroxyl, an option of potential importance in the synthesis of carbohydrate derivatives.

TABLE I

^{1}H NMR chemical shifts (δ in ppm, J in Hz) of monosaccharides [a]

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OH	Ac	*t*-BuCO
1	5.67 (d; 8.4)	5.19 (t)	5.32 (t)	5.13 (t)	3.83 (m)	4.12 (d)	4.09 (dd)			1.18; 1.15; 1.12; 1.09×2
2	5.61 (d; 8.3)	4.98 (t)	3.75 (d)	4.91 (t)	3.79 (d)	4.12 (d)	4.12 (d)	2.66 (d)		1.18; 1.15; 1.14; 1.13
3	5.65 (d; 7.8)	5.11 (t)	5.11 (t)	3.50 (tt)	3.64 (m)	4.42 (dd)	4.29 (dd)	3.02 (d)		1.20; 1.17; 1.15; 1.10
4	5.98 (s)	5.24 (bs)	5.32 (dd)	5.52 (t)	4.00 (m)	4.17 (dd)	4.10 (bd)			1.25; 1.24; 1.19; 1.15; 1.10
5	5.81 (s)	5.44 (m)	5.14 (dd)	5.44 (m)	3.82 (m)	4.17 (dd)	4.17 (bd)			1.27; 1.20; 1.14; 1.13; 1.09
6	5.72 (s)	4.13 (d)	4.95 (dd)	5.38 (t)	3.78 (m)	4.12 (m)	4.12 (m)			1.20; 1.16×2; 1.14
7	5.71 (s)	4.12 (bd)	4.80 (dd)	3.66 (dt)	3.62 (m)	4.37 (d)	4.37 (d)			1.21; 1.20; 1.18
8	6.09 (s)	5.06 (s)	5.14 (d)	4.30 (t)	5.33 (m)	4.38 (dd)	4.14 (dd)			1.22; 1.20×2; 1.19; 1.14
10	5.61 (d; 8.4)	5.42 (t)	4.95 (dd)	3.98 (d)	3.85 (t)	4.25 (d)	4.25 (d)			1.14; 1.13; 1.12; 1.07
11	5.52 (d; 8.0)	3.99 (t)	4.87 (dd)	3.96 (bs)	3.87 (t)	4.29 (dd)	4.23 (dd)	2.46 (s)		1.23; 1.20; 1.16
14	5.68 (d, 10.5)	5.14 (t)	5.34 (t)	5.09 (t)	3.85 (m)	4.11 (d)	4.11 (d)		1.93 (s)	1.15; 1.12; 1.10; 1.09
15	5.68 (d; 8.9)	5.14 (t)	5.30 (t)	5.17 (t)	3.82 (m)	4.14 (d)	4.14 (d)		1.99 (s)	1.19; 1.16; 1.10×2
16	5.80 (s)	5.50 (d)	5.12 (dd)	5.38 (t)	3.81 (m)	4.22 (bd)	4.12 (dd)		2.14 (s)	1.20; 1.15×2; 1.10
17	5.67 (d; 9.4)	5.37 (t)	5.11 (dd)	5.43 (d)	4.04 (m)	4.14 (m)	4.04 (m)		2.13 (s)	1.16; 1.13; 1.09×2
25	6.48 (d; 3.6)	5.06 (dd)	5.43 (t)	3.56 (tt)	4.07 (m)	4.39 (dd)	4.32 (dd)	3.21 (d)		1.18×3; 1.11
26	4.51 (d; 7.3)	4.97 (m)	4.95 (t)	3.48 (bd)	3.48 (bd)	4.37 (d)	4.27 (dd)	2.89 (s)		1.21; 1.20; 1.15

[a] All spectra were measured in $CDCl_3$.

TABLE II

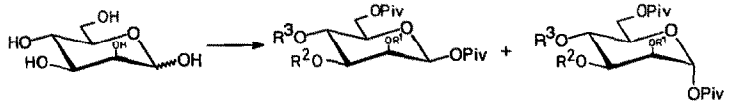
^{13}C NMR chemical shifts (δ in ppm) of monosaccharides [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	*t*-Bu*C*O	Ac	$(CH_3)_3C$	$(CH_3)_3C$	CH_3
1	91.83	70.08	72.31	67.72	72.75	61.44	177.94; 176.97; 176.34; 176.28×2		38.70	27.05	
2	91.56	72.69	74.19	70.63	72.72	61.71	178.04; 177.91; 177.54; 176.48		38.72	26.95	
3	91.88	75.12	69.62	69.57	74.90	62.45	179.06; 178.82; 176.40×2		38.72	27.08	
4	90.72	68.22	69.37	64.55	71.19	61.71	177.88; 177.25; 176.67; 176.46; 175.40		38.81	27.10	
5	90.69	68.16	71.01	64.76	73.19	61.52	177.91; 177.03; 176.85; 176.49; 175.82		38.81	27.04	
6	91.61	68.34	73.17	64.94	73.36	61.86	177.98; 177.53; 176.63; 175.86		38.89	27.05	
7	91.63	68.51	75.21	65.53	75.15	62.99	178.85; 178.55; 175.91		38.90	27.10	
8	99.07	80.89	75.63	82.06	69.09	62.47	177.69; 177.09×2; 176.97; 176.27		38.75	26.98	
10	92.26	67.66	73.03	66.87	73.12	61.96	178.25; 177.28; 176.40×2		38.67	27.00	
11	94.35	68.64	75.06	66.99	72.99	61.86	178.49; 178.26; 176.79		38.80	27.06	
14	91.80	69.96	72.42	67.82	72.97	61.43	177.86; 176.64; 176.43; 176.31	169.63	38.75	27.05	20.45
15	91.93	70.02	72.45	68.32	72.81	61.85	177.85; 177.12; 176.22×2	168.96	38.79	27.08	20.58
16	90.32	68.17	70.60	65.08	73.24	61.57	177.99; 177.36; 177.68; 176.73	169.66	38.90	26.80	20.49
17	92.29	67.90	70.96	66.84	71.79	60.86	177.71; 176.94; 176.38×2	169.66	38.76	26.99	20.55
25	92.79	69.31	72.01	69.18	72.69	62.69	178.82; 178.67; 177.18×2		38.70	26.98	

[a] All spectra were measured in $CDCl_3$.

1 $R^1 = R^2 = R^3 = Piv$
2 $R^1 = R^3 = Piv$; $R^2 = H$
3 $R^1 = R^2 = Piv$; $R^3 = H$
14 $R^1 = R^3 = Piv$; $R^2 = Ac$
15 $R^1 = R^2 = Piv$; $R^3 = Ac$
20 $R^1 = R^3 = Piv$; R^2 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl
21 $R^1 = R^2 = Piv$; R^3 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl

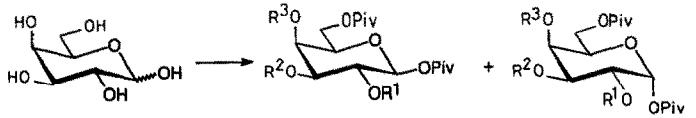
Scheme 1.



5 $R^1 = R^2 = R^3 = Piv$
6 $R^2 = R^3 = Piv$; $R^1 = H$
7 $R^2 = Piv$; $R^1 = R^3 = H$
16 $R^2 = R^3 = Piv$; $R^1 = Ac$
22 $R^2 = R^3 = Piv$; R^1 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl

4 $R^1 = R^2 = R^3 = Piv$

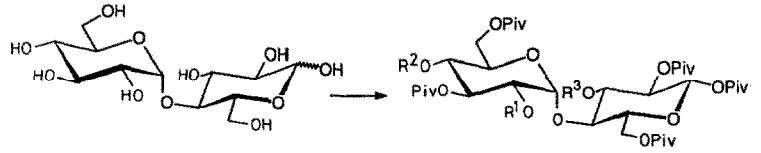
Scheme 2.



9 $R^1 = R^2 = R^3 = Piv$
10 $R^1 = R^2 = Piv$; $R^3 = H$
11 $R^2 = Piv$; $R^1 = R^3 = H$
17 $R^1 = R^2 = Piv$; $R^3 = Ac$
23 $R^1 = R^2 = Piv$; R^3 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl

8 $R^1 = R^2 = R^3 = Piv$

Scheme 3.



12 $R^1 = Piv$; $R^2 = R^3 = H$
13 $R^1 = R^2 = R^3 = H$
18 $R^1 = Piv$; $R^2 = R^3 = Ac$

Scheme 4.

TABLE III

^{1}H NMR chemical shifts (δ in ppm, J in Hz) of disaccharides [a]

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′	H-2′
12	5.60 (d; 9.5)	4.83 (d)	3.74 (t)	3.63 (t)	3.68 (m)	4.38 (d)	4.18 (d)	5.55 (d)	4.78 (dd)
13	5.50 (d; 10.8)	4.86 (t)	3.80 (m)	3.52 (m)	3.58 (m)	4.35 (d)	4.10 (d)	5.00 (d)	3.58 (m)
18	5.70 (d; 9.6)	5.00 (t)	5.24 (t)	4.01 (t)	3.78 (m)	4.50 (dd)	4.28 (dd)	5.40 (d)	4.70 (dd)
20	5.57 (d; 8.7)	5.20 (t)	4.09 (t)	4.94 (t)	3.76 (m)	4.11 (dd)	4.03 (d)	4.71 (d; 8.7)	4.86 (t)
21	5.61 (d; 8.8)	5.05 (t)	5.26 (t)	3.92 (t)	3.71 (m)	4.57 (dd)	4.10 (dd)	4.50 (d; 8.8)	4.84 (t)
22	5.66 (s)	4.30 (d)	4.81 (dd)	5.14 (m)	3.80 (m)	4.16 (dd)	4.12 (d)	4.78 (d; 7.6)	5.20 (m)
23	5.57 (d; 8.3)	5.20 (t)	5.05 (m)	4.07 (m)	3.83 (m)	4.16 (d)	4.16 (d)	4.53 (d; 8.7)	5.05 (m)

Compound	H-3′	H-4′	H-5′	H-6′a	H-6′b	CH_3	*t*-BuCO
12	5.30 (t)	3.40 (t)	3.87 (bd)	4.42 (d)	4.21 (d)		1.17; 1.15; 1.14; 1.11×3
13	4.91 (t)	3.28 (t)	3.80 (m)	4.35 (d)	4.10 (d)		1.22; 1.19; 1.18; 1.16; 1.14
18	5.40 (m)	5.10 (t)	3.92 (m)	4.17 (dd)	4.07 (dd)	2.04; 1.98	1.22; 1.19; 1.16; 1.13; 1.09×2
20	5.02 (t)	5.03 (t)	3.62 (m)	4.31 (dd)	4.03 (d)	0.06; 2.00; 1.98; 1.95	1.23; 1.19; 1.17; 1.16
21	5.08 (t)	4.95 (t)	3.61 (m)	4.20 (dd)	4.04 (d)	2.05; 1.99; 1.98; 1.94	1.19; 1.14; 1.11; 1.09
22	5.12 (m)	5.06 (m)	3.56 (m)	4.23 (dd)	3.97 (d)	2.03; 2.00; 1.99×2	1.24; 1.17; 1.14; 1.13
23	5.05 (m)	5.01 (m)	3.54 (m)	4.16 (d)	4.16 (d)	2.02; 2.00; 1.97; 1.96	1.19; 1.13; 1.12; 1.05

[a] All spectra were measured in $CDCl_3$.

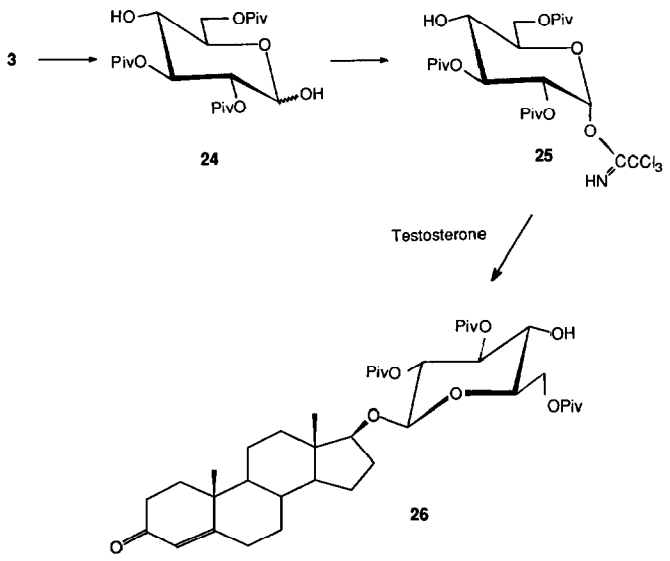
TABLE IV

^{13}C NMR chemical shifts (δ in ppm) of disaccharides [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
12	91.19	72.75	76.19	77.70	73.17	62.77	96.93	70.45	71.26	69.53	71.51	62.53
13	96.70	71.58	71.58	81.76	73.18	62.36	101.93	71.58	75.91	68.38	74.90	62.77
18	91.46	70.42	74.48	71.63	73.60	62.17	94.65	70.91	68.86	68.13	68.96	61.92
20	91.68	72.09	61.80	72.98	72.86	61.80	100.45	72.72	67.78	67.78	71.85	62.14
21	91.68	70.45	71.26	73.93	73.78	61.19	99.20	71.57	72.94	68.10	72.27	61.82
22	91.80	72.94	71.94	72.52	73.42	61.81	100.65	65.14	71.02	69.05	72.23	61.47
23	92.01	67.69	73.10	73.39	72.77	63.10	100.57	70.84	68.50	67.69	71.90	61.53

Compound	*t*-Bu*C*O	CH_3CO	$(CH_3)_3C$	$(CH_3)_3C$	CH_3
12	179.25; 178.70; 178.52; 177.91; 177.76; 176.36		38.86	27.07	
13	183.94; 180.82; 179.37; 177.70; 176.50		38.86	27.00	
18	177.90; 177.50; 177.00; 176.60; 176.20×2	169.48; 168.94	38.82	27.01	20.95; 20.61
20	178.25; 176.58×2; 175.60	170.50; 170.19; 169.26; 169.18	38.80	27.10	20.70
21	177.40; 176.82; 176.52; 176.21	170.36; 170.08; 169.24; 168.75	38.66	27.10	20.50
22	177.94; 176.79; 176.27; 175.73	170.53; 170.24; 169.30; 169.15	38.70	27.00	20.65
23	177.94; 177.34; 176.36; 176.12	170.51; 170.12; 169.30; 169.12	38.65	27.00	20.50

[a] All spectra were measured in $CDCl_3$.



Scheme 5.

EXPERIMENTAL

General data.—Column chromatography was performed on Silica Gel S (Riedel-de Haën). TLC was performed on Silica Gel 60 F_{254} (Merck), using 1:3 acetone–hexane as eluant. Pyridine was dried over KOH; all other solvents were dried over basic alumina (Fisher Chemical). NMR spectra were measured on a Bruker AM-400 instrument equipped with an Aspect 3000 computer. Products that were formed in a yield $\leq 8\%$ are not discussed in the Experimental section although some of them were purified and fully characterized.

*1,2,4,6-Tetra-*O*-pivaloyl-β-*D*-glucopyranose* (**2**) *and 1,2,3,6-tetra-*O*-pivaloyl-β-*D*-glucopyranose* (**3**).—To a stirred solution of dry $CHCl_3$ (1.7 mL) and dry pyridine (1 mL) was added pivaloyl chloride (1.05 mL, 8.6 mmol, 6.2 equiv) dropwise at room temperature under N_2. Anhydrous D-glucose (Merck) (250 mg, 1.4 mmol) was added and the reaction was followed by TLC at 35°C. After 7.5 h at 35°C, **2** and **3** (R_f 0.41 and 0.38, respectively) had become the major component in the mixture. The solvent was removed under reduced pressure and the mixture extracted with ether (3 × 5 mL). The organic fractions were combined and washed with M H_2SO_4 (5 mL), aq 10% $CuSO_4$ (2 × 3 mL), satd aq $NaHCO_3$ (5 mL), and water (5 mL). The solution was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The crude mixture was separated by column chromatography (CH_2Cl_2 and 8:1 CH_2Cl_2–EtOAc) to give 195 mg (27%) of **2** (R_f 0.41), 280 mg (39%) of **3**, (R_f 0.38), and 100 mg (14%) of 1,2,3,4,6-penta-*O*-pivaloyl-β-D-glucopyranose (**1**, R_f 0.50). The overall yield of isolated esterified glucose was 600 mg (84%).

1,3,4,6-Tetra-O-pivaloyl-β-D-mannopyranose (**6**).—The reaction was carried out as described for the preparation of **2**, using anhyd D-mannose (Fluka) (250 mg, 1.4 mmol). The mixture was maintained at 35°C and the reaction followed by TLC. After 23 h, **6** (R_f 0.40) had become the major component in the mixture. The reaction was quenched, and the products were separated by column chromatography (CH_2Cl_2 and 8:1 CH_2Cl_2–EtOAc) to give 430 mg (59%) of **6** (R_f 0.40); 205 mg (27%) of 1,2,3,4,6-penta-*O*-pivaloyl-α-D-mannopyranose (**4**, R_f 0.55) and 1,2,3,4,6-penta-*O*-pivaloyl-β-D-mannopyranose (**5**, R_f 0.52), which were separated easily in a ratio of 1:2.7; and 60 mg (8%) of 1,3,6-tri-*O*-pivaloyl-β-D-mannopyranose (**7**, R_f 0.21). The overall yield of isolated esterified mannose was 750 mg (99%).

1,2,3,6-Tetra-O-pivaloyl-β-D-galactopyranose (**10**).—The reaction was carried out as described for **2**, using anhyd D-galactose (Fluka) (250 mg, 1.4 mmol). The mixture was maintained at 35°C and followed by TLC. After 2 h, **10** (R_f 0.38) had become the major component in the mixture. The reaction was quenched and the products were separated by column chromatography (CH_2Cl_2 and 8:1 CH_2Cl_2–EtOAc) to give 420 mg (58%) of **10** (R_f 0.38), 120 mg (14%) of 1,2,3,4,6-penta-*O*-pivaloyl-α-D-galactopyranose (**8**, R_f 0.55), and 100 mg (16%) of 1,3,6-tri-*O*-pivaloyl-β-D-galactopyranose (**11**, R_f 0.21). The overall yield of isolated esterified galactose was 640 mg (88%).

1,2,6-Tri-O-pivaloyl-4-O-(2,3,6-tri-O-pivaloyl-α-D-glucopyranosyl)-β-D-glucopyranose (**12**).—The reaction was carried out as described for the preparation of **2**, using anhyd maltose (250 mg, 0.73 mmol) and pivaloyl chloride (0.9 mL, 7.5 mmol, 10.3 equiv). The mixture was maintained at 35°C and the reaction followed by TLC. After 7 h, **12** (R_f 0.36) became the major component in the mixture. The reaction was quenched and worked up as described for **2**. The crude mixture was separated by column chromatography (CH_2Cl_2, 8:1 CH_2Cl_2–EtOAc, and 6:1 CH_2Cl_2–EtOAc) to give 425 mg (70%) of **12** (R_f 0.36) and 70 mg (11%) of 1,2,6-tri-*O*-pivaloyl-4-*O*-(3,6-di-*O*-pivaloyl-α-D-glucopyranosyl)-β-D-glucopyranose (**13**, R_f 0.20). The overall yield of isolated esterified maltose was 565 mg (92%).

3-O-Acetyl-1,2,4,6-tetra-O-pivaloyl-β-D-glucopyranose (**14**).—To a stirred solution of **2** (45 mg, 0.087 mmol) in dry pyridine (0.1 mL) was added Ac_2O (0.1 mL). The mixture was kept at room temperature overnight, and worked up as described for **2**. Column chromatography using CH_2Cl_2 as eluant gave **14** (45 mg, 93%).

4-O-Acetyl-1,2,3,6-tetra-O-pivaloyl-β-D-glucopyranose (**15**).—Compound **3** (35 mg, 0.07 mmol) was acetylated as described for **14**, to give **15** (44 mg, 92%).

2-O-Acetyl-1,3,4,6-tetra-O-pivaloyl-β-D-mannopyranose (**16**).—Compound **6** (45 mg 0.087 mmol) was acetylated as described for **14**, to give **16** (45 mg, 93%).

4-O-Acetyl-1,2,3,6-tetra-O-pivaloyl-β-D-galactopyranose (**17**).—Compound **10** (50 mg, 0.1 mmol) was acetylated as described for **14**, to give **17** (49 mg, 90%).

3-O-Acetyl-4-O-(4-O-acetyl-2,3,6-tri-O-pivaloyl-α-D-glucopyranosyl)-1,2,6-tri-O-pivaloyl-β-D-glucopyranose (**18**).—Compound **12** (160 mg, 0.19 mmol) was acetylated as described for **14**, to give **18** (150 mg, 85%).

1,2,4,6-Tetra-O-pivaloyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (**20**).—2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[12] (**19**; 0.2 g, 0.4 mmol) and **2** (100 mg, 0.2 mmol) were added to dry CH_2Cl_2 (6 mL) and dried 3A molecular sieves (0.2 g). The mixture was stirred under N_2 at room temperature for 2 h, BF_3 etherate (20 μL, 0.16 mmol) was added, and the reaction kept at room temperature overnight. The mixture was washed with satd aq $NaHCO_3$ (2 mL) and water (2 mL), and dried ($MgSO_4$). The solvents were removed under reduced pressure and the crude mixture was chromatographed using 5% ether in $CHCl_3$ as eluant to give **20** (120 mg, 72%).

1,2,3,6-Tetra-O-pivaloyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (**21**).—Compound **3** (0.5 g, 1 mmol) was converted into **21** (0.36 g, 84%) as described for **20**.

1,3,4,6-Tetra-O-pivaloyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-mannopyranose (**22**).—Compound **6** (0.2 g, 0.4 mmol) was converted into **22** (40 mg, 23%) as described for **20**.

1,2,3,6-Tetra-O-pivaloyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-galactopyranose (**23**).—Compound **10** (0.2 g, 0.4 mmol) was converted into **23** (80 mg, 49%) as described for **20**.

2,3,6-Tri-O-pivaloyl-β-D-glucopyranose (**24**).—Compound **3** (0.2 g, 0.4 mmol) was dissolved in DMF (1 mL) and hydrazine acetate (80 mg, 0.9 mmol) was added to the solution under N_2. The mixture was kept at 50°C for 18 h and worked up as described[11]. The product was chromatographed over silica gel, using 6:1 CH_2Cl_2–EtOAc as eluent, to give **24** (105 mg, 60%).

2,3,6-Tri-O-pivaloyl-α-D-glucopyranosyl trichloroacetimidate (**25**).—Compound **24** (140 mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under N_2. To the solution were added CCl_3CN (0.07 mL, 0.7 mmol) and Cs_2CO_3 (0.01 g, 0.03 mmol), and the mixture was stirred overnight at room temperature and worked up as described[11]. The crude product was chromatographed over silica gel, using CH_2Cl_2 as eluant, to give **25** (130 mg, 55%).

Androst-4-en-3-on-17-β-yl 2,3,6-tri-O-pivaloyl-β-D-glucopyranoside (**26**).—The coupling of **25** (70 mg, 0.12 mmol) with testosterone (23 mg, 0.08 mmol) was carried out as described for **20**. The product was isolated by chromatography to give **26** (75 mg, 85%).

REFERENCES

1 R.R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 212–235.
2 J.M. Küster and I. Dyong, *Liebigs Ann. Chem.*, (1975) 2179–2189.
3 H. Kunz and A. Harreus, *Liebigs Ann. Chem.*, (1982) 41–48.
4 S. Tomić-Kulenović and D. Keglević, *Carbohydr. Res.*, 85 (1980) 302–306.
5 D. Becker and N. Galili, *Tetrahedron Lett.*, 33 (1992) 4775–4778.
6 D. Ljevakvić, S. Tomić, and J. Tomašić, *Carbohydr. Res.*, 230 (1992) 107–115.
7 M.S. Chowdhary, L. Hough, and A.C. Richardson, *J. Chem. Soc., Perkin Trans. 1*, (1984) 419–427.
8 R.C. Garcia, L. Hough and A.C. Richardson, *Carbohydr. Res.*, 200 (1990) 307–317.

9 I.M. Vazquez, I.M.E. Thiel, and J.O. Deferrari, *Carbohydr. Res.*, 26 (1973) 351–356.
10 I.M. Vazquez, I.M.E. Thiel, and J.O. Deferrari, *Carbohydr. Res.*, 47 (1976) 241–244.
11 P. Zimmermann, R. Bmmer, T. Bär, and R.R. Schmidt, *J. Carbohydr. Chem.*, 7 (1988) 435–452.
12 F.J. Urban, B.S. Moore, and R. Breitenbach, *Tetrahedron Lett.*, 31 (1990) 4421–4424.
13 M.E. Chacón-Fuertes and M. Martín-Lomas, *Carbohydr. Res.*, 43 (1975) 51–56.