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A Practical Synthesis of 2,3,4,6-Tetra-*O*-acetyl-1-*O*-(2-propenyl)-β-D-glucopyranoside Using $ZnCl_2$

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Abstract:

2,3,4,6-Tetra-*O*-acetyl-1-*O*-(2-propenyl)-β-D-glucopyranoside (1a), which is a useful raw material in the synthesis of a bioactive agent, has been synthesized in 50% yield by reacting β-D-glucose pentaacetate and 3 mol equiv of an allyl alcohol with 0.9 mol equiv of $ZnCl_2$ in toluene at 80 °C for 2 h followed by recrystallization from diisopropyl ether. This method is suitable for the large-scale preparation of 1a due to its efficiency, safety, and cost-effectiveness.

Introduction

2,3,4,6-Tetra-*O*-acetyl-1-*O*-(2-propenyl)-β-D-glucopyranoside (**1a**) is known to be a useful raw material in the syntheses of a bioactive agent, an irreversible inhibitor of yeast hexokinase,[1] and recently reported, 3-(6-deoxy-6-sulfoglucopyranosyl)acylglycerol derivatives as immunosuppressants.[2] Some syntheses of **1a** have been reported.

For example, Lee has reported the synthesis of **1a** from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, excess allyl alcohol, and 1.1 equiv of mercuric cyanide in 74.5% yield.[3] A previous report used a catalytic amount of silver oxide, instead of mercuric cyanide, with chloroform as the solvent to produce **1a** in 65% yield.[4]

Furthermore, β-D-glucose pentaacetate (**2**) in dichloromethane or in refluxing benzne was alkylated by the various alcohols in the presence of stannic chloride to give alkyl β-D-glucopyranoside tetraacetates.[5,6] Upon the reaction with an allyl alcohol in the presence of stannic chloride in dichloromethane, β-D-mannose pentaacetate produced the corresponding allyl glycosides as a mixture of α-/β-anomers.[7]

However, these reported methods are considered unsuitable due to the toxicity of the reagents and economic and environmental concerns. Large-scale production is needed using an efficient, safe, and cost-effective process. We have studied the allylation of **2**, and we now report the practical synthesis of **1a** for a raw material for synthesis of 3-(6-deoxy-6-sulfoglucopyranosyl)acylglycerol derivatives as immunosuppressants.[2]

Table 1. **Results of the allylation of 2 by $SnCl_4$[a]**

	allyl alcohol[b] mol equiv	solvent	temp (°C)	reaction time (h)	ratio of **1a**/**1b** by HPLC	isolated yield of **1a** (%)
1	1.0	CH_2Cl_2	25	2	75/25	32
2	2.0	toluene	35	3	40/60	*c*

[a] 1.0 mol equivalent of $SnCl_4$ for **2** (50 mmol) was used. [b] Mole equivalent value of allyl alcohol for **2**. [c] **1a** was not isolated.

Table 2. **Results of the allylation of 2 in various amounts of $ZnCl_2$[a]**

	$ZnCl_2$ mol equiv	solvent	temp (°C)	reaction time (h)	ratio of **1a**/**1b** by HPLC	isolated yield of **1a** (%)
1	1.0	benzene	80	2	90/10	40
2	0.9	benzene	80	2	92/8	45
3	0.8	benzene	80	2	90/10	41

[a] 3.0 mol equiv of allyl alcohol for **2** (50 mmol) was used.

Results and Discussion

Initially, we attempted the coupling reaction of β-D-glucose pentaacetate **2** and allyl alcohol in dichloromethane with $SnCl_4$, according to the above-described literature.[5] The result was not practically acceptable with regard to the selectivity of the α/β-anomeric ratio and the isolated yield (run 1 in Table 1). In the case of changing to toluene as the solvent, the selectivity and yield were not improved (run 2 in Table 1). We next used $ZnCl_2$ as a Lewis acid, which is classified as borderline acid[8] and easier to handle than $SnCl_4$. The amount of $ZnCl_2$ in benzene as a solvent has been investigated, and 0.9 mol equiv of $ZnCl_2$ gave the best result (run 2 in Table 2). The solvent and reaction temperature were fixed in benzene at 80 °C, according to a previous report,[5a,6] because this reaction did not proceed at temperatures below 50 °C in toluene. Furthermore, the optimal amount of allyl

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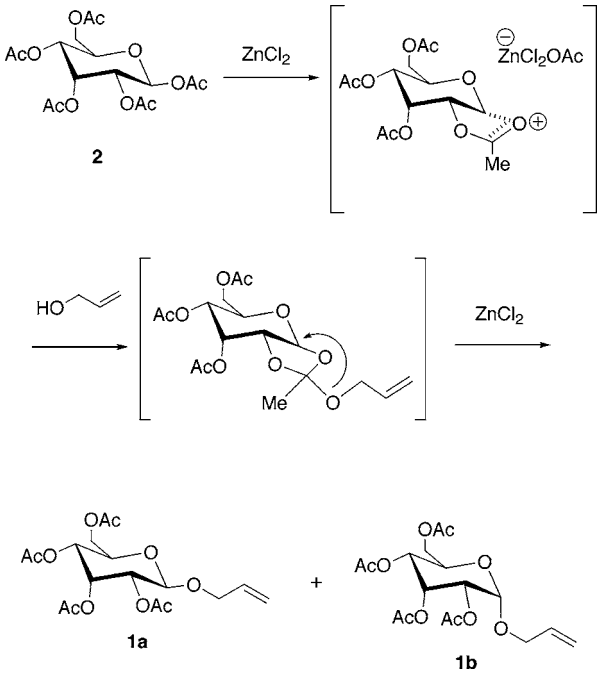
Table 3. **Results of the allylation of 2 in various mol equiv of the allyl alcohol[a]**

	allyl alcohol mol equiv	solvent	temp (°C)	reaction time (h)	ratio of **1a**/**1b** by HPLC	isolated yield of **1a** (%)
1	1.1	benzene	80	2	80/20	32
2	1.1	benzene	80	9	68/32	20
3	2.0	benzene	80	2	82/18	40
4	3.0	benzene	80	2	92/8	45
5	3.0	benzene	80	20	59/41	15
6	3.0	toluene	80	2	93/7	47
7	3.0	toluene	80	10	46/54	*b*

[a] 0.9 mol equiv of $ZnCl_2$ for **2** (100 mmol) was used. [b] **1a** was not isolated.

Scheme 1. **Allylation of *β*-D-glucose pentaacetate 2 using $ZnCl_2$**



alcohol was investigated, and thus 3 mol equiv of allyl alcohol gave the best result (run 4 in Table 3). Once again, the solvent was changed to toluene instead of benzene (run 6 in Table 3), because benzene has a higher toxicity than toluene. Thus, *β*-D-glucose pentaacetate, 3 mol equiv of allyl alcohol, and 0.9 mol equiv of $ZnCl_2$ in toluene at 80 °C for 2 h produced 2,3,4,6-tetra-*O*-acetyl-1-*O*-(2-propenyl)-*β*-D-glucopyranoside (**1a**) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(2-propenyl)-α-D-glucopyranoside (**1b**) in a 93/7 ratio by HPLC. Purification by recrystallization from alcohols was not successful, but recrystallization from diisopropyl ether gave **1a** with 99% purity in 47% isolated yield (shown in Experimental Section). The rationalization of this reaction could be explained according to the literature;[5a,9] thus, in the presence of allyl alcohol and $ZnCl_2$, **2** gave the corresponding 1,2-*trans*-glucoside **1a**, presumably via the formation of a 1,2-orthoesther intermediate, and subsequent rearrengement (Scheme 1). The extension of reaction times led to increasing proportions of α-anomer **1b** due to anomerisation (run 7 in Table 3).

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The α-anomer, **1b** could be purified by silica gel column chromatography, and its spectra were obtained (shown in Experimental Section).

In large-scale production, we have produced 7.55 kg of **1a** with 99% purity in 50% yield from 15.0 kg of **2** using the above-described method without difficulty.

Experimental Section

β-D-Glucose pentaacetate was purchased from Tokyo Kasei. All reagents and solvents were obtained from commercial sources and used without further purification. For determining the melting points, a Yanagimoto micro melting apparatus was used, and the values are uncorrected. The boiling points are uncorrected values. NMR was run on a Bruker DRX-500. The ^1H and ^{13}C NMR were measured at 500 and 125 MHz, respectively. The NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard. The chemical shifts were given in δ (ppm). IR: Nicolet Avatar 360 FT-IR. MS: Hitachi M-80A mass spectrometer at 70 eV. HPLC: Hitachi L-6200; column: Cosmosil 5C-18AR-II, 4.6 mm × 250 mm; eluent: CH_3CN/0.2% aqueous H_3PO_4 (60/40); flow rate: 1.0 mL/min; detector: Hitachi L-4000 (220 nm). Retention times **1a** 9.8 min, **1b** 10.2 min.

Scale-Up Procedure for 2,3,4,6-Tetra-*O*-acetyl-1-*O*-(2-propenyl)-*β*-D-glucopyranoside (1a). In a 200-L glass vessel, toluene (120 L) was added with stirring, and then $ZnCl_2$ (5.23 kg, 38.18 mol), *β*-D-glucose pentaacetate **2** (15.0 kg, 38.43 mol), and the allyl alcohol (6.7 kg, 115.33 mol) were added. The mixture was heated at 80 °C for 2 h and immediately cooled to 5 °C. Then water (30 L) was added. The organic layer was separated and washed with 5% Na_2CO_3 solution (30 L) and 5% NaCl solution (30 L). After the solvent was removed under reduced pressure, an oily residue (13.8 kg) was obatined. The residue was dissolved in diisopropyl ether (60 L) at 50 °C and cooled to 15 °C. The formed crystalline material was filtered and dried at 40 °C under reduced pressure (35 Torr) to give 2,3,4,6-tetra-*O*-acetyl-1-*O*-(2-propenyl)-*β*-D-glucopyranoside (**1a**) (7.55 kg, 50%) as colourless crystals. Purity was 99% by HPLC. Mp 85−86 °C (lit.[1] 86 °C, lit.[3] 88 °C). $[\alpha]^{23}_D = -25.0°$ ($c = 1$, $CHCl_3$) (lit.[3] $[\alpha]^{25}_D = -25.8°$ ($c = 5$, $CHCl_3$). ^1H NMR 2.01 (3H, s, CH_3CO_2), 2.04 (3H, s, CH_3CO_2), 2.05 (3H, s, CH_3CO_2), 2.09 (3H, s, CH_3CO_2), 3.63−3.72 (1H, m, OCH_2-CH═), 4.06−4.14 (1H, m, OCH_2CH═), 4.16 (1H, d, J = 2.5 Hz, H-5), 4.26 (1H, dd, J = 12.3, 4.8 Hz, H-6), 4.35 (1H, dd, J = 13.2, 4.8 Hz, H-6′), 4.56 (1H, d, J = 2.5 Hz, H-1), 5.02 (1H, dd, J = 9.6, 8.0 Hz, H-3), 5.10 (1H, dd, J = 9.9, 9.5 Hz, H-4), 5.20−5.23 (2H, m, H-2, CH═CH_2), 5.28 (1H, dd, J = 17.3, 1.7 Hz, CH═CH_2), 5.82−5.86 (1H, m, CH═CH_2); ^{13}C NMR 20.56 (CH_3), 20.58 (CH_3), 20.63 (CH_3), 20.70 (CH_3), 61.94 (CH_2), 68.44 (CH), 69.99 (CH_2), 71.28 (CH), 71.77 (CH), 72.85 (CH), 99.55 (CH), 117.62 (CH_2), 133.28 (CH), 169.29 (CO), 169.36 (CO), 170.26 (CO), 170.64 (CO); IR ($CHCl_3$) 3020, 2972, 2878, 2401, 1751, 1648 cm^{-1}; SI-MS (*m*/*e*): 411 $[M + Na]^+$, 389 $[M + H]^+$, 331, 307, 289, 271, 243, 229, 211.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-(2-propenyl)-α-D-glucopyranoside (1b). A small amount of the mother liquor of recrystallized **1a** was concentrated in a vacuum and purifi-

cated by column chromatography (silica gel, eluent: ethyl acetate/*n*-hexane = 1:15) to give 2,3,4,6-tetra-*O*-acetyl-1-*O*-(2-propenyl)-α-D-glucopyranoside (**1b**). Purity was 98% by HPLC. Mp 51−54 °C (lit.[1] 55−56 °C). $[\alpha]^{23}_{D} = +131.8°$ ($c = 1.1$, $CHCl_3$) (lit.[1] $[\alpha]^{30}_{D} = +141°$ ($c = 1$, $CHCl_3$)). ^{1}H NMR 2.01 (3H, s, CH_3CO_2), 2.03 (3H, s, CH_3CO_2), 2.07 (3H, s, CH_3CO_2), 2.09 (3H, s, CH_3CO_2), 3.99−4.11 (3H, m, H-6, OC*H*$_2$CH═), 4.16−4.22 (1H, m, H-5), 4.27 (1H, dd, $J = 12.3$, 4.5 Hz, H-6′), 4.90 (1H, dd, $J = 10.3$, 3.7 Hz, H-2), 5.07 (1H, dd, $J = 10.1$, 9.7 Hz, H-3), 5.11 (1H, d, $J = 3.7$ Hz, H-1), 5.23 (1H, dd, $J = 10.4$, 1.4 Hz, CH═C*H*$_2$), 5.32 (1H, dd, $J = 16.4$, 1.6 Hz, CH═C*H*$_2$), 5.51 (1H, dd, $J = 10$, 9.7 Hz, H-4), 5.82−5.92 (1H, m, C*H*═CH$_2$); ^{13}C NMR 20.51 (CH_3), 20.57 (CH_3), 20.58 (CH_3), 20.61 (CH_3), 61.80 (CH_2), 67.28 (CH), 68.49 (CH), 68.71 (CH_2), 70.08 (CH), 70.66 (CH), 94.77 (CH), 118.05 (CH_2), 133.02 (CH), 169.50 (CO), 169.97 (CO), 170.01 (CO), 170.52 (CO); IR ($CHCl_3$) 3023, 2970, 2401, 2877, 1741, 1647 cm^{-1}; SI-MS (*m*/*e*): 411 $[M + Na]^+$, 389 $[M + H]^+$, 331, 307, 289, 271, 243, 229, 211.

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