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Note

An improved method for the preparation of 3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranose 1,2,4-orthopivalate

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Abstract

The synthetic route to 3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranose 1,2,4-orthopivalate (**1**), which was previously established, was shortened by introducing two novel reactions, regioselective pivaloylation with dibutyltin oxide in toluene for the regioselective activation of hydroxyl groups, and intramolecular orthoesterification with benzenesulfonyl chloride and triethylamine in dichloromethane. Compound **1** was obtained in 58.8% overall yield from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (**2**) via four reaction steps.

Keywords: 3-*O*-Benzyl-6-*O*-pivaloyl-α-D-glucopyranose 1,2,4-orthopivalate; Regioselective pivaloylation; Intramolecular orthoesterification; Cellulose synthesis

There are many functionalized cellulose derivatives. Hydroxypropyl cellulose has liquid crystal properties,[1] methyl or carboxymethyl celluloses show thermoreversible gelation,[2] Na-cellulose sulfates have film-forming properties and biological activities,[2] and so on.

The structure and properties of partially functionalized celluloses—from natural cellulose or from chemosynthesis—are controlled by the degree of polymerization (DP), the degree of substitution (DS), and the functionalization pattern. The pattern of functionalization includes the distribution within the anhydroglucose unit along the polymer chain and between the chains. However, much remains unknown about the relationship between the molecular structures of cellulose derivatives and their properties.

For these studies, and for the molecular design of advanced materials from cellulose, it is important to be able to prepare regioselectively substituted cellulose derivatives bearing desired functional groups on the desired hydroxyl groups in the repeating anhydroglucose units of the polymers.

At present, regioselectively 6-*O*- and 2,3-di-*O*-substituted cellulose derivatives[3–5] have been prepared from natural cellulose via tritylation at the 6-*O*-position with subsequent derivatization. Recently, a method for the preparation of 3-*O*-substituted cellulose using the thexyldimethylsilyl group was reported by Koschella et al.,[6] but other regioselectively substituted cellulose derivatives, such as 2-*O*-, 3,6-di-*O*- or 2,6-di-*O*-substituted celluloses, could be scarcely prepared by their methods.

On the other hand, synthesis of cellulose has been reported starting from 3,6-di-*O*-benzyl-, and 3-*O*-benzyl-6-*O*-pivaloyl-α-D-glucopyranose 1,2,4-orthopivalate (**1**) by a cationic ring-opening polymerization.[7,8] The cellulose derivatives obtained can be converted to other regioselectively substituted celluloses. Particularly, 2-*O*-, 3,6-di-*O*- or 2,6-di-*O*-substituted celluloses can be prepared from the synthetic cellulose intermediates, because the two secondary hydroxyl groups at the C-2 and C-3 positions in the repeating anhydroglucose units on the cellulose chain are already protected with ester and ether groups, respectively, and both of which can be selectively deprototected. Thus, chemically synthesized cellulose is extremely useful.

3-*O*-Benzyl-6-*O*-pivaloyl-α-D-glucopyranose 1,2,4-orthopivalate (**1**), the starting monomer for the synthesis of cellulose, is also a valuable compound for preparing various other orthopivalate derivatives that lead to regioselectively substituted celluloses, as described in our previous report.[9] Compound **1** has been synthesized from the commercially available 1,2:5,6-di-*O*-isopropylidene-

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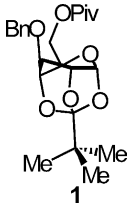
α-D-glucopyranose (**2**) via eight reaction steps, i.e., benzylation, *O*-dediisopropylidenation, benzylidenation, pivaloylation, debenzylidenation, selective pivaloylation, selective depivaloylation, and intramolecular orthoesterification.[8,10] However, the total yield of compound **1** from compound **2** was low, about 19%. A synthetic route to compound **1** that had fewer steps and a greater overall yield is desired.

In this paper, an improved method for the preparation of compound **1** is described, and two novel reactions are discussed.



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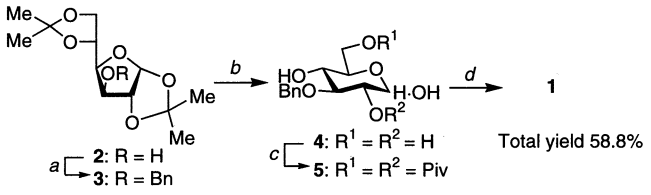
General overview.—An improved synthetic route for compound **1** is shown in Scheme 1. We describe here two novel reactions, the first of which is the regioselective pivaloylation at the 2-*O*- and 6-*O*-positions of 3-*O*-benzyl-D-glucopyranose (**4**), and the second is the intramolecular orthoesterification of 3-*O*-benzyl-2,6-di-*O*-pivaloyl-D-glucopyranose (**5**).



Scheme 1. Reagents and conditions: (a) $PhCH_2Br$, NaH, *t*-Bu_4NI, THF, 0 °C, 5 h; (b) Dowex 50-W (H^+), 1:3 EtOH–H_2O, reflux, 5 h, 93% (two steps); (c) PivCl, pyridine, Bu_2SnO, CH_3Ph, 4 Å MS, 105 → −10 °C, 2 h, 80%; (d) $BuSO_2Cl$, Et_3N, CH_2Cl_2, rt → reflux, 1 h, 79%.

Regioselective pivaloylation.—Compound **4** was prepared from commercially available 1,2:5,6-di-O-isopropylidene-α-D-glucopyranose (**2**) by benzylation and subsequent *O*-dediisopropylidenation with cation-exchange resin in 93% overall yield.

Regioselective pivaloylations of compound **4** with pivaloyl chloride in pyridine[11] or pyridine–chloroform mixed solvent system were tried, but compound **5** was not obtained, although 6-*O*- and 1,6-di-*O*-pivaloyl derivatives were produced in 41 and 51% yield, respectively. In diethyl ether solvent,[12] 6-*O*- and 1,6-di-*O*-pivaloyl derivatives were also produced about 60 and 30% yield, respectively, without compound **5**.

Then, we examined the selective activation of hydroxyl groups for regioselective pivaloylation of compound **4**. Dibutyltin oxide is a useful reagent for the selective activation of equatorial, cis-hydroxyl groups for subsequent regioselective esterification or etherification.[13–19] On the other hand, the selectivity of the pivaloylation reaction for compound **4** was found to be accomplished at lower reaction temperatures, i.e., below at least −10 °C from the results of our preliminary experiments. Thus, benzene, which has been generally used for azeotropic removal of water, is not a suitable solvent for the preparation of a cyclic tin intermediate with dibutyltin oxide, because the reaction mixture solidifies during the subsequent pivaloylation, which is carried out below −10 °C.

Thus, the best regioselective pivaloylation reaction was accomplished under the following reaction conditions. Compound **4** was treated with two equivalents of dibutyltin oxide in toluene at 105 °C to convert it into the bisdibutylstannylene acetal intermediate (Fig. 1), which was subsequently reacted with pivaloyl chloride and pyridine in the presence of powdered 4 Å molecular sieves at −10 °C to afford compound **5** in 80% yield. The structure of compound **5** was confirmed by comparison of its ^1H NMR data with those reported previously.[10] Thus, pivaloylation occurred under these conditions with high regioselectivity at the O-2 and O-6 of compound **4**.

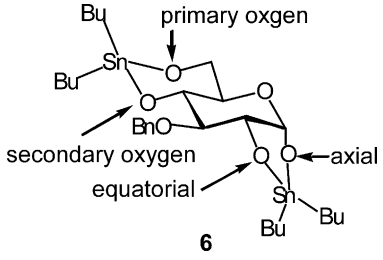


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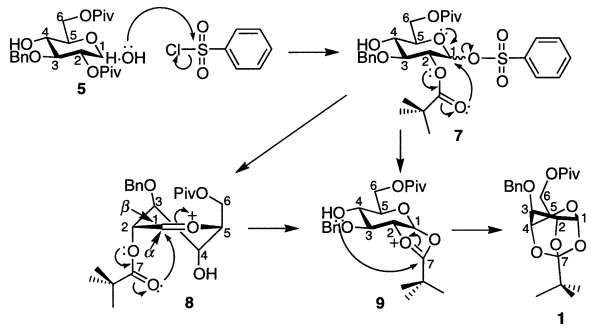
Fig. 1. Plausible structure of the intermediate stannylene acetal.

In this reaction, another important factor in obtaining such high selectivity along with high yield is to use more than two equivalents of dibutyltin oxide with compound **4**; otherwise, the high selectivity with high yield is lost. Therefore, the structure of the dibutylstannylene acetal intermediate is considered to be structure **6**, shown in Fig. 1. Consequently, the selectivity for O-6 is probably explained by the normal preference of a 4,6-*O*-dibutylstannylene acetal to react at the primary oxygen atom[16] and that for O-2 by the preference of a dibutylstannylene acetal cis-fused to a five-membered ring to react at the equatorial oxygen atom.[14] These results provide further evidence that esters of pyranose rings do not rearrange at room temperature under stannylene acetal reaction conditions[17] unlike those on acyclic 1,2-diols.[18,19]

Intramolecular orthoesterification.—Conventional intramolecular orthoesterification of compound **5**, conducted by refluxing with *N*,*N*′-carbonyldiimidazole in a large amount of benzene (1 g/130 mL) to avoid intermolecular reactions, yielded compound **1** in 58% yield.[8]



Scheme 2. Proposed reaction mechanism for orthoesterification.

In this reaction, the 1-*O*-carbonylimidazole group may act as a leaving group for the orthoesterification by dehydration.[7,8] Then, we tried another reagent for the dehydration of OH-1 in compound **5**. Both *N*,*N*′-dicyclohexyl- and *N*,*N*′-diisopropylcarbodiimides, which are popular reagents for ester and peptide syntheses,[20,21] were tried, but the expected **1** was not obtained. The use of thionyl chloride and pyridine in toluene gave compound **1** in 36% yield, but the starting material still remained. Finally, three kinds of sulfonyl chlorides, methane-, *p*-toluene-, and benzenesulfonyl chlorides, were examined. The reaction with *p*-toluene- and benzenesulfonyl chlorides produced compound **1** in 18 and 79% yields, respectively, although methanesulfonyl chloride gave none of the product. Thus, benzenesulfonyl chloride was found to be the most suitable reagent for the dehydration of OH-1 leading to the formation of the orthopivalate **1**.

The structure of compound **1** was determined by ^{1}H and ^{13}C NMR spectroscopy. The spectral data for compound **1** were completely identical with the literature data.[8] Thus, novel orthoesterification conditions were established.

The following reaction mechanism to form the orthoester is proposed as shown in Scheme 2. Initially, benzenesulfonyl chloride reacts at the C-1 oxygen atom to yield compound **7**. The carbonyl oxygen atom at the C-2 position attacks at the C-1 position from the α-side to form a dioxacarbenium ion intermediate **9**, either directly from **7** or via intermediate **8**, and then the hydroxyl group at the C-4 position in compound **9** attacks the C-7 position, resulting in an intramolecular cyclization to compound **1**.

Thus, compound **1** can be synthesized from D-glucose in five steps. The present method gives a higher yield of compound **1** via fewer steps than the conventional process.[8,10]

We have improved the synthetic method for compound **1** by introducing two novel reactions. Selective pivaloylation at the 2-*O*- and 6-*O*-positions was accomplished via the dibutylstannylene acetal intermediate to afford compound **5** in high yield without having to use a blocking–deblocking technique. A novel orthoesterification reaction with benzenesulfonyl chloride and triethylamine enables us to synthesize compound **1** in high yield. Consequently, compound **1** is obtained in 58.8% overall yield from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (**2**) via four reaction steps.

1. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were taken with a Varian INOVA 300 FT-NMR instrument (300 MHz) with tetramethylsilane (Me_4Si) as the internal standard in chloroform-*d*. Chemical shifts (δ) and coupling constants (J) are given in value (ppm) and Hz, respectively. Optical rotations were measured at 25 °C using a JASCO Dip-1000 digital polarimeter. Products were purified on a silica gel column chromatography (Wakogel® C-200, Wako Pure Chemical Industries, Ltd.). The standard workup for reaction mixtures consisted of extraction with EtOAc, washing with brine, drying over Na_2SO_4, and concentration of the organic extract in vacuo.

*Preparation of 3-*O*-benzyl-*D*-glucopyranose* (**4**).—To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (**2**, 50 g, 192 mmol) in THF (225 mL), 60% NaH dispersed in mineral oil (9.22 g, 0.23 mol), and tetrabutylammonium iodide (7.09 g, 19.2 mmol) were added at 0 °C. Benzyl bromide (25.1 mL, 210 mmol) was then added dropwise at 0 °C. The solution was stirred at rt for 5 h. After addition of MeOH (1 mL), the reaction mixture was worked up by the standard procedure. The product was separated on a silica gel column (16 g, 40 × 30 mm) eluted with 1:19 EtOAc–hexane to give compound **3** as a yellow oil (ca. 67 g, 100% recovery yield). The oil was used for the subsequent step without further purification.

Crude compound **3** (67 g, 192 mmol) and Dowex 50-W (H^+) (cation-exchange resin, Dow Chemical Co.) (27 g, wet weight) were stirred in 1:3 EtOH–water (200 mL) at reflux for 5 h. After the reaction was completed, the reaction mixture was neutralized with NaOMe, and then filtered. The solvent (EtOH) was removed under reduced pressure. The residual water layer was washed with EtOAc, and then the water was removed by lyophilization to give compound **4** as a white solid (48.1 g, 93%), which was crystallized from EtOAc to give colorless crystals: mp 123–125 °C, lit.[22] 134–135 °C; $[\alpha]_D^{25}$ +16.2 → +44.1° (*c* 0.5, water), lit.[22] +21.6 → +43.2°; Anal. Calcd for $C_{23}H_{32}O_7$: C, 57.77; H, 6.71. Found: C, 57.49; H, 6.55.

*Preparation of 3-*O*-benzyl-2,6-di-*O*-pivaloyl-*D*-glucopyranose* (**5**).—Compound **4** (5.0 g, 18.5 mmol)

and dibutyltin oxide (9.2 g, 37.0 mmol) in toluene (200 mL) were gradually heated to 105 °C until the reaction mixture become homogeneous and clear. To the clear solution, powdered 4 Å molecular sieves (4.0 g) were added. The mixture was cooled to −10 °C. Pyridine (3.95 mL, 48.8 mmol) was added, followed by the dropwise addition of pivaloyl chloride (5.46 mL, 44.4 mmol) in toluene (36 mL). After 2 h, MeOH (0.75 mL) was added. The solvent was removed to give a yellow oil that was purified on a silica gel column (97 g, 40 × 180 mm) eluted with CH_2Cl_2, and then 1:2 EtOAc–hexane. The combined eluent was evaporated to give compound **5** as a slightly yellow oil (6.5 g, 80%): ^{1}H NMR ($CDCl_3$): δ 1.16–1.28 (broad s, 18 H, H-piv), 7.26–7.35 (m, 5 H, Ar).

*Preparation of 3-*O*-benzyl-6-*O*-pivaloyl-α-*D*-glucopyranose 1,2,4-orthopivalate* (**1**).—To a solution of compound **5** (3.7 g, 8.4 mmol) in CH_2Cl_2 (37.0 mL), triethylamine (5.8 mL, 42.2 mmol), and benzenesulfonyl chloride (2.1 mL, 16.8 mmol) were added at 0 °C. The solution was stirred at rt for 0.5 h, and then refluxed for 0.5 h. The reaction mixture was concentrated to give a wine-red oil that was purified on a silica gel column (100 g, 40 × 190 mm) eluted with 1:1 CH_2Cl_2–hexane, and then CH_2Cl_2. The eluent was evaporated to give compound **1** as a slightly yellow syrup (2.8 g, 79%), which was crystallized from MeOH to give colorless crystals: mp 72.5–73.5 °C, lit.[8] 73.1–73.6 °C; $[\alpha]_D^{25}$ +31.2° (*c* 1.0, $CHCl_3$), lit.[8] +31.2°; ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 9 H, H-orthopiv), 1.23 (s, 9 H, H-piv), 3.95 (broad d, 1 H, $J_{3,4}$ 4.5 Hz, H-4), 4.16 (dd, 1 H, $J_{2,3}$ 2.1, $J_{3,4}$ 4.5 Hz, H-3), 4.31–4.41 (m, 2 H, H-6), 4.39–4.43 (m, 1 H, H-2), 4.50 (broad t, 1 H, $J_{5,6}$ 6.3 Hz, H-5), 5.76 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 4.63 (s, 2 H, $CH_2C_6H_5$), 7.26–7.38 (m, 5 H, Ar). ^{13}C NMR: δ 97.6 (C-1), 64.4, 71.3, 71.5, 72.0, 72.2, 75.3 (C-2, C-3, C-4, C-5, C-6, $CH_2C_6H_5$), 123.1 (orthopivalate quaternary carbon), 27.2 [pivaloyl–C(CH_3)$_3$], 38.8 [pivaloyl–C(CH$_3$)$_3$], 24.9 [orthopivalate–C(CH_3)$_3$], 35.7 [orthopivalate–C(CH$_3$)$_3$], 127.7, 128.1, 128.7, 137.4 (Ar), 178.2 (C=O); Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.60; H, 7.76.

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