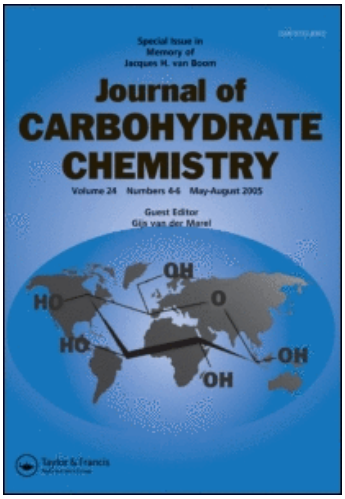

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A ONE-STEP PROCEDURE FOR FACILE PREPARATION OF D-GLUCOPYRANOSIDES WITH A FREE 2-OH FROM *O*-PERACETYLATED β-D-GLUCOPYRANOSE

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ABSTRACT

Glycosylations and deacetylations of 2-*O*-acetyl of *O*-peracetylated β-D-glucopyranose were realized in one step by reactions with 4.0 equivalents of alcohols and 1.5 equivalents of trifluoroborane etherate. Thus, various β-D-glucopyranosides with a free hydroxyl group on C-2 were conveniently prepared and applied for synthesis of Glc1→2 linked disaccharides.

INTRODUCTION

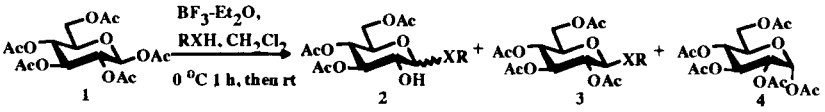
Glc1→2 linked oligosaccharide moieties commonly occur in natural medicinal plants, especially saponins. In order to simplify the chemical synthesis of such oligosaccharides, it is important to be able to prepare conveniently protected D-glucopyranosides having the C-2 hydroxyl group unprotected.[2] Several methods[3-6] have already been developed for preparations of glucosides having a free hydroxyl group on C-

2, but all of them are multi-step procedures involving several steps of regioselective protections and deprotections of monosaccharides, which makes syntheses of the target oligosaccharides tedious and of comparatively low yield. We report here a new, one steps high yielding, facile method for preparation of various 3,4,6-tri-*O*-acetyl-β-D-glucopyransides with a free 2-OH starting from *O*-peracetylated β-D-glucopyranose. The glucosides obtained are important intermediates for chemical synthesis of numerous natural oligosaccharides containing the 1→2Glc fragment.[7]

RESULTS AND DISCUSSION

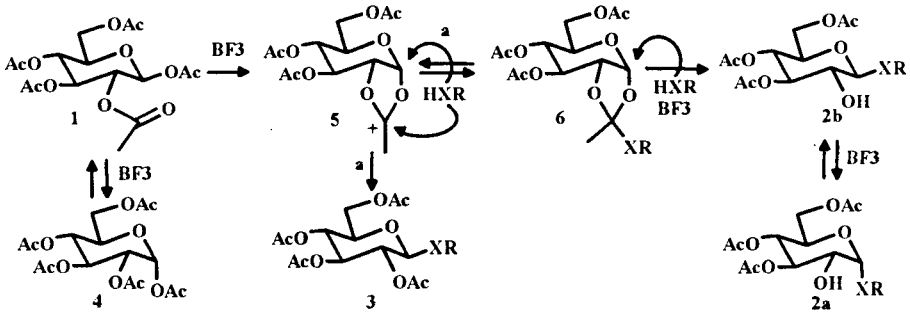
Reactions of *O*-peracetylated monosaccharides with one equivalent of alcohol in the presence of Lewis acids, such as BF_3-Et_2O, TMSOTf and $AgClO_4$, generally afford their glycosides **3** (**Scheme 1**).[8] However, deprotection of the 2-*O*-acyl group has also been occasionally observed as a side reaction.[9] It has recently been found that treatment of *O*-peracetylated β-D-glucopyranose with an excess amount of allylic alcohol in the presence of trifluoroborane etherate could promote deacetylation of the 2-*O*-acetyl group during glycosylation, and afford allyl glucosides with a free C-2 hydroxyl group (**2a**) as a major product.[10] We have, therefore, studied effects of various reaction conditions on product yields and revealed that an optimal yield (63%, based on **1**) of **2a** was obtained with a molar ratio of **1**, allyl alcohol and trifluoroborane etherate being 1.0 : 4.0 : 1.5. Except for **2a**, compound **4**, the α-anomer of the starting material **1**, was also isolated in 21% yield from the reaction mixture, but only a very small amount of glycosylation product **3a** was observed by TLC.

In order to check whether the above phenomena is of general significance, we have further investigated the reactions of **1** with other alcohols such as benzyl alcohol and isopropyl alcohol, and with thiol under the same conditions. As shown in **Scheme 1**, satisfactory results were also obtained with these alcohols and ethanethiol. Reaction of **1** with benzyl alcohol gave **2b** in good yield (73%) and with ethanethiol and isopropyl alcohol afforded **2c** (43%) and **2d** (52%) in acceptable yields together with some glycosylation products **3c** (14%) and **3d** (10%), respectively. However, all of the reactions also afforded a substantial amount of **4** (24-26%). Among the products **2a-d**,



a. XR = $OCH_2CH{=}CH_2$	63%(α:β 1:4)	trace	21%
b. XR = OCH_2Ph	73%(β)	trace	24%
c. XR = SEt	43% (β)	14%	25%
d. XR = $OCHMe_2$	52% (β)	10%	26%

Scheme 1

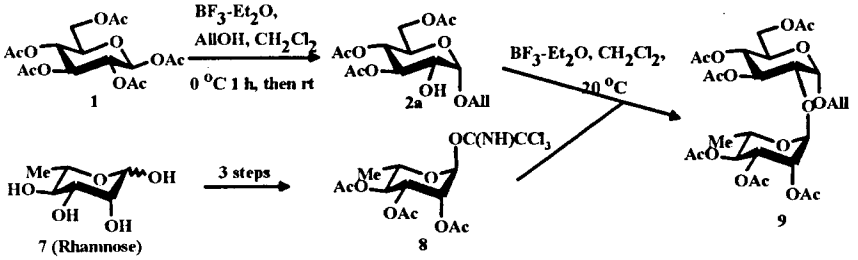


Scheme 2

β-anomers were major, but the α:β ratios in the products increased with prolonged reaction time. In addition, it should be noted that the reactions of **1** with active alcohols such as allylic alcohol and benzyl alcohol gave the corresponding products (**2a** and **2b**) in good yield.

Although the true reaction path is still obscure, a probable mechanism is suggested in **Scheme 2**. It is supported by the reported results[9] that the reactions proceed through a key ortho-ester intermediate **6**, as well as by ortho-ester products[10] isolated in some similar reactions. Obviously, β-anomer and ratio of peracetylated monosaccharide to alcohol are of great importance for practical utilization of the reactions. Experimental results have also shown that compound **4** was rather stable under the reaction conditions above, and therefore, some amount of **4** was isolated in all related reactions.

To demonstrate the convenience of this procedure for synthesis of complex oligosaccharides with Glc1→2 linked disaccharide units, we have successfully synthesized



Scheme 3

a protected disaccharide **9**, **Allyl 3,4-Di-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside,** one of naturally occurring saponin disaccharides,[7] in only 6 steps starting from D-glucose and L-rhamnose (**Scheme 3**).

CONCLUSION

In short, glycosylations together with deacetylation of 2-*O*-acetyl of *O*-peracetylated β-D-glucose were realized with a one-step procedure. The method presented here is, to date, the shortest and most convenient one for preparations of **2**. All of the compounds **2a-c** are useful intermediates for complex oligosaccharide synthesis, as demonstrated by the synthesis of a natural saponin Glc1→2 linked disaccharide moiety **9.**

EXPERIMENTAL

General methods. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter at ambient temperature (25 °C). TLCs were performed on pre-coated plates of Silica Gel HF_{254} (0.5 mm, Qingdao, China) and detected by 10% H_2SO_4 in methanol. Flash column chromatography was performed on Silica Gel H (400 mesh). ^{1}H-NMR spectra were recorded at 300 MHz on a Bruker AM-300 spectrometer with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. IR spectra were recorded with a Shimadzu IR-440 spectrophotometer, using potassium bromide disks for

solid samples and film for liquid samples. Mass spectra were performed on a VG QUATTRO MS instrument.

General Procedure for the Preparations of Various Glucosides with Free 2-OH (2). To a mixture of *O*-peracetylated β-D-glucose (**1**, 0.195 g, 0.5 mmol), which was prepared from D-glucose in acetic anhydride-sodium acetate, and dried alcohols (2.0 mmol) or ethanethiol in anhydrous dichloromethane (4.00 mL) was added freshly-distilled trifluoroborane etherate (0.10 mL, 0.75 mmol) under nitrogen atmosphere at 0 °C. The reaction solution was stirred at 0 °C for 1 h, at room temperature overnight, poured into ice-water, and then extracted with ethyl acetate. The combined extracts were concentrated under diminished pressure and the residues were easily purified by flash column-chromatography to afford products **2**, **3** and **4**.

Allyl 3,4,6-Tri-*O*-acetyl-α-and β-D-glucopyranoside (2a): colorless syrup; yield, 63%; $[\alpha]_D$ +75.8° (*c* 0.9, $CHCl_3$); IR(film) 3455 (OH), 1750 (C=O) cm^{-1}; **2a-α**: ^1H NMR δ 5.95 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.34 (m, 1H, $CH_2CH=C\underline{H_2}$), 5.26 (m, 1H, $CH_2CH=C\underline{H_2}$), 5.21 (dd, 1H, $J_{3,4} = J_{4,5} = 9.8$ Hz, H-4), 4.99 (dd, 1H, $J_{2,3} = 9.8$ Hz, H-3), 4.95 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.27 (m, 1H, $OC\underline{H_2}CH=$), 4.23 (dd, 1H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 12.3$ Hz, H-6a), 4.08 (m, 1H, $OC\underline{H_2}CH=$), 4.05 (dd, 1H, $J_{5,6b} = 2.3$ Hz, H-6b), 3.96 (ddd, 1H, H-5), 3.66 (dd, 1H, H-3), 2.08, 2.07 and 2.03 (3×s, 3H each, 3×OAc); **2a-β**: ^1H-NMR δ 5.92 (m, 1H, $C\underline{H}=CH_2$), 5.33 and 5.23 (2×m, 1H each, $CH=C\underline{H_2}$), 5.11 (dd, 1H, $J_{4,5} = J_{3,4} = 9.4$ Hz, H-4), 4.99 (dd, 1H, $J_{2,3} = 9.7$ Hz, H-3), 4.43 (d, 1H, $J_{1,2} = 7.7$ Hz, H-1), 4.37 (m, 1H, $OC\underline{H_2}CH=$), 4.34 (dd, 1H, $J_{5,6a} = 4.9$ Hz, $J_{6a,6b} = 12.1$ Hz, H-6a), 4.18 (m, 1H, $OC\underline{H_2}CH=$), 4.11 (dd, 1H, $J_{5,6b} = 2.3$ Hz, H-6b), 3.71 (ddd, 1H, H-5), 3.59 (dd, 1H, H-2), 2.09, 2.05 and 2.02 (3×s, 3H each, 3×OAc); MS: *m/z* 346 (M^+-1), 289 (M^+-OAll);

Anal. Calcd for $C_{15}H_{22}O_9$ (346.33): C, 52.02; H, 6.40. Found: C, 52.13; H 6.75.

Benzyl 3,4,6-Tri-*O*-acetyl-β-D-glucopyranoside (2b): colorless syrup; yield, 73%; $[\alpha]_D$ +37.8° (*c* 0.9, $CHCl_3$); IR(film): 3450 (OH), 1750 (C=O) cm^{-1}; ^1H NMR δ 7.36 (m, 5H, Ph), 5.10 (dd, 1H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 5.05 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-3), 4.90 and 4.79 (2×d, 2H, J = 11.6 Hz, $OC\underline{H_2}Ph$), 4.44 (d, 1H, $J_{1,2} = 7.7$ Hz, H-1), 4.29 (dd, 1H, $J_{5,6a} = 4.7$ Hz, $J_{6a,6b} = 12.3$ Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b} = 2.1$ Hz, H-6b), 3.67

(ddd, 1H, H-5), 3.62 (dd, 1H, H-2), 2.10, 2.06 and 2.02 (3×s, 3H each, 3×OAc); MS: *m/z* 397 (M^+-1), 289 (M^+-OBn).

Anal. Calcd for $C_{19}H_{24}O_9$ (396.39): C, 57.57; H, 6.10. Found: C, 57.82; H, 6.15.

Ethyl 3,4,6-Tri-*O*-acetyl-1-thio-α-D-glucopyranoside (2c): pale-yellow solid; mp 70-72 °C; yield, 43%; $[\alpha]_D$ -23.8° (*c* 0.9, $CHCl_3$); IR(film) 3450 (OH), 1750 (C=O) cm^{-1}; ^1H NMR δ 5.05 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4), 4.96 (dd, 1H, $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 4.48 (d, $J_{1,2}$ = 8.2 Hz, H-1), 4.44 (dd, 1H, $J_{5,6a}$ = 3.9 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.34 (dd, 1H, $J_{5,6b}$ = 2.0 Hz, H-6b), 3.59 (dd, 1H, H-2), 3.55 (ddd, 1H, H-5), 2.70 (q, 2H, J = 7.3 Hz, SCH_2), 2.11, 2.09, 2.06 (3×s, 3H each, 3×OAc), 1.27 (t, 3H, $SCH_2C\underline{H}_3$); MS: *m/z* 331(M^+-1-H_2O), 289 (M^+-SCH_2CH_3).

Anal. Calcd for $C_{14}H_{22}O_8S$ (350.39): C, 48.00; H, 6.33. Found: C, 48.45; H, 6.34.

Isopropyl 3,4,6-Tri-*O*-acetyl-β-D-glucopyranoside (2d): colorless syrup; yield, 52%; $[\alpha]_D$ +126.7° (*c* 0.9, $CHCl_3$); IR(film) 3450 (OH), 1750 (C=O) cm^{-1}; ^1H NMR δ 5.05 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 4.90 (t, 1H, $J_{2,3}$ = 9.7 Hz, H-3), 4.54 (d, 1H, $J_{1,2}$ = 8.1, H-1), 4.49 (dd, 1H, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.32 (dd, 1H, $J_{5,6b}$ = 1.9 Hz, H-6b), 3.93 (m, 1H, OC<u>H</u>), 3.60 (dd, 1H, H-2), 3.51 (ddd, 1H, 5-H), 2.14, 2,10, 2.06 (3×s, 3H each, 3×OAc), 1.24 [d, 6H, J = 6.3 Hz, $OCH(C\underline{H}_3)_2$]; MS: *m/z* 289 [M^+-$OCH(CH_3)_2$].

Anal. Calcd for $C_{15}H_{24}O_9$ (348.30): C, 51.73; H, 6.95. Found: C, 51.90; H, 7.15.

Allyl 3,4-Di-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (9). A mixture of allyl 3,4-di-*O*-acetyl-α-D-glucopyranoside **2a-α** (0.274 g, 1.0 mmol), *O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl) trichloroacetimidate **7** (0.520 g, 1.2 mmol), freshly prepared from 2,3,4-tri-*O*-acetyl-L-rhamnopyranose, molecular sieves 4A (0.200 g) in dry dichloromethane (10.0 mL) was stirred at room temperature for 1 h and was then, cooled down to -20 °C and trifluoroborane-etherate (0.66 mL, 0.5 mmol) was then added dropwise. The reaction was stirred at -20 °C for 2 h and at room temperature for 2 h, and then quenched with aq sodium hydrogen carbonate solution. Usual work-up and purification of the product as above gave **9** (0.518 g, 95%) as a colorless solid: mp 48-49 °C; [α] +22.1° (*c* 0.9, $CHCl_3$); IR(film) 1750 (C=O) cm^{-1}; ^1H NMR δ 5.95 (m, 1H, $CH_2C\underline{H}=CH_2$), 5.47 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 5.37 (m,

1H, $CH_2CH=C\underline{H}_2$), 5.25 (m, 1H, $CH_2CH=C\underline{H}_2$), 5.21 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-3), 5.09 (dd, 1H, $J_{1',2'}$ = 1.8 Hz, $J_{2',3'}$ = 3.30 Hz, H-2'), 5.05 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 9.9 Hz, H-4'), 4.99 (dd, 1H, $J_{2',3'}$ = 3.6 Hz, H-3'), 4.98 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.83 (d, 1H, H-1'), 4.27 (m, 1H, $C\underline{H}_2CH=CH_2$), 4.23 (m, 1H, $C\underline{H}_2CH=CH_2$), 4.15 (dd, 1H, $J_{5,6a}$ = 2.4 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.01 (dd, 1H, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.97 (dq, 1H, $J_{5',6'}$ = 6.4 Hz, H-5'), 3.72 (dd, 1H, H-2), 3.71 (ddd, 1H, H-5), 2.13, 2.08, 2.07, 2.04, 2.02, 1.98 (6×s, 3H each, 6×OAc), 1.16 (d, 3H, $C\underline{H}_3$-6'); MS: *m/z* 561 (M^+-$CH_2CH=CH_2$).

Anal. Calcd for $C_{27}H_{38}O_{16}$ (618.59): C, 52.43; H, 6.15. Found: C, 52.39; H, 6.14.

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