JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

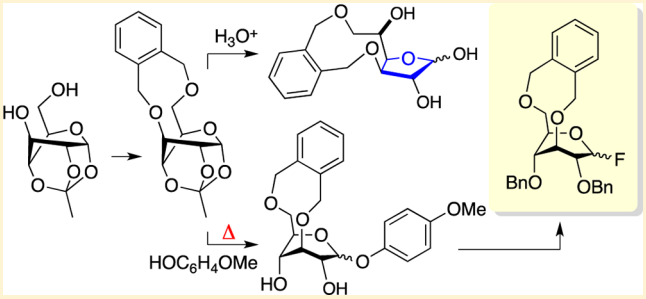
Synthesis of 3,6-*O*-(*o*-Xylylene)glucopyranosyl Fluoride, an Axial-Rich Glycosyl Donor of β-Glycosylation

Noriaki Asakura,† Atsushi Motoyama, Takuya Uchino, Kotaro Tanigawa, and Hidetoshi Yamada*

School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337, Japan

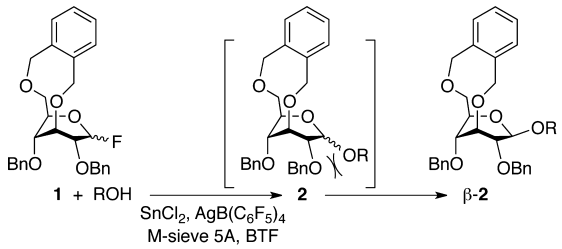
Supporting Information

ABSTRACT: Despite the reported complete β-selectivity in glycosylation with 2,4-di-*O*-benzyl-3,6-*O*-(*o*-xylylene)-glucopyranosyl fluoride, its preparation has been inefficient. This paper describes an improved route for the donor, including the formation of the 3,6-bridge on 1,2,4-orthoacetylglucose, the preparation of which was also refined, along with a discovered feature that the 3,6-bridged glucose prefers the furanose form. Although this feature made the synthesis of the desired glucopyranosyl donor difficult, application of thermal glycosylation solved the problem. With a modifiable intermediate, the improved availability of the donor would expand the applications.



Realization of advanced and stable stereoselectivity in chemical glycosylation has been a fundamental challenge for synthetic organic chemists for many years. Among the variety of methods for realizing stereoselectivity, stereocontrol on the basis of conformational locking of pyranose rings is one developing area of research,[1−3] Theoretical calculations have also indicated the significance of the conformational control.[4−7] Locking the conformation to the inverted form of pyranose rings has been a typical approach.[8−14] Ring inversion produces carbohydrates possessing more axial substituents, which are called axial-rich forms.[15−19] To lock a conformation into an axial-rich form, steric repulsion between bulky silyl groups has often been applied.[8−12,18−31] The axial-rich form has enhanced the reactivity of glycosyl donors.[18,19] In contrast, a reduction in reactivity[12,32] and migration of the silyl groups[23] due to their intense steric hindrance have also been observed in some instances, which suggests a brittleness of the locking method of conformation.

We recently reported a completely β-selective glycosylation based on the development of a new axial-rich glycosyl donor.[33] This donor, 2,4-di-*O*-benzyl-3,6-*O*-(*o*-xylylene)glucopyranosyl fluoride (**1**), reacts with various alcohols in a $SnCl_2$−$AgB(C_6F_5)_4$ catalytic system to providing only the corresponding glucosides β-**2** through convergent isomerization from the α-isomer to the β-isomer (eq 1).[34] The one-way isomerization was attributed to steric repulsion between the α-anomeric oxygen and the axially oriented 2-oxygen. The orientation was forced by the conformational lock due to the *o*-xylylenebridge. This conformational locking system exhibited merits over the system using silyl protecting groups because of its reduced steric bulkiness and its structural robustness. In addition, the *o*-xylylene group can be removed by hydrogenolytic cleavage together with benzyl groups.



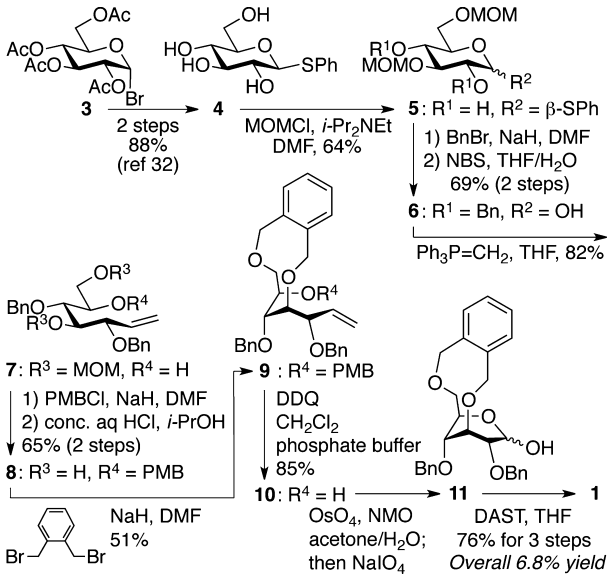
(1)

Despite the exhibited efficiency of **1** in β-glycosylation, its preparation remained unpolished. The preparation required 13 steps from acetobromoglucose (**3**), including pyranose ring opening as in **7** (Scheme 1), which made the formation of the 3,6-bridge possible, and reconstruction of the pyranose ring, which was the transformation from **10** to **11**.[33,35] Therefore, a rationalized synthetic route for **1** was indispensable to utilize the β-glycosylation. In this study, we describe a drastic rationalization of the synthesis of **1** along with new knowledge that the equilibrium between the furanose and pyranose forms is tilted toward the furanose form almost entirely when glucose possesses an *o*-xylylene 3,6-bridge.

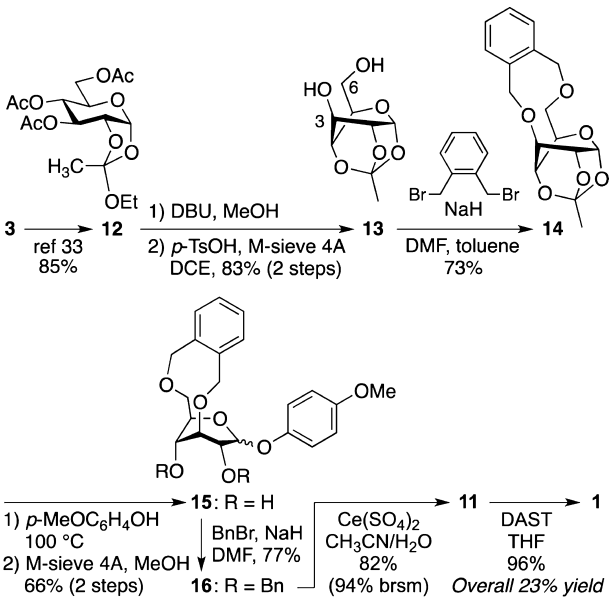
The rationalized synthetic route to **1** is summarized in Scheme 2. A salient feature of this route is the employment of 1,2,4-orthoacetyl-D-glucose (**13**), the pyranose ring of which is locked to the axial-rich conformation. This conformation allows the formation of the 3,6-*O*-(*o*-xylylene) bridge without opening of the pyranose ring. For ease of comparing the overall yield of the new route with that of the previous one, the scheme commences with **3**, which is the precursor of ethyl orthoacetate **12**.[36] Although the transformation of **12** to **13** was known,[37−42]

Received: June 27, 2013
Published: August 28, 2013

Scheme 1. Previous Synthetic Route to 1



Scheme 2. New Synthetic Route to 1



we improved this step in terms of yield and reproducibility. Tethering the 3,6-diol of **13** to the *o*-xylylene group gave **14**. The orthoester was cleaved to afford **15** through introduction of the *p*-methoxyphenyl group followed by removal of the remaining acetyl group. The reason for the adoption of this unusual method for cleavage of the orthoester group will be discussed later. Diol **15** was then benzylated to provide **16**, the *p*-methoxyphenyl group of which was removed by treatment with cerium(IV) sulfate to produce **11**.[33] The use of cerium(IV) sulfate as a one-electron oxidant gave a better yield and purity of pyranose **11** than the use of ceric ammonium nitrate, which is usually applied for oxidative removal of the group.[43−45] The yield of the fluorination of **11** was 96%. The advantages of this route over the previous one are (1) the smaller number of steps, (2) the higher overall yield (23% from **3**), and (3) the creation of diol **15** as a synthetic intermediate, which might allow variety in modification.

In the new route, the following three steps are noteworthy. The first is the improvement in the synthesis of the known compound **13**, which allowed a 74% yield from **12** on a reaction scale of 20 g. The second is the development of optimized reaction conditions to give **14** through intramolecular formation of the *o*-xylylene bridge on **13** on a reaction scale of 2 g, reducing the intermolecular formation of *o*-xylylene ethers. The third is the removal of the orthoester group of **14** by thermal glycosylation with *p*-methoxyphenol. The following paragraphs describe details of the above.

Bochkov and co-workers first reported the synthesis of **13** through intramolecular transorthoesterification of 1,2-methyl-orthoacetyl-D-glucopyranose catalyzed by *p*-toluenesulfonic acid.[37−41] However, the reproducibility and yield were low. These problems were solved by the rational use of basic and acidic properties of molecular sieves (M-sieve).[42] However, this synthetic method was too expensive for the large-quantity synthesis of **13** because a 10 g scale reaction needed 100 g of M-sieve 5A.

In the present work, these problems were overcome by application of the method for the synthesis of 1,2,4-orthopivaloylxylose reported by Nakatsubo et al.[46] The main feature of this method is its reaction conditions, in which the removal of the acetyl groups with DBU is followed by the addition of *p*-TsOH to the crude deacetylated product without removal of DBU. The mixing of DBU and *p*-TsOH might generate suitable acidic conditions to prepare the 1,2,4-orthopivaloyl moiety. Application of the reaction conditions to **12** increased the efficiency of obtaining **13** to 83% and 74% yield on 1 and 20 g scale reactions, respectively.

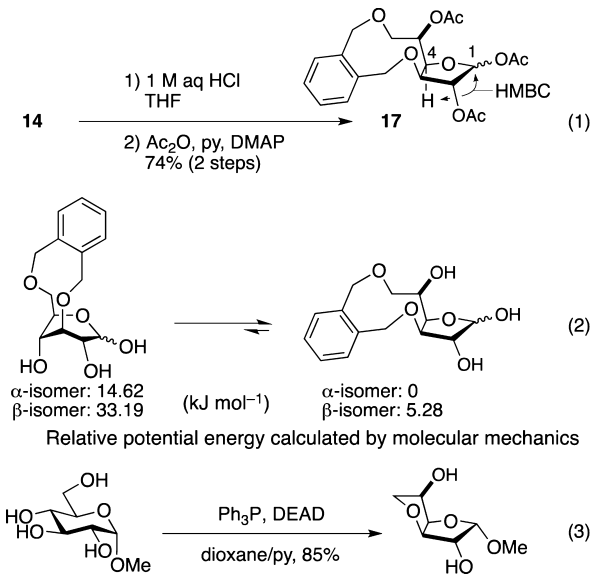
The efficiency increase was also supported by the discovery of an improved method for chromatographic purification of **13**. Compound **13** can be purified by recrystallization, but the yield is poor.[40] Although silica gel degrades **13** because the orthoester moiety is prone to be hydrolyzed, pretreatment of the silica gel with Et_3N eliminated the degradation. As eluents, a mixture of toluene and MeOH made the separation effective. Elution with *n*-hexane/EtOAc required more than 3 times the quantity of the eluent required with toluene/MeOH. The improvement in chromatographic purification stabilized the yield and reproducibility of this step.

In the formation of the *o*-xylylene bridge on **13**, the order of mixing the reagents and substrates and the rates of their additions were important. The optimal reaction conditions involved synchronized additions of a solution of *α*,*α*′-*o*-dibromoxylene in DMF (0.1 mM) and a solution of **13** in toluene (0.09 mM) to a stirred mixture of NaH in toluene (0.12 M) at 85 °C. The rate of addition was 1 mL/min for both solutions. This protocol stabilized the reproducibility of **14** to give a yield of more than 70% when starting from 2 g of **13**. The following protocols provided **14** in poor yield with significant amounts of byproducts, including dimers: (1) reaction at lower temperature, (2) addition of a solution of **13** in DMF to a mixture of *α*,*α*′-*o*-dibromoxylene and NaH in toluene, and (3) addition of a solution of *α*,*α*′-*o*-dibromoxylene in DMF to a mixture of NaH and **13** in toluene.

For the preparation of **15**, the unusual thermal glycosylation was adopted to remove the orthoester. The adoption was due to the exclusive production of the corresponding furanosyl isomer when the orthoester was removed under common hydrolysis conditions. Hence, the hydrolysis of **14** with hydrochloric acid followed by acetylation provided furanose **17** (eq 1 in Scheme 3). The furanose structure was confirmed

dx.doi.org/10.1021/jo401395h | J. Org. Chem. 2013, 78, 9482−9487

Scheme 3. Pyranose−Furanose Equilibrium of 3,6-*O*-(*o*-Xylylene)glucose



by observed HMBC between C-1 and H-4 for both the α- and β-isomers of **17**. Molecular force field calculations confirmed that the α-furanose was the most stable isomer, followed by the β-furanose, among the four possible isomers of 3,6-*O*-(*o*-xylylene)glucose (eq 2 in Scheme 3).[47] The potential energies of the pyranoses were clearly higher than those of the furanoses.

The equilibrium between furanose and pyranose forms has scarcely been discussed when glucose possesses a bridge between the 3- and 6-oxygens. All that is known is that 3,6-anhydroglucose prefers the furanose form (eq 3 in Scheme 3).[48,49] Therefore, the result of the present study provides fundamental knowledge for sugar chemistry, namely, that glucose exists as the furanose form when the *o*-xylylene group bridges the 3- and 6-oxygens, although this feature was adverse to our synthesis.

If a pyranose form with a 3,6-*O*-(*o*-xylylene) bridge is desired, the hydroxyl groups at the 1- and 4-positions should not be unprotected at the same time (eq 2 in Scheme 3). The thermal glycosylation of **14** with *p*-methoxyphenol (Scheme 2) was discovered during efforts aimed at removing the orthoester group while keeping its pyranose form intact. Thermal glycosylation is a method of glycosylation that involves heating a glycosyl donor and acceptor without solvent.[50] Thus, heating of a mixture of **14** and *p*-methoxyphenol cleaved the orthoester part without the pyranose−furanose isomerization. The cleaved orthoester group remained as an acetyl group on O-2. The acetyl group was removed by methanolysis using M-sieve 4A[42,51] to give diol **15** as a 1/3 mixture of anomers.

In summary, we have drastically improved the synthetic route to **1**, the glucosyl donor for the completely β-selective glycosylation reaction. The *o*-xylylene bridge of **1** was constructed on 1,2,4-orthoacetylglucose, which eliminated the need for pyranose ring opening and reclosing processes involved in the previous synthetic route. In addition, we found that glucose prefers the furanose form when the 3- and 6-oxygens are bridged by the *o*-xylylene group. This fact provided fundamental chemical knowledge but also represented a major problem for the synthesis of the desired pyranose derivative. This problem was solved by thermal glycosylation, which enabled the cleavage of the 1,2,4-orthoester while keeping the pyranose form intact. As a result, **1** was synthesized from **3** in nine steps in 23% overall yield. The improved availability of **1** and the modifiable synthetic intermediate **15** should expand the applications utilizing conformationally locked carbohydrates.

EXPERIMENTAL SECTION

General Methods. All of the commercially available reagents were used without further purification. When necessary, glassware was dried under reduced pressure by heating with a heat gun and solvents were distilled prior to use. Reaction mixtures were magnetically stirred. Concentration was performed under reduced pressure.

Reactions were monitored by TLC and MS. Anhydrous $MgSO_4$ was used to dry the organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence is represented as "the general drying procedure" in the experimental methods provided below.

TLC was performed on Merck precoated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light or by immersion into a solution of 2% anisaldehyde and 5% H_2SO_4 in ethanol or a solution of 10% phosphomolybdic acid in ethanol, followed by heating at ca. 200 °C. Column chromatography (CC) was performed on Merck silica gel 60 (63−200 or 40−63 μm) or Kanto Chemical silica gel 60 N (spherical, neutral, 40−50 or 63−210 μm). An Et_3N-treated SiO_2 column was prepared as follows. A slurry obtained by mixing SiO_2 with 10% (v/v) Et_3N/*n*-hexane was poured into a glass tube with a cotton plug at the bottom. After sedimentation of SiO_2, the solvent was eluted off to the upper line of SiO_2. The indicated eluent was then gently added to replace the Et_3N-containing *n*-hexane.

The melting points were uncorrected. Optical rotations were determined with a 100 mm cell at 589 nm. IR spectra were recorded with a spectrophotometer equipped with an ATR sampling unit, and the major absorbance bands are reported in wavenumbers (cm^{-1}).

The ^1H NMR (400 MHz) data are indicated by chemical shifts (δ), with the multiplicity, the coupling constant(s) (J), and the integration in parentheses in that order. The multiplicities are abbreviated follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The ^{13}C NMR (100 MHz) data are reported as chemical shifts (δ) with the hydrogen multiplicities obtained from DEPT spectra in parentheses. The multiplicities are abbreviated as follows: s, C; d, CH; t, CH_2; and q, CH_3. When the number of carbons is more than one, the number is given in the parentheses after the H multiplicity.

1,2,4-Orthoacetyl-α-D-glucopyranose (13). Synthesis on a 1 g scale: A mixture of ethyl orthoacetate **12** (1.0 g, 2.66 mmol) and DBU (405 mg, 2.66 mmol) in MeOH (20 mL) was stirred for 30 min at 25 °C. After concentration, the residue was dissolved in DCE (28 mL). To this solution were added activated M-sieve 4A (710 mg) and *p*-TsOH·H_2O (19 mg, 99.9 μmol). After the mixture was refluxed for 6.5 h, $NaHCO_3$ was added. The mixture was filtered through a cotton−Celite pad. After concentration of the filtrate, the residue was purified by CC (10 g of Et_3N-treated SiO_2, toluene/MeOH 25/1 to 10/1) to give **13**[36] (449 mg, 83% yield) as a colorless syrup.

Synthesis on a 20 g scale: A mixture of ethyl orthoacetate **12** (20.5 g, 54.5 mmol) and DBU (12.4 g, 81.6 mmol) in MeOH (500 mL) was stirred for 20 min at 25 °C. After concentration, the residue was dissolved in DCE (545 mL). To this solution were added activated M-sieve 4A (16.4 g) and *p*-TsOH·H_2O (518 mg, 2.72 mmol). After the mixture was refluxed for 18 h, it was filtered through a cotton−Celite pad to remove M-sieve 4A. After concentration, the filtrate was purified by CC (300 g of Et_3N-treated SiO_2, toluene/MeOH 25/1 to 10/1) to give **13** (8.23 g, 74% yield) as a colorless syrup.

1,2,4-Orthoacetyl-3,6-*O*-(*o*-xylylene)-α-D-glucopyranose (14). To a stirred mixture of NaH (60% in mineral oil, 1.57 g; 942 mg of NaH, 39.3 mmol) in toluene (330 mL) were added dropwise a solution of α,α'-*o*-dibromoxylene (2.80 g, 10.6 mmol; ***caution***: highly lachrymatory and toxic by inhalation and in contact with skin) in DMF (109 mL) and a solution of 1,2,4-orthoacetyl-α-D-glucopyranose (**13**) (2.01 g, 9.79 mmol) in toluene (109 mL) at 85 °C. Two syringe

dx.doi.org/10.1021/jo401395h | J. Org. Chem. 2013, 78, 9482−9487

pumps were used for these additions; the addition rate was 1 mL/min for both, and thus, the addition required 109 min. The mixture was further stirred for 1 h at 85 °C after the end of the addition. The reaction was quenched by addition of H_2O (150 mL). From this aqueous mixture, the organic layer was separated and washed with H_2O. After the general drying procedure, the crude product was purified by CC (40 g of Et_3N-treated SiO_2, *n*-hexane/EtOAc 15/1 to 10/1) to give **14** (2.21 g, 73% yield) as a white amorphous solid. Mp 131−133 °C; $[\alpha]_D^{24}$ +126.9 (*c* 1.09, $CHCl_3$); IR 3009, 2953, 2899, 2859, 1134, 1082, 1048, 752 cm^{-1}; ^1H NMR (C_6D_6) δ 7.03−6.96 (m, 2H), 6.93−6.86 (m, 2H), 5.56 (d, *J* = 4.9 Hz, 1H), 5.52 (d, *J* = 10.1 Hz, 1H), 4.91 (d, *J* = 9.4 Hz, 1H), 4.61 (br d, *J* = 3.1 Hz, 1H), 4.47 (dd, *J* = 4.3, 2.1 Hz, 1 H), 4.18 (d, *J* = 10.1 Hz, 1 H), 4.11 (dd, *J* = 4.9, 2.1 Hz, 1H), 3.88 (d, *J* = 9.4 Hz, 1H), 3.85 (dd, *J* = 4.3, 1.8 Hz, 1H), 3.61 (dd, *J* = 14.2, 1.4 Hz, 1H), 3.53 (dd, *J* = 14.2, 3.1 Hz, 1H), 1.72 (s, 3 H); ^{13}C NMR (C_6D_6) δ 138.0 (s), 136.7 (s), 128.7 (d), 128.7 (d), 127.8 (d), 127.4 (d), 119.9 (s), 98.1 (d), 79.7 (d), 74.8 (t), 74.1 (d), 72.3 (d), 71.9 (t), 70.5 (d), 69.3 (t), 20.9 (q); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{18}O_6Na$ 329.1001, found 329.1010.

4-Methoxyphenyl 3,6-*O*-(*o*-Xylylene)-D-glucopyranoside (15). A mixture of *p*-methoxyphenol (3.06 g, 24.6 mmol) and 1,2,4-orthoacetyl-3,6-*O*-(*o*-xylylene)-α-D-glucopyranose (**14**) (1.44 g, 4.70 mmol) was heated to 100 °C. The melted mixture was stirred for 9 h at 100 °C. After being cooled, the mixture was diluted with MeOH (25 mL). To the mixture, activated M-sieve 4A[42] (4.5 g) was added. After being refluxed for 12 h, the mixture was filtered through a cotton−Celite pad to remove the M-sieve. After concentration, the residue was purified by CC (45 g of SiO_2, *n*-hexane/EtOAc 7/2 to 1/3) to give α-**15** (334 mg, 19% yield) and β-**15** (853 mg, 47% yield), both as colorless amorphous solids.

Data for α-**15**: mp 61−64 °C; $[\alpha]_D^{24}$ −40.3 (*c* 0.62, $CHCl_3$); IR 3422, 2932, 2878, 1509, 1217, 1115, 1032, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.20 (m, 4H), 6.96 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 6.80 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 5.52 (d, *J* = 2.3 Hz, 1H), 5.02 (d, *J* = 9.9 Hz, 1H), 4.89 (d, *J* = 12.6 Hz, 1H), 4.74 (d, *J* = 12.6 Hz, 1H), 4.54 (d, *J* = 9.9 Hz, 1H), 4.39 (br dd, *J* = 7.3, 6.2 Hz, 1H), 4.33 (br d, *J* = 8.9 Hz, 1H), 4.15−4.07 (m, 4H), 3.91 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.75 (s, 3H), 3.07 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 156.5 (s), 150.6 (s), 137.2 (s), 136.1 (s), 131.3 (d), 130.1 (d), 129.1 (d), 128.5 (d), 118.0 (d, 2C), 114.8 (d, 2C), 93.9 (d), 79.5 (d), 75.2 (d), 74.2 (t), 70.4 (d), 70.1 (t), 68.7 (t), 63.4 (d), 55.8 (q); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{24}O_7Na$ 411.1420, found 411.1432.

Data for β-**15**: mp 88−90 °C; $[\alpha]_D^{24}$ −61.1 (*c* 1.04, $CHCl_3$); IR 3407, 2907, 2874, 1509, 1217, 1111, 1090, 1051, 1036, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24−7.12 (m, 4H), 6.96 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 6.82 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 5.44 (d, *J* = 10.3 Hz, 1H), 5.16 (d, *J* = 5.3 Hz, 1H), 5.15 (d, *J* = 10.3 Hz, 1H), 4.69 (m, 1H), 4.54 (d, *J* = 10.3 Hz, 1H), 4.42 (d, *J* = 10.3 Hz, 1H), 4.13 (br dd, *J* = 3.9, 2.5 Hz, 1H), 4.07 (br dd, *J* = 8.5, 5.3 Hz, 1H), 3.99 (dd, *J* = 13.3, 3.9 Hz, 1H), 3.94 (dd, *J* = 13.3, 2.5 Hz, 1H), 3.86 (br d, *J* = 3.4 Hz, 1H), 3.77 (s, 3H), 2.84 (d, *J* = 8.5 Hz, 1H), 2.45 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.0 (s), 151.2 (s), 137.0 (s), 136.2 (s), 129.6 (d), 128.9 (d), 128.0 (d), 127.8 (d), 117.8 (d, 2C), 114.5 (d, 2C), 102.3 (d), 83.1 (d), 78.5 (d), 74.9 (t), 74.5 (d), 71.2 (t), 70.3 (t), 64.6 (d), 55.7 (q); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{24}O_7Na$ 411.1420, found 411.1433.

4-Methoxyphenyl 2,4-Di-*O*-benzyl-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (16). To a stirred solution of diol **15** (172 mg, 440 μmol) and NaH (60% in mineral oil, 120 mg; 72 mg of NaH, 3.0 mmol) in DMF (8.0 mL) was added BnBr (301 mg, 1.76 mmol) at rt. After the mixture was stirred for 5 h at 80−85 °C, the reaction was quenched by addition of saturated NH_4Cl(aq) (2.0 mL). After dilution of the mixture with H_2O (40 mL), the aqueous mixture was extracted with EtOAc. The combined organic layers were successively washed with H_2O and brine. After the general drying procedure, the mixture was purified by CC (10 g of SiO_2, *n*-hexane/EtOAc 19/1 to 4/1) to afford **16** (194 mg, 77% yield) as a yellow syrup. Some fractions contained the pure β-anomer (β-**16**), which allowed for its characterization. Mp 68−70 °C; $[\alpha]_D^{24}$ +11.0 (*c* 1.29, $CHCl_3$); IR 3063, 3029, 2903, 2872, 1455, 1215, 1113, 1044, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.26 (m, 10H), 7.21−7.10 (m, 4H), 6.94 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 6.81 (d with small long-range couplings, *J* = 9.2 Hz, 2H), 5.57 (d, *J* = 9.9 Hz, 1H), 5.27 (d, *J* = 6.6 Hz, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 4.81 (d, *J* = 12.1 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.45 (br s, 1H), 4.35 (d, *J* = 10.1 Hz, 1H), 4.30 (d, *J* = 9.9 Hz, 1H), 4.22 (br s, 1H), 4.01 (br d, *J* = 2.8 Hz, 1H), 3.90 (br d, *J* = 6.6 Hz, 1H), 3.83 (br d, *J* = 13.5 Hz, 1H), 3.79 (br d, *J* = 13.5 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1 (s), 151.4 (s), 138.6 (s), 138.0 (s), 137.1 (s), 136.5 (s), 129.6 (d), 128.6 (d), 128.6 (d, 2C), 128.4 (d, 2C), 128.0 (d), 127.9 (d, 2C), 127.9 (d, 2C), 127.8 (d, 2C), 127.7 (d), 118.0 (d, 2C), 114.6 (d, 2C), 101.2 (d), 83.1 (d), 82.3 (d), 75.4 (d), 75.0 (t), 72.9 (t), 72.0 (t), 70.6 (t), 70.5 (t), 70.3 (d), 55.8 (q); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{36}O_7Na$ 591.2359, found 591.2345.

2,4-Di-*O*-benzyl-3,6-*O*-(*o*-xylylene)-D-glucopyranose (11). A mixture of 4-methoxyphenyl glucoside **16** (194 mg, 341 μmol) and $Ce(SO_4)_2$ (560 mg, 1.69 mmol) in CH_3CN (5.0 mL) and H_2O (2.5 mL) was stirred for 19 h at rt. The reaction was quenched by the addition of 10% $Na_2S_2O_3$(aq) (15 mL). The mixture was extracted with EtOAc. The combined organic layers were successively washed with H_2O and brine. After the general drying procedure, the mixture was purified by CC (10 g of SiO_2, *n*-hexane/EtOAc 19/1 to 3/2) to afford **11** (129 mg, 82% yield) and **16** (23.7 mg, 12% yield) as a white solid and a yellow syrup, respectively.

Data for **11** (major isomer): mp 117−119 °C; $[\alpha]_D^{25}$ +97.5 (*c* 0.64, $CHCl_3$); IR 3409, 3029, 2903, 2870, 1455, 1115, 1028, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.28 (m, 10H), 7.22−7.12 (m, 4H), 5.52 (d, *J* = 9.8 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 5.04 (d, *J* = 4.6 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.40 (br dd, *J* = 3.0, 1.8 Hz, 1H), 4.34 (d, *J* = 10.1 Hz, 1H), 4.32 (d, *J* = 9.8 Hz, 1H), 4.18 (br d, *J* = 3.4 Hz, 1H), 3.96 (d, *J* = 3.0 Hz, 1H), 3.83 (br d, *J* = 13.6 Hz, 1H), 3.77 (dd, *J* = 13.6, 3.4 Hz, 1H), 3.59 (dd, *J* = 4.6, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.6 (s), 138.0 (s), 137.0 (s), 136.5 (s), 129.6 (d), 128.7 (d), 128.5 (d, 3C), 128.4 (d, 2C), 127.8 (d, 6C), 127.6 (d), 96.2 (d), 84.2 (d), 83.0 (d), 75.3 (d), 74.7 (t), 72.5 (t), 71.8 (t), 70.6 (t), 70.4 (t), 70.3 (d); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{30}O_6Na$ 485.1940, found 485.1941.

2,4-Di-*O*-benzyl-3,6-*O*-(*o*-xylylene)-D-glucopyranosyl fluoride (1). A mixture of **11** (473 mg, 1.02 mmol) and *N*,*N*-diethylaminosulfur trifluoride (DAST) (322 mg, 2.00 mmol) in THF (20 mL) was stirred for 40 min at rt. MeOH (5 mL) was then added, and the mixture was concentrated. The residue was dissolved in EtOAc. The solution was successively washed with H_2O, saturated $NaHCO_3$(aq), and brine. After the general drying procedure, the mixture was purified by CC (15 g of SiO_2, *n*-hexane/EtOAc 97/3 to 4/1) to afford **1** (457 mg, 96% yield) as a mixture of anomers (α/β = 1/6). The ^1H and ^{13}C NMR spectral data were identical to the reported data.[33]

3,6-*O*-(*o*-Xylylene)-1,2,5-tri-*O*-acetyl-D-glucofuranose (17). A mixture of orthoacetylglucopyranose **14** (100 mg, 327 μmol) in THF (0.65 mL) and 1.0 M hydrochloric acid (1.3 mL) was stirred for 15 min at rt. After the addition of saturated $NaHCO_3$(aq) (3 mL), the aqueous mixture was extracted with EtOAc. The general drying procedure provided a crude product that was used for the next reaction without further purification. A mixture of the crude product, pyridine (92 μL, 1.1 mmol), Ac_2O (0.22 mL 2.3 mmol), and DMAP (7.99 mg, 6.54 μmol) was stirred for 40 min at rt. After the addition of 1.0 M hydrochloric acid (5 mL), the aqueous mixture was extracted with EtOAc. The combined organic layer was successively washed with 1 M hydrochloric acid, water, and brine. After the general drying procedure, the mixture was purified by CC (2 g of SiO_2, *n*-hexane/EtOAc 8/1 to 6/1) to give **17** (100 mg, 74% yield, α/β = 1/1) as an amorphous solid. A part of the anomeric mixture was separated by HPLC (column, YMC-Pack R&D SIL, R-SIL-5, 250 mm × 20 mm; eluent, *n*-hexane/EtOAc = 4/1; flow rate, 1.8 mL/min; detection, UV 254 nm; retention times, 35 min for α-**17** and 28 min for β-**17**).

dx.doi.org/10.1021/jo401395h | J. Org. Chem. 2013, 78, 9482−9487

Data for α-**17**: mp 38−39 °C; $[\alpha]_D^{23}$ −26.9 (*c* 0.53, $CHCl_3$); IR 2925, 2852, 1740, 1435, 1368, 1217, 1124, 1051, 1005, 960, 886, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.22 (m, 4H), 6.05 (d, *J* = 2.1 Hz, 1H), 5.42 (dd, *J* = 5.3, 2.1 Hz, 1H), 5.31 (ddd, *J* = 3.7, 3.7, 1.4 Hz, 1H), 5.07 (d, *J* = 11.0 Hz, 1H), 4.97 (d, *J* = 10.7 Hz, 1H), 4.79 (d, *J* = 10.7 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.56 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.32 (dd, *J* = 6.2, 5.3 Hz, 1H), 3.91 (d, *J* = 3.7 Hz, 2H), 2.15 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5 (s), 170.1 (s), 169.9 (s), 137.1 (s), 135.6 (s), 130.3 (d), 130.1 (d), 128.9 (d), 128.4 (d), 98.9 (d), 81.4 (d), 80.8 (d), 80.1 (d), 75.2 (d), 73.9 (t), 73.6 (t), 69.9 (t), 21.6 (q), 21.1 (q), 21.0 (q); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{24}O_9Na$ 431.1318, found, 431.1331.

Data for β-**17**: mp 36−37 °C; $[\alpha]_D^{25}$ +54.5 (*c* 0.60, $CHCl_3$); IR 2925, 1740, 1435, 1371, 1216, 1137, 1112, 1075, 1043, 1007, 930, 892, 781, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.19 (m, 4H), 6.35 (d, *J* = 4.6 Hz, 1H), 5.30−5.24 (m, 2H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.88 (d, *J* = 12.1 Hz, 1H), 4.77 (d, *J* = 10.1 Hz, 1H), 4.69−4.64 (m, 2H), 4.56 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.87 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.75 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 170.1 (s), 169.6 (s), 136.9 (s), 135.6 (s), 130.9 (d), 130.0 (d), 129.0 (d), 128.6 (d), 92.5 (d), 80.2 (d), 76.3 (d), 75.4 (d), 74.0 (t), 73.4 (d), 73.0 (t), 67.9 (t), 21.3 (q), 21.1 (q), 20.7 (q); HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{24}O_9Na$ 431.1318, found, 431.1334.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hidetosh@kwansei.ac.jp.

Present Address

[†]N.A.: Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

JSPS A-STEP (Grant AS231Z04872D) and KAKENHI (Grant 22550047) partially supported this work.

■ REFERENCES

(1) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209.
(2) Christina, A. E.; Muns, J. A.; Olivier, J. Q. A.; Visser, L.; Hagen, B.; van den Bos, L. J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Eur. J. Org. Chem.* **2012**, 5729−5737.
(3) Satoh, H.; Manabe, S. *Chem. Soc. Rev.* **2013**, *42*, 4297−4309.
(4) Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765−774.
(5) Nukada, T.; Bérces, A.; Wang, L.; Zgierski, M. Z.; Whitfield, D. M. *Carbohydr. Res.* **2005**, *340*, 841−852.
(6) Ionescu, A. R.; Whitfield, D. M.; Zgierski, M. Z. *Carbohydr. Res.* **2007**, *342*, 2793−2800.
(7) Kumar, R.; Whitfield, D. M. *J. Org. Chem.* **2012**, *77*, 3724−3739.
(8) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663−666.
(9) Ikeda, T.; Yamada, H. *Carbohydr. Res.* **2000**, *329*, 889−892.
(10) Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021−1023.
(11) Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **2001**, *123*, 11870−11882.
(12) Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 1573−1576.
(13) Furukawa, T.; Hinou, H.; Nishimura, S. *Org. Lett.* **2012**, *14*, 2102−2105.
(14) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *J. Org. Chem.* **2013**, *78*, 7234−7238.
(15) Balley, W. F.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798−1806.
(16) Mehta, G.; Ramesh, S. S. *Eur. J. Org. Chem.* **2005**, 2225−2238.
(17) Sivapriya, K.; Chandrasekaran, S. *Carbohydr. Res.* **2006**, *341*, 2204−2210.
(18) Pedersen, C. M.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222−9235.
(19) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465−2467.
(20) Yamada, H.; Nakatani, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **1999**, *40*, 5573−5576.
(21) Tius, M. A.; Bush-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181−5184.
(22) Walford, C.; Jackson, R. F. W.; Rees, N. H.; Clegg, W.; Heath, S. L. *Chem. Commun.* **1997**, 1855−1866.
(23) Broddefalk, J.; Bergquist, K.-E.; Kihlberg, J. *Tetrahedron* **1998**, *54*, 12047−12070.
(24) Ichikawa, S.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **1999**, *121*, 10270−10280.
(25) Abe, H.; Shuto, S.; Tanura, S.; Matsuda, A. *Tetrahedron Lett.* **2001**, *42*, 6159−6161.
(26) Abe, H.; Terauchi, M.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 7439−7447.
(27) Marzabadi, C. H.; Anderson, J. E.; Gonzalez-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 15163−15173.
(28) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 9207−9209.
(29) Okajima, K.; Mukae, T.; Imagawa, H.; Kawamura, Y.; Nishizawa, M.; Yamada, H. *Tetrahedron* **2005**, *61*, 3497−3506.
(30) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328−5329.
(31) Ohtani, T.; Sakai, S.; Takada, A.; Takahashi, D.; Toshima, K. *Org. Lett.* **2011**, *13*, 6126−6129.
(32) Yamada, H. *Trends Glycosci. Glycotechnol.* **2011**, *23*, 122−133.
(33) Okada, Y.; Asakura, N.; Bando, M.; Ashikaga, Y.; Yamada, H. *J. Am. Chem. Soc.* **2012**, *134*, 6940−6943.
(34) Abbreviations used in addition to those in "The Journal of Organic Chemistry Guidelines for Authors (Updated July 2012).": BTF, benzotrifluoride; CC, column chromatography; DAST, *N*,*N*-diethylaminosulfur trifluoride; M-sieve, molecular sieves.
(35) Ikeda, Y.; Nagao, K.; Tanigakiuchi, K.; Tokumaru, G.; Tsuchiya, H.; Yamada, H. *Tetrahedron Lett.* **2004**, *45*, 487−489.
(36) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199−2204.
(37) Bochkov, A. F.; Voznyi, Y. V.; Kalinevich, V. M.; Shashkov, A. S.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 415−420.
(38) Bochkov, A. F.; Voznyi, Y. V.; Chernetskii, V. N.; Dashunin, V. M.; Rodionov, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 420−423.
(39) Moradei, O. M.; du Mortier, C.; Cirelli, A. F. *Arkivoc* **2005**, *2005* (xii), 189−194.
(40) Bochkov, A. F.; Voznyi, Y. V.; Chernetskii, V. N.; Dashunin, V. M.; Rodionov, A. V. *Russ. Chem. Bull.* **1975**, *24*, 348−351.
(41) Bochkov, A. F.; Voznyi, Y. V.; Kalinevich, V. M.; Shashkov, A. S.; Kochetkov, N. K. *Russ. Chem. Bull.* **1975**, *24*, 343−347.
(42) Asakura, N.; Hirokane, T.; Hoshida, H.; Yamada, H. *Tetrahedron Lett.* **2011**, *52*, 534−537.
(43) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291−6292.
(44) Mori, M.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1989**, *30*, 1273−1276.
(45) Wuts, P. G. M.; Greene, T. W. In *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, NJ, 2007; p 100.
(46) Hori, M.; Nakatsubo, F. *Carbohydr. Res.* **2001**, *332*, 405−414.

(47) Each model was optimized in the "conformer distribution" mode using MMFF calculations as implemented in Spartan '08 for Mac software.
(48) Castro, B. R. *Org. React.* **1983**, *29*, 82.
(49) Grynkiewicz, G. *Pol. J. Chem.* **1979**, *53*, 2501−2515.
(50) Nishizawa, M.; Shimomoto, W.; Momii, F.; Yamada, H. *Tetrahedron Lett.* **1992**, *33*, 1907−1908.
(51) Mizuno, M.; Kobayashi, K.; Nakajima, H.; Koya, M.; Inazu, T. *Synth. Commun.* **2002**, *32*, 1665−1670.

dx.doi.org/10.1021/jo401395h | *J. Org. Chem.* 2013, 78, 9482−9487