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Useful Intermediates, 3-*C*-Dichloromethyl Furanose Derivatives, for the Synthesis of Branched-Chain Functionalized Sugars

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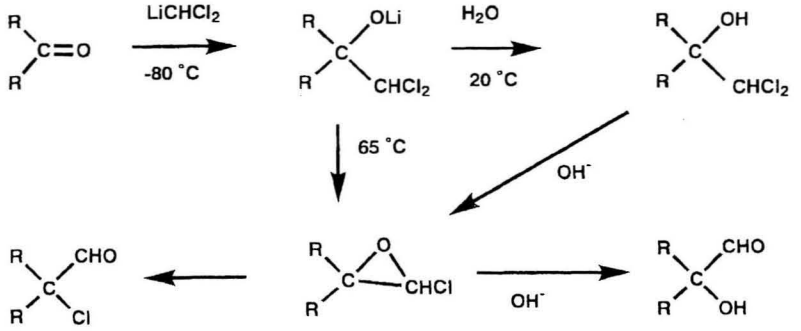
A few novel branched-chain functionalized sugars, which have important functions such as hydroxy, hydro, chloro, or azido at the quaternary carbon, were stereoselectively prepared in good yield via the same intermediary 3-*C*-,3-*O*-chloromethylene- or 3-*C*-dichloromethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-furanose derivatives.

Numerous new branched-chain sugars as the glycosidic component of antibiotics during the past two decades have stimulated extensive research on the chemistry and biochemistry of sugars. Most of the branched-chain sugars found in nature have a polar substituent at the branching carbon-atom (Type A); tertiary alcohols are the most common, and in several instances an amino or nitro group is attached to the branching carbon atom. In a few cases naturally occurring branched-chain sugars have no substituent at the branching carbon atom (Type B). In general, various branched-chain sugars have been synthesized by applying a Grignard reaction, Reformatsky reaction, Wittig reaction as well as organolithium, nitromethane, diazomethane, and cyanohydrin syntheses to suitable glycosidulose.[1] In 1988, Thang et al.[2] reported an elegant approach for synthesizing branched-chain sugars using chloromethyl *p*-tolyl sulfone. In 1969, Köbrich et al.[3] reported that the reaction of a 2,2-dichloroethanol derivative with KOH gave an 2-hydroxy aldehyde derivative in good yield via the corresponding spiro chlorooxirane derivative. In that report, ring opening with the hydroxide anion was described as seeming to occur with complete regiospecificity at the β-carbon with respect to the chloro group (Scheme 1). Unfortunately, they did not discuss the stereochemical course of this reaction. The authors were inspired by Köbrich's work in constructing any type of naturally occurring functionalized branched-chain sugars, and tried to study the stereochemical course of this reaction.

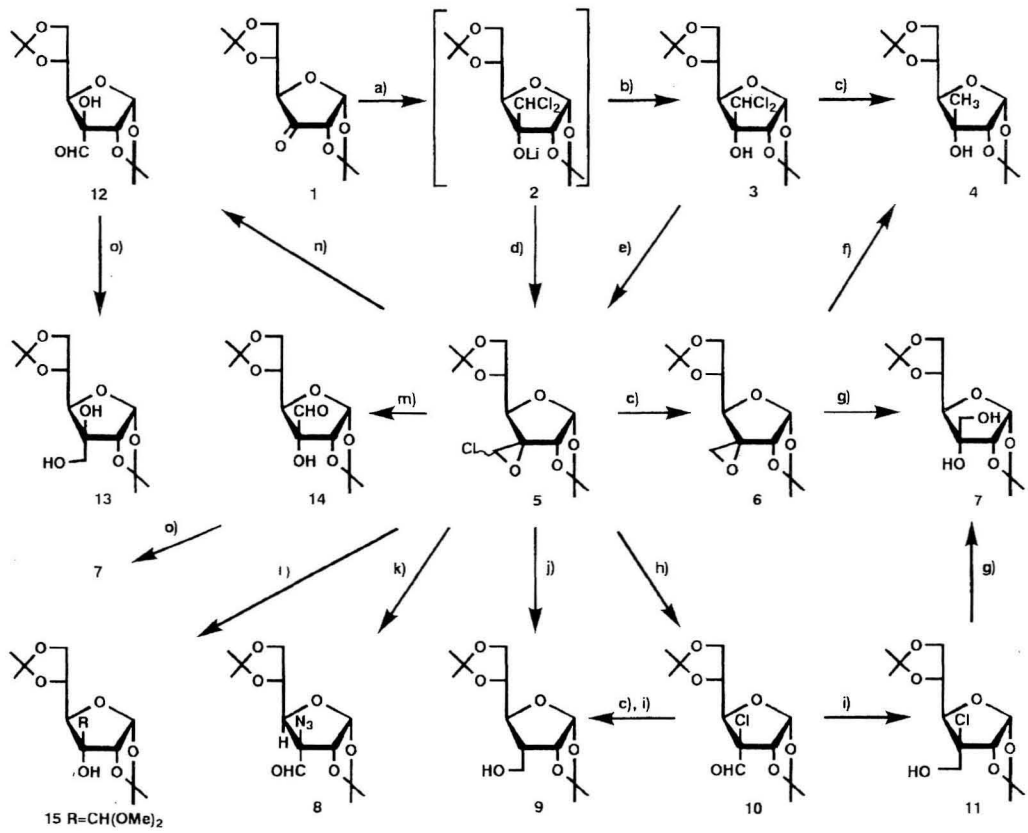
In a previous paper,[4] the authors communicated on a facile and effective simple reagent, dichloromethyllithium, for the synthesis of various functionalized branched-chain sugars, which were easily converted into almost all types of naturally occurring types. This paper describes the details concerning the communication, additional new data, as well as a suggestion concerning the stereochemical course of Köbrich's work using 3-*C*-dichloromethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**) (Scheme 2).

Results and Discussion

The reaction of 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)[5] with dichloromethyllithium (2.0 mol amt.) in oxolane at −78 °C, subsequently quenched with a saturated ammonium chloride solution, gave the corresponding dichloromethyl derivative (**3**) in 88% yield via **2**. On the other hand, the reaction mixture was worked up after heating at 65 °C to give 3,1′-anhydro-3-*C*-(1′-chloro-1′-hydroxymethyl)-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) in 94% yield via **2**. Compound **5** was also derived from **3** by a treatment with 1,8-diazabicyclo[5.4.0]undec-

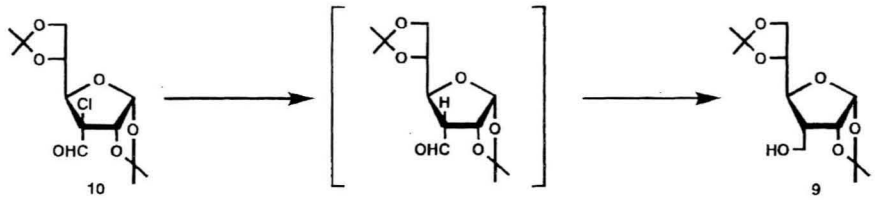


Scheme 1.

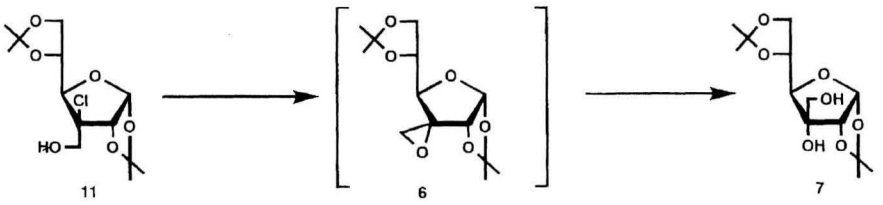


Scheme 2. a) LDA, CH_2Cl_2, oxolane, −78 °C b) H_2O, r.t. c) *n*-Bu_3SnH, AIBN, toluene, reflux. d) 65 °C. e) DBU, DMSO, r.t. f) $LiAlH_4$, oxolane, r.t. g) NaOH aq, 1,4-dioxane, reflux. h) NaOAc, 15-crown-5, HMPT, 70 °C. i) $NaBH_4$, aq MeOH, r.t. j) $NaBH_4$, DMSO, 80 °C. k) NaN_3, 15-crown-5, HMPT, 70 °C. l) NaOMe, HMPT, 70 °C. m) *n*-Bu_4NOH aq, DMSO, r.t. n) CsOAc, 18-crown-6, toluene, reflux. o) $NaBH_4$, MeOH, r.t.

7-ene (DBU) in dimethyl sulfoxide (DMSO) in 82% yield. The configuration of **3** was confirmed by a derivation into a known 3-*C*-methyl derivative, 1,2 : 5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**4**)[6] in 87% yield by radical reduction [tributyltin hydride, 2,2′-azobis(isobutyronitrile) (AIBN)/toluene]. The structure of **5** was also confirmed by derivation into 3,1′-anhydro-3-*C*-(1′-hydroxymethyl)-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**6**)[7] with tributyltin hydride and AIBN in 81% yield. Compound **6** is difficult to synthesis by the previously used common methods (a reaction of **1** with diazomethane or oxidation of the 3-*C*-methylene derivative of **1** with *m*-chloroperbenzoic acid) owing to the ring expansion and/or reverse stereoselectivity. An alkali hydrolysis of **6** gave the corresponding hydroxymethyl derivative, 3-*C*-hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**7**),[8] in quantitative yield. Compound **6** was treated with lithium aluminum hydride ($LiAlH_4$) to also give the 3-*C*-methyl derivative **4** in 83% yield. Kirrmann et al.[9] reported that chlorooxiranes can be obtained from the 2,2-dichloroethanol derivatives by a treatment with alkali under carefully chosen conditions (Scheme 1). The reaction of **3** with nucleophiles seems to easily progress via **5** under the reaction conditions, because both reactions **3** and **5** give the same products and almost the same yield. It is therefore possible to use **3** instead of **5** in reactions with nucleophiles. A treatment of **3** or **5** with NaN_3 (10 mol amt.) and 15-crown-5 in hexamethylphosphoric triamide (HMPT) at 70 °C gave 3-azido-3-deoxy-3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**) in 81% (from **3**) and 85% (from **5**) yield, the configuration of which was supported by NMR (NOE; 10%, between formyl proton and H-4 proton). Compound **8** is easily derived into the 3-amino-3-deoxy-3-*C*-methyl branched-chain sugar, which has usually been synthesized by the long steps from **1** (via cyanohydrin and spiro epimino derivative). The 3-deoxy derivative, 3-deoxy-3-*C*-hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**9**) was derived by reducing **3** with $NaBH_4$ in DMSO at 80 °C in 65% yield. The structure of **9** was clarified by acetylation (acetyl derivative of **9**: ^{1}H NMR $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 10.0 Hz). Compound **9** has usually been synthesized by hydroboration of the corresponding 3-*C*-methylene derivative of **1**. The reaction of **3** with NaOAc (10 mol amt.) and 15-crown-5 in HMPT at 70 °C gave an unexpected chlorine-migrated product, 3-chloro-3-deoxy-3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**10**) instead of a tertiary acetoxy derivative, in 83% yield. Kirrmann et al. also reported[9] on a rearrangement of the alkoxides into 2-chloro aldehydes, which proceeds via the unstable chlorooxiranes



Scheme 3.



Scheme 4.

(Scheme 1). The structure of **10** was confirmed as follows. A radical reduction of **10** with tributyltin hydride in toluene at 110 °C gave 3-deoxy-3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose in the form of a hydrate, which was reduced (without purification) with $NaBH_4$ in MeOH at room temperature to give the corresponding 3-deoxy derivative **9** in 82% yield (2 steps) (Scheme 3). On the other hand, a hydride reduction of **10** with $NaBH_4$ in MeOH–H_2O (2 : 1) at room temperature gave 3-chloro-3-deoxy-3-*C*-hydroxymethyl-1, 2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**11**) in 97% yield. The structure of **11** was clarified by a derivation into its acetyl derivative. Compound **11** was then treated with 0.1 M NaOH (1 M = 1 mol dm^{-3}) in 1,4-dioxane–H_2O (1 : 1) under reflux conditions to give **7** via **6** in 70% yield (Scheme 4). It seemed that the reactivity of NaOAc was not sufficient to compare it with that of the other nucleophiles. Therefore, the authors tried to use more effective CsOAc[10] instead of NaOAc, as follows. Compound **3** was treated with CsOAc (10 mol amt.) and 18-crown-6 (7.0 mol amt.) in toluene under reflux conditions to give the corresponding unstable 2-hydroxy aldehyde, 3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**), in 36% yield. Compound **12** easily formed its hydrate via the corresponding 3-acetoxy derivative (accompanied by a cleavage of the acetyl group), but was too unstable to purify. It is noteworthy that this type of acetyl group seems to be easily cleaved by a weak base.[11] The configuration of **12** was confirmed by derivation into 3-epimer of **7**, 3-*C*-hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**).[8] On the other hand, the reaction of **3** with *n*-Bu_4NOH (40% in water, 5.2 mol amt.) was carried out in DMSO at room temperature for a short time (30 s), and the epimeric 2-hydroxy aldehyde, 3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**14**), was obtained in 61% yield. Since compound **14** was also too unstable to purify, its structure was confirmed by derivation into **7** by a treatment with $NaBH_4$ in MeOH, of which the physical data were identical with that obtained from **6**. Although compound **14** has usually been synthesized by the reaction of **1** with nucleophiles, such as vinyl or bis(alkylthio)methyl derivatives, its epimer **12** has been difficult to synthesis, due to its reverse stereoselectivities. In contrast to the above reaction using *n*-Bu_4NOH, the reaction of **3** with NaOMe (10 mol amt.) in HMPT at 70 °C gave 3-*C*-dimethoxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (**15**) in 93% yield. The branched-chain sugars (**8**, **9**, **10**, **12**, and **14**) have useful functions, such as azido, hydro, chloro, or hydroxy, at the quaternary carbon, and are converted to branched-chain sugars of type A and B, respectively (Scheme 2). Among the above-mentioned functional groups, the azido group can be easily converted into an amino or nitro group, and the formyl group can be converted into a hydroxymethyl, methyl, 1-hydroxyethyl, acetyl, 2-hydroxyacetyl, 1,2-dihydroxyethyl, high alkyl, or carboxyl group, all of which are found in nature.

In conclusion, the ring opening of spiro chlorooxirane with a nucleophile, such as N_3^-, H^-, Cl^- (NaOAc, 1,2-migration of chlorine), or AcO^- (CsOAc), occurs with complete regiospecificity and S_N2 fashion at the β-carbon with respect to the chloro group. However, in the case of OH^- or OMe^-, the reaction occurs at the α-carbon. The different regiospecificity may be attributed to the reactivities of nucleophiles to this type of epoxide. That is, nucleophiles such as OR^-, OH^-, and SR^-, having a strong nucleophilicity (nearly equal to strong base), react at the α-carbon, which has a lower electron density than that of the β-carbon. In the case of weak nucleophiles (their conjugate acids are rather stronger), the epoxy oxygen first coordinates to acid; the reaction then proceeds via the favorable β-carbenium intermediate (stabilized by two alkyl groups) rather than the α-carbenium intermediate (destabilized by chlorine). Of course, even the β-carbenium ion is not sufficiently stable to react in S_N1 fashion. As mentioned above, these results may provide an answer regarding the stereochemical course of Köbrich's work[3] (OH^- reacts at α-carbon or β-carbon with respect to the chloro group), which did not consider the configurations of the products. Thus, the method proposed herein may promise wide applications to the preparation of functionalized branched-chain sugars whose branching car-

bon is on the sterically hindered side. Especially, two modes of reactions of the 3-*C*-dichloromethyl furanose derivative, or the corresponding spiro chlorooxirane, either with CsOAc or with *n*-Bu_4NOH may provide a convenient method for the selective preparation of each epimeric 2-hydroxy aldehyde derivative.

Experimental

All melting points were uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 40 °C. The optical rotations were measured in a 0.5 dm tube with a JASCO DIP-140 polarimeter in chloroform. ^{1}H NMR spectra were recorded in chloroform-*d* with a JEOL EX-90, FX-200, EX-270, or A-500 spectrometer. IR spectra were recorded with a Hitachi 270-30 spectrometer. Elemental analyses were performed on a Perkin–Elmer 240 C or 2400 II elemental analyzer. The chemical shifts, coupling constants, and IR frequencies were recorded in δ, Hz, and cm^{-1} units, respectively. Column chromatography was performed on silica gel (Silica gel 60, 70—230 mesh, Merck). Thin-layer chromatography (TLC) on silica gel (Silica gel $60F_{254}$, Merck) was used to monitor the reactions and to certify the purity of the reaction products.

1,2 : 5,6-Di-*O*-isopropylidene-3-*C*-dichloromethyl-α-D-allofuranose (3). To a stirring solution of diisopropylamine (770 mg, 7.61 mmol) in oxolane (100 cm^3) was added butyllithium (1.64 M solution in hexane, 4.8 cm^3, 7.87 mmol) at −78 °C under argon, and stirred for 30 min; then, abs dichloromethane (3.24 g, 38.1 mmol) in oxolane (5.0 cm^3) was added dropwise for 3 min and stirred for 3 min. To the above reaction mixture, 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)[5] (982 mg, 3.80 mmol) in oxolane (10.0 cm^3) was added dropwise for 5 min and stirred until the disappearance of **1** on TLC (hexane/ethyl acetate = 2/1). The reaction mixture was poured into a saturated ammonium chloride solution, extracted with chloroform (100 $cm^3 \times 1$, 10 $cm^3 \times 5$), washed with brine (20 $cm^3 \times 2$), dried over anhydrous magnesium sulfate, and evaporated to give a residue. The residue was purified on a column of silica gel (hexane/ethyl acetate = 3/1—2/1) to give **3** (1.15 g, 88% yield), which was recrystallized from ether-hexane. **3**: Mp 134—135 °C (recrystallized from Et_2O–hexane); $[\alpha]_D^{24}$ +27.7° (*c* 1.0, $CHCl_3$); IR 3476 cm^{-1} (OH); ^{1}H NMR (FX-200) δ = 6.23 (1H, s, H-3′), 5.93 (1H, d, $J_{1,2}$ = 4.2 Hz, H-1), 4.80 (1H, d, H-2), 4.41 (1H, ddd, $J_{4,5}$ = 9.8 Hz, $J_{5,6}$ = 5.9 Hz, $J_{5,6'}$ = 4.2 Hz, H-5), 4.14 (1H, dd, $J_{6,6'}$ = 8.8 Hz, H-6), 4.01 (1H, d, H-4), 3.95 (1H, dd, H-6′), 3.51 (1H, s, OH), 1.61, 1.47, 1.44, and 1.36 (3H×4, each s, isop-Me). Found: C, 45.26; H, 5.64%. Calcd for $C_{13}H_{20}Cl_2O_6$: C, 45.49; H, 5.87%.

1,2 : 5,6-Di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (4). A reaction mixture of **3** (33 mg, 0.096 mmol), tributyltin hydride (280 mg, 0.96 mmol, 10 mol amt.), and AIBN (1.6 mg, 0.0098 mmol) in dry toluene (3.0 cm^3) was refluxed under argon until the disappearance of the **3** on TLC. To the reaction mixture, saturated potassium fluoride solution (5.0 cm^3) was added and stirred for 30 min to produce a precipitate. After the precipitate was filtered off, the separated organic layer was dried over anhydrous magnesium sulfate and evaporated to give a known compound **4**, which was purified on a column of silica gel (hexane/ethyl acetate = 3/1). The yield was 87% (23 mg). The physical constants of **4** were identical to that reported.[6]

Synthesis of 4 from 6 (Reduction with $LiAlH_4$). To a solution of **6** (12 mg, 0.044 mmol) in oxolane (5.0 cm^3) was added $LiAlH_4$ (9.0 mg, 0.24 mmol); the mixture was then stirred at room temperature for 1 h. The excess hydride was carefully decomposed with water, and then poured into a saturated aq ammonium chloride solution. The water layer was extracted with chloroform. The combined extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **4**, which was purified as mentioned above. The yield was 83% (10 mg).

3,1′-Anhydro-3-*C*-(1′-chloro-1′-hydroxymethyl)-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (5). In a similar manner as that mentioned in the synthesis of compound **3**, the alkoxide intermediate (**2**) was prepared; the reaction mixture was kept at 65 °C for 15 min, then filtered through a charcoal bed, and evaporated to give **5**, which was purified on a column of silica gel (hexane/ethyl acetate = 4/1). The yield was 94% (291 mg). **5**: Syrup; $[\alpha]_D^{24}$ +49.6° (*c* 0.8, $CHCl_3$); ^{1}H NMR (EX-90) δ = 5.93 (1H, d, $J_{1,2}$ = 4.2 Hz, H-1), 5.74 (1H, s, H-3′), 4.77 (1H, d, H-2), 4.19—3.85 (4H, m, H-4, H-5, H-6, and H-6′), 1.61, 1.43, 1.39, and 1.32 (3H×4, each s, isop-Me). Found: C, 51.24; H, 6.13%. Calcd for $C_{13}H_{19}ClO_6$: C, 50.90; H, 6.24%.

Compound **5** was also derived from **3** by a treatment with DBU in DMSO in 82% yield, as follows. To a stirring solution of **3** (50 mg, 0.15 mmol) in DMSO (1.0 cm^3), DBU (27 mg, 0.18 mmol, 1.2 mol amt.) was added at room temperature. The reaction mixture was kept for 24 h at room temperature [there was no change on TLC (hexane/ethyl acetate = 2/1)], then diluted with ethyl acetate (20 cm^3), washed with a saturated aqueous ammonium chloride solution (10 $cm^3 \times 1$) and with water (10 $cm^3 \times 1$), and evaporated to give a syrup. The syrup was treated on a column of silica gel (hexane/ethyl acetate = 1/2) to remove DMSO and DBU; however, the mixture of **5** and **3** was difficult to separate [only one spot on TLC (hexane/ethyl acetate = 2/1)]. The mixture of **5** and **3** was recovered almost quantitatively and ^{1}H NMR data showed that the purity of **5** was 82%. Therefore, the yield of **5** was ca. 82%.

3,1′-Anhydro-3-*C*-(1′-hydroxymethyl)-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (6). The reaction mixture of **5** (87 mg, 0.28 mmol), tributyltin hydride (825 mg, 2.83 mmol), and AIBN (23 mg, 0.14 mmol) was refluxed (for ca. 1 h) under argon until the disappearance of **5** on TLC (hexane/ethyl acetate = 1 : 1). To the reaction mixture, saturated potassium fluoride solution (5.0 cm^3) was added and stirred for 30 min to produce a precipitate. After the precipitate was filtered off, the separated organic layer was dried over anhydrous magnesium sulfate and evaporated to give **6**, which was purified on a column of silica gel (hexane/ethyl acetate = 2/1–ethyl acetate only). The yield was 81% (62 mg). The structure of **6** was confirmed by comparison of ^{1}H NMR data with that of 3-epimer.[7] **6**: Syrup; $[\alpha]_D^{25}$ +82.2° (*c* 0.8, $CHCl_3$); ^{1}H NMR (EX-270) δ = 5.87 (1H, d, $J_{1,2}$ = 4.0 Hz, H-1), 4.43 (1H, d, H-2), 4.25 (1H, d, $J_{4,5}$ = 6.9 Hz, H-4), 4.09—3.89 (3H, m, H-5, H-6, and H-6′), 3.39 (1H, d, $J_{3'a,3'b}$ = 5.2 Hz, H-3′a), 2.97 (1H, d, H-3′b), 1.63, 1.41, 1.37, and 1.32 (3H×4, each s, isop-Me). Found: C, 57.37; H, 7.10%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

3-*C*-Hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (7). The reaction mixture of **6** (12 mg, 0.044 mmol) and sodium hydroxide (18 mg, 0.45 mmol) in a mixed solvent (2 cm^3, 1, 4-dioxane–H_2O= 1/1) was refluxed (for 4 h) until the disappearance of **6** on TLC (hexane/ethyl acetate = 1/1). The reaction mixture was extracted with chloroform (25 cm^3), washed with water (5.0 $cm^3 \times 1$), dried over anhydrous magnesium sulfate, and evaporated to give pure **7** quantitatively (13 mg). **7**: Syrup; $[\alpha]_D^{25}$ +19.0° (*c* 1.2, $CHCl_3$); IR 3442 cm^{-1} (OH); ^{1}H NMR (A-500) δ = 5.78 (1H, d, $J_{1,2}$ = 4.0 Hz, H-1), 4.57 (1H, d, H-2), 4.18 (1H, ddd, $J_{4,5}$ = 7.6 Hz, $J_{5,6}$ = 6.4 Hz, $J_{5,6'}$ = 5.8 Hz, H-5), 4.09 (1H, dd, $J_{6,6'}$ = 8.5 Hz, H-6), 3.95 (1H, dd, H-6′), 3.91 (1H, dd, $J_{3'a,OH'}$ = 7.6 Hz, $J_{3'a,3'b}$ = 11.9

Hz, H-3′a), 3.86 (1H, d, H-4), 3.56 (1H, ddd, $J_{3'b,OH}$ = 0.9 Hz, $J_{3'b,OH'}$ = 8.9 Hz, H-3′b), 2.95 (1H, d, OH), 2.44 (1H, dd, OH′), 1.60, 1.47, 1.38, and 1.36 (3H×4, each s, isop-Me). Found: C, 53.83; H, 7.51%. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64%. The configuration of **7** was confirmed by comparison of ^{1}H NMR data with that of 3-epimer.[8)]

Synthesis of 7 from 11 (Hydrolysis with Aqueous NaOH). The reaction mixture of **11** (50 mg, 0.16 mmol) and sodium hydroxide (65 mg, 1.6 mmol) in a mixed solvent (16 cm^3, 1,4-dioxane/H_2O = 1/1) was refluxed (for 12 h) until the disappearance of **11** on TLC (hexane/ethyl acetate = 1/1). The reaction mixture was evaporated to ca. a half volume and extracted with chloroform (25 cm^3). The extract was washed with water (5.0 cm^3 × 1), dried over anhydrous magnesium sulfate, and evaporated to give pure **7** (33 mg). The yield was 70%.

3-Azido-3-deoxy-3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (8). The reaction mixture of **3** (100 mg, 0.29 mmol), sodium azide (190 mg, 2.92 mmol), and 15-crown-5 (40 mg) in HMPT (2.0 cm^3) was stirred at 70 °C for 3.5 h under argon until the disappearance of **3** on TLC (hexane/ethyl acetate = 2/1). The reaction mixture was diluted with toluene, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **8**, which was purified on a column of silica gel (hexane/ethyl acetate = 1/4). The yield was 81% (74 mg). In a similar way to that mentioned above, compound **8** was also obtained from **5** in 85% yield. **8**: Syrup; $[\alpha]_D^{24}$ +76.9° (*c* 1.8, $CHCl_3$); IR 2120 cm^{-1} (N_3) and 1736 cm^{-1} (C=O); ^{1}H NMR (FX-200) δ = 9.67 (1H, s, CHO), 5.94 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 4.63 (1H, d, H-2), 4.55 (1H, d, $J_{4,5}$ = 8.5 Hz, H-4), 4.23 (1H, ddd, $J_{5,6}$ = 3.7 Hz, $J_{5,6'}$ = 5.9 Hz, H-5), 4.15 (1H, dd, $J_{6,6'}$ = 8.6 Hz, H-6′), 4.04 (1H, dd, H-6), 1.61, 1.38, 1.33, and 1.31 (3H×4, each s, isop-Me). Found: C, 50.04; H, 6.31; N, 13.30%. Calcd for $C_{13}H_{19}N_3O_6$: C, 49.83; H, 6.11; N, 13.41%.

3-Deoxy-3-*C*-hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (9). The reaction mixture of **3** (50 mg, 0.15 mmol) and $NaBH_4$ (56 mg, 1.5 mmol) in DMSO (0.5 cm^3) was stirred at 80 °C until the disappearance of **3** on TLC (for 18 h). The reaction mixture was poured into brine, extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **9**, which was purified on a column of silica gel (hexane/ethyl acetate = 5/1). The yield was 65% (27 mg). **9**: Syrup; $[\alpha]_D^{24}$ +32.7° (*c* 2.0, $CHCl_3$); IR 3490 cm^{-1} (OH); ^{1}H NMR (FX-200) δ = 5.74 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.75 (1H, dd, $J_{2,3}$ = 4.6 Hz, H-2), 4.21—3.80 (6H, m, H-3′a, H-3′b, H-4, H-5, H-6, and H-6′), 3.28 (1H, m, OH), 2.12 (1H, m, H-3), 1.52, 1.45, 1.37, and 1.31 (3H×4, each s, isop-Me). Found: C, 57.13; H, 8.28%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%.

Synthesis of 9 from 10 (Reduction with Tributyltin Hydride and $NaBH_4$). The reaction mixture of **10** (68 mg, 0.22 mmol), tributyltin hydride (323 mg, 1.11 mmol, 5.0 mol amt.), and AIBN (18 mg, 0.11 mmol, 0.5 mol amt.) in toluene (5.0 cm^3) was refluxed (for ca. 30 min) under argon until the disappearance of **10** on TLC (hexane/ethyl acetate = 2/1). After the reaction mixture was separated on a preparative TLC (hexane/ethyl acetate = 2/1) to give the corresponding dechlorinated compound, the product was immediately reduced with $NaBH_4$ (56 mg, 1.5 mmol) at room temperature in methanol (5.0 cm^3). The reaction mixture was evaporated, extracted with ethyl acetate, washed with water, and dried over anhydrous magnesium sulfate; the organic layer was then evaporated to give **9**, which was purified on a column of silica gel (hexane/ethyl acetate = 5/1). The yield was 82% (2 steps, 50 mg). The physical constants were identical to those mentioned above.

Acetyl Derivative of 9. The reaction mixture of **9** (26 mg, 0.095 mmol) and acetic anhydride (1.0 cm^3) in pyridine (1.0 cm^3) was stirred at room temperature until the disappearance of **9** on TLC. To the reaction mixture, ethanol and toluene were added and coevaporated to give the corresponding acetyl derivative in quantitative yield (30 mg). Syrup; $[\alpha]_D^{24}$ +74.3° (*c* 0.9, $CHCl_3$); IR 1746 cm^{-1} (C=O); ^{1}H NMR (FX-200) δ = 5.80 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.72 (1H, dd, $J_{2,3}$ = 4.6 Hz, H-2), 4.50 (1H, dd, $J_{3,3'a}$ = 4.9 Hz, $J_{3'a,3'b}$ = 11.0 Hz, H-3′a), 4.21 (1H, dd, $J_{3,3'b}$ = 11.0 Hz, H-3′b), 4.18—3.82 (3H, m, H-5, H-6, and H-6′), 3.78 (1H, dd, $J_{3,4}$ = 10.0 Hz, H-4), 2.27 (1H, dddd, H-3), 2.08 (3H, s, OAc), 1.52, 1.41, 1.34, and 1.34 (3H×4, each s, isop-Me). Found: C, 57.33; H, 7.64%. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65%.

3-Chloro-3-deoxy-3-*C*-formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (10). The reaction mixture of **3** (100 mg, 0.29 mmol), NaOAc (239 mg, 2.91 mmol), and 15-crown-5 (40 mg) in HMPT (2.0 cm^3) was stirred at 70 °C under argon for 24 h until the disappearance of **3**. The reaction mixture was directly separated on a column of silica gel (hexane/ethyl acetate = 1/3) to give **10**, which easily formed its hydrate and was too unstable to purify. The yield was 83% (74 mg). Therefore, only IR and ^{1}H NMR data were measured, as described below. **10**: Syrup; IR 1740 cm^{-1} (C=O); ^{1}H NMR (FX-200) δ = 9.60 (1H, s, CHO), 5.99 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 4.80 (1H, d, H-2), 4.67 (1H, d, $J_{4,5}$ = 8.1 Hz, H-4), 4.30 (1H, ddd, $J_{5,6}$ = 5.6 Hz, $J_{5,6'}$ = 4.4 Hz, H-5), 4.15 (1H, dd, $J_{6,6'}$ = 9.0 Hz, H-6), 4.09 (1H, dd, H-6′), 1.59, 1.38, 1.33, and 1.31 (3H×4, each s, isop-Me). A further confirmation of the structure of **10** was achieved by derivation into the corresponding hydroxymethyl derivative (**11**), as follows.

3-Chloro-3-deoxy-3-*C*-hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (11). To a solution of **10** (50 mg, 0.16 mmol) in methanol (2.0 cm^3) was added $NaBH_4$ (61 mg, 1.6 mmol) in water (1.0 cm^3) and stirred at room temperature until the disappearance of **10** on TLC. The reaction mixture was poured into brine, extracted with chloroform, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **11**, which was purified on a column of silica gel (hexane/ethyl acetate = 1/1). The yield was 97% (49 mg). **11**: Syrup; $[\alpha]_D^{25}$ +22.4° (*c* 1.1, $CHCl_3$); IR 3472 cm^{-1} (OH); ^{1}H NMR (FX-200) δ = 5.89 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.74 (1H, d, H-2), 4.46—3.96 (6H, m, H-3′a, H-3′b, H-4, H-5, H-6, and H-6′), 1.54, 1.44, 1.36, and 1.34 (3H×4, each s, isop-Me). Found: C, 50.19; H, 6.55%. Calcd for $C_{13}H_{21}ClO_6$: C, 50.57; H, 6.86%.

Acetyl Derivative of 11. The reaction mixture of **11** (10 mg, 0.032 mmol) and acetic anhydride (0.5 cm^3) in pyridine (0.5 cm^3) was stirred at room temperature until the disappearance of **11** on TLC. To the reaction mixture, ethanol and toluene were added and coevaporated to give the corresponding acetoxymethyl derivative in quantitative yield (12 mg). Syrup; $[\alpha]_D^{25}$ +29.6° (*c* 1.5, $CHCl_3$); IR 1746 cm^{-1} (C=O); ^{1}H NMR (FX-200) δ = 5.87 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.71 and 4.32 (1H×2, ABq, $J_{A,B}$ = 12.2 Hz, H-3′a and H-3′b), 4.36 (1H, ddd, $J_{4,5}$ = 8.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{5,6'}$ = 4.4 Hz, H-5), 4.11 (1H, dd, $J_{6,6'}$ = 9.3 Hz, H-6), 4.01 (1H, dd, H-6′), 3.91 (1H, d, H-4), 2.12 (3H, s, OAc), 1.51, 1.41, 1.32, and 1.32 (3H×4, each s, isop-Me). Found: C, 51.69; H, 6.38%. Calcd for $C_{15}H_{23}ClO_7$: C, 51.36; H, 6.61%.

3-*C*-Formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (12). The reaction mixture of **3** (100 mg, 0.29 mmol), CsOAc (560 mg, 2.92 mmol, 10 mol amt.), and 18-crown-6 (550 mg, 2.08 mmol, 7.0 mol amt.) in dry toluene (5 cm^3) was refluxed for 5 h until the disappearance of **3** on TLC (hexane/ethyl acetate = 3/1). The reaction mixture was then poured into a saturated aqueous ammonium chloride solution (20 cm^3), extracted with ethyl acetate (3 times),

washed with brine and water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a syrupy product, which was separated on a preparative TLC (hexane/ethyl acetate = 5/1) to give **12**. The yield was 30 mg (36%). Compound **12** easily formed its hydrate, and was too unstable to purify. Therefore, only IR and ^{1}H NMR data were measured, as described below. **12**: Syrup; IR 3460 (OH) and 1730 cm^{-1} (C=O); ^{1}H NMR (EX-270) δ = 9.76 (1H, d, $J_{CHO,OH}$ = 1.0 Hz, CHO), 5.93 (1H, d, $J_{1,2}$ = 3.3 Hz, H-1), 4.49 (1H, d, $J_{4,5}$ = 8.9 Hz, H-4), 4.45 (1H, d, H-2), 4.25 (1H, ddd, $J_{5,6}$ = 5.9 Hz, $J_{5,6'}$ = 4.3 Hz, H-5), 4.11 (1H, dd, $J_{6,6'}$ = 8.9 Hz, H-6), 4.06 (1H, dd, H-6′), 3.76 (1H, d, OH), 1.61, 1.35, 1.32, and 1.27 (3H×4, each s, isop-Me).

3-*C*-Hydroxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (13). The reaction mixture of **12** (30 mg, 0.10 mmol) and $NaBH_4$ (39 mg, 1.0 mmol, 10 mol amt.) in methanol (5.0 cm^3) was stirred at room temperature for 1 h. It was then partially evaporated after the addition of a saturated ammonium chloride solution, extracted with chloroform, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **13** in quantitative yield (31 mg), of which the physical data were identical with that reported.[8)]

3-*C*-Formyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (14). To a solution of **3** (100 mg, 0.29 mmol) in DMSO (7.0 cm^3) was added tetrabutylammonium hydroxide (40 wt % solution in water, 1.0 cm^3, 1.5 mmol, 5.2 mol amt.) at room temperature; the reaction mixture was kept for a very short time until the disappearance of **3** (30 s). It was poured into a saturated aqueous ammonium chloride solution (20 cm^3), extracted with ethyl acetate (3 times), washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated to give a syrupy product, which was separated on a preparative TLC (hexane/ethyl acetate = 3/1) to give **14**. The yield was 61% (51 mg). Compound **14** easily formed its hydrate and was too unstable to purify. Therefore, only IR and ^{1}H NMR data were measured, as described below. **14**: Syrup; IR 3488 cm^{-1} (OH) and 1730 cm^{-1} (C=O); ^{1}H NMR (EX-270) δ = 9.81 (1H, s, CHO), 5.95 (1H, d, $J_{1,2}$ = 3.9 Hz, H-1), 4.45 (1H, d, H-2), 4.23 (1H, ddd, $J_{4,5}$ = 6.3 Hz, $J_{5,6}$ = 6.3 Hz, $J_{5,6'}$ = 6.3 Hz, H-5), 4.11 (1H, d, H-4), 4.07 (1H, dd, $J_{6,6'}$ = 8.6 Hz, H-6), 3.96 (1H, dd, H-6′), 3.53 (1H, s, OH), 1.62, 1.44, 1.39, and 1.33 (3H×4, each s, isop-Me).

Reduction of 14 with $NaBH_4$ into 7. The reaction mixture of **14** (50 mg, 0.17 mmol) and $NaBH_4$ (66 mg, 1.7 mmol, 10 mol amt.) in methanol (5.0 cm^3) was stirred at room temperature for 1 h. It was then partially evaporated after the addition of saturated ammonium chloride solution, extracted with chloroform, washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **7** in quantitative yield (50 mg). The physical data were identical to that obtained from **6** or **11**.

3-*C*-Dimethoxymethyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (15). To a solution of **3** (33 mg, 0.096 mmol) in HMPT (1.0 cm^3) was added a solution of sodium methoxide (sodium 22 mg, 0.96 mmol in methanol 1.0 cm^3) and stirred at 70 °C under argon for 24 h until the disappearance of **3** on TLC. The reaction mixture was directly purified on a column of silica gel (ether only) to give **15** in 93% yield (30 mg). **15**: Mp 89.0—90.5 °C (recrystallized from ether–hexane); $[\alpha]_D^{24}$ +3.9° (*c* 0.6, $CHCl_3$); IR 3520 cm^{-1} (OH); ^{1}H NMR (FX-200) δ = 5.71 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 4.61 (1H, d, H-2), 4.54 (1H, s, H-3′), 4.22 (1H, ddd, $J_{4,5}$ = 8.3 Hz, $J_{5,6}$ = 4.4 Hz, $J_{5,6'}$ = 6.1 Hz, H-5), 4.10 (1H, dd, $J_{6,6'}$ = 8.8 Hz, H-6′), 3.93 (1H, dd, H-6), 3.92 (1H, d, H-4), 3.66 and 3.47 (3H×2, each s, OMe×2), 2.90 (1H, s, OH), 1.58, 1.46, 1.38, and 1.37 (3H×4, each s, isop-Me). Found: C, 53.87; H, 7.88%. Calcd for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84%.

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