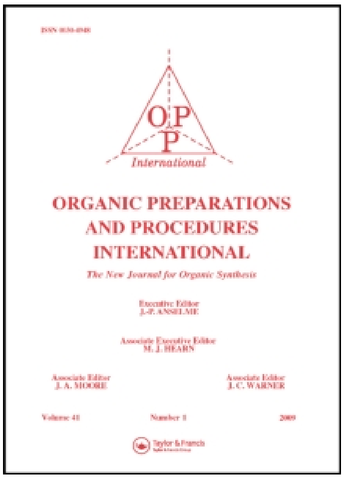

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Masuo Funabashi[a]; Yukinori Ooshiro[a]
[a] Department of Chemistry, Faculty of Sciences, Chiba University, Inage-ku, Chiba, JAPAN

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A MULTI-GRAM SYNTHESIS OF 1,2:5,6-DI-*O*-ISOPROPYLIDENE-3-*C*-TRIMETHYLSILYLMETHYL-α-D-ALLOFURANOSE. AN IMPROVED PREPARATION OF 3-*C*-HYDROXYMETHYL-α-D-GLUCO- AND 3-*C*-METHYL-α-D-ALLOFURANOSE DERIVATIVES

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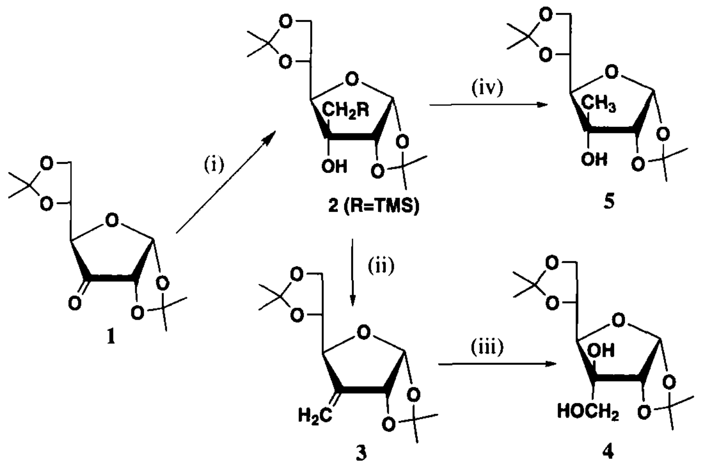
Masuo Funabashi* and Yukinori Ooshiro

Department of Chemistry, Faculty of Sciences, Chiba University
Yayoi-cho, 1-33, Inage-ku, Chiba 263-8522, JAPAN

The use of carbohydrates as chiral building blocks in natural product synthesis is still a challenging area of contemporary synthetic organic chemistry. As part of our work on branched-chain sugars and cyclitols related to natural products such as amipurimycin,[1] paniculide C,[2] and tetrodotoxin,[3] we required a large amount of 3-*C*-hydroxymethyl-α-D-glucofuranose derivative (**4**),[4] for which a key-intermediate is 1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose (**3**).[5] Compound **3** has been prepared from a 3-ulose derivative **1**[6] by the conventional Wittig reaction using methyltriphenylphosphonium bromide and *n*-butyllithium (or sodium hydride). However, the large-scale preparation of **3** *via* a Wittig reaction is not amenable in terms of yield (65-73%) and the handling of a large amount of *n*-butyllithium; in addition, the time-consuming purification of **3** by column chromatography requires a large amount of silica gel.

Therefore, we now describe, an improved, large-scale preparation of **3** *via* a facile Peterson olefination of 1,2:5,6-di-*O*-isopropylidene-3-*C*-trimethylsilylmethyl-α-D-allofuranose (**2**),[7] which was obtained in large quantity in high yield (>90%) by reacting **1** (50g scale) with (trimethylsilylmethyl)magnesium chloride. In contrast to unstable and syrupy **1**, compound **2** is shelf-stable and crystalline and may be converted into 3-*C*-methylene derivative **3** in better than 95% yield by simple heating with sodium hydride in THF for 3 hrs. The work-up is very simple and the product may be used directly for the next reaction without purification.



i) (trimethylsilylmethyl)magnesium chloride, THF, 1hr ii) NaH, THF, reflux, 3 hrs
iii) OsO_4, NMO, aq Acetone, 48 hrs iv) 1-propanol, aq KOH (1.0M), reflux, 5 hrs

Thus, a large-scale dihydroxylation[8] of **3** was smoothly effected with 4-methylmorpholine N-oxide (NMO) in the presence of catalytic amount of OsO_4 to afford an excellent yield (92%) of 3-*C*-hydroxymethyl-α-D-glucofuranose derivative (**4**), which is sufficiently pure for further manipulations. At the same time, we wish to mention a very simple procedure to obtain 3-*C*-methyl-α-D-allofuranose derivative (**5**) *via* a facile protiodesilation, which has scarcely been applied[9] so far to unactivated β-hydroxyalkylsilanes. Simple heating a solution of **2** in 1-propanol in the presence of aqueous potassium hydroxide (1.0M) gave 3-*C*-methyl-α-D-allofuranose derivative (**5**) exclusively in a 90% yield. The total yield (84%) of **5** from **1** was much better than that of the conventional Grignard reaction[10] (56-65%) with **1**. Interestingly, no formation of the olefin **3** was observed at all, probably because homo-Brook rearrangement[9] effectively occurred in this condition. The general applicability of such reaction conditions to various β -hydroxyalkylsilanes is now under investigation and will be reported in due course.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on JEOL spectrometers (JNM-GSX 400 MHz) for solutions in $CDCl_3$ containing tetramethylsilane as the internal reference. Mass spectra were measured on a JEOL JMS-HX110 mass spectrometer. Melting points were determined on a Yazawa micro melting-point apparatus BY-2 and are uncorrected. Optical rotations were determined at 23° on a JASCO DIP-140 digital polarimeter; the temperature of the optical rotation of compounds **4** and **5** were not reported in the references cited. Column chromatography was performed by the flash technique on silica gel (Wakogel C-300).

1,2:5,6-Di-*O*-isopropylidene-3-*C*-trimethylsilylmethyl-α-D-*allo*-hexofuranose (2).- To a solution of (trimethylsilylmethyl)magnesium chloride prepared from trimethylsilyl-methyl chloride (31 g, 0.252 mol) and magnesium (5 g, 0.21 mol) in dry THF (150 mL), was gradually added during 30-40 min a solution of the compound **1** [freshly prepared[6] from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (50 g, 0.194 mol)] in dry THF (150 ml). The reaction mixture was then heated gently at reflux for 20 min, cooled, and poured into ice water (700 mL) containing NH_4Cl (21 g). The precipitate was collected, washed with ice water, and recrystallized from ethanol to afford lustrous white crystals (48.3 g). From the filtrate was isolated a second crop (8.0 g, recrystalized from ethanol). The total yield is 56.3 g (85%, 2 steps), mp. 135-136°, *lit.*[7] mp. 128-130°; $[\alpha]_D^{23}$ = +28° (*c* 0.50, ethyl acetate), *lit.*[7] $[\alpha]_D^{20}$ = +16.9° (*c* 0.68, chloroform). Fab-MS: m/e 347 (M+1), 331(M-15), ^{1}H NMR: δ 0.15 (s, 9H, $\underline{CH}_3$-Si), 0.65 (d, 1H, C-$\underline{CH}_2$-Si- , J= 14.9 Hz), 1.15 (d, 1H, C-$\underline{CH}_2$-Si-), 1.36, 1.38, 1.46, 1.60 (s, 12H, $\underline{CH}_3$-C), 2.60 (s, 1H, OH), 3.77(d, 1H, H_4, $J_{4,5}$=7.64 Hz), 3.95 (dd, 1H, H_{6a}, $J_{6a,,6b}$=8.3 Hz), 4.11 (dd, 1H, H_{6b}), 4.17 (m, 1H, H_5), 4.27 (d, 1H, H_2, $J_{1,2}$=3.66 Hz), 5.70 (d, 1H, H_1).

Anal. Calcd for $C_{16}H_{30}O_6Si$: C, 55.46; H, 8.73. Found: C, 55.60; H, 8.85

3-*C*-Hydroxylmethyl-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-hexofuranose (4).- To a solution of **2** (34.6 g, 0.10 mol) in dry THF (200 mL) was added under an atmosphere of argon, sodium hydride (2.6 g, 0.11 mol) obtained by washing the oily reagent twice with hexane. The reaction mixture was then heated gently to reflux for 3 hrs and cooled to a room temperature, quenched with methanol (10 mL) and water (5 mL) successively. The resultant pale-brown solution was concentrated *in vacuo* to a syrupy residue, which was treated with ethyl acetate (200-250 mL) and water (100 mL). The organic layer was immediately washed with water, dried over anhydrous $MgSO_4$, and concentrated to a nearly pure syrup (**2:** 25 g, 97%). To a solution of **2** (25 g, 0.098 mol) dissolved in an aqueous acetone (215 mL of acetone and 50 mL of distilled water), was added OsO_4 (100 mg) and NMO (50% aqueous solution, 27 g). The reaction mixture was stirred vigorously at room temperature for 48 hrs. After the disappearance of **3** monitored by tlc, a solution of sodium sulfite (16 g in 50 mL distilled water) was added to the pale yellow reaction solution, and the precipitate was filtered off. The filtrate was then concentrated *in vacuo* to about one-third of its volume, and extracted with ethyl acetate (100 mL x 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to a crystalline mass (28.1 g, 96%), mp. 84-86° A portion of the nearly pure crystals was recrystallized from ethanol and hexane to afford fine white needles, mp. 87-88°, *lit.*[4c] mp. 86-87°,; $[\alpha]_D^{23}$ = +30° (*c* 0.45, ethyl acetate), *lit.*[4c] $[\alpha]_D$ = +25° (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ 1.31, 1.37, 1.46, 1.52 (s, 12H, $\underline{CH}_3$-C), 3.17-3.20 (m, 2H, H_4 and OH), 3.77 (m, 3H, $\underline{CH}_2\underline{OH}$ at C-3'), 4.07 (dd, 1H, $H_{6a,}$ $J_{5,6a}$= 4.8 Hz), 4.18 (dd, 1H, H_{6b}, $J_{5,6b}$= 6.2 Hz , $J_{6a,6b}$= 8.9 Hz), 4.41 (d, 1H, H_2, $J_{1,2}$ = 3.6 Hz), 5.88 (d, 1H, H_1).

1,2:5,6-Di-*O*-isopropylidene-3-*C*-methyl-α-D-*allo*-hexofuranose (5).- A suspension of **2** (346 mg, 1.0 mmol) in a mixture of 1-propanol (10 mL) and aq KOH (1.0 M,3 mL) was heated to reflux for 5 hrs. After the disappearance of **2** monitored by tlc (toluene:ethyl acetate = 5:1), the solution was neutralized with acetic acid, concentrated *in vacuo* to a crystalline residue, which was treated with ethyl acetate and water. The organic layer was then washed with water, dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **5** (247 mg, 90%), mp.102-104°., a part of which was recrystallized from ether/petroleum ether gave white needles, mp. 104-105°, *lit.*[10a] mp. 105-107°; $[\alpha]_D^{23}$ + 28° (*c* 0.24, ethyl acetate), *lit.*[10a] $[\alpha]_D$ = +22° (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.29, 1.35, 1.37, 1.45 (s, 12H, $\underline{CH}_3$-C), 1.60

(s, 3H, $\underline{CH}_3$ at C-3), 2.69 (s, 1H, OH), 3.78 (d, 1H, H_4, $J_{4,5}$= 7.4 Hz), 3.93 (m, 1H, H_5), 4.11 (m, 2H, H_{6a} and H_{6b}), 4.18 (d , 1H, H_2, $J_{1,2}$= 3.62 Hz), 5.71 (d, 1H, H_1).

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