BCSJ

Document type: Article

Selected Paper

One-Step Conversion to a Disubstituted Cyclopentenone from 2-Deoxy-D-Glucose and Application to Synthesis of Prostaglandin E_1 Methyl Ester

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Received: August 28, 2018; Accepted: September 20, 2018; Web Released: November 10, 2018

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Abstract

We have developed a facile one-step conversion of 2-deoxy-D-glucose to form a disubstituted cyclopentenone through catalyst-free hydrothermal reaction under mild conditions. The use of 2-deoxy-D-glucose in one-pot conversion is to provide the formation of a carbon five-membered ring instead of the common biomass-derived furans such as furfural, 5-HMF, etc. The cyclopentenone has a potential to be a building block for the preparation of chemical products. As one example, we successfully demonstrated the synthesis of prostaglandin E_1 methyl ester.

Keywords: Biomass | Hydrothermal reaction | Total synthesis

1. Introduction

Consumption of natural resources, e.g. fossil fuels, is steadily increasing and subsequently leading to severe environmental pollution among other consequences. A known alternative to fossil fuels is the use of degraded biomass products. Currently biomass resources are converted to products by chemical methods using sub- and supercritical fluids,[1] acids,[2] catalysts[3] or enzymes.[4] Many compounds can be obtained via initial production of glucose from crops such as sugarcane and corn, including ethanol,[5] carboxylic acids,[4b,6] furfural,[2b,4a] etc. Due to enormous previous efforts, the syntheses of almost all products that can be obtained from direct conversion of cellulosic-biomass resources, especially natural monosaccharides such as glucose and fructose, has been made clear.[1d] And thus, production of new substances with higher synthetic value from biomass resources would be surely beneficial. Therefore, we aimed at the creation of new materials other than furans, bioethanol and carboxylic acids which have been widely reported, and using them for application to fine chemicals. We have looked for procedures that could allow the preparation of useful compounds from deoxy sugars, such as 2-deoxy-D-glucose (2-DG) (**1**). The preparation methods of **1** have been reported previously, and the overall yield is over 50% from glucose.[7] Also, **1** is one of the most easily available industrial deoxy sugars. In addition, their transformations are much less studied compared to those of glucose. In this paper, we describe the first demonstration of one-step conversion to 4-hydroxy-2-(hydroxymethyl)cyclopent-2-en-1-one (**2**) from **1** by hydrothermal treatment (Figure 1). The reactants include water and **1** without any catalyst at lower temperature and pressure than those usually applied in general biomass conversion processes.[1] Elliott *et al*. reported synthesis of **2** in 3.5% overall yield through ten reaction steps from quinic acid.[8] Meanwhile, our environmentally friendly method provides **2** from an aqueous solution of **1** in one-pot. In addition, this method significantly enhances yield of **2** to 80%, the maximum conversion possible from **1**.

2. Experimental

Materials. 2-Deoxy-D-glucose was purchased from Carbosynth Limited, phosphorus tribromide (PBr_3), chlorotri-

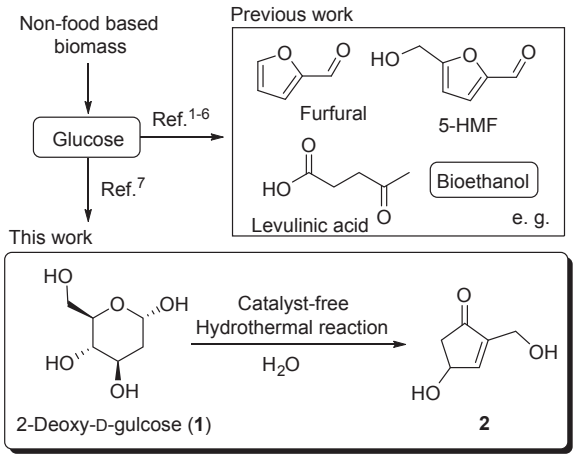


Figure 1. Strategy of biomass utilization.

ethylsilane (TESCl), trimethylamine (Et_3N), 4-dimethylaminopyridine (DMAP), diethylamine ($HNEt_2$), methyl 6-bromohexanoate, sodium iodide (NaI), triethylborane (Et_3B), tributyltin hydride (n-Bu_3SnH) methanol (MeOH) and anhydrous solvents for organic synthesis, including CH_2Cl_2, tetrahydrofuran (THF), and diethyl ether (Et_2O) were purchased from Wako Pure Chemical Industries, pyridinium p-toluenesulfonate (PPTS) was purchased from Tokyo Chemical Industry Co., (*S*)-(−)-1-octyn-3-ol (97% *ee*), lithium 2-thienylcyanocuprate and aluminum oxide, activated, basic, Brokmann Grade I (Al_2O_3) were obtained from Sigma-Aldrich. Silica gel plates (60F-254) for thin layer chromatography were purchased from Merck. Silica gel 60N (230–400 mesh) for flash chromatography was purchased from Kanto Chemical. All reagents were used without further purification. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere with dry solvents. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). Visualization of the developed chromatograms was performed by UV absorbance and aqueous cerium ammonium molybdate. Flash chromatography was performed on Kanto Chemical silica gel 60N (230–400 mesh) with the indicated solvent systems.

Instruments. Optical rotations were recorded on a Jasco DIP-1000 polarimeter. Infrared spectra (IR) were recorded on a Jasco FT/IR-4100 spectrometer using ATR. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE-400 III spectrometer and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ at δ 7.26 ppm for ^{1}H, δ 77.16 for ^{13}C NMR, $(CD_3)_2CO$ (Acetone-d_6) at δ 2.05 ppm for ^{1}H, δ 29.8, 206.3 for ^{13}C NMR). High-resolution mass spectrometry (HR-MS) was performed using a Bruker MicrOTOF-Q II-S1 using electrospray ionization (ESI). High performance liquid chromatography (HPLC) was performed using YMC LC-Forte/R100. Gas chromatography (GC) was performed using an Agilent Technologies 7890B/5977A MSD.

Experimental Produces. Optimized Procedure for Catalyst-Free Hydrothermal Reaction and Isomerization: A solution of 2-DG (**1**) (10 g, 60.9 mmol) in distilled water (250 mL) was poured into a tube bomb reactor (304L-HDF4-300, 300 mL, Swagelok, Co.) and sealed tightly. The reactor was placed in a pre-heated dry oven (DO-450PA, AS ONE Co.) at 140 °C, and left standing without stirring at the same temperature. After 22 hours, it was taken out of the oven and cooled in water rapidly to terminate the reaction. The reaction mixture including the solid removed from the reactor was frozen for aggregation. The mixture, thawed at room temperature, was filtered twice (retained particle diameter, 1.0 and 0.2 μm) and the solid (insoluble char) was removed. Concentration *in vacuo* to remove water gave a residue as a brown paste. The activated basic alumina with the same amount of residue and 10 w/v % distilled water were added to the residue and stirred at 50 °C. After 5 hours, the resultant mixture was diluted with 2-propanol (25 mL × 4) and filtered (filter paper, 0.4 μm) to remove the alumina. In this case, the alumina was used not only for isomerization but also for purification. Concentration in vacuum gave the racemic **2** (6.3 g, 49.2 mmol, 80%) as a single isomer. TLC (EtOAc): $R_f = 0.22$; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.18 (dd, $J = 2.0$, 18.4 Hz, 1H), 2.72 (dd, $J = 6.0$, 18.4 Hz, 1H), 4.21 (s, 2H), 4.91–4.92 (m, 1H), 7.36–7.37 (m, 1H) ppm; ^{13}C NMR (100 Mz, acetone-d_6): δ 45.9, 56.8, 68.6, 147.6, 157.7, 205.4 ppm; IR(neat): 1701, 3276 cm^{-1}; HR-MS (ESI-TOF): m/z calcd. for $C_6H_9O_3$ ($[M + H]^+$), 129.0546; found, 129.0552; (*R*)-**2**, $[\alpha]_D^{26} = +33.0$ (c = 1.0 in ethanol). The optical rotation was in agreement with those previously published;[8] (*S*)-**2**, $[\alpha]_D^{18} = -34.3$ (c = 1.0 in ethanol).

Compound 4: PBr_3 (59 μL, 0.62 mmol) was added to a stirred solution of (*R*)-**2** (227 mg, 1.77 mmol) in THF (5.9 mL) at 0 °C, and the mixture was stirred at the same temperature. After 5 min, Et_3N (0.49 mL, 3.54 mmol) and $HNEt_2$ (0.37 mL, 3.54 mmol) were added to the same pot, and the mixture was stirred at room temperature for 15 min. Finally, TESCl (0.39 mL, 2.30 mmol) was added to the reaction mixture, and further stirred 30 min at room temperature (If the reaction is stopped halfway or does not proceeded, the temperature is set above 30 °C.) All reactions were monitored by TLC (AcOEt). The reaction was quenched with saturated H_2O. The resulting mixture was extracted with AcOEt (2 × 10 mL). The combined extracts were washed with brine (10 mL) then dried with $MgSO_4$. Concentration in *vauco* afforded a residue, which was purified by column chromatography (hexane/EtOAc 1:1 → 2:1) to give **4** (219 mg, 0.734 mmol, 42%) as a pale yellow oil. TLC (hexane:EtOAc, 1:2 v/v): $R_f = 0.40$ (broad); $[\alpha]_D^{26} = +18.7$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.65 (dd, $J = 8.0$, 15.8 Hz, 6H), 0.96–1.04 (m, 15H), 2.32 (dd, $J = 2.0$, 18.4 Hz, 1H), 2.47–2.53 (m, 4H), 2.77 (dd, $J = 6.0$, 18.2 Hz, 1H), 3.15–3.25 (m, 2H), 4.90–4.92 (m, 1H), 7.24–7.25 (m, 1H) ppm; ^{13}C NMR (100 Mz, $CDCl_3$) δ 4.8, 6.9 12.1, 45.9, 47.4, 47.5, 68.8, 145.1, 158.9, 206.2 ppm; IR(neat): 1147, 1716, 2960 cm^{-1}; HR-MS (ESI-TOF): m/z $C_{16}H_{32}NO_4Si$ ($[M + H]^+$) calcd. for 298.2197, found 298.2196.

Compound 6: n-BuLi (1.55 M, 0.25 mL, 0.39 mmol) was added to a stirred solution of vinyl iodide (145 mg, 0.39 mmol) prepared from (*S*)-(−)-1-octyn-3-ol in Et_2O (1.3 mL) at −78 °C under argon atmosphere. After 2 hours, lithium 2-thienylcyanocuprate (0.25 M, 1.57 mL, 0.39 mmol) was added to the reaction and stirring further continued for 30 minutes at the same temperature to allow formation of mixed cuprate **5**.[9e] A solution of **4** (106 mg, 0.35 mmol) in Et_2O (1.5 mL) was added

dropwise at −78 °C. The mixture was stirred for 20 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with hexane (2 × 10 mL). The combined extracts were washed with brine (10 mL) then dried with Na_2SO_4. Concentration *in vauco* afforded a residue, which was purified by column chromatography (hexane/EtOAc 60:1 → 40:1) to give **6** (114 mg, 0.243 mmol, 70%) as a colorless oil. TLC (hexane:EtOAc, 20:1 v/v): $R_f = 0.33$; $[\alpha]_D^{22} = -40.8$ (c = 0.30 in $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.56–0.62 (m, 12H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.93–0.97 (m, 18H), 1.26–1.51 (m, 8H), 2.34 (dd, $J =$ 6.4, 17.8 Hz, 1H), 2.63 (dd, $J = 6.4$, 17.8 Hz, 1H), 3.30–3.33 (m, 1H), 4.10–4.15 (m, 2H), 5.24–5.25 (m, 1H), 5.45–5.65 (m, 2H), 6.12–6.13 (m, 1H) ppm; ^{13}C NMR (100 Mz, $CDCl_3$) δ 4.9, 5.1, 6.9, 7.0, 14.2, 22.8, 25.2, 32.0, 38.7, 47.1, 54.6, 72.79, 72.83, 77.4, 119.5, 127.6, 137.7, 146.8, 203.7 ppm; IR(neat): 1149, 1427, 1731, 2360, 2954 cm^{-1}; HR-MS (ESI-TOF): m/z $C_{26}H_{48}O_3Si_2Na$ ($[M + Na]^+$) calcd. for 487.3034, found 487.3029.

Compound 8: Triethylborane (47 µL, 0.047 mmol) was added to a stirred solution of **6** (210 mg, 0.47 mmol), **7** (358 mg, 1.40 mmol) and tributyltin hydride (0.38 mL, 1.40 mmol) in toluene (1.5 mL) at −20 °C under argon atmosphere. The mixture was stirred for 3 hours at the same temperature. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 50:1 → 20:1) to give **8** (158 mg, 0.262 mmol, 56%) as a colorless oil. TLC (hexane:EtOAc, 10:1 v/v): $R_f = 0.40$; $[\alpha]_D^{22} = -29.0$ (c = 0.24 in $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.55–0.62 (m, 12H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.92–0.99 (m, 18H), 1.21–1.63 (m, 18H), 1.91–1.97 (m, 1H), 2.18 (dd, $J = 8.0$, 18.4 Hz, 1H), 2.28 (t, $J = 7.6$ Hz, 2H), 2.42–2.49 (m, 1H), 2.62 (ddd, $J =$ 1.2, 7.2, 18.2 Hz, 1H), 3.66 (s, 3H), 4.1–4.13 (m, 2H), 5.49–5.61 (m, 2H) ppm; ^{13}C NMR (100 Mz, $CDCl_3$) δ 4.9, 5.1, 6.7, 6.9, 7.1, 14.2, 22.8, 25.1, 25.2, 26.8, 28.0, 29.1, 29.3, 29.7, 32.0, 34.2, 38.7, 51.6, 53.2, 53.9, 73.0, 77.4, 129.0, 136.3, 174.4, 216.5 ppm; HR-MS (ESI-TOF): m/z $C_{33}H_{64}O_5Si_2Na$ ($[M + Na]^+$) calcd. for 619.4184, found 619.4203.

PGE$_1$-Methyl Ester (9): PPTS (0.63 mg, 2.5 µmol) was added to a stirred solution of **8** (50.0 mg, 0.084 mmol) in acetone (0.83 mL) and water (0.17 mL). After 6 hours stirring at room temperature, acetone was removed in vacuo and the residue was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with brine (5 mL) then dried with $MgSO_4$. Concentration in *vauco* afforded a residue, which was purified by column chromatography (Et_2O/MeOH 50:1) to give **9** (25.2 mg, 0.0684 mmol, 82%) as a colorless oil. TLC (Et_2O:MeOH, 50:1 v/v): $R_f = 0.23$; $[\alpha]_D^{22} = -46.8$ (c = 0.93 in MeOH), [lit $[\alpha]_D^{22} = -55.6$ (c = 0.33 in MeOH)]; ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.89 (t, $J = 6.4$ Hz, 3H), 1.21–1.69 (m, 18H), 1.96–2.04 (m, 1H), 2.17–2.38 (m, 5H), 2.73 (ddd, $J =$ 1.2, 7.2, 18.4 Hz, 1H), 3.22 (brs, 1H), 3.66 (s, 3H), 4.01–4.14 (m, 2H), 5.52–5.70 (m, 2H) ppm; ^{13}C NMR (100 Mz, $CDCl_3$) δ 14.2, 22.8, 25.0, 25.3, 26.7, 27.8, 29.0, 29.5, 31.8, 34.1, 37.5, 46.0, 51.6, 54.6, 54.9, 72.0, 73.1, 131.9, 136.9, 174.5, 214.8 ppm; HR-MS (ESI-TOF): m/z $C_{21}H_{36}O_5Na$ ($[M + Na]^+$) calcd. for 391.2455, found 391.2459. The spectroscopic data and the optical rotation were in agreement with those previously published.[10]

Conversion to 2 from IV: An aqueous solution (3 w/v %) of IV prepared form tri-*O*-acetyl-D-glucal[11] was poured into a sealed reactor and sealed tightly. The rector was placed in a previously heated dry oven at 160 °C and left standing without stirring at same temperature. After 4 hours, the reactor was taken out of the oven and cooled in water rapidly to terminate the reaction. The resulting mixture was filtered to remove the solid. Concentration *in vacuo* gave a crude residue as a brown paste. The ratio of **2**/**3** was 1:0.4 according to ^{1}H NMR measurements (see Supporting Information).

GC-FID Measurements: Column, HP-INNOWAX 19091N-113; injection, 250 °C; Detection (FID), 250 °C; presser, 88.0 kP; He flow late, 2.5 mL min^{-1}; linear velocity, 42 cm sec^{-1}; split flow late, 14 mL min^{-1}, conditions; 80 °C (2 min)-(10 °C min^{-1})-100 °C (2 min)-(10 °C min^{-1})-245 °C (5 min); retention time, **2** and **3**, 22.0 min.

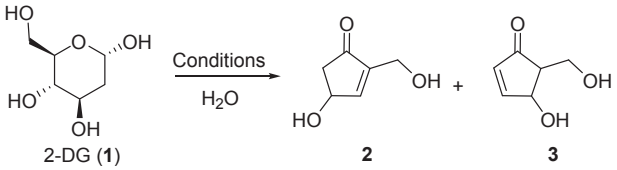
HPLC Measurements: CHIRAL ART Cellulose-SC (5 µm, ϕ 30.0 I.D. × 250 mm YMC CO., LTD.); column temperature, room temperature; mobile phase, hexane/*i*-propanol (v/v) = 50/50 for 20 min; flow rate, 13 mL min^{-1}; sample concentration, 5 mg mL^{-1}; injection volume, 4.5 mL; UV absorbance was monitored at 220 nm; retention times, (*S*)-**2**, 12.9 min; (*R*)-**2**, 14.4 min.

Optical Resolution *via* HPLC: CHIRAL ART Cellulose-SC (5 µm, ϕ 30.0 I.D. × 250 mm, YMC CO., LTD.); column temperature, room temperature; mobile phase, hexane/*i*-propanol (v/v) = 50/50 for 20 min; flow rate, 13 mL min^{-1}; sample amount, 1.0 g; sample concentration, 40 mg mL^{-1}; injection volume, 2.0 mL at a time; UV absorbance was monitored at 220 nm; collection, (*S*)-**2**, 492 mg, 14.7 min; (*R*)-**2**, 489 mg, 17.8 min.

3. Results and Discussion

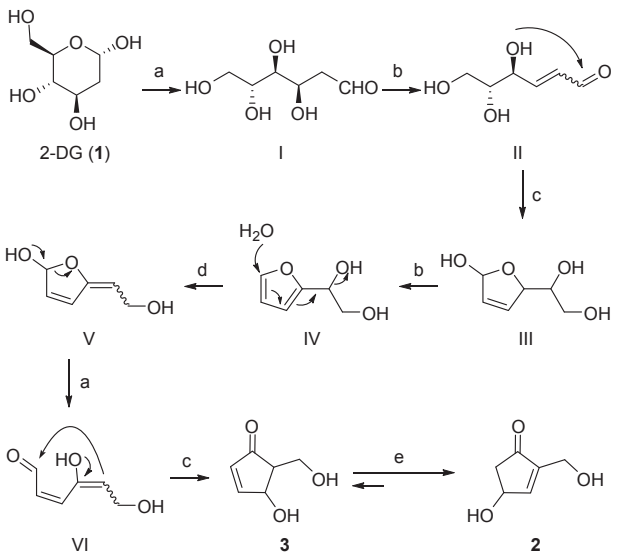
Hydrothermal conversion of glucose, fructose, cellulose, etc. into products has been investigated under sub- (150–374 °C) and supercritical (374–500 °C) conditions.[1,12] Since the temperature ramping rate and the reaction time greatly affect the yield of the product and quantity of by-products, there are still many difficulties in the conversion of saccharides into products using batch reaction systems. On the other hand, flow reaction systems have been recently used for controlling the reaction conditions.[13] However, this equipment must strictly manage reaction time at high temperatures and pressures, so other solutions are essential. We have found that **2** can be obtained from 2-DG (**1**) by hydrothermal reaction at 160 °C or lower without any catalyst. Since the retro-aldol reaction of **1** is suppressed under these conditions, the dehydration reactions of **1** and its intermediates are selectively enhanced. We have also optimized the reaction conditions to achieve the highest yield, as follows. Table 1 shows the conditions for conversion of **1** into **2**. In our experiments, we fixed the concentration of the reactants, and varied the reaction time and temperature. The reaction of **1** was conducted in a tube bomb reactor with an inner volume of 150 mL. An aqueous solution (100 mL) of **1** (3.0 g) was loaded into the reactor. The reactor was sealed and placed in a constant temperature drying oven controlled at the reaction temperature (140 °C and 160 °C). After the reaction, the reactor was removed from the oven and rapidly quenched in an ice-water bath. The reaction mixture was filtered with a 0.22 µm mem-

Table 1. Investigation of reaction condition[a]



Entry	Temp.(°C)	Time (h)	Yield (%)[b]	Ratio (**2**:**3**)[c]
1	160	7	74	1 : 0.3
2	160	14	63	-
3	160	28	37	-
4	140	14	67	-
5	140	28	80	1 : 0.3
6	140	56	55	-
7	140	94	41	-

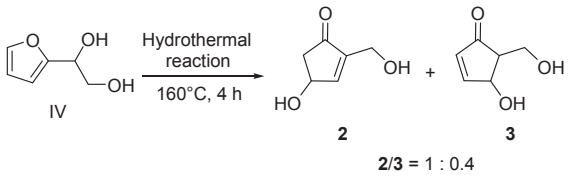
(a) Unless stated otherwise, reactions were performed as follows: 2-DG (**1**) (3.0 g) in H_2O (100 mL) at indicated temperature and for indicated time without stirring. (b) Yield of **2** including **3** was determined by GC-FID analysis. (c) Ratio of **2** and **3** was determined by ^{1}H NMR analysis.



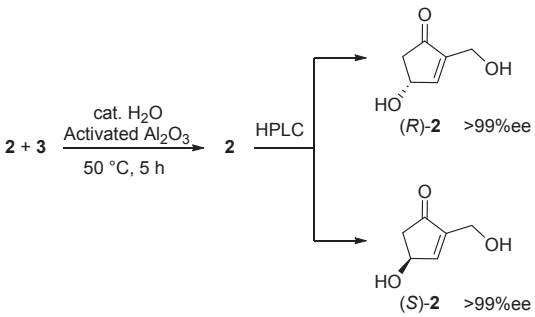
Scheme 1. Reaction mechanism: (a) Ring opening; (b) Dehydration; (c) Cyclization; (d) Dehydration/Hydration; (e) Equilibrium reaction.

brane filter. The products in the filtered solution were identified by GC-FID.

Under high yield conditions (Entry 1 and 5), a crude mixture **2** and its isomer **3** was obtained and the ratio of **2**/**3** was 1:0.3 according to ^{1}H NMR measurements (see Supporting Information). The following reaction mechanism could be the reason for the resultant isomers (Scheme 1). At the beginning, unsaturated ketone is formed by dehydration (I → II); and the followed cyclization results in IV (II → III → IV). After that, the furan ring is opened by hydration and cyclized to form a carbon five-membered ring (IV → V → VI → **3**). Finally, in the presence of water, an equilibrium reaction occurs between **2** and **3**, however, the amount of **2** is higher due to its thermodynamic stability. This hypothesis was verified from the experimental results described below. When the hydrothermal

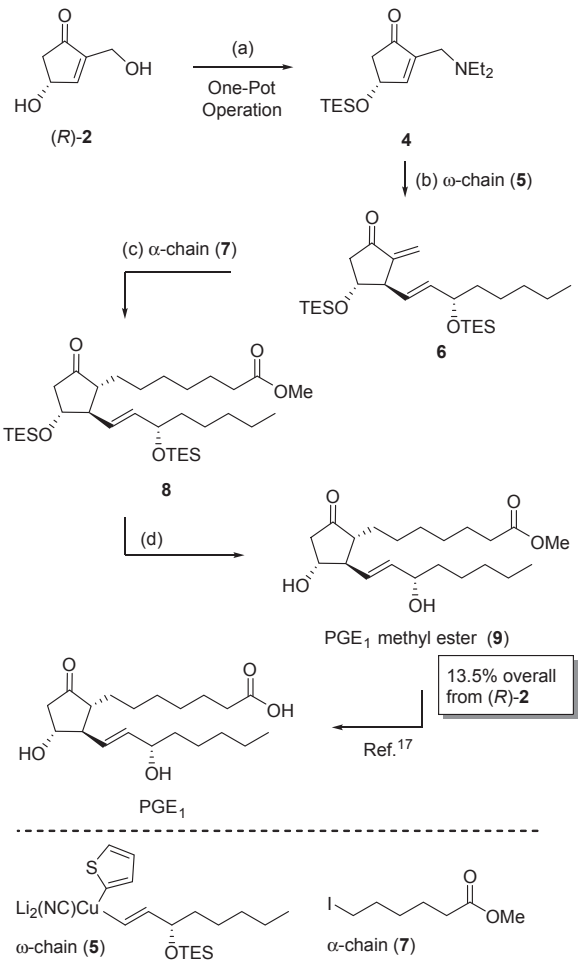


Scheme 2. Conversion to **2** and **3** from intermediate IV. Ratio of **2** and **3** was determined by ^{1}H NMR analysis.



Scheme 3. Isomerization by alumina and purification *via* HPLC.

reaction was stopped for 1 hour at 160 °C, presence of the intermediate IV in the reaction solution was confirmed by ^{1}H NMR measurements. Therefore, we have synthesized the intermediate IV by a known method[11] and performed its hydrothermal reaction at 160 °C. Monitoring the reaction by TLC and ^{1}H NMR measurements, we found that IV completely disappeared in 4 hours and the mixture of **2** and **3** was produced as mentioned in Table 1 (Scheme 2). Unfortunately, the isomers were not separable by silica gel column chromatography. Several methods of isomerization of substituted cyclopentenones have been previously reported. A method of isomerization using activated alumina was applied due to simplicity of the process.[14] An amount of activated basic alumina equivalent in weight was added to the mixture of **2** and **3** together with a small amount of water and the resultant mixture was heated at 50 °C for the isomerization of **3** to **2**, accompanied by the removal of alumina from the reaction mixture to give a single isomer **2** as a racemate (Scheme 3). The product was purified via high-performance liquid chromatography (HPLC) to yield (*R*)-**2** and (*S*)-**2** separately (see Supporting Information). The optical rotation of (*R*)-**2**, $[\alpha]_D^{26} = +33.0$ (c = 1.0 in ethanol), a matched previous report for (*R*)-**2**, $[\alpha]_D = +50$ (c = no data in ethanol),[8] but the sign of optical rotation of (*S*)-**2**, $[\alpha]_D^{19} = -34.3$ (c = 1.0 in ethanol) was opposite. We strongly believe that 2 has potential to be a key building block for the preparation of chemical products such as natural products, pharmaceuticals, flavors, etc.[14,15] In particular, many natural products which have physiological activity having C4-position substituted cyclopentenones as a central block or segments are known. As one example for application to the synthesis of natural products, we focused on prostaglandins which are currently produced enzymatically by using cyclooxygenase type I (COX-I) and type II (COX-II).[16] A lot of prostaglandins and derivatives have been synthesized and used as drugs.[9] Herein, we have demonstrated that **2** is a useful compound for achieving formal synthesis of prostaglandin E_1 (PGE_1)



Scheme 4. Synthesis of prostaglandin E_1 methyl ester (**9**). Reagents and Conditions: (a) Phosphorus tribromide (PBr_3), THF, 0 °C, 15 min; diethylamine, trimethylamine, room temperature (r.t.), 15 min; TESCl (TES = triethylsilyl), r.t., 30 min (42%, one-pot, 3 steps); (b) ω-chain (**5**), Et_2O, −78 °C, 20 min (70%); (c) α-chain (**7**), Triethylborane (Et_3B), *n*-Bu_3SnH, toluene, −20 °C, 3 h (56%); (d) Pyridinium *p*-toluenesulfonate (PPTS), acetone-H_2O (4:1), r.t., 6 h (82%).

(Scheme 4). **2** has two allyl-alcohol substituents: 2-hydroxylmethyl and 4-hydroxyl groups. First, we attempted to synthesize the core frame **4** step by step, but it was impossible to isolate each of them because of instability of the intermediates. Therefore, **4** was synthesized in a one-pot operation. This reaction is made up of three stages, 1) regioselective primary bromination with the minimum required amount of phosphous tribromide, 2) replacement of diethylamino and bromo groups, and 3) silylation of the secondary hydroxyl group. In this reaction, the second stage is particularly interesting. This conversion proceeds by double Michael addition and E_1cb elimination.[9d,17] As a result, we have successfully obtained **4** in 42% overall yield from (*R*)-**2** without any evaporation or solvent exchange. In addition, **4** was synthesized without isomerization under the same condition by using (*R*)-**2** obtained *via* optical resolution of **2** by HPLC. The key intermediate **4** is fairly similar to the key compound in the synthesis of PGE_1 reported by Sato *et al*.[9d] Therefore, we followed this synthetic approach: the two-component coupling process of Sato *et al*. Cuprate (**5**) was prepared from (*S*)-1-octyn-3-ol (97% *ee*)[9e] and (2-thieny)Cu(CN)Li reacted with **4** to produce the adduct **6**.[9d,9e,18] The conjugated adduct **8** was produced from **6** and the known α-chain unit (**7**) by radical reaction.[19] According to the report of Sato *et al.*, stereoselectivity was poor under heating. Furthermore, when tris(trimethylsilyl)silane or Et_3SiH were used as a hydride source, the substrate decomposed. Therefore, we carried out the reaction using *n*-tributyltin at low temperature, to obtain **8** stereoselectively. However, the chemical yield was moderate (56%) due to decomposition of product. The yield was further decreased when the reaction time was extended. On the other hand, when the reaction time was shortened, **6** remained. Finally, desilylation under mild conditions produced PGE_1 methyl ester (**9**). Its spectroscopic properties were identical with those described previously.[10] As reported by Spur *et al*, PGE_1 can be prepared from **9**.[18] In addition, we believe that **6** could be also reacted with organometallic reagents as reported previously.[20]

4. Conclusion

In conclusion, we have developed a novel method which avoids the use of catalysts, high pressure and high temperature, and produced **2** from 2-DG (**1**) in a one-pot operation. In addition, the reaction mechanism under hydrothermal treatment was elucidated. The key intermediate **4** obtained from (*R*)-**2** was used to prepare PGE_1 methyl ester (**9**). We also believe that if **2** were to be widely known, there could be more valuable and useful products produced from **2** as a building block. Currently, we are pursuing the conversion of products closer to biomass origin, such as glucose, into **2** to obtain large-scale processes for industrial applications. In addition, development of optical resolution method without using chiral HPLC is promoted for reduce the manufacturing costs is under way. These accomplishments demonstrate an example of the conscious use of an unnatural sugar. In addition, we proved that it is possible to create a more valuable compound by modifying some functional groups rather than directly utilizing biomass resources such as glucose. We are convinced that pushing forward research on conversion of modified sugars will lead to discovery of more valuable compounds in the field of biomass chemistry.

We would like to thank Emeritus Profs. Masahiro Hirama, Hachiro Nakanishi, Kunio Arai, and Assoc. Prof. Hiroshi Tada of Tohoku University and Dr. Hideo Hattori of FromSeeds Co., who provided fruitful discussion. We are very grateful to Prof. Fumi Nagatsugi, Prof. Hidetoshi Oikawa, Assoc. Prof. Ilya D. Gridnev, Assistant Prof. Anh T. N. Dao of Tohoku University and Dr. Kiyotaka Hatakeda of AIST, for their help on the compound measurements. This work was performed under the Cooperative Research Program of Network Joint Research Center for Materials and Devices.

Supporting Information

Copies of the ^{1}H NMR, ^{13}C NMR, HPLC analysis and GC-FID analysis of materials. This material is available on http://dx.doi.org/10.1246/bcsj.20180241.

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