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Formation of Five-Membered Carbocycles from D-Glucose: A Concise Synthesis of 4-Hydroxy-2-(hydroxymethyl)cyclopentenone

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Abstract

A concise synthesis of 4-hydroxy-2-(hydroxymethyl)cyclopentenone (**1**) has been accomplished from D-glucose by a three-step sequence that features a catalyst-free hydrothermal reaction of D-glucal, which is readily obtained from D-glucose. Optimization of the reaction conditions for synthesizing **1** was performed by changing the temperature and reaction time. The treatment of D-glucal under the optimal conditions, i.e., at 120 °C for 24 h, provided **1** in the highest isolated yield of 61%. **1** would become a versatile intermediate for the synthesis of various fine chemicals having a cyclopentenone structure from cellulosic biomass.

Keywords: Glucose conversion | Hydrothermal reaction | Biomass feedstock

1. Introduction

Cellulose is the main component of plant biomass resources and is therefore the most important consideration in the development of synthetic methods that convert biomass-derived feedstocks into valuable fine chemicals.[1–4] Cellulose is a polymeric compound composed of D-glucose units linked by β-1,4-glycosidic bonds. Accordingly, the hydrolysis of cellulose into D-glucose by homogeneous,[5] heterogeneous,[6] and enzymatic methods[7] has been intensively investigated as a means to produce D-glucose and its derivatives, including bioethanol,[8] sorbitol,[9] and 5-hydroxymethyl furfural (5-HMF).[10] However, these research efforts focused on the direct conversion of D-glucose, whereas our group has investigated the transformation of deoxy sugars that can be synthesized from D-glucose into valuable compounds.

Very recently, we reported the synthesis of 4-hydroxy-2-(hydroxymethyl)cyclopentenone (**1**). This disubstituted cyclopentenone can be obtained by hydrothermal reaction from 2-deoxy-D-glucose (2-DG), which is one of the most readily available industrial deoxy sugars.[11] Furthermore, the synthesis of prostaglandin E_1 methyl ester was achieved in six steps from **1**. Thus, we consider that **1** is a potential key synthetic intermediate not only for prostaglandins but also for a range of other bioactive compounds.

Many kinds of five-membered carbocyclic natural products have been discovered, including litseaverticillols, parthenin, and pentenomycins. These compounds have been previously synthesized via analogs of **1** as key intermediates (Figure 1).[12,13] However, analogs of **1** are currently synthesized from compounds derived from petroleum resources.[13] Therefore, the development of an efficient synthesis method for **1** from plant biomass resources would contribute to the industrial production of fine chemicals from non-petroleum resources using **1** as a feedstock.

Accordingly, in the present study, we developed a method for efficient synthesis of **1** from D-glucose—one of the most abundant biomass resources on Earth. We present a concise synthesis of **1** from D-glucose via a three-step reaction that involves the quantitative conversion of D-glucose into D-glucal

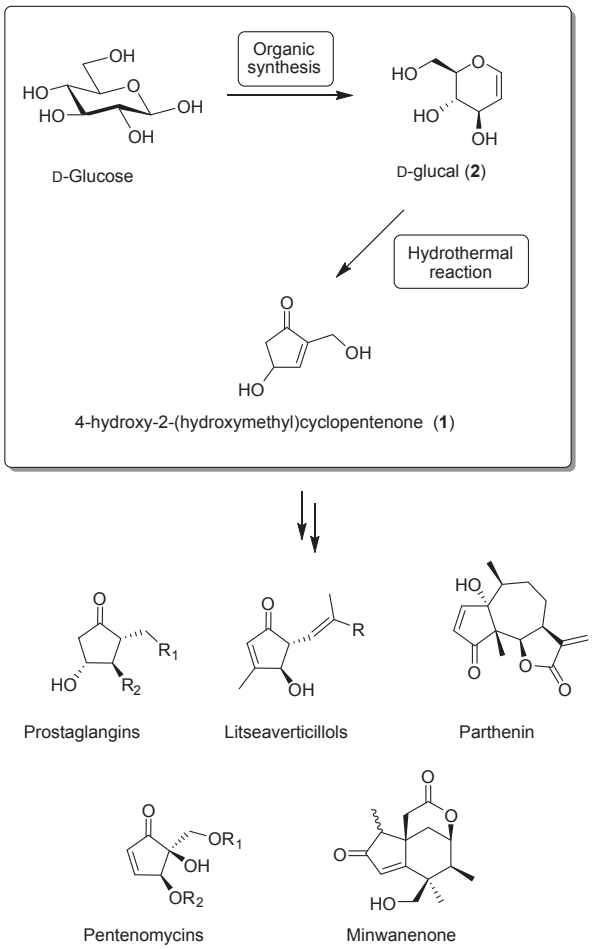


Figure 1. Synthesis of 4-hydroxy-2-(hydroxymethyl)cyclopentenone (**1**) from D-glucose and representative natural products containing the cyclopentenone structure.

and subsequent construction of the cyclopentenone structure via a catalyst-free hydrothermal reaction.

2. Experimental

Materials. D-Glucose, acetic anhydride (Ac_2O), copper(II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$), sodium hydrogen carbonate ($NaHCO_3$), and acetic acid (AcOH) were purchased from FUJIFILM Wako Pure Chemical Corporation. Sodium acetate (NaOAc), zinc powder, anhydrous magnesium sulfate ($MgSO_4$), anhydrous sodium sulfate (Na_2SO_4), methanol (MeOH), and ethyl acetate (EtOAc) were purchased from Nacalai Tesque, Inc. Hydrogen bromide (30% in AcOH, ca. 5.1 M) and sodium methoxide (NaOMe) were purchased from Tokyo Chemical Industry Co. Hydrogen chloride (HCl, 1.25 M in MeOH) was purchased from Sigma-Aldrich Co. Chloroform-*d* ($CDCl_3$) and acetone-d_6 were purchased from Acros Organics and Kanto Chemical Co., respectively. SEPABEADS^{TM} SP207 was purchased from Mitsubishi Chemical Corporation. Silica gel 60 F_{254} for thin-layer chromatography (TLC) was purchased from Merck Millipore. Silica gel 60 N (230–400 mesh) for flash chromatography was purchased from Kanto Chemical Co., Inc. All reagents were used without further purification. Sealed reactor (40 mL) was purchased from ACRAFT.

Instruments. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE-400 spectrometer. High-resolution mass spectrometry (HR-MS) was performed with a Bruker micrOTOF-Q II-S1 by electrospray ionization time of flight (ESI-TOF) reflectron experiment. Fourier Transform Infrared (FT-IR) spectra were performed by FT-IR-4200 (Jasco Corp.). Pellet samples for FT-IR were fabricated using KBr.

General Organic Synthesis Methods. Reactions were monitored by analytical TLC performed on 0.25-mm silica gel plates. Visualization of the developed plates was performed using UV absorbance at 254 nm and *p*-anisaldehyde solution. Flash chromatography was performed using silica gel with the indicated solvent systems. NMR spectra were calibrated using the residual undeuterated solvent as an internal reference ($CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C NMR; CD_3OD at 3.31 ppm for ^{1}H and at 49.00 ppm for ^{13}C NMR; acetone-d_6 at δ 2.05 ppm for ^{1}H and at δ 29.8 and 206.3 for ^{13}C NMR). The following abbreviations are used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

Tri-*O*-acetyl-D-glucal (2).[14,15] To a suspension of D-glucose monohydrate (2.00 g, 11.1 mmol) in Ac_2O (6.3 mL, 66.6 mmol) was added HBr in AcOH (ca. 5.1 M, 3.2 mL, 16.1 mmol) at room temperature. The reaction mixture was maintained for 2.5 h with vigorous stirring, during which time the suspended solid went into solution. This solution was then treated with additional HBr in AcOH (ca. 5.1 M, 9.0 mL, 46.0 mmol), and the resulting solution was stirred at room temperature for 16 h. Anhydrous NaOAc (3.6 g, 43.9 mmol) was then added to neutralize the excess HBr, and this mixture was added to a suspension of zinc power (11.6 g, 177 mmol), $CuSO_4 \cdot 5H_2O$ (0.799 g, 3.20 mmol), and anhydrous NaOAc (1.98 g, 23.0 mmol) in a mixture of water (10 mL) and AcOH (15 mL). The resultant reaction mixture was stirred vigorously at room temperature for 3 h. The solid was then removed by filtration and washed first with EtOAc and then with water. The organic layer of the filtrate was washed with saturated aqueous $NaHCO_3$ and brine and then dried (anhydrous Na_2SO_4). The solvent was removed under reduced pressure to provide tri-*O*-acetyl-D-glucal (**2**) (3.00 g, 11.0 mmol, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.05 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 4.20 (1H, dd, J = 12.0, 3.2 Hz), 4.24–4.28 (1H, m), 4.40 (1H, dd, J = 12.0, 8.0 Hz), 4.85 (1H, dd, J = 6.0, 3.2 Hz), 5.23 (1H, dd, J = 7.6, 5.6 Hz), 5.33–5.36 (1H, m), 6.47 (1H, dd, J = 6.0, 1.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.8, 20.9, 21.1, 61.4, 67.2, 67.5, 74.0, 99.0, 145.7, 169.7, 170.5, 170.7 ppm.

D-Glucal (3).[16–20] To a solution of tri-*O*-acetyl-D-glucal (1.1 g, 4.00 mmol) in MeOH (20 mL) was added NaOMe (10.8 mg, 0.2 mmol), and the mixture was stirred at room temperature for 5 h. The solution was then neutralized with 1.25 M HCl in MeOH and the solvent was concentrated under reduced pressure. The residue was purified using silica gel column chromatography with EtOAc to obtain D-glucal (**3**) (0.573 g, 3.92 mmol, 98%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.57 (1H, dd, J = 9.6, 7.2 Hz), 3.70–3.74 (1H, m), 3.79 (1H, dd, J = 12.0, 5.6 Hz), 3.88 (1H, dd, J = 12.0, 1.2 Hz), 4.12 (1H, ddd, J = 6.8, 2.0, 2.0 Hz), 4.68 (1H, dd, J = 6.4, 2.0 Hz), 6.35 (1H, dd, J = 6.0, 1.6 Hz) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ = 62.2, 70.5, 70.8, 80.3, 104.5, 144.9 ppm.

4-Hydroxy-2-(hydroxymethyl)cyclopentenone (1).[11] The crude D-glucal (**3**) (*ca.* 4.00 mmol) in distilled water (20 mL) was poured into a sealed reactor. The reactor was placed in a preheated dry oven at 100–160 °C and allowed to stand without stirring for 1–72 h. After the period of time indicated, the reactor was removed from the oven and cooled in water to terminate the reaction. The reaction mixture was filtered, and the filtrate was applied to a column of SEPABEADS^{TM} SP207 (15 g) to remove coloring components. The product was eluted with water (500 mL), which was then removed under reduced pressure, and the residue was purified using silica gel column chromatography (EtOAc/MeOH = 20:1) to obtain **1**, **4**, and **5** as a colorless oil. **1**: ^{1}H NMR (400 MHz, acetone-d_6): δ 2.18 (1H, dd, $J = 18.4$, 2.0 Hz), 2.72 (1H, dd, $J = 18.4$, 6.0 Hz), 4.07 (1H, t, $J = 5.6$ Hz), 4.21–4.23 (2H, m), 4.46 (1H, d, $J = 6.0$ Hz), 4.90–4.94 (1H, m), 7.36–7.37 (1H, m) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ 46.0, 56.9, 68.7, 147.7, 157.7, 205.4 ppm. HR-MS (ESI-TOF): m/z calcd. for $C_6H_9O_3$ ($[M + H]^+$), 129.0546, found 129.0552. **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (1H, brs), 2.53 (1H, brs), 3.88–3.90 (2H, m), 4.82 (1H, t, $J = 5.6$ Hz), 6.33–6.34 (1H, m), 6.36 (1H, dd, $J = 6.4$, 1.6 Hz), 7.40 (1H, dd, $J = 1.6$, 0.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1, 68.4, 107.1, 110.4, 142.4, 153.6 ppm.

Isomerization Reaction 4 into 1. To the mixture of **1** and **4** was added the same amount of activated basic alumina and 10 w/v % of distilled water was added to the mixture and stirred at 50 °C for 5 h. The resultant mixture was diluted with 2-propanol (25 mL × 4) and filtered (filter paper, 0.4 µm) to remove the alumina. The solvent was removed under reduced pressure to provide **1** as a single isomer in quantitative yield.

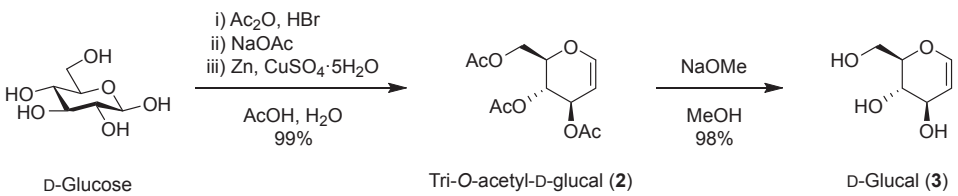
Conversion to 1 and 4 from 5. A solution of furan **5** (363 mg, 2.83 mmol) in distilled water (14 mL) was poured into a sealed reactor. The reactor was placed in a preheated dry oven at 120 °C and allowed to stand without stirring for 12 h. After the reaction, the same purification procedure for synthesis of **1** was performed to provide a mixture of **1** and **4** (152 mg, 1.19 mmol, 42%) as colorless oil.

3. Results and Discussion

As shown in Scheme 1, our synthesis of **1** begins with the transformation of D-glucose into tri-*O*-acetyl-D-glucal (**2**) and removal of the acetyl group of **2** to obtain D-glucal (**3**) according to the literature.[14–20] Briefly, D-glucose was converted into **2** with 99% yield by a one-pot, three-step procedure that involved acetylation with acetic anhydride in HBr/AcOH followed by transformation of the anomeric acetates to the corresponding bromides with additional HBr/AcOH and finally reductive elimination of the 1-bromo and 2-acetoxy groups with $Zn/CuSO_4 \cdot 5H_2O$ in AcOH/water containing NaOAc. Then, deprotection of the acetyl group of **2** using NaOMe/MeOH affords **3** in 98% yield.

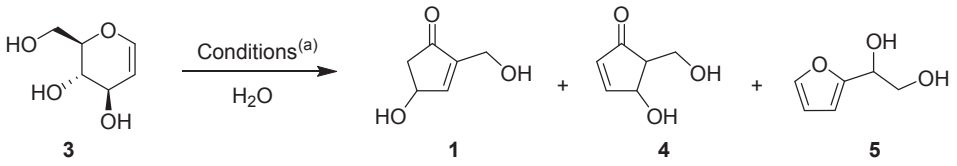
Table 1 shows the conditions for the conversion of **3** into **1**. In the hydrothermal treatments, the concentration of **3** was fixed at 0.2 M and the reaction conditions were optimized by changing the temperature and reaction time. An aqueous solution of **3** was loaded into a sealed reactor and placed in a constant-temperature drying oven at a reaction temperature in the range 100–160 °C. After the reaction, the reactor was rapidly cooled in an ice-water bath and the reaction mixture was filtered to remove any insoluble solids. The filtrate was loaded onto a resin column and eluted with water several times until it became colorless. After removal of water and purification of the residue by silica gel chromatography, cyclopentenone **1** was afforded with its isomer **4**. **1** and **4** were not separable, however, the isomerization of **4** to **1** was achieved using activated alumina to afford a single isomer. After hydrothermal reaction, the solid which was not soluble in general organic solvents was obtained as byproduct. The FT-IR spectrum of the insoluble solid showed the existence of carbonyl and hydroxy groups similar to that of **1** (Figure S1). Thus, the insoluble solid was predicted as the polymerized compounds of **1** or **4**. At the lower temperatures of 100 and 120 °C (Entries 1–13), a long reaction time was required to maximize the yield of **1**. At the condition of 100 °C for 72 h (Entry 7), Formation of insoluble solid (22 mg) was observed and consequently we assessed that it would be difficult to improve the yield with reaction times longer than 72 h at 100 °C. At the higher temperatures of 140 and 160 °C (Entries 14–24), the maximal yield was achieved in a relatively short time, though the decomposition of products proceeded faster than at low temperatures. Overall, the reaction at 120 °C for 24 h (Entry 12) afforded **1** in the highest isolated yield of 61%. Hence, **1** was synthesized in 59% yield over three steps from D-glucose while the total yield of **1** in the previous report was 36% over five steps.[11,21] In addition, even if the reaction volume was 10 fold greater, **1** was obtained in 55% yield at the optimized reaction condition (See Supporting Information).

The ratio of cyclopentenone **1** and its isomer **4** was determined by ^{1}H NMR. A significant difference was observed in the ratio depending on the reaction time. For shorter reaction times, the **1**/**4** ratio was very similar. Conversely, for longer reaction times, the amount of **1** produced was significantly higher. This result indicates that an equilibrium between **1** and **4** in the presence of water is established with time, and that the thermodynamically more stable **1** can be preferentially obtained by extending the reaction duration. In fact, according to DFT calculations, **1** showed higher thermodynamic stability than **4** (Figure S6). When the reaction was stopped before the formation of the cyclopentenone was completed, furan **5** was



Scheme 1. Synthesis of D-glucal (**3**).

Table 1. Effect of the reaction temperature and reaction time on the yields of **1**.



Entry	Temp. (°C)	Time (h)	Solid (mg)	Yield (%)[b]	Ratio (**1**/**4**)[c]	**5** (%)[d]
1	100	1	7	n.d.	-	1
2		3	5	n.d.	-	7
3		7	0	n.d.	-	21
4		12	6	16	1 : 2.16	24
5		24	1	32	1 : 0.88	17
6		48	2	31	1 : 0.15	14
7		72	22	50	1 : 0.11	2
8	120	1	3	n.d.	-	15
9		3	1	n.d.	-	11
10		7	4	24	1 : 0.87	20
11		12	22	52	1 : 0.57	6
12		24	23	61	1 : 0.17	1
13		48	95	41	1 : 0.04	0.3
14	140	1	3	n.d.	-	3
15		3	0	42	1 : 1.20	7
16		7	35	55	1 : 0.41	1
17		12	37	55	1 : 0.12	1
18		24	66	47	1 : 0.06	0
19	160	1	3	n.d.	-	11
20		3	20	30	1 : 0.19	14
21		5	63	47	1 : 0.10	1
22		7	74	54	1 : 0.04	0
23		12	145	43	1 : 0.06	0
24		24	199	21	1 : 0.06	0

(a) Unless stated otherwise, reactions were performed as follows: An aqueous solution of D-Glucal (**3**) (4.0 mmol) in H_2O (20 mL, 0.2 M) at indicated temperature and for indicated time without stirring. (b) Isolated yield of **1** including **4**. (c) Ratio of **1** and **4** was determined by ^1H NMR analysis. (d) Isolated yield of **5**. n.d. = not detected.

found to be present in significant amounts. The conversion of **3** into **5** has been reported by treatment of **3** with $FeCl_3$.[22] Hydrothermal reaction of isolated **5** at 120 °C for 24 h afforded **1** and **4** in 42% yield. Therefore, we regarded **5** as one of the intermediates during the conversion of **3** into **1**. In addition, the specific optical rotation of **5** isolated after hydrothermal reaction observed racemic $\{[\alpha]_D^{23} = +0.04$ (c = 1.0 in $CHCl_3)\}$, whereas the value of **5** prepared by the reaction with $FeCl_3$ was $[\alpha]_D^{23} = +32.9$ (c = 1.0 in $CHCl_3$); lit.[23] $[\alpha]_D = +36.0$ (c = 1.0 in $CHCl_3$).

Given these experimental facts, we constructed a reaction mechanism of the synthesis of **1** (Figure 2). Firstly, 2-DG is formed by a hydration reaction of **3**, and then dehydration of 2-DG affords α,β-unsaturated aldehyde. When the aldehyde forms *Z*-isomer, cyclization occurs and following dehydration of the cyclized product affords the intermediate furan **5**. After that, the furan ring is opened by hydration and cyclized by intramolecular aldol reaction to form a five-membered carbocycle **4** (pathway A). At the same time, retro reaction also occurs to form racemic **5** (pathway B). Finally, an equilibrium reaction occurs between **1** and **4**, and then thermodynamically more stable **1** can be preferentially obtained.

4. Conclusion

A new concise synthesis of 4-hydroxy-2-(hydroxymethyl)-cyclopentenone (**1**) was achieved from D-glucose through a

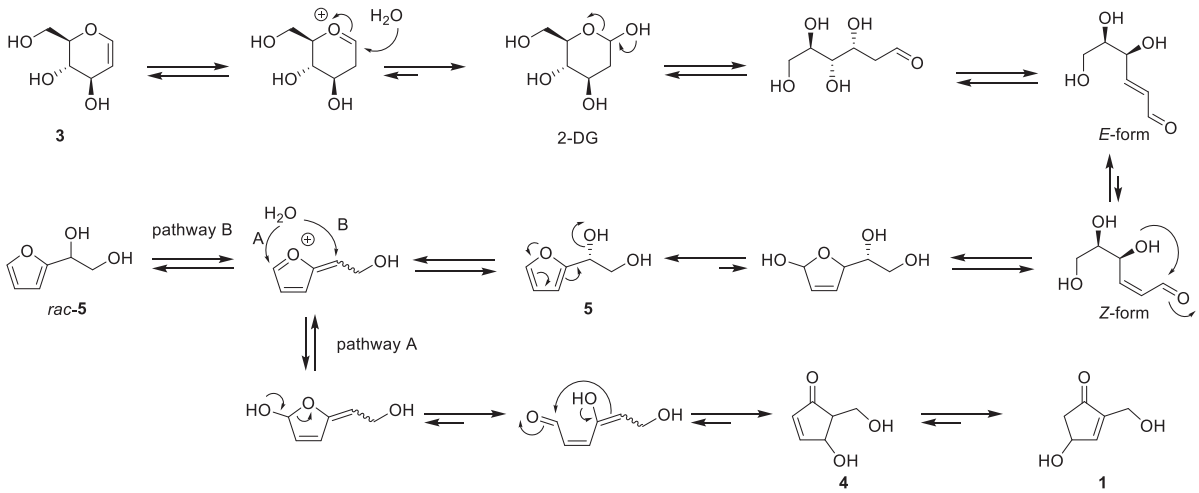


Figure 2. Proposed reaction mechanism of the synthesis of **1**.

three-step conversion in 59% overall yield. For the hydrothermal reaction of D-glucal (**3**) to **1**, the key reaction, reaction conditions in the temperature range 100–160 °C and the reaction time range 1–72 h were assessed in order to optimize the yield. The reaction at a temperature of 120 °C for 24 h afforded **1** from D-glucal in the highest isolated yield of 61% in the present study. The main advantage of the present study is that we succeeded in the short-step synthesis of five-membered carbocyclic compound from D-glucose instead of the common biomass-derived furans such as sorbitol or 5-HMF, etc. We believe that **1** would become a versatile intermediate for the production of various fine chemicals using cellulosic biomass as a feedstock. The synthesis of different cyclopentenones from **1** is now in progress in our group to realize the production of fine chemicals based on non-petroleum resources.

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Supporting Information

^{1}H and ^{13}C NMR spectra are available on https://doi.org/10.1246/bcsj.20190063.

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