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Synthesis of Levoglucosenone

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Levoglucosenone was synthesized from D-galactose via reductive decarboxylation as a key reaction. Among the catalysts used for the key reaction, hydrous zirconium oxide was found to have the best activity.

Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose, **1**) is known as a major product of the acid-catalyzed pyrolysis of cellulose and its related carbohydrates.[1] **1** is an optically active enone and its other functional groups, that is, hydroxy and carbonyl groups, are protected by intramolecular acetal. Therefore, **1** has been interesting to synthetic organic chemists and has been used as a starting material for optically active compounds.[2] The preparation of **1** was conventionally carried out at 300—500 °C with phosphoric acid derivatives, however, the yield of **1** was very low. Since it was difficult to heat the voluminous solid reactant (cellulose etc.) homogeneously, **1** could not be obtained efficiently on a large scale. Furthermore, a large volume of the residue was always left in the reactor.

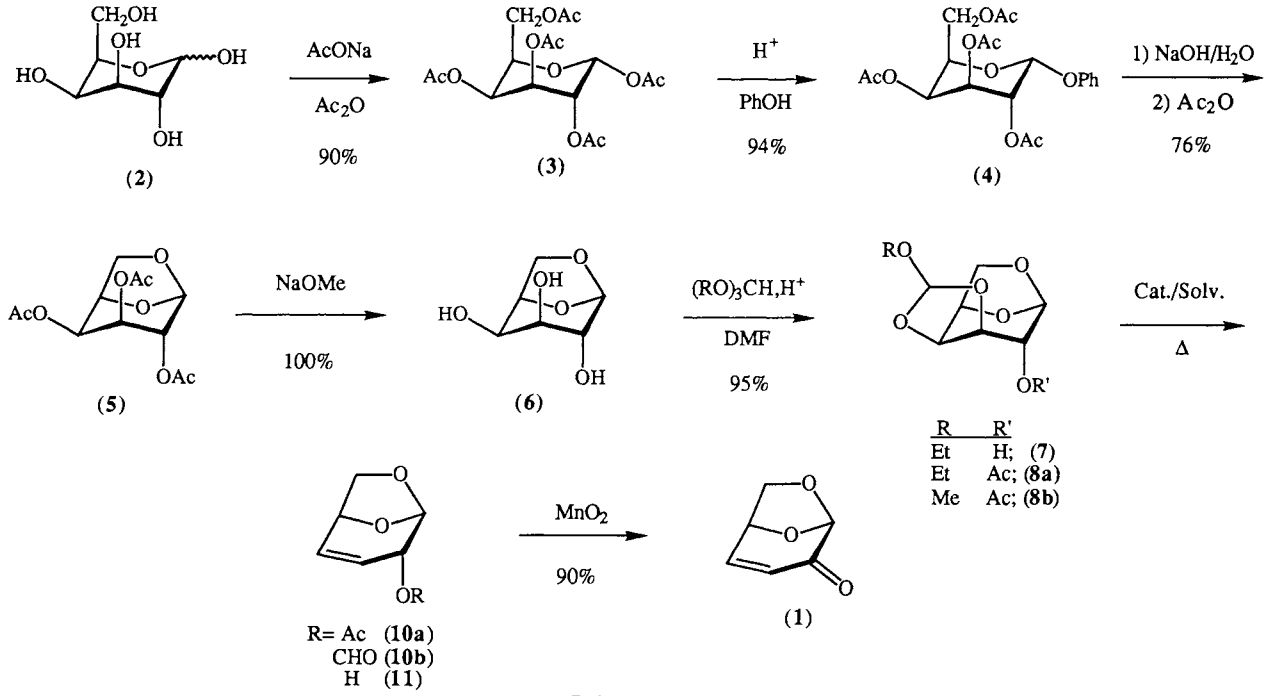
In this paper, we report that **1** is synthesized from D-galactose (**2**). The synthetic route is shown in Scheme 1, which includes the catalytic reductive decarboxylation of the acetoxyacetal derivative as a key reaction. Several catalysts were examined for the key reaction, and hydrous zirconium oxide resulted as the best catalyst.

Phenyl 2,3,4,6-tetraacetyl-β-D-galactopyranoside (**4**) was prepared by the reaction of 1,2,3,4,6-pentaacetyl-β-D-galactopyranose (**3**), which was derived from **2** in 90% yield,[3] with phenol in 94% yield, and 1,6-anhydro-2,3,4-triacetyl-β-D-galactopyranose (**5**) was obtained in 76% yield by the treatment of **4** with aqueous sodium hydroxide at 100°C followed by the acetylation with acetic anhydride in a manner similar to the preparation of 1,6-anhydro-2,3,4-triacetyl-β-D-glucopyranose.[4] After deacetylation of **5** by sodium methoxide, 1,6-anhydro-β-D-galactopyranose (**6**) reacted with 4 equivalents of triethyl orthoformate in N,N-dimethylformamide in the presence of one drop of sulfonic acid at room temperature for 12 h. The reaction mixture was neutralized by aqueous sodium bicarbonate, and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give 95% of 1,6-anhydro-β-D-galactopyranose 3,4-ethoxyacetal (**7**) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ= 1.23 (3H, t), 3.59 (2H, m),

3.60 (1H, dd), 3.83 (1H, d), 3.92 (1H, s), 4.25 (1H, d), 4.50 (1H, t), 4.63 (1H, t), 5.37 (1H, s), 5.75 (1H, s); ^{13}C NMR ($CDCl_3$): δ= 14.7 (q), 60.8 (t), 63.4 (t), 68.8 (d), 69.5 (d), 71.2 (d), 74.4 (d), 100.8 (d), 114.4 (d).

In order to purify **7**, acetylation was carried out with acetic anhydride in pyridine and a quantitative yield of 1,6-anhydro-2-acetyl-β-D-galactopyranose 3,4-ethoxyacetal (**8a**) was obtained as a needle; mp 94.0–94.5 °C; $[\alpha]_D$ -8.9 (c 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ= 1.28 (3H, t, J= 7.1 Hz), 2.12 (3H, s), 3.64 (1H, dd, J= 5.9, 7.6 Hz), 3.74 (2H, m), 4.08 (1H, d, J= 6.7 Hz), 4.42 (1H, t, J= 6.1 Hz), 4.56 (1H, t, J= 5.5 Hz), 4.60 (1H, d, J= 6.1 Hz), 4.98 (1H, s), 5.39 (1H, s), 5.75 (1H, s), ^{13}C NMR ($CDCl_3$): δ= 15.2 (q), 21.0 (q), 61.3 (t), 63.8 (t), 69.9 (d), 70.5 (d), 72.1 (d), 72.6 (d), 98.9 (d), 114.9 (d), 169.5 (s). The 3,4-methoxyacetal derivative (**8b**) was also synthesized in a similar manner as described above; ^1H NMR ($CDCl_3$): δ= 2.13(3H, s), 3.34 (3H, s), 3.65 (1H, dd, J= 4.2, 7.9 Hz), 3.90 (1H, d, J= 7.9 Hz), 4.21 (1H, d, J= 6.7 Hz), 4.56 (1H, dd, J= 4.2, 5.7 Hz), 4.62 (1H, dd, J= 5.7, 6.7 Hz), 4.98 (1H, s), 5.40 (1H, s), 5.79 (1H, s); ^{13}C NMR ($CDCl_3$): δ= 21.1 (q), 52.8 (q), 63.8 (t), 69.9 (d), 70.4 (d), 72.1 (d), 72.7 (d), 98.9 (d), 115.7 (d), 169.4 (s).

The catalytic reductive decarboxylations of **7**, **8a**, and **8b** were carried out under the following conditions; in a 25 cm^3 round-bottom flask, 0.5 mmol of **7**, **8a**, or **8b** was dissolved in the solvent (4 cm^3) with 0.1 mmol of decane as an internal standard. After adding 1.0 g of the catalyst, the content was refluxed for 4 h, and the products were analyzed by gas chromatography. The yields of 1,6-anhydro-2-acetyl-3,4-dideoxy-β-D-erythro-hex-3-enopyranose (**10a**) or its 2-formyl derivative (**10b**) are listed in Table 1. The structure of **10a** was determined by ^1H and ^{13}C NMR after distillation; bp 64 °C (2 mmHg), $[\alpha]_D$ -232.4 (c 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$): δ=

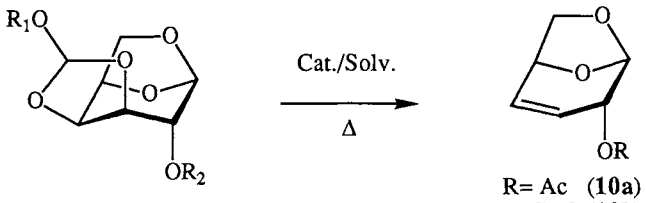


Scheme 1.

2.03 (3H, s), 3.67 (1H, d, J= 6.7 Hz), 3.63 (1H, ddd, J= 1.2, 6.7, 4.0 Hz), 4.67 (1H, d, J=3.9 Hz), 4.69 (1H, dd, J= 4.7, 4.0 Hz), 5.46 (1H, bs, J= 1.9 Hz), 5.70 (1H, ddd, J= 1.9, 3.9, 9.9 Hz), 6.26 (1H, ddd, J= 1.1, 4.7, 9.9 Hz); ^{13}C NMR ($CDCl_3$): δ= 21.2 (q), 66.6 (t), 69.3 (d), 70.6 (d), 100.4 (d), 122.9 (d), 132.6 (d), 170.0 (s).

Among the examined catalysts, hydrous zirconium oxide[5] served as the best catalyst for the reductive decarboxylation of **7**, **8a**, and **8b**; and **10a** or **10b** was

Table 1. The Reductive Decarboxylations of **7**, **8a**, and **8b**[a]



R_1 = Et R_2 = H (**7**)
Et Ac (**8a**)
Me Ac (**8b**)
Et Ms (**12**)

R= Ac (**10a**)
CHO (**10b**)
Ms (**13**)

Reactant	Catalyst	Solvent	Product	Yield/%
7	-	Ac_2O	**10a**	8
7	Zr[b]	Ac_2O	**10a**	88
7	Zr-4[c]	Ac_2O	**10a**	63
7	SiO_2	Ac_2O	**10a**	10
7	Al_2O_3	Ac_2O	**10a**	20
7	Zeolite	Ac_2O	**10a**	15
7	Ti[d]	Ac_2O	-	tr.
7	Py	Ac_2O	**10a**	1.3
8a	AcOH	Ac_2O	**10a**	55
8a	Zr[b]	Ac_2O	**10a**	86
8a	H_2SO_4	Ac_2O	-	0
8a	H_3PO_5	Ac_2O	**10a**	6
8a	$TiCl_4$	Ac_2O	**10a**	8
8a	-	DMF	-	0
8a	Zr[b]	DMF	**10b**	55
8a	Zr[b]	Tol.	-	tr.
8a	Zr[b]	Xyl.	-	0
8a	Zr[b]	Diglyme	-	0
8a	Zr[b]	Dioxane	-	0
8a	Zr[b]	Tol.+Ac_2O[e]	**10a**	27
8b	Zr[b]	Ac_2O	**10a**	85

a) Reactant; 0.5 mmol, Solvent; 4 cm^3, Catalyst; 0.1 g, Reflux for 4 h. b) Hydrous zirconium oxide calcined at 300 °C. c) Hydrous zirconium oxide calcined at 400 °C. d) Hydrous titanium oxide e) Toluene : Ac_2O = 1 : 1.

obtained in a high yield. The preparation of 1,6-anhydro-3,4-dideoxy derivative (**13**) was reported to be obtained by the reductive decarboxylation of ethoxyacetal derivative (**12**),[6] however, the yield of **13** was very low because of the high reaction temperature (150–180 °C) needed. In our catalytic method, the reaction temperature was relatively low (ca. 110 °C), and a yield of over 80% could be reached. These reactions were reported to be difficult to proceed directly from **6** *via* **7** without protection of the hydroxy group,[6] however, they could proceed effieciently by our method. The best result was obtained by use of acetic anhydride as a solvent.

After deacetylation of **10a** by sodium methoxide, 1,6-anhydro-3,4-dideoxy-β-D-erythro-hex-3-enopyranose (**11**) was oxidized by manganese dioxide by use of the reported method,[7] and **1** was obtained in 80% yield.

In conclusion, the method shown in Scheme 1 was useful for the preparation of **1** on a large scale, and the total yield of **1** from **2** was relatively high (ca. 50%). It was considered that our synthetic method could lead to the advance of synthetic chemistry utilizing levoglucosenone as a starting material.

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