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Note

Magnesium-mediated Wittig reagent-promoted Stereoselective synthesis of L-Sorbopyranoses from D-Glucopyranoses

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ABSTRACT

L-Sorbose is an important rare sugar that exists in some natural products and widely used in pharmaceutical and chemical industries. Herein, two simple and practical routes were developed using cheap magnesium (II) for the synthesis of 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose from 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose with high stereoselectivity and yield. The first route involved the intramolecular hydride shift from C5 to the C1 of the glucopyranose precursor. Wittig reagent ($PPh_3CHCOOBn$) was used to combined with Mg(II) to promote this isomerization reaction from D-glucopyranose to L-sorbopyranose in the alternative route.

1. Introduction

Carbohydrates are essential functional groups in many natural products, drug intermediates, and fine chemicals, as well as exhibit extremely diverse activities in numerous biological processes such as immune responses, inflammatory, microbial virulence, and so on [1,2]. According to the classification of International Society of Rare Sugars (ISRS), mannose, xylose, glucose, galactose, ribose, fructose, xylose and arabinose of all possible pentoses and hexoses are considered to occur abundantly in nature, while other 9 pentoses and 20 hexoses are categorized as rare sugars due to the limited amounts in nature [3]. Some rare sugars such as tagatose and sorbose have very high commercial importance irrespective of their shallow natural occurrence and have been widely used as food additives, cosmetics, fuel and medicines [4]. Besides, L-sorbose is one of the most important natural rare sugars as the L-carbohydrates. L-Sorbose is primarily used as a starting material for the preparation of vitamin C in pharmaceutical industry [5]. The biotransformation of D-sorbitol by *Gluconobacter suboxydans* into L-sorbose is a key step towards the synthesis of vitamin C by Reichstein method [6]. A series of work has been reported on this biotransformation process [7–9], however, the synthesis of ketopyranoses by modifying the appropriate aldose derivatives remains an undisclosed problem in carbohydrate chemistry. Hence, the development of simple and practical chemical methods with high efficiency and stereoselectivity would increase the availability of rare sugars for furnishing carbohydrate research and understanding the functions of carbohydrates [10].

The general synthetic routes for L-sorbose are outlined in Scheme 1. Some approaches toward L-sorbose have been reported previously. In 1989, Casiraghi group reported the conversion of 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose into 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose using a large molar excess of *tert*-butoxide magnesiumbromides (5 equiv) [11]. A hard accessible catalyst with a high amount (5 equiv) was required for this method (Scheme 1A). In 1996, Iadonisi group presented a simple transformation of aldohexopyranose to ketohexopyranose induced by air-oxidized samarium diiodide. However, dry air is necessary for this transformation, and the stereoselectivity was very poor with the mixture of α and β anomers (Scheme 1B) [12,13]. Very recently, Gounder group developed a heterogeneous isomerization reaction to prepare L-sorbose using titanium zeolites [14]. These reports inspire us to explore the alternative strategy to access L-sorbose with high stereoselectivity and yield by a homogeneous sub-stoichiometric manner. We envisioned two routes to synthesize 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose from 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose using cheap Mg^nBu_2. The first route involved magnesium (II)-mediated intramolecular isomerization of the glucopyranose precursor toward sorbopyranose. The other route used Wittig reagent combined with Mg(II) to promote this isomerization process (Scheme 1C).

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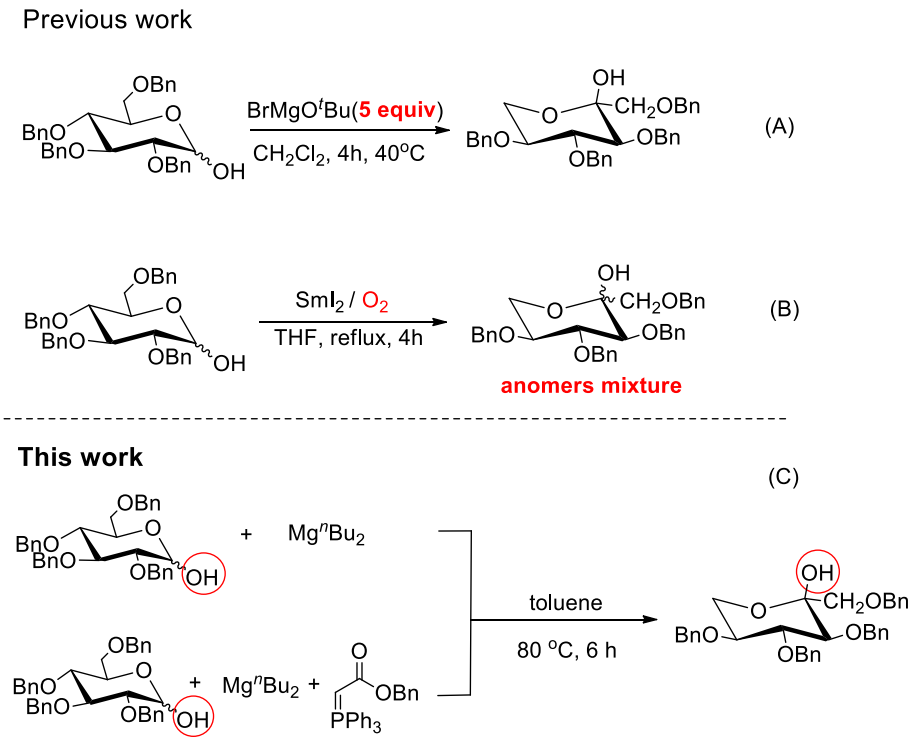


Scheme 1. Synthesis of 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose.

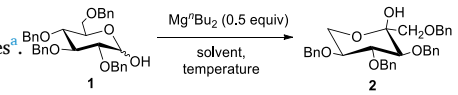
2. Result and discussion

Initially, 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose **1** and Mg^nBu_2 (0.5 equiv) were used for optimizing the reaction conditions. As shown in Table 1, the desired product **2** could be acquired under non-polar solvents such as toluene, DCE, CH_2Cl_2, and dioxane (Table 1, entries 1–4). Using toluene as solvent gave the best yield (80%) at 80 °C (Table 1, entry 1). L-Sorbose **2** could not be obtained when polar solvents were used, including CH_3CN, DMSO, and DMF (Table 1, entries 5–7). Different temperatures also affected the yield of L-Sorbose and maximum yield was obtained at 80 °C (Table 1, entries 8–10). Changing the loading of Mg^nBu_2 could not further increase the yield of L-sorbose (Table 1, entries 11–12).

Subsequently, different Wittig reagents and their amounts were screened to promote this isomerization process in Table 2. If 10 mol% of benzyl 2-(triphenylphosphoranylidene) acetate was used as the additive, the yield of **2** would be increased from 80% to 92% (Table 2, entry 1). The yield could be slightly declined using ethyl 2-(triphenylphosphoranylidene) acetate and methyl 2-(triphenylphosphoranylidene) acetate as Wittig reagents (Table 1, entries 2–3). However, this transformation would become very sluggish using ethyl 2-(triphenylphosphoranylidene) propanoate as Wittig reagent and D-glucose was still left (Table 1, entry 4). Compared to alkyl Wittig reagents, 1-phenyl-2-(triphenylphosphoranylidene) ethanone could promote this reaction albeit the lower yield (Table 2, entry 5). In addition, the amount of Wittig reagents also affected the yield of L-sorbose. When 5 mol% of benzyl 2-(triphenylphosphoranylidene) acetate was used as the additive, the yield of **2** would be dropped from 92% to 78% (Table 2, entry 6). More amounts of Wittig reagent (40 mol% and 100 mol%) could not increase the yield and even slowed the reaction using stoichiometric

Table 1

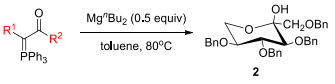
Optimization of different solvents and temperatures[a].

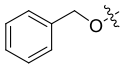
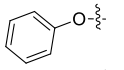
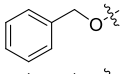
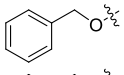
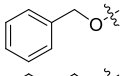
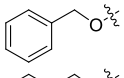
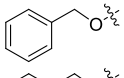
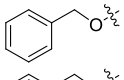
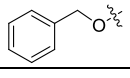


Entry	Solvent	Temperature (°C)	Yield (%)[b]
1	Toluene	80	80
2	DCE	80	78
3	CH_2Cl_2	40	46
4	Dioxane	80	34
5	CH_3CN	80	trace
6	DMSO	80	trace
7	DMF	80	trace
8	Toluene	40	55
9	Toluene	60	68
10	Toluene	100	73
11[c]	Toluene	80	43
12[d]	Toluene	80	72

[a] The reaction conditions: 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose **1** (0.1 mmol), Mg^nBu_2 (0.05 mmol), solvent (1 mL), temperature for 6 h.
[b] The yield was determined by HPLC analysis.
[c] 0.25 equiv Mg^nBu_2 was used.
[d] 1.0 equiv Mg^nBu_2 was used.

Table 2
Optimization of Wittig reagents with different amounts[a].



Entry	R^1	R^2	Wittig reagent Amount (mol%)	Yield (%)[b]
1	H		10.	92
2	H	H_3CH_2CO	10	83
3	H	H_3CO	10	86
4	CH_3	H_3CH_2CO	10	54
5	H		10	79
6	H		5	78
7	H		40	85
8	H		100	21
9[c]	H		10	49
10[d]	H		10	68
11[e]	H		10	77
12[f]	H		10	78

[a] Standard conditions: 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose **1** (0.1 mmol), Mg^{n}Bu$_2$ (0.05 mmol), toluene (1 mL), 80 °C for 6 h.
[b] The yield was determined by HPLC analysis.
[c] 0.25 equiv Mg^{n}Bu$_2$ was used.
[d] 1.0 equiv Mg^{n}Bu$_2$ was used.
[e] The reaction was performed at 60 °C for 6 h.
[f] The reaction was performed at 100 °C for 6 h.

Wittig reagent, which may due to the formation of *C*-glycoside as by-product (Table 2, entries 7–8). The Mg^{n}Bu$_2$ loading and reaction temperature were further screened, and the yield would be dropped excluding the standard conditions (Table 2, entries 9–12).

Next, we explored the gram-scale preparation of L-sorbose in Scheme 2. The isomerization reaction could be performed on the gram scale. Treating with **1** (2 mmol, 1.08 g) by Mg^{n}Bu$_2$ (0.5 equiv), L-Sorbose **2** was isolated in 76% yield after column purification (Scheme 2A). If additional benzyl 2-(triphenylphosphoranylidene) acetate (10 mol%) was added to the mixture as additive, **2** was isolated in 87% yield after column purification (Scheme 2B). Surprisingly, *C*-glycoside (**2'**) could also be acquired as by-product after column purification, which hinted that Wittig reagent may promote the isomerization transformation from aldehydo-sugar intermediates [15].

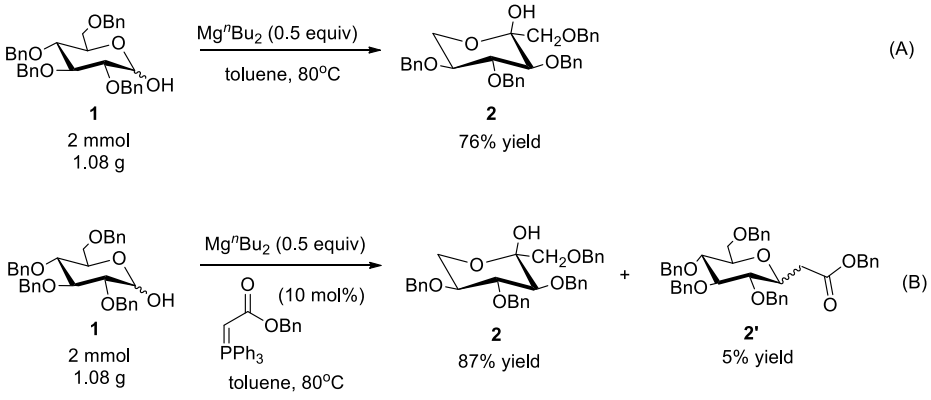
Based on above results, a general mechanism for this isomerization reaction is proposed in Scheme 3. Initially, Mg^{n}Bu$_2$ could coordinate with the two oxygen of 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose (**1**) to afford intermediate **A**. Then the aldehydo-sugar complex (**B**) is formed by a ring opening process from intermediate **A**. An intramolecular hydride shift occurs from C5 to C1 of the glucopyranose precursor (C2 to C6 of the sorbopyranose product) to give the keto-sugar complex (**C**) by a formal Meerwein-Ponndorf-Verley/Oppenauer reaction. 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose (**2**) could be acquired from the keto-sugar complex (**C**). The driving force of this transformation may attribute to the different stability of sorbose (**2**) and glucose (**1**). We found Wittig reagent reacted with the aldehydo-sugar complex (**B**) to generate intermediate **D**, which may simultaneously accelerate the ring-opening process from intermediate **A** to aldehydo-sugar complex (**B**). *C*-glycoside (**2'**) could be obtained from intermediate **D** as by-product.

3. Conclusion

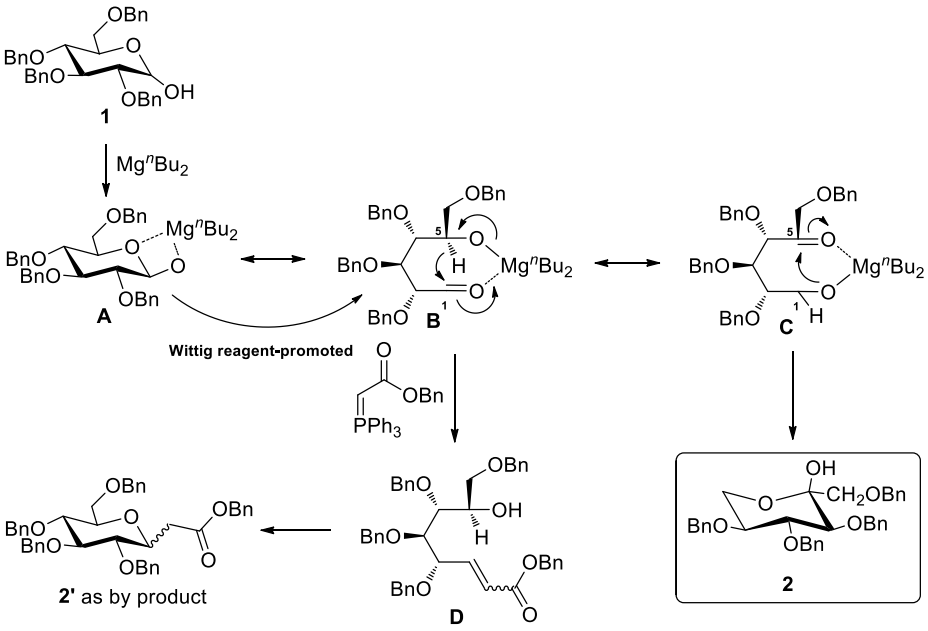
In summary, we have developed two novel methods for the synthesis of 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose using cheap magnesium (II). The first route involved the intramolecular hydride shift from C5 to C1 of the glucopyranose precursor. The other route used Wittig reagent combined with magnesium (II) to promote this isomerization reaction from 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose to 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose. Both approaches are very simple and practical with high stereoselectivity and yield. It could potentially be used for the large-scale synthesis of L-sorbose in pharmaceutical and chemical industries.

4. Experimental section

General Experimental Methods. Unless otherwise noted, all reactions in non-aqueous media were conducted in glassware that had been oven dried prior to use. Anhydrous solutions were transferred *via* an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Thin layer chromatography was performed using precoated silica gel plates and visualized with UV light at 254 nm. Flash column chromatography was performed with silica gel (40–60 μm). ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Bruker Avance II 400 MHz or Bruker Avance III 500 MHz recorded in ppm (δ) downfield of TMS ($\delta = 0$) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet(t), quartet (q), quintet (quint), multiplet (m), and broad (br) with coupling constants (*J*) in hertz (Hz). High resolution mass spectra



Scheme 2. Synthesis of 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose.



Scheme 3. Proposed mechanism for the magnesium-mediated isomerization reaction.

(HRMS) were performed by Agilent apparatus on an Electron Spray Injection (ESI) mass spectrometer.

General procedure for the synthesis of 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose (**2**).

Method I: To the solution of 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose (**1**) (1.08 g, 1 equiv, 2 mmol) in toluene (20 mL) was added Mg^{n}Bu$_2$ (1 mL, 1.0 mol/L, 0.5 equiv, 1 mmol) slowly. The mixture was heated to 80 °C for 6 h, then quenched by saturated NH_4Cl solution (20 mL). The mixture was extracted with EtOAc. The combined organic extracts were washed by brine, dried over anhydrous $NaSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/hexane) gave 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose (**2**) (821 mg, 76% yield) as colorless oil.

Method II: To the solution of 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose (1) (1.08 g, 1 equiv, 2 mmol) in toluene (20 mL) was added Mg^{n}Bu$_2$ (1 mL, 1.0 mol/L, 0.5 equiv, 1 mmol) and benzyl 2-(triphenylphosphoranylidene) acetate (82 mg, 10 mol%, 0.2 mmol). The mixture was heated to 80 °C for 6 h, then quenched by saturated NH_4Cl solution (20 mL). The mixture was extracted with EtOAc. The combined organic extracts were washed by brine, dried over anhydrous $NaSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) gave 1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose (**2**) (940 mg, 87% yield) as colorless oil and benzyl 2-((*3S*,*5R*,*6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl) acetate (**2'**) (67 mg, 5% yield) as white solid.

1,3,4,5-*tetra*-*O*-benzyl-L-sorbopyranose (2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.15 (m, 18H), 7.17–7.15 (m, 2H), 4.96 (d, J = 12.0 Hz, 1H), 4.84 (t, J = 12.0 Hz, 2H), 4.73 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.56–4.48 (m, 3H), 3.95 (t, J = 8.0 Hz, 1H), 3.78–3.75 (m, 2H), 3.65–3.62 (m, 1H), 3.48 (d, J = 12.0 Hz, 1H), 3.40 (d, J = 12.0 Hz, 1H), 3.32 (d, J = 12.0 Hz, 1H), 3.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.3, 137.8, 137.4, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 97.4, 82.8, 78.7, 78.5, 75.8, 75.4, 73.8, 73.2, 71.9, 61.0. HRMS (ESI-TOF) *m/z* calcd for $C_{34}H_{36}O_6$ $(M + H)^+$ 541.2590, found 541.2594. All the spectra matched with those previously reported [11].

2-((*3S*,*5R*,*6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)acetate (2') White solid (4:1 anomers mixture). ^{1}H NMR (400 MHz, $CDCl_3$) for major anomer (α anomer) δ 7.37–7.12 (m, 23H), 7.17–7.12 (m, 2H), 5.22 (t, J = 4.0 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 4.86–4.81 (m, 2H), 4.74 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.59–4.54 (m, 1H), 4.50–4.46 (m, 3H), 4.05–4.01 (m, 1H), 3.97 (t, J = 12.0 Hz, 1H), 3.89–3.78 (m, 1H), 3.72–3.68 (m, 1H), 3.65–3.56 (m, 3H), 3.05 (d, J = 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 138.7, 138.6, 138.5, 138.4, 138.3, 138.1, 138.0, 137.9, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 98.2, 97.5, 92.8, 91.3, 84.6, 83.2, 81.8, 80.1, 79.8, 77.9, 77.8, 75.7, 75.1, 74.9, 74.7, 73.5, 72.2, 72.0, 71.7, 71.3, 70.4, 69.7, 69.0, 68.7. HRMS (ESI-TOF) *m/z* calcd for $C_{43}H_{44}O_7$ $(M + Na)^+$ 695.2985, found 695.2990.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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