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Simple and efficient synthesis of 2,5-anhydro-D-glucitol

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ABSTRACT

The synthesis of 2,5-anhydro-D-glucitol is described via intramolecular cyclization of diepoxide using ammonium formate in MeOH by a microwave-assisted reaction. The overall yield was 32% from D-mannitol derivative involving seven steps.

Furanose sugars are essential components of nucleic acids and were considered a central core for the development of antiviral and antitumor drugs, which also encompass uncommon natural nucleosides. These nucleosides contain the furanose-linked pyrazole or imidazole, isolated from *Streptomyces*,[1] being pyrazomycin (**1**), a potential anti-HIV agent, and showdomycin (**2**) which has antitumor and antibacterial properties (Fig. 1).[2]

The fructose analogue 2,5-anhydro-D-mannitol (**3**), is a valuable furanose sugar involved in the inhibition of gluconeogenesis[3] and glucogenolysis,[4] and the increase of food intake in rats (Fig. 1),[5] whereas 2,5-anhydro-D-glucitol (**4**) and its derivatives have been described as an antitumor agent, able to inhibit tumor cell growth,[6] as well as being a phytotoxic agent[7,8] (Fig. 1). Furthermore, compound **4** has been used as a key intermediate in the synthesis of natural products, such as (+)-muscarine[9] and D-chitaric acid.[10]

The classical method established for the synthesis of 2,5-anhydro-D-glucitol (**4**) and its corresponding derivatives is based on the acid dehydration of D-mannitol, which results in a non-separable mixture of three anhydride derivatives resulting in compound **4** (45% of the mixture), as revealed by gas chromatography analysis.[11,12] An attempt to isolate compound **4** through isopropylidenation and tritylation of these mixed anhydrides gave 2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol, which was deprotected by acid hydrolysis to yield **4** in approximately 15% overall yield.[11] A slight improvement in the yield involving an alternative derivative of **4**, 2,5-anhydro-1,3-*O*-isopropylidene-D-glucitol, was accomplished by treating these mixed anhydrides with acetone under acid catalysis followed by either high vacuum fraction distillation[13] or dry column vacuum chromatography.[8] Similar low yields were also achieved by treatment of the di-*O*-methyl diepoxide **5** (Fig. 2), prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol in four steps,[14] with either hydrogen bromide or chiral (salen)Co^{III} complex to provide 2,5-anhydro-6-bromo-6-deoxy-D-glucitol (16%)[15] or 2,5-anhydro-3,4-di-*O*-methyl-D-glucitol (12%),[16] respectively. Alternatively, *5-endo-tet* cyclization of 2,3-epoxy alcohols, **6** or **7** (Fig. 2), starting from L(+)-diethyl tartarate and allyl bromide or *cis*-but-2-ene-1,4-diol, respectively, were also effective in producing **4** with approximately 21% overall yield, when performed from **7** (eight steps).[17]

In addition, silylation of methyl fructo-furanoside or pyranoside, followed by treatment with triethylsilane and trimethylsilyl

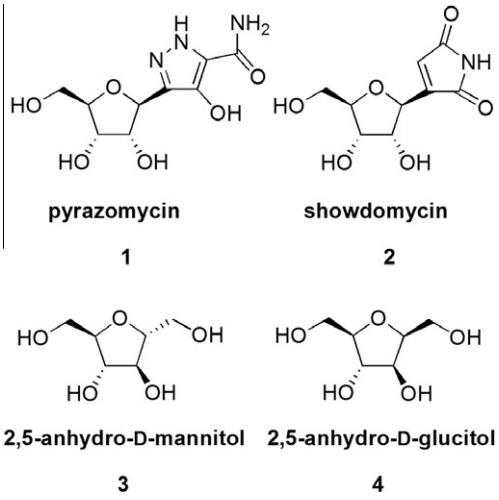

Figure 1. Structures of furanose sugars with relevant biological activity.

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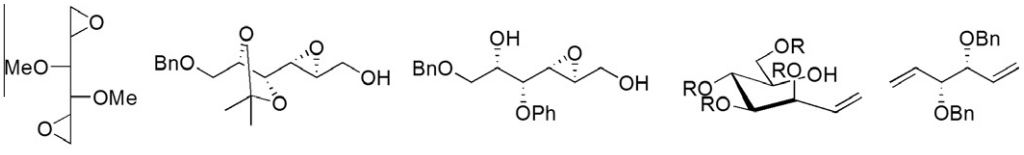


5 6 7 8 9

Figure 2. Important intermediates applied to the synthesis of 2,5-anhydro-D-glucitol (**4**).

trifluoromethanesulfonate for reductive cleavage gave **4** in 19% yield,[18] while regio- and stereoselective cyclization of manno open olefin **8** (Fig. 2) allowed the preparation of deuterium labeling in different positions of **4** from protected D-mannose in four steps, with approximately 12% overall yield.[19] Finally, oxidative cyclization of 1,5-diene **9** using OsO_4, prepared from D-mannitol (three steps), gave the intermediate 2,5-anhydro-3,4-di-*O*-benzyl-D-glucitol, which was converted into either compound **4** or D-chitaric acid with approximately 42% and 13% overall yields, respectively.[10]

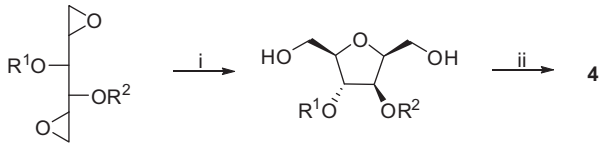
However, to the best of our knowledge the synthesis of compound **4** from diepoxide derivatives with ammonium formate under microwave conditions has not been described. In this Letter, an alternative route to obtain 2,5-anhydro-D-glucitol (**4**) is reported from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol via intramolecular cyclization of diepoxide **10** using ammonium formate in a microwave-assisted reaction (Scheme 1).

The protection of hydroxyl groups of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was achieved by treatment with benzyl bromide and NaH in the presence of Bu_4NI, after purification in silica gel chromatography (96% yield).[20] The cleavage of the isopropylidene group was undertaken by treatment with MeOH/HCl, instead of AcOH 70%,[20] yielding the corresponding product with 98% yield.[21,22] The 1- and 6-positions were selectively protected with TBDMS group followed by functionalization of secondary hydroxyl groups (2- and 5-positions) using mesyl chloride. The crude product was used in the next step without any purification.[23] Treatment of this compound with MeOH/HCl, followed by KOH gave diepoxide **10** by intramolecular S_N2 reaction (52% yield), involving inversion of configuration at C-2 and C-5 (Scheme 1).[23] Compound **10**, which is an important intermediate in the synthesis of glycosidase azasugar inhibitors (1-deoxynojirimycin and polyhydroxylated pyrrolidines),[23] was converted into the furanose derivative **11** by treatment with ammonium formate in MeOH at 90 °C for 1 h under microwave irradiation with 65% yield after purification in silica gel chromatography (Scheme 1).[24] The first step of this reaction involves the regioselective opening of 1,2-epoxide of **10** followed by the *O*-cyclization leading to glucitol **11**. Alternatively, ammonium formate has been described to reduce alkyl linear 1,2-epoxides to produce saturated alcohols in the presence of a palladium catalyst.[25]

In order to check the influence of the solvents on solubility, stability of the reactants, and cyclization rates, the reaction was also performed in 1,4-dioxane, THF, DMF, and H_2O using the same reaction conditions applied to MeOH (90 °C for 1 h under microwave irradiation). Despite the moderate yield (41%) of **11** achieved in the reaction using a mixture of MeOH/H_2O (8:2), diepoxide **10** was not converted into the product **11** in the majority of the experiments, being quantitatively recovered from the reaction mixture, with exception of the use of DMF, which also led to the degradation of **10**. Additionally, the effect of the protective group on the cyclization reaction was pursued using two derivatives of **10**, containing either free hydroxyl groups at 3- and 4-positions, as exemplified for compound **12**, or 3,4-isopropylidene group in the place of the original 3,4-dibenzyl protective group of **10**, such as compound **13**. Thus, a time controlled hydrogenolysis of **10** (10 min) gave the diol **12** in 78% yield after purification by chromatography column, which was treated with acetone and zinc chloride to give isopropylidene **13** (20% yield).[26] While the cyclization of diol **12** in the presence of ammonium formate required 2 h to give 2,5-anhydro-D-glucitol (**4**) in 22% yield, instead 1 h for the corresponding 3,4-dibenzyl **10** to produce **11** (65%), attempts to convert compound **13** into glucitol derivative under similar reaction conditions provided just a complex mixture.

Finally, the hydrogenation reaction of glucitol **11** in the presence of Pd/C afforded 2,5-anhydro-D-glucitol (**4**) in quantitative yield (Scheme 1).[27]

In conclusion, 2,5-anhydro-D-glucitol (**4**) was successfully prepared via intramolecular cyclization reaction of dibenzyl diepoxide **10**, in the presence of ammonium formate, with overall yield of 32% in seven steps from 1,2:5,6-di-*O*-isopropyllidene-D-mannitol.



10 $R^1 = R^2 =$ Bn
12 $R^1 = R^2 =$ H
13 $R^1, R^2 = C(CH_3)_2$

11 $R^1 = R^2 =$ Bn

Scheme 1. Synthesis of 2,5-anhydro-D-glucitol (**4**). Reagents and conditions: (i) HCO_2NH_4, MeOH, MW, 90 °C, 65%; (ii) H_2, Pd/C, AcOH, MeOH, 100%.

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24. *Procedure for the synthesis of 3,4-dibenzyloxy-2,5-dihydroxymethyl-tetrahydrofuran (**11**):* ammonium formate (0.019 g, 0.3062 mmol) was added to a solution of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-l-iditol (**10**) (0.050 g, 0.1531 mmol) in MeOH (0.5 mL). The mixture was stirred at 90 °C for 1 h under microwave irradiation then concentrated in vacuum. Purification of the crude product by silica gel chromatography, eluting with CH_2Cl_2 and methanol (9:1), provided 3,4-dibenzyloxy-2,5-dihydroxymethyl-tetrahydrofuran (**11**) (0.034 g, 65%) as a yellow oil: R_f 0.3 (toluene/ethyl acetate 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 10H, Ar H); 4.64–4.57 (m, 3H, CH_2Ph); 4.45 (d, 1H, *J* 11.8, CH_2Ph); 4.15–4.11 (m, 3H, H-5, H-3, H-4); 4.04–4.02 (m, 1H, H-2); 3.91 (dd, 1H, *J* 11.9, 4.5, H-6b); 3.85–3.82 (m, 2H, H-6a, H-1b); 3.68 (dd, 1H, *J* 11.9, 4.0, H-1a); 2.65 (sl, OH). 13C NMR (125 MHz, $CDCl_3$) δ 137.8 (C-Ph); 137.3 (C-Ph); 128.8 (C-Ph); 128.7 (C-Ph); 128.3 (C-Ph); 128.2 (C-Ph); 128.0 (C-Ph); 127.8 (C-Ph); 84.3, 84.0, 83.1, 80.6 (C-2, C-3, C-4, C-5); 72.3 (CH_2Ph); 72.2 (CH_2Ph); 62.9 (C-1); 61.7 (C-6). The data are in good agreement with literature values.[10]
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27. *2,5-Anhydro-D-glucitol (**4**):* ^{1}H NMR (500 MHz, D_2O) δ 4.09 (dd, 1H, *J* 4.3, 2.5, H-4); 4.03 (dd, 1H, *J* 7.0, 4.3, H-5); 3.92 (dd, 1H, *J* 4.3, 2.5, H-3); 3.75 (1H, m, H-2); 3.73 (dd, 1H, *J* 12.0, 4.3, H-6b); 3.68 (dd, 1H, *J* 12.0, 3.8, H-1b); 3.65 (dd, 1H, *J* 12.0, 7.0, H-6a); 3.60 (dd, 1H, *J* 12.1, 6.0, H-1a). ^{13}C NMR (125 MHz, D_2O) δ 85.0, 81.3, 78.4, 77.3 (C-2, C-3, C-4, C-5); 62.1, 60.5 (C-1, C-6). ESI-MS *m*/*z*, calcd for $C_6H_{12}O_5$ $[M+Na]^+$ 187.0582, found 187.0577. The data are in good agreement with literature values.[10,19]