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Short communication

SHORT COMMUNICATION

First and efficient synthesis of 4-[((3,4-dihydroxybenzoyl)-oxy)methyl]phenyl *β*-D-glucopyranoside, an antioxidant from *Origanum vulgare*

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Abstract: 4-[((3,4-Dihydroxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside (DBPG, **1**), a polyphenolic glycoside previously isolated from oregano (*Origanum vulgare* L.) in 0.08 % isolated yield, was synthesized in five chemical steps with 41.4 % overall yield. First, 4-(hydroxymethyl)phenyl *β*-D-glucopyranoside 2,3,4,6-tetraacetate (**4**) was obtained in 53.2 % yield by selective glycosylation of 4-hydroxybenzyl alcohol (**3**) with 2,3,4,6-tetra-*O*-acetyl-*α*-D--glucopyranosyl bromide (**2**) in a mixture of chlorobenzene and aqueous CsOH using triethylbenzylammonium chloride (TEBAC) as a phase transfer catalyst. Then, this product was esterified with 3,4-diacetoxybenzoyl chloride (**7**) to generate 4-[((3,4-diacetoxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside 2,3,4,6-tetraacetate (**8**) in 95 % yield. Finally, selectively global deacetylation of **8** was performed in a mixture of dibutyltin oxide and methanol under reflux to afford **1** in 94.8 % yield.

Keyword: 4-[((3,4-dihydroxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside; synthesis; glycosylation; antioxidant; dibutyltin oxide.

INTRODUCTION

As an extensively used herb in China and a common herb in the Western diet, oregano (*Origanum vulgare* L.) is believed to display antithrombin, anti--*Helicobacter pylori*, antimicrobial, antibiotic, antihyperglycemia and antioxidant effects.[1,2] 4-[((3,4-Dihydroxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside (DBPG) (Fig. 1), a polyphenolic glycoside, was identified as a major constituent of oregano (*Origanum vulgare* L.). Previous and recent studies showed that DBPG exhibits free radical scavenging activity,[3] antioxidant and cytoprotective effects on liver and skin cells.[4] Therefore, it is plausible to speculate the pos-

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sibility of employing DBPG as an additive to food and cosmetics for antioxidant-mediated health. However, conventional access to DBPG *via* extraction from oregano is not only a time-consuming and expensive process, but also a challenging procedure due to the extremely low content (only 0.08 %) and the ever-increasing shortage of oregano.

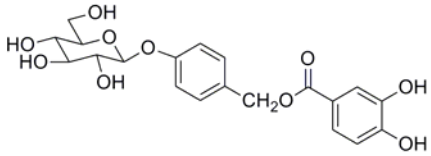
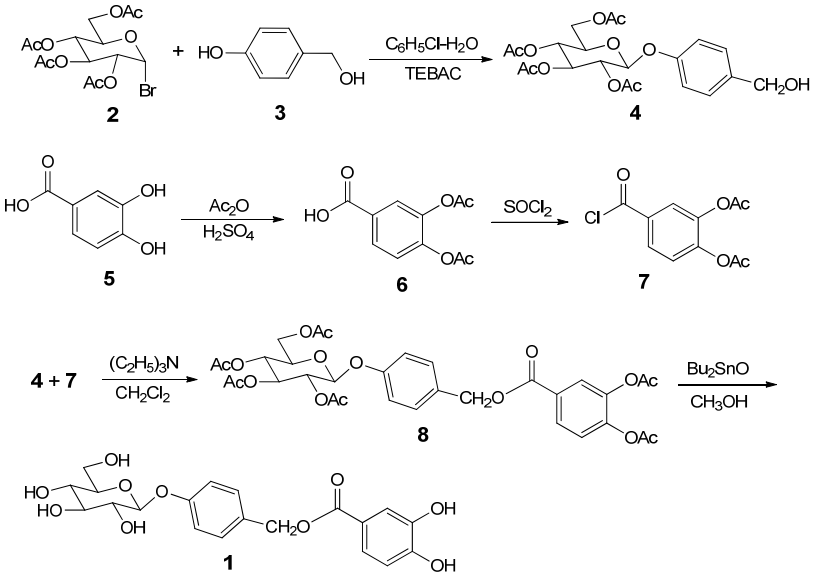


Fig. 1. Structure of DBPG **1**.

To circumvent these problems associated with the extraction of DBPG from oregano, herein, a first and efficient chemical synthesis of DBPG is presented (Scheme 1), in which 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **2** was employed as a glycosyl donor.



Scheme1. First and efficient synthesis of DBPG (**1**).

RESULTS AND DISCUSSION

As shown in Scheme 1, 4-(hydroxymethyl)phenyl β-D-glucopyranoside 2,3,4,6-tetraacetate (**4**), a key intermediate for the synthesis of DBPG, was synthesized according to the literature[5] with some modifications, such as replacement of sodium hydroxide by cesium hydroxide and substitution of chloroform for chlorobenzene. Then, selective glycosylation of 4-hydroxybenzyl alcohol (**3**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) was performed in the

system chlorobenzene–aqueous CsOH in the presence of triethylbenzylammonium chloride (TEBAC) as a phase transfer catalyst. Preliminary experiments were conducted to find the optimal conditions leading to the highest yield of compound **4**, and it was found that the optimal molar ratio of compounds **2**, **3** and TEBAC was 1:2:0.8 in terms of highest yield of **4**. Thus, compound **4** was prepared by heating the reaction mixtures at 60 °C for 4.5 h in a yield of 53.2 %, an increase of 14.2 % over that previously reported.[5]

With the intermediate **4** in hand, 3,4-diacetoxybenzoic acid (**6**) was prepared in 86.5 % yield by reaction of 3,4-dihydroxybenzoic acid (**5**) with acetic anhydride using conc. H_2SO_4 as a catalyst according to literature[6] with some modifications, such as replacement of ethyl acetate–hexane by ethyl ether–petroleum ether (60–90 °C) as the recrystallization solvent. Next, 3,4-diacetoxybenzoyl chloride (**7**) was prepared by reaction of **6** with thionyl chloride and stored hermetically for further employment. Subsequently, coupling of the thus-obtained **7** with **4** afforded 4-[((3,4-diacetoxybenzoyl)oxy)methyl]phenyl β-D--glucopyranoside 2,3,4,6-tetraacetate (**8**) in 95 % yield. Of special note is that triethylamine was employed as an acid scavenger in this coupling process because of the acid-sensitivity of the glycosidic bond of **8**. Finally, global deacetylation of **8** gave rise to 4-[((3,4-diacetoxybenzoyl)oxy)methyl]phenyl β-D-glucopyranoside (**1**). While global deacetylation of **8** using the conventional NaOMe/MeOH reagent combination (Zemplen conditions) in carbohydrate chemistry afforded **1**, methyl 3,4-dihydroxybenzoate as by-product was observed in this process, thus leading to poor yield of **1** and difficulty in purification of **1**. To obviate the formation of the by-product in the global deacetylation of **8** under Zemplen conditions, conversion of **8** into **1** by exclusive global deacetylation of **8** was performed using dibutyltin oxide (DBTO) as a catalyst and methanol as the solvent.[7] The ^{1}H-NMR data for the title compound **1** is presented in the Supplementary material to this paper. Efforts were made to optimize the conditions for the synthesis of **1** by varying the molar ratio of compound **8** to DBTO, and it was found that the appropriate mole ratio of **8** to DBTO was 4:1 in terms of reaction time and facile purification of **1**. Under this condition, compound **1** was obtained in 94.8 % yield by refluxing the reaction mixture in methanol for 6 h. Notably, down-regulating the mole ratio of **8** to DBTO could shorten the reaction time, but disfavored the purification of compound **1** concurrent with DBTO. Therefore, striking a balance between the reaction time and easiness of purification of **1** is advisable.

EXPERIMENTAL

Materials and methods

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 4-hydroxybenzyl alcohol, 3,4--dihydroxybenzoic acid, acetic anhydride, thionyl chloride, dibutyltin oxide and triethylbenzylammonium chloride were obtained from Qingdao Justness Reagent Company (China). All

solvents were obtained commercially and used without further purification unless otherwise stated.

Instrumentation

The melting points were measured with a digital melting point apparatus (WRS-1B). The optical rotations were measured with JASCO P1030 polarimeter. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III400 spectrometer, operating at 400 MHz for protons and 100 MHz for carbons. 2D NMR techniques (^{1}H–^{1}H-COSY and ^{1}H–^{13}C-HSQC) were used for full assignment of the spectra. All compounds were confirmed by physical and spectral methods.

The physical, analytic and spectral data are given in the Supplementary material to this paper.

Synthesis of 4-(hydroxymethyl)phenyl β-*D-glucopyranoside 2,3,4,6-tetraacetate (**4**)*

A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**, 12.30 g, 30 mmol) in 120 mL chlorobenzene was added to a solution of 4-hydroxybenzyl alcohol (**3**, **7**.44 g, 60 mmol), CsOH (8.99 g, 60 mmol) and triethylbenzylammonium chloride (5.4 g, 24 mmol) in 100 mL H_2O. The mixture was then stirred at 60 °C for 4.5 h, after which it was cooled to room temperature and the chlorobenzene layer separated, washed with 80 mL saturated K_2CO_3 solution, 80 mL H_2O and dried over anhydrous Na_2SO_4. The filtrate was concentrated under vacuum to give a yellowish syrupy crude product **4**, which was purified by crystallization from 95 % ethanol to afford the desired compound **4** as a white solid. Yield: 53.2 %.

*Synthesis of 3,4-diacetoxybenzoic acid (**6**)*

To a stirred suspension of 3,4-dihydroxybenzoic acid (**5**, 6.16 g, 40 mmol) in 19 mL acetic anhydride was added 0.2 mL of concentrated sulfuric acid. Then, the suspension was stirred at 70 °C until a clear solution was obtained, indicating completion of the reaction. The resulting clear solution was poured into 200 mL of cold water and stirred until the crude 3,4--diacetoxybenzoic acid (**6**) had precipitated completely. The white crude precipitate **6** was collected by filtration, washed with 50 mL of 95 % ethanol and purified by recrystallization from Et_2O–PE (3:2, *V*/*V*) to obtain the desired 3,4-diacetoxybenzoic acid (**6**) as white crystals. Yield: 86.5 %.

*Synthesis of 3,4-diacetoxybenzoyl chloride (**7**)*

A mixture of 3,4-diacetoxybenzoic acid (**6**, 2.38 g, 10 mmol) and thionyl chloride (25 mmol, 1.81 mL) was stirred at 40 °C for 5 h. The mixture was then distilled under vacuum to remove the excess thionyl chloride, leaving a yellowish oily residue (**7**). Anhydrous CH_2Cl_2 (6 mL) was added to the residue **7**, which was then poured into a dried 10 mL dropping funnel for further employment.

4-[((3,4-Diacetoxybenzoyl)oxy)methyl]phenyl β-*D-glucopyranoside 2,3,4,6-tetraacetate (**8**)*

To a stirred mixture of 4-(hydroxymethyl)phenyl *β*-D-glucopyranoside 2,3,4,6-tetra-acetate (**4**, 4.54 g 10 mmol) and triethylamine (11 mmol, 1.1 mL) in 30 mL dried CH_2Cl_2 was added dropwise the already-made 3,4-diacetoxybenzoyl chloride (**7**) within 0.5 h. Upon completion of the dropwise addition, the mixture was kept stirring for 5 h at room temperature to give a brown solution. The resulting brown solution was diluted with 50 mL CH_2Cl_2 and washed successively with 100 mL H_2O, 100 mL aq. $NaHCO_3$ and 100 mL brine, and dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure to afford crude 4-[((3,4-Diacetoxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside 2,3,4,6-tetraacetate (**8**) as

brown solid. Recrystallization of the crude **8** from absolute ethanol gave the desired **8** as white crystals. Yield: 95 %.

4-[((3,4-Dihydroxylbenzoyl)oxy)methyl]phenyl β-*D-glucopyranoside (**1**)*

A stirred mixture of 4-[((3,4-Diacetoxybenzoyl)oxy)methyl]phenyl *β*-D-glucopyranoside 2,3,4,6-tetraacetate (**8**, 5.39 g, 8 mmol) and dibutyltin oxide (0.5 g, 2 mmol) in 50 mL methanol was refluxed for 6 h, and then the mixture was concentrated under vacuum to provide crude product **1**. Recrystallization of crude **1** from absolute ethanol afforded the desired **1** as white crystals. Yield: 94.8 %

CONCLUSIONS

In summary, a chemical synthesis of DBPG in five chemical steps was developed for the first time with 41.4 % overall yield. This synthetic route to DBPG has the advantages of operational simplicity as well as facile separation and purification by recrystallization throughout the whole procedure.

SUPPLEMENTARY MATERIAL

The physical, analytic and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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Извод

ПРВА ЕФИКАСНА СИНТЕЗА 4-[((3,4-ДИХИДРОКСИБЕНЗОИЛ)ОКСИ)МЕТИЛ]-ФЕНИЛ-*β*-D-ГЛУКОПИРАНОЗИДА, АНТИОКСИДАНТА ИЗ *Origanum vulgare*

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4-[((3,4-Дихидроксибензоил)окси)метил]фенил-*β*-D-глукопиранозид (DBPG, **1**), полифенолни глукозид, који је раније изолован из оригана (*Origanum vulgare* L.) у приносу 0,08 %, синтетисан је у пет реакционих корака у укупном приносу од 41,4 %. Прво је 4-(хидроксиметил)фенил-*β*-D-глукопиранозид-2,3,4,6-тетраацетат (**4**) добијен у приносу 53,2 % селективним гликозиловањем 4-хидроксибензил-алкохола (**3**) помоћу 2,3,4,6-тетра-*O*-ацетил-*α*-D-глукопиранозил-бромида (**2**), у смеши хлорбензена и воденог раствора CsOH у присуству триетилбензиламонијум-хлорида (TEBAC) као катализатора фазног прелаза. Потом је производ естерификован 3,4-диацетоксибензоил-хлоридом (**7**) чиме је добијен 4-[((3,4-диацетоксибензоил)окси)метил]фенил-*β*-D-глукопиранозид-2,3,4,6-тетраацетат (**8**) у приносу од 95 %. На крају, селективно укупно деацетиловање деривата **8** извршено је у смеши дибутил-калај-оксида у метанолу, уз загревање на температури кључања, при чему је добијен дериват **1** у приносу 94,8 %.

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