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Proposed total synthesis of the potential antidiabetic compound 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one

Kexin Li

Shanxi Medical University, NO.56 xinjian south road, Taiyuan Shanxi 030001, China

likelsie44@gmail.com

Abstract. Insulin analogs are currently the most often prescribed medications for treating type 2 diabetes mellitus (T2DM). However, because of the inherent flaws of the medications and the restrictions of the administration methods, there is no comprehensive plan for managing diabetes. As a result, it's crucial to research comprehensive treatment plans based on the available medications and the traits of T2DM. Natural products play as key role in drug discovery. Although many articles have been published on the antidiabetic potential of natural products, few natural product-based molecules have been approved for the treatment of T2DM. It has been established that the compound 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one from Nigella glandulifera Freyn et Sint (N. glandulifera) possesses antidiabetic activity, but little attention has been dedicated to its total synthesis. Herein, we attempt to reveal a new total synthesis of 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one. The synthesis is simple, with few steps, and has potential for industrialization.

Keywords: 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one, Natural products, Total synthesis, T2DM, Antidiabetic activity

1. Introduction

Natural products have long been recognized as a significant source of inspiration for drug discovery, and because of their immense structural diversity and wide range of biological activity, they play a vital role in drug development [1]. Among them, the bioactivity of plant-derived compounds has many functions to treat and overcome a wide range of diseases and fatalities, including diabetes and cancer [2,3].

People with diabetes mellitus (DM) experience many different types of effects, ranging from the immediate danger of a severe hyperglycemic hyperosmolar coma, ketoacidosis, or metabolic disturbances caused by severe hypoglycemia to serious long-term complications in the large and small arterial vessels, as well as lifelong challenges to quality of life due to a variety of psychosocial issues [4]. Type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM) are the three subtypes of DM [5]. Absolute insulin shortage and pancreatic cell death are hallmarks of T1DM, whereas insulin resistance (IR) and inadequate insulin production are the main causes of T2DM [6,7]. Blood glucose levels in GDM can be raised during pregnancy (though this is most likely to happen after week 24), and this usually subsides after delivery [5]. People with diabetes are mainly T2DM, who

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represent approximately around 90% of the total population [8]. Previous research has established that common disease of middle age and the elderly, T2DM diagnosis rates are getting older every year, with a definite tendency towards younger age groups [9].

Currently, insulin, insulin analogs, non-insulin oral hypoglycemic medicines, and other newly developed therapy methods are the most often used medications in the clinical treatment of diabetes [5].

For overall glycemic control, insulin therapy is the most effective treatment, reducing HbA1c concentrations by 1.5-2% [10]. Insulin analogs are synthetically manufactured by modifying the amino acid sequence in human insulin in order to mimic as closely as possible the normal endogenous insulin secretion and action [11]. The class of medications known as oral hypoglycemics includes insulin secretagogues, biguanides, insulin sensitizers, etc [12]. Other emerging treatment strategies include nano-based diabetes therapy, insulin pump, pancreatic islet cell transplantation, and more [5]. Because of the shortcomings of the medications themselves as well as the restrictions placed on the methods of administration, such as the negative side effects of prolonged subcutaneous injections and the various challenges posed by oral administration, there is no effective treatment for diabetes mellitus. Therefore, it is crucial to create effective new medications and investigate full treatment approaches based on the characteristics of medications and diabetes mellitus [13].

Although many articles have been published on the antidiabetic potential of natural products, there are very few examples of molecules based on natural products that have been approved for use as antidiabetic drugs. Metformin, discovered based on a natural compound, galegine from the plant Galega officinalis, is one of the few examples of an antidiabetic drug developed from a natural compound and clinically approved. It is a first-line treatment option for patients with T2DM unless there are specific contraindications, such as for patients with impaired renal function [14]. And it has been demonstrated that metformin has a significant effect on the cell survival of HepG2 cells and high glucose-induced IR-HepG2 cells [15]. It can be used as a positive control group to evaluate the anti-glycemic activity of substance.

Nigella glandulifera Freyn et Sint (N. glandulifera) is frequently added to naan as a spice. Alopecia and hair-blacking, urethral calculi, hypogalactia, heat stranguria, amnesia, amenorrhea, edema, and bronchial asthma were all can be treated with the water decoction of N.glandulifera in traditional Uighur medicine [16]. The binding affinity of two compounds, α-hederin and negillicine, isolated from Nigella glandulifer, to the RNA-dependent RNA polymerase (RdRp) enzyme active site of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) could be considered for use in a sustained drug development strategy against SARS-CoV-2 [17].

A additional constituent of it, 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one, was isolated in 2006 from Fungus Stereum sp. by Li's group [18]. Additionally, the IR-HepG2 cell model was used to assess its hypoglycemic activity. To develop an IR model using human hepatoblastoma HepG2 cells, metformin was chosen as a positive control because it could encourage hepatic glucose consumption in IR HepG2 cells. The results showed that it had higher glucose consumption at different concentrations than the positive control of metformin. These findings illustrate the antidiabetic activity of it [19]. However, although the compound has been isolated over 16 years ago, and in 2022, its function of promoting glucose consumption by IR-HepG2 cells for the treatment of T2DM has been demonstrated, little attention has been paid to the total synthesis of it. Herein, we attempted to disclose a new method for the total synthesis of 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one, shown in Figure 1.

2. Method

We first synthesized 5-bromo-3-methylene-1,3-dihydroisobenzofuran-4,6-diol (4) and (3-methylbut-2-en-1-yl) boronic acid (6) and planned to couple the two known compounds by Suzuki-Miyaura Cross Coupling reaction [20].

Product 4 was prepared in three steps from resorcinol (1). Initially 1 was subjected to an electrophilic bromination reaction with NBS to give 2-bromobenzene-1,3-diol (2). Then, under high pressure ambient circumstances, a Kolbe-Schmitt type reaction was achieved by combining an organic base with

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resorcinols [21]. The equivalent salicylic acid derivatives, 3-bromo-2,4-dihydroxybenzoic acid (3), were produced by nucleophilic addition to carbon dioxide after hydroxyphenol derivatives 2 were treated with DBU in a carbon dioxide environment. Subsequently the cyclic palladium intermediate obtained by carboxyl-directed carbon-hydrogen bond activation could be oxidized by the solvent CH2Br2 to give the o-alkylated product, followed by the SN2 reaction to give the cyclic lactone 4. [22]. Product 6 was then obtained from compound 3-methylbut-2-en-1-ol (5) by a boronization reaction [23]. Finally, the total synthesis of 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one (7) was achieved by taking advantage of the high functional group selectivity of Suzuki-Miyaura Cross Coupling reaction.

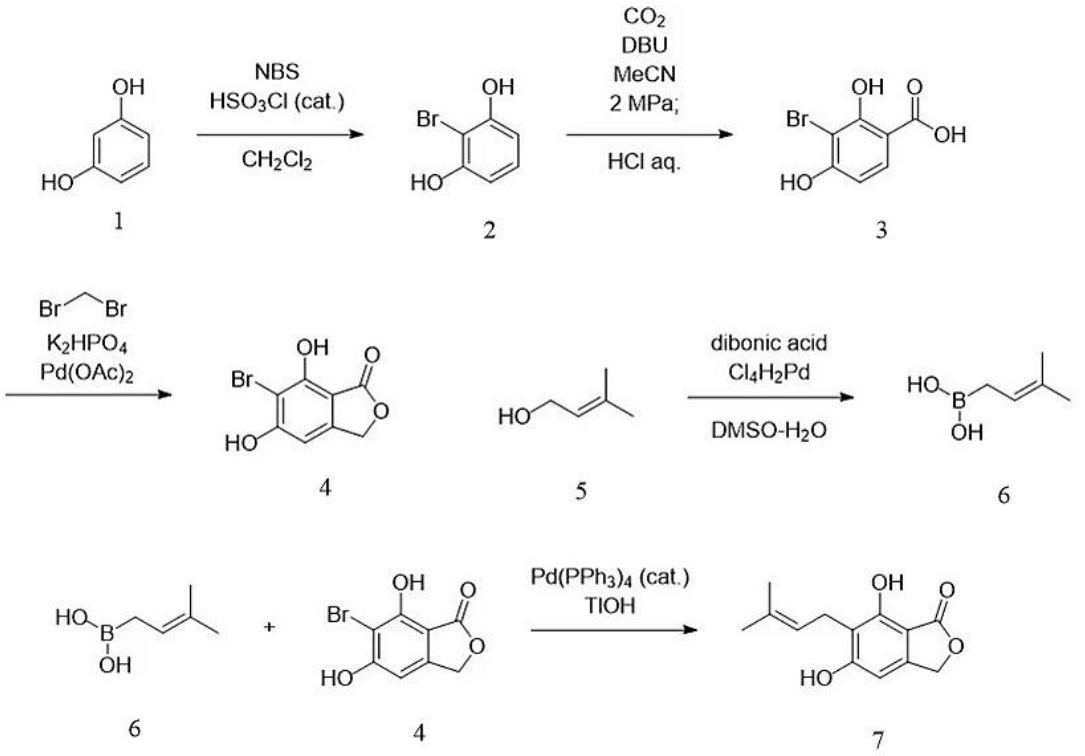

Figure 1. Proposed total synthesis of 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one

3. Conclusion

The method successfully utilized existing structurally simple compounds and constructed the proposed total synthetic route by using Suzuki-miyaura cross-coupling reaction. To successfully present a new complete synthesis technique for 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one. The synthesis method has a few steps and it is easy to follow. The conditions for all reaction types are relatively easy to control and the cost is also comparatively low, which makes it potential for industrialization in the future. It is expected to be applied to the synthesis of drugs based on this compound in the future, as well as the development of type 2 diabetes drugs, providing new ideas for type 2 diabetes drug development.

In future work, the proposed synthesis scheme needs to be studied experimentally to confirm its feasibility. After the product has been synthesized, it needs to be spectroscopically analyzed and compared with the natural sample to verify the identity of the synthesized product with the natural sample. After the complete synthesis of 5,7-dihydroxy-6-(3-methybut-2-enyl)-isobenzofuran-(13H)-one has been accomplished, additional research can be done to enhance the synthetic pathways and the reaction conditions in order to provide larger yields and more effective procedures.

In conclusion, the total synthesis method is highly feasible.

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