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Microwave-Mediated Chiral Synthesis of O-Glycosides of β-Lactams

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ABSTRACT

Microwave-mediated optically active O-glycosides of anticancer β-lactams is synthesized by cycloaddition reaction of an activated carbohydrate acid with an imine. The stereochemistry differences of the products under microwave-induced reaction and classical method is not significant in contrast to other known available methods.

KEYWORDS

β-Lactams, Anticancer compounds, Chirality, Carbohydrate, Ketene.

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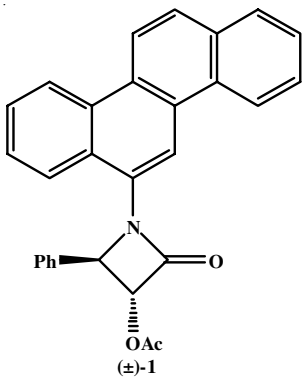
INTRODUCTION

There is a high demand for new anticancer agents with high activity against cancer cells but minimum toxicity in non-cancerous cells. Studies toward apoptotic pathways with new types of molecules including β-lactams are the most important objectives [1-3]. Despite excellent progress in the development of anticancer agents, synthesis of compounds with low toxicity and high potency against cancer cells remains a great challenge. β-Lactam molecules have been used as the most powerful anti-bacterials and other therapeutic drugs for many years [4-11]. Therefore, preparation of β-lactams as novel anticancer agents has received attention in recent years [12-19]. We have been actively involved in the preparation of diverse β-lactams for many years [20-24]. Microwave-induced reactions have shown a great promise in the synthesis of β-lactams and altering their configurations [25-27]. The alteration of the configuration of β-lactam molecules at C-3 and C-4 position of the ring is of great importance because we have demonstrated a specific *trans*-isomer is more active than the other [17]. We report here chiral synthesis of anticancer β-lactam starting from 6-chrysenyl imine using cycloaddition reaction with an activated chiral carbohydrate derivative by microwave-mediated reaction. These two isomeric compounds were prepared by classical method using the same starting materials in almost 1:1 ratio [17]. Interestingly, microwave-induced reaction of 6-chrysenyl imine and the same carbohydrate derivative afforded an identical ratio of two chiral compounds reported earlier [17]. This reaction is interesting since it has been demonstrated that microwave irradiation method alters the formation of *trans* diastereomer over *cis* diastereomer in racemic compounds [28-37]. But no alteration of the diastereomeric ratios of the two

trans isomer of the chiral β-lactams is noted with optically active substrates.

In our previous publications, we demonstrated synthesis and biological study of a number of anticancer β-lactams [12-19]. To prepare chiral β-lactam (**1**) and to identify its effectiveness against various cancer cell lines, the present study was initiated. The main goal was to prepare the active enantiomer of this compound [17]. Optically active compound showed better medicinal profiles and selectivity than the racemic version of the same compound against blood, skin, ovary, colon, prostate and breast cancer cell lines [17].



Structure of chiral β-lactam (**1**)

Reaction of acyloxy, alkoxy and nitrogen-containing acid chloride with diaryl imines in general produced *cis*-β-lactams following Staudinger cycloaddition reaction. But, polyaromatic imines derived from polyaromatic amines and monocyclic aromatic aldehydes with these acid chlorides in the presence of triethylamine produced *trans*-β-lactams exclusively [12-19].

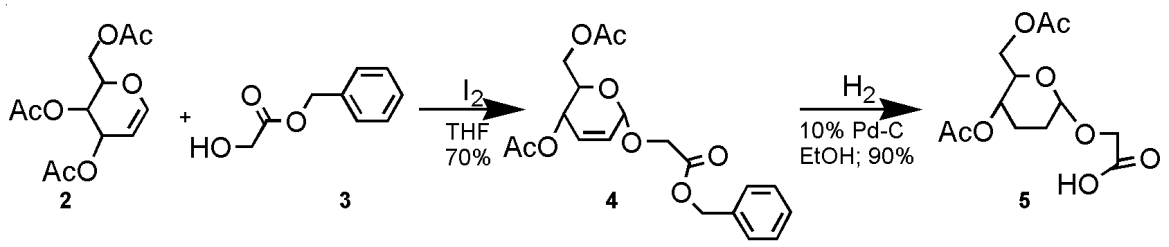
Due to the anticancer properties of racemic β-lactam (for example, **1**), a method for the preparation of optically active compounds was devised. Cycloaddition of imines with optically active and racemic ketenes was investigated [20-24,35,36]. A carbohydrate-based approach was found suitable to obtain both enantiomers of anticancer β-lactams [17,36]. Enantiospecific synthesis of *cis*-hydroxy β-lactam using α-O-glycoside as the ketene component was known with a diaryl imine [36]. However, these studies failed to predict the absolute configuration of the resulting β-lactam ring. For example, it seemed that the absolute configuration of the β-lactam ring does not depend on the stereochemistry of the anomeric center of the sugar unit, which serves as the ketene precursor.

EXPERIMENTAL

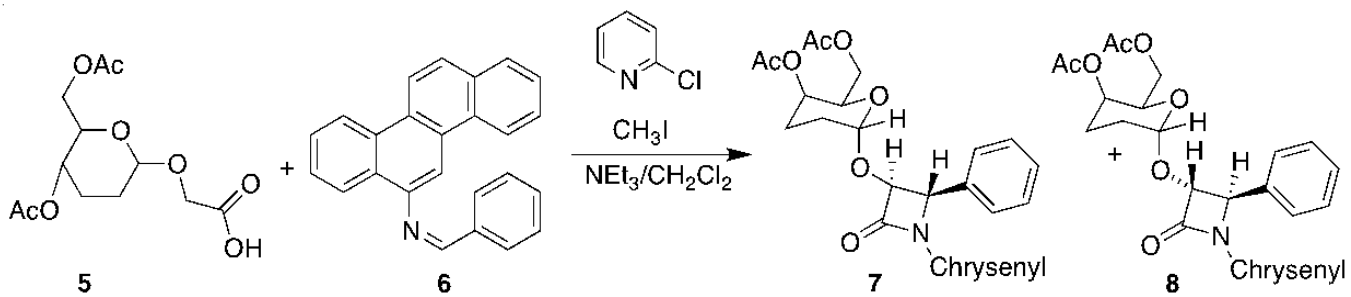
The desired α-glycoside was prepared by molecular iodine-catalyzed reaction of 3,4,5-tri-O-acetyl D-glucal (**2**) with benzyl glycolate (**3**). A single glycoside (**4**) was obtained from this reaction in good yield. Hydrogenolysis of the benzyl ester and the hydrogenation of the alkene in compound **4** were performed with Pd/C and hydrogen gas to produce sugar containing 2,3-deoxy acid (**5**) in excellent yield (**Scheme-I**).

Reaction of the activated acid **5** with imine **6** produced a mixture of diastereomeric O-glycosides of *trans* β-lactams **7** and **8** in a ratio of 45:55 [17]. This reaction was completed within 12 h. In a separate experiment, the reaction of **5** and **6** was performed using the same reagent and dichloroethane in a microwave oven for 6 min at 50 °C at 300 watt. Surprisingly, a mixture of two diastereomeric O-glycosides of *trans* β-lactams **7** and **8** was obtained in 1:1 ratio in 75 % yield (**Scheme-II**). The analytical data of **7** and **8** was identical with our previous reported data [17]. Domestic microwave oven was also used for this reaction. It was necessary to maintain the temperature of the reaction below 55 °C using a heat sink. The process of using heat sink in domestic microwave oven is known in the literature and demonstrated in our earlier publications [23,25,26]. The isomeric ratios of the *trans* β-lactams **7** and **8** remained identical in automatic or domestic microwave-induced reactions.

It has been hypothesized that high power microwave irradiation may alter the transition state structure that is formed in a reaction between ketene and imine [28-35]. This alteration then would produce minor isomer as the major stereoisomer.



Scheme-I



Scheme-II

Clearly, our current results indicate that microwave irradiation can accelerate the synthesis of β-lactams, but it has no role in controlling the absolute stereochemistry of these products. This trend was observed in our earlier studies with optically active imines of different structures [20,23]. High power irradiation failed to alter the product distribution in two specific examples. The diastereomers **7** and **8** afforded two optically active hydroxy β-lactams *via* acid-induced removal of the carbohydrate system and acetylation experiment as described in our previous publication [20-24]. One of them was proved to be promising anticancer agent [17].

RESULTS AND DISCUSSION

The stereochemical results of the microwave-induced cycloaddition reaction confirm our earlier results with optically active starting materials when chirality was induced by the carbon part of the imine [20,23]. This study also proves that high power microwave radiation has no effects on the absolute stereochemistry of the β-lactam formation reaction when chirality of the ring was induced by the ketene component. This will enhance further examinations of the transition state structures of Studinger cycloaddition reaction toward β-lactam formation.

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