Synthesis of proposed structure of rennellianone B: A study on rearrangement of anthraquinonyl propargyl ether toward 2*H*-pyranoanthraquinone

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PII: S0040-4039(16)31736-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.12.080
Reference: TETL 48492

To appear in: *Tetrahedron Letters*

Received Date: 2 December 2016
Revised Date: 21 December 2016
Accepted Date: 28 December 2016

Please cite this article as: Han, Y.T., Synthesis of proposed structure of rennellianone B: A study on rearrangement of anthraquinonyl propargyl ether toward 2*H*-pyranoanthraquinone, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.12.080

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of proposed structure of rennellianone B: A study on rearrangement of anthraquinonyl propargyl ether toward 2*H*-pyranoanthraquinone

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This paper is dedicated to Professor Young-Ger Suh on the occasion of his 65th birthday

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Rennellianone B
Pyranoanthraquinone
Claisen rearrangement
Hydroarylation
Anthraquinonyl propargyl ether

ABSTRACT

Rennellianone B was originally reported as a natural 2*H*-pyranoanthraquinone, isolated from the root of *Rennellia elliptica* Korth. An efficient synthesis of the proposed structure of rennellianone B was accomplished, starting from alizarin. The key feature of the synthesis involves the Claisen rearrangement of the anthraquinonyl propargyl ether intermediate to provide a 2*H*-pyranoanthraquinone moiety. In addition, intensive studies on rearrangement reaction conditions of anthraquinonyl propargyl ether toward the 2*H*-pyranoanthraquinone skeleton were described.

Introduction

Anthraquinones (9,10-dioxoanthracenes) are widely found in nature, and an important class of natural and synthetic compounds with strong and broad varieties of biological efficacies including anticancer, anti-inflammatory, anti-tyrosinase, antibacterial, and antiviral effects.[1] In this connection, anthraquinone has been regarded as an attractive scaffold in terms of both synthetic and medicinal chemistry.[2] Recently, rennellianone B **1**, a 2*H*-pyranoanthraquinone, was isolated by Osman *et al*. from the root of *Rennellia elliptica* Korth, used as traditional medicine in South East Asia.[3] It was also revealed that several anthraquinones isolated from R. *elliptica* have therapeutically useful properties.[4] Considering not only therapeutic properties of anthraquinones and R. *elliptica*, as mentioned above, but also its structure embedded with a privileged benzopyran substructure,[5] rennellianone B is strongly expected to possess therapeutically useful biological activities.

As shown in Figure 1, it was envisioned that the 2*H*-pyran moiety of rennellianone B **1** could be readily synthesized from anthraquinonyl propargyl ether **2** *via* a rearrangement reaction such as transition metal-catalyzed intramolecular hydroarylations[6] and a Claisen rearrangement.[7] In addition, the rearrangement precursor **2** was expected to be conveniently prepared from alizarin **3**, a natural 1,2-dihydroxyanthraquinone, *via* consecutive etherification reactions. Herein, it is reported that the concise synthesis of a proposed structure of rennellianone B via Claisen-rearrangement, as well as investigations on the rearrangement of an anthraquinonyl propargyl ether intermediate toward a 2*H*-pyranoanthraquinone skeleton.

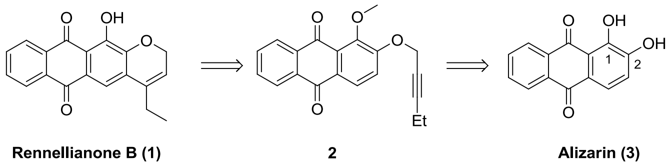

Figure 1. Proposed structure of rennellianone B and its retrosynthetic analysis

Results and Discussion

Synthesis of rennellianone B commenced with the selective protection of a 2-hydroxyl group of alizarin **3** to provide anthraquinonyl propargyl ether, a precursor of rearrangement reaction (Scheme 1). Etherification of **3** with chloroethyl methyl ether using Hunig's base afforded 2-ethoxymethyoxy alizarin **4** in high yield without regioisomeric 1-ethoxymethyoxy alizarin. Methylation of the **4** gave a high yield of the 1-methyl ether **5**, which was then subjected to deprotection using concentrated hydrochloric acid to afford alizarin-1-methyl ether **6**, a natural analog of alizarin. All of the spectral data of the synthetic alizarin-1-methyl ether **6** were identical to those of the reported data.[8] The key intermediate, anthraquinonyl propargyl ether **2**, could be obtained in high yield by propargylation of the **6** with 1-bromo-2-pentyne. On the other hand, the propargylation of alizarin **3** without a protection group at 1-hydroxyl group afforded only regioisomeric mixtures along with di-ether as previously reported.[9] Thermal Claisen rearrangement of