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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

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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.

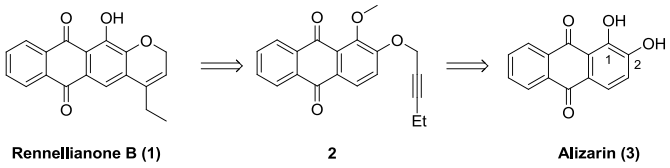
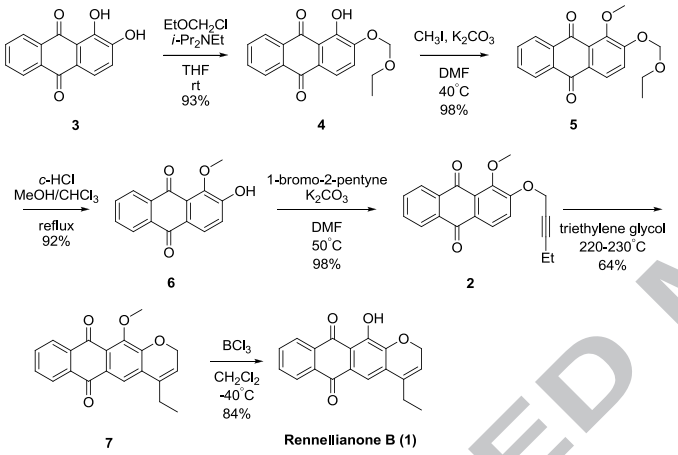


Figure 1. Proposed structure of rennellianone B and its retrosynthetic analysis

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

anthraquinonyl propargyl ether **2** in triethylene glycol at 220–230°C afforded the pyranoanthraquinone **7** in moderate yield (64%). Demethylation of the **7** using boron trichloride readily afforded the proposed structure of rennellianone B **1**. Synthesis of the proposed structure of **1** was accomplished in 6 steps (44% yield) from cheap and readily available alizarin. The structure of the 2*H*-pyran moiety of synthesized **1** was assigned and confirmed by 2D-NMR analysis including nuclear overhauser effect spectroscopy (NOESY) and correlation spectroscopy (COSY). Selected correlations and spectra are shown in Figure 2. However, it was hard to confirm that the reported structure by Osman *et al*. is identical with synthetic **1**, because previous ^{13}C-NMR data of **1** were reported incompletely probably due to the use of a small quantity of the isolated compound (0.5 mg).[3] Although ^{1}H-NMR and ^{13}C-NMR in this study differed slightly from the reported data, considering comprehensive NMR spectra analysis on the synthetic **1** as well as all of the synthetic intermediates including known alizarin methyl ether **6**, assignment in this paper seems to be more reasonable.



Scheme 1. Synthesis of proposed structure of rennellianone B

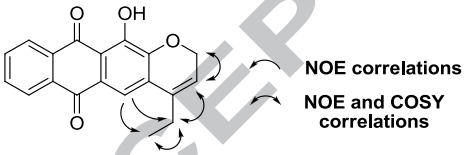
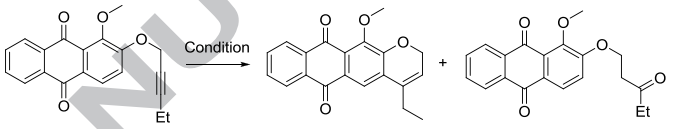


Figure 2. Selected NOE and COSY correlations for synthesized rennellianone B.

Construction of 2*H*-pyranoanthraquinone skeleton by rearrangement of anthraquinonyl propargyl ether **2** was a formidable task. Traditionally, cyclization of arene-alkyne substrate toward benzopyran moiety has been accomplished by either Claisen rearrangement or electrophilic intramolecular hydroarylation using a transition metal catalyst such as Pt(IV), In(III).[6] Based on the previous studies, intramolecular hydroarylation of anthraquinonyl propargyl ether **2** was initially attempted (entry 1–6, Table 1). Indium(III)-catalyzed hydroarylation[6a] in CH_2Cl_2 at room temperature using 5 mol % InI_3 (entry 1) did not provide any products. Instead, the starting anthraquinonyl propargyl ether **2** was recovered. It was also observed that modifications in the loading amount of catalyst, reaction temperature and solvent did not promote the indium(III)-catalyzed hydroarylation (entry 2–4). Platinum(IV)-catalyzed hydroarylation[6d] also did not afford the desired intramolecular hydroarylation product **7**, but resulted in a mixture of side products. Interestingly, ketone **8**, probably resulted from unintended intramolecular hydroarylation with trace vapor, was observed among the diverse undesired products (entry 5–6). This observation seemed to imply that the electron-deficient anthraquinone moiety is not nucleophilic enough to react with the alkyne-platinum complex.[10] Next, the Claisen-rearrangement reaction of anthraquinonyl propargyl ether **2** was investigated focused on solvent and reaction temperature. When the anthraquinonyl propargyl ether **2** was heated at 180°C in $PhNEt_2$ (entry 7) and triethylene glycol (TEG) (entry 8), only starting **2** was recovered. The desired pyranoanthraquinone **7** could be obtained in moderate yield (64%) when the **2** was heated for 4 h at a higher temperature (220–230°C; entry 10) in TEG. While Claisen rearrangement in $PhNEt_2$ at a higher temperature (refluxed; entry 9) afforded an unidentifiable mixture of side products.

Table 1. Study on the synthesis of 2*H*-pyranoanthraquinone from propargyl ether



No.	Catalyst (mol%)	Condition[a]	Result
Intramolecular hydroarylation reactions			
1	InI_3 (5)	CH_2Cl_2, rt, 12h	No reaction
2	InI_3 (20)	CH_2Cl_2, rt, 12h	
3	InI_3 (20)	CH_2Cl_2, reflux, 12h	
4	InI_3 (20)	toluene, reflux, 12h	
5	$PtCl_4$ (5)	dioxane, rt, 12h	Mixture of side products including **8**[b]
6	$PtCl_4$ (5)	dioxane, reflux, 4h	
Claisen rearrangement reactions			
7		$PhNEt_2$, 180°C, 12h	No reaction
8		TEG, 180°C, 12h	No reaction
9		$PhNEt_2$, reflux, 12h	An unidentifiable mixture of side products
10		TEG, 220–230°C, 4h	**7** (64%)[c]

[a] 0.05 M solution of **2**; [b] Yield of **8** was not dertermined; [c] Isolated yield.

Conclusion

In summary, this article describes an efficient synthesis of the proposed structure of rennellianone B via Claisen rearrangement of an anthraquinoyl propargyl ether intermediate, easily prepared from cheap and readily available natural 1,2-dihydroxyanthraquinone alizarin. The spectral data of the synthesized rennellianone B did not agree with previous report. A 2*H*-pyran moiety of the synthesized rennellianone B was confirmed by careful 2D-NMR analysis. To find the appropriate reaction condition for the synthesis of the 2*H*-pyranoanthraquinone skeleton, intensive studies on the intramolecular hydroarylation and Claisen rearrangement

reaction of anthraquinoyl propargyl ether were performed, and it was hypothesized that electron-deficient anthraquinone would be an inadequate nucleophile for hydroarylation of alkynes. To my best knowledge, this study is the first example of synthesis of 2*H*-pyranoanthraquinone from anthraquinonyl propargyl ether. And, it would be helpful in the synthesis of derivatives of 2*H*-pyranoanthraquinone.

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Supplementary Material

Supplementary data (experimental section and copies of spectra for all of compounds) associated with this article can be found, in the online version, at http://

Graphical Abstract

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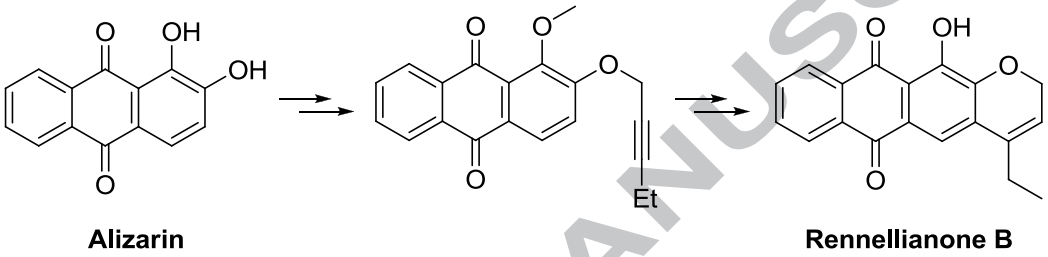

Alizarin **Rennellianone B**

Highlights

- The efficient synthesis of the proposed structure of rennellianone B was presented.
- The first practical example of the Claisen rearrangement of anthraquinonyl propargyl ether toward 2*H*-pyranoanthraquinone.
- Study on the rearrangement of anthraquinonyl propargyl ether toward pyranoanthraquinone skeleton was also described.