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PII: S0040-4039(16)30271-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.03.049
Reference: TETL 47437

To appear in: *Tetrahedron Letters*

Received Date: 29 January 2016
Revised Date: 10 March 2016
Accepted Date: 15 March 2016

Please cite this article as: Li, Y., Yu, B., Wang, R., Efficient synthesis of rottlerin and its two subunits, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.03.049

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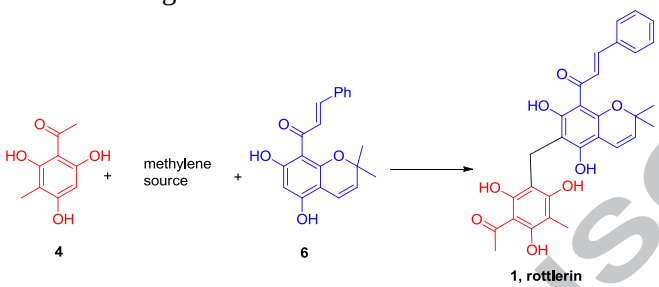

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Efficient synthesis of rottlerin and its two subunits

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
rottlerin
total synthesis
phenol-aldehyde condensation
ortho- quinone methide
gram-scale

ABSTRACT

Rottlerin, a natural product isolated from *Mallotus philippensis*, is associated with a range of biological activities. Its chemical structure is featured by two different substituted phloroglucinol units linked by a methylene group. In this study, we accomplished a total synthesis of rottlerin using phenol-aldehyde condensation as the key reaction. By our method, gram-scale preparation of the two structural subunits was achieved, and rottlerin was obtained in a longest eight linear step with 20% overall yield. Our study provides a practical solution for obtaining the sample of rottlerin in an efficient way.

Introduction

Mallotus philippensis, also known as "Kamala tree", is distributed widely in the rainforests of Southeast Asia.[1-3] It has long been valued as the source of dyeing material known as Kamala, which is also a rich source of biologically active compounds.[4-8] Rottlerin (**1**), also called mallotoxin, is a chromenochalcone isolated from Kamala along with other structurally related molecules, such as kamalachalcones and acylphloroglucinol derivatives.[9] Rottlerin began to attract the public attention as a useful compound with pharmaceutical potential in 1994, when Gschwendt *et. al*[10] showed it to be a specific inhibitor of protein kinase C delta (PKCδ). Since then, rottlerin has been used as a PKC-δ inhibitor in a number of biological assays related to PKC-δ.[11] Other bioactivities of rottlerin have also been discovered in recent years, such as cytotoxicity against four human cancer cell lines,[1] autophagy-inducer in chronic lymphocytic leukemia cells and human pancreatic cancer stem cell,[12] inhibition of human T cell responses,[13] abrogation of reactive oxygen species production in hepatic stellate cells,[14] neuroprotective agent in cell culture and animal models,[15] activator of potassium channel,[16] and prevention of histamine-induced H1-receptor gene expression in HeLa cells.[17]

Isolation of rottlerin from the kamala fruit extract is difficult. It typically results in different levels of purity as many structurally similar natural products also exist in the source. In ~~addition,~~ rottlerin is found to be somewhat unstable. "Rottlerone change",[18] discovered during trials of synthesis of rottlerin analogues, reveals its sensitivity in both acidic and basic conditions (**Figure 1**). Therefore, rottlerin is often sold in small quantities at high price. Difficulty in obtaining available samples has certainly put a limitation on the research related to rottlerin.

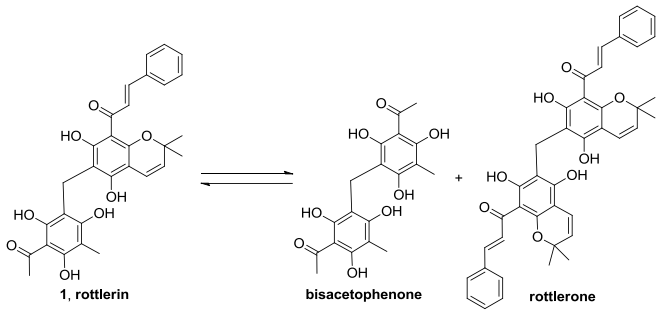

Figure 1. Chemical structure of rottlerin (**1**) and the "rottlerone change" reaction.

The first total synthesis of rottlerin was reported by Kumar *et al* in late 2015 (**Scheme 1**).[19] They used phloroacetophenone as the common starting material. Acetophenone (**4**) was obtained through formylation and Clemmensen reduction in 63% yield. Chromene (**6**) was prepared in three steps with known methods[20] and then aldol condensation and deprotection in five steps with yield up to 63% (computed by assuming that the first three steps were fully complete). Then, **6** was converted into a tertiary amine (**7**) with Eschenmoser's salt in 88% yield. Finally, **7** was used as

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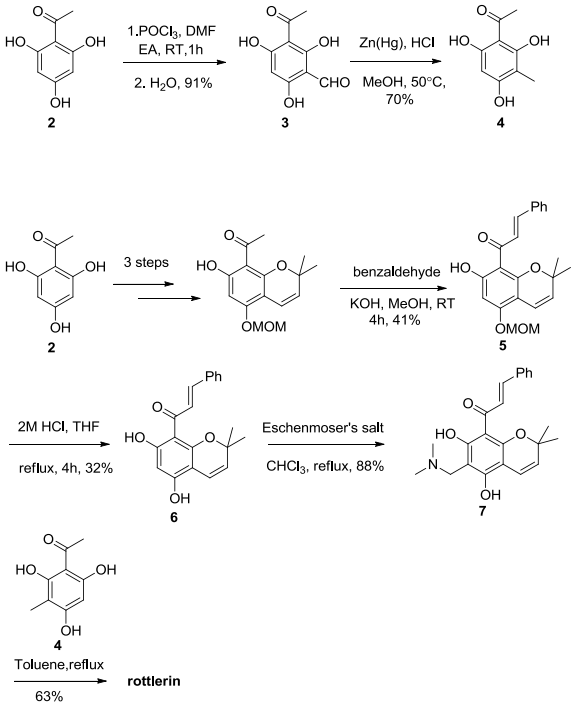
the precursor to prepare an *o*-quinone methide, which then went through Michael addition with the corresponding acetophenone (**4**) to obtain rottlerin in 63% yield. The overall yield by their synthetic route was up to 4.6%.

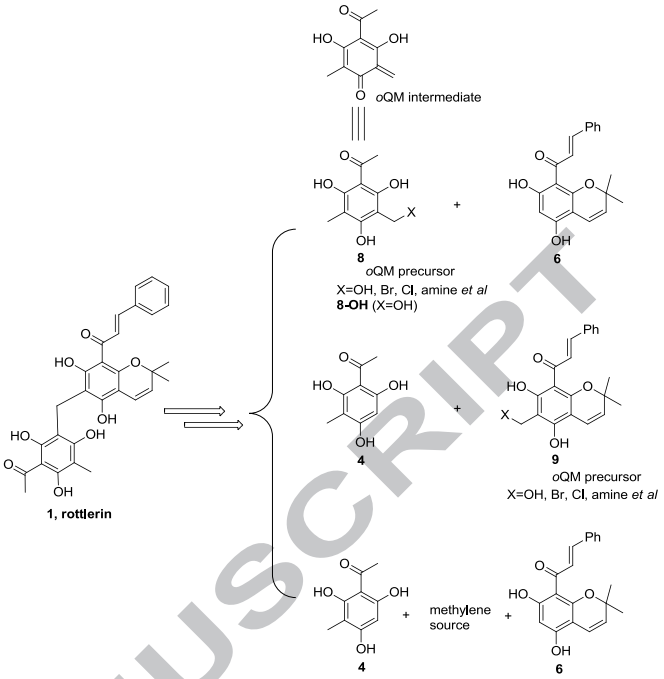


Scheme 1. The first total synthesis of rottlerin reported by Kumar *et al*.[19]

By an independent effort, we have developed an efficient synthetic route for obtaining rottlerin, which is somewhat different from Kumar's method. In particular, our route is featured by high-yield synthesis of the two main structural subunits of rottlerin, i.e. **4** and **6**, where **6** was prepared in seven steps with 47% overall yield and **4** was prepared in three steps with 67% overall yield. Both subunits could be prepared at the gram scale. Finally, the classic phenol-aldehyde condensation was adopted to produce rottlerin in 42% yield, which provides an alternative approach to the linkage of two subunits through an *ortho*-quinone methide (*o*QM) mediated reaction.

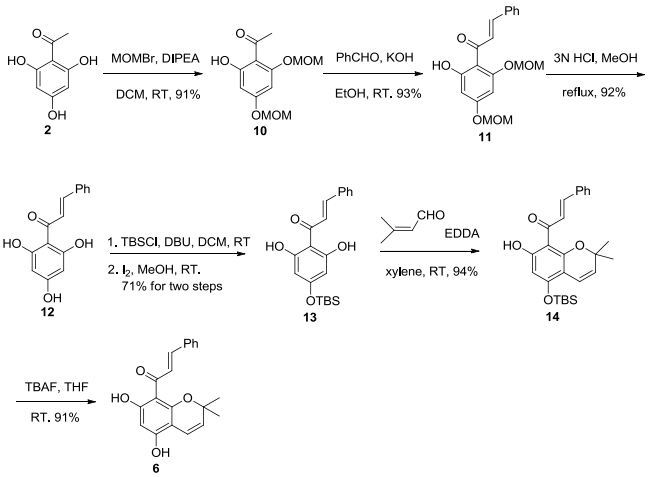
Results and Discussion

The structure of rottlerin (**1**) contains a chalcone skeleton and phloroglucinol and chromene rings (**Figure 1**). Unlike other symmetrical phloroglucinol dimers,[21] rottlerin has a pseudodimeric structure that two phloroacetophenone derived aryl cores are linked by a methylene bridge. If the chromene and acetophenone scaffolds are available, connection of them to yield rottlerin can be accomplished via an *ortho*-quinone methide (*o*QM) mediated reaction (the first two retrosynthetic routes in **Scheme 2**) or a direct phenol-formaldehyde condensation (the last route in **Scheme 2**). In either way, obtaining the two subunits in an efficient way is the primary task. The *o*QM intermediate strategy has long been applied to the total synthesis of many natural products.[22] As mentioned in the Introduction section, Kumar *et al*. has accomplished total synthesis of rottlerin through the second route in **Scheme 2**. In this paper, we will mainly describe our efforts on exploring the other two routes.



Scheme 2. Retro-synthetic analysis of rottlerin.

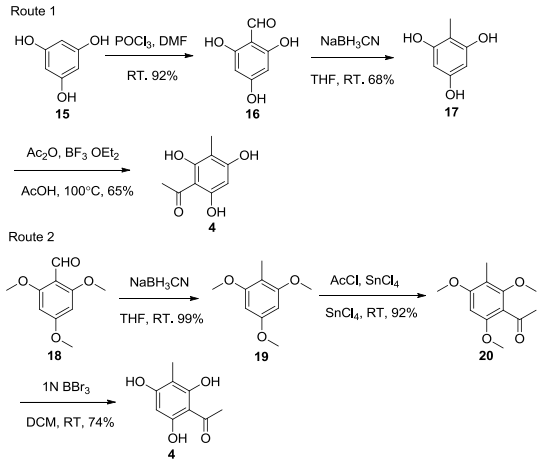
The chromene scaffold exists in the structures of many natural products, but no efficient preparation of it has been reported. Here, we developed an efficient route for obtaining this useful scaffold (**Scheme 3**). Our method began with protection of phloro-acetophenone (**2**) with MOM groups. It then underwent condensation with benzaldehyde to give **11**. After that, the two MOMs were removed using 3N hydrochloric acid to obtain **12** in 92% yield. Treatment of **12** with TBSCl provided a fully protected product, and without purification, it was deprotected selectively by iodine in methanol at room temperature to produce **13** in two-step 71% yield. EDDA-catalyzed chromene cyclization of **13** produced **14**.[23] Here, EDDA (ethylenediamine diacetic acid) was prepared by acid-base neutralization of 1 equiv of ethylenediamine and 2 equiv of acetic acid. Then, removal of the TBS group in **14** with TBAF in THF produced **6**. Through this route, compound **6** could be prepared in seven steps with 47% overall yield. This route could be accomplished at the gram scale (see the Supporting Information).



Scheme 3. Synthesis of chromene **6**

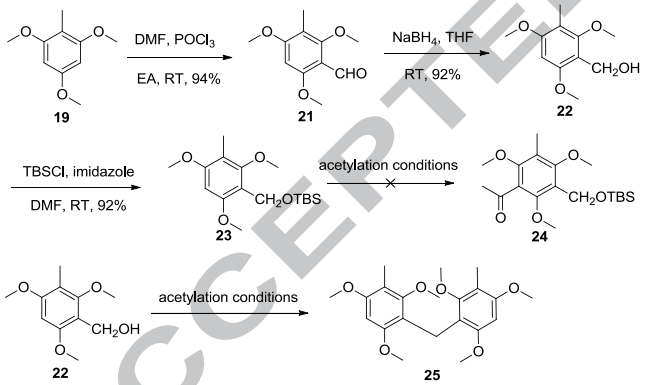
Our synthesis of acetophenone started with phloro-acetophenone (**15**). Vilsmeier−Haack formylation and subsequent reduction with sodium cyanoborohydride produced **17**. Then, it was acetylated into **4** using acetic anhydride and boron trifluoride diethyl etherate in 65% yield. Another alternative route was as

follows: 2, 4, 6-trimethoxybenzoaldehyde (**18**) was reduced into **19**, followed by acetylation to form **20** in 92% yield. Finally, removal of three methyl groups by boron tribromide solution at room temperature produced **4** in 74% yield (**Scheme 4**), and acetophenone **4** was obtained in three steps with an overall yield as high as 67%. Both routes could be accomplished at the gram scale (see the Supporting Information).



Scheme 4. Synthesis of acetophenone **4**.

After obtaining **4**, we first attempted to obtain the *o*QM precursor **8-OH**. A few hydroxymethylation reactions[24] were attempted, but unfortunately no desired product was observed. Besides, our attempts of acetoxymethylation,[25] chloro-methylation,[26] and amine methylation[27] of **4** all failed. We assumed that this may be explained by the interference of the naked hydroxyl groups to the desired reaction. Thus, hydroxyl protected **20** was tested as reactants under the same conditions. However, no reaction was observed either.



Scheme 5. Attempts on acetylation of **22** and **23**.

Next, we turned to another possible synthetic route of **8-OH** by introducing hydroxymethyl group before acetylation (**Scheme 5**). Compound **19** was formylated using Vilsmeier−Haack reagent to produce aldehyde **21** in 94% yield. Reduction of **21** with sodium borohydride produced alcohol **22**, which was then protected with TBS group to give **23**. Acetylation of both **22** and **23** were unsuccessful with a few attempted conditions (Ac_2O–BF_3OEt_2; AcCl–$SnCl_4$; AcCl–$AlCl_3$; Ac_2O–TMSOTf). Only the dimer product **25** was isolated, which proved the high activity of phenol ring. Such a reaction probably takes place via a retro Friedel−Crafts mechanism prompted by cation-π interactions to generate formaldehyde. Similar phenomenon was reported by Chiba *et al*.[28] These failed attempts demonstrate that the acetophenone-derived *o*QM precursor is not suitable for the synthesis of rottlerin because it is difficult to obtain.

The third synthetic route shown in **Scheme 2** seems to be feasible since the key factors in phenol-aldehyde condensation[29] are methylene source and acid. We conducted the condensation of **4** and **6** using four different methylene reagents (**Table 1**). In most cases, no reaction between the reactants and paraformaldehyde, dimethoxymethane, or chloromethyl methyl ether was observed, indicating the low reactivity of releasing the active methylene intermediate. To tackle this problem, a variety of Brønsted acids were examined. Finally, we found that by using formalin (30 equiv) and concentrated sulphuric acid in ethanol at the room temperature, rottlerin was obtained in 42% yield along with two homogeneous dimers as the result of the "rottlerone change" reaction (**Figure 1**). Nevertheless, all three products could be easily isolated by regular chromatography.

Conclusions

We accomplished a total synthesis of rottlerin in a modular manner by starting from readily available materials. Our synthetic route requires a longest eight linear step in a total of 11 steps, which results in an overall yield of 20%. Compared to the method reported by other researchers, our synthetic route is more efficient, and the two major structural subunits of rottlerin can be prepared in the gram scale. Although condensation of the two subunits also yields two homogeneous dimers as by-products, they can be separated from rottlerin easily by chromatography. Efficient production of the sample of rottlerin will hopefully facilitate the studies on its biological or pharmaceutical indications.

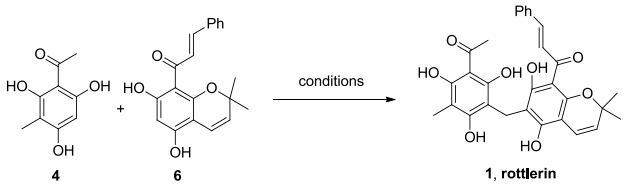
Acknowledgement

The authors thank Dr. Marc J. Adler at the Northern Illinois University and Dr. Sandip B. Bharate at the Indian Institute of Integrative Medicine for sharing their experience in the synthesis of rottlerin. The authors are grateful for the financial supports from the National Natural Science Foundation of China (grant #81430083, #81172984, #21472227 to Prof. R. Wang) and the Science and Technology Development Foundation of Macao SAR (Grant #055/2013/A2 to Prof. R. Wang).

Supplementary Data

Experimental procedures, characterization Data, ^1H and ^{13}C NMR spectra of rottlerin, two homogeneous dimers of the rottlerone change, as well as allbn bn of the key intermediates mentioned in this paper.

Table 1. Phenol-aldehyde condensation and the results.



4 6 1, rottlerin

Entry	Conditions	Result
1	37% HCHO (30 equiv), conc HCl (10 equiv), RT	13%
2	37% HCHO (30 equiv), conc H_2SO_4 (15 equiv), RT	42%
3	37% HCHO (30 equiv), AcOH (30 equiv), RT	< 5%
4	MOMCl (10 equiv), conc HCl (10 equiv), RT	No Product
5	$(CH_2O)_n$ (30 equiv), conc H_2SO_4 (15 equiv), RT	No Product
6	$CH_2(OMe)_2$ (30 equiv), conc H_2SO_4 (15 equiv), RT	No Product
7	37% HCHO (30 equiv), TsOH (10 equiv), RT	<10%

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