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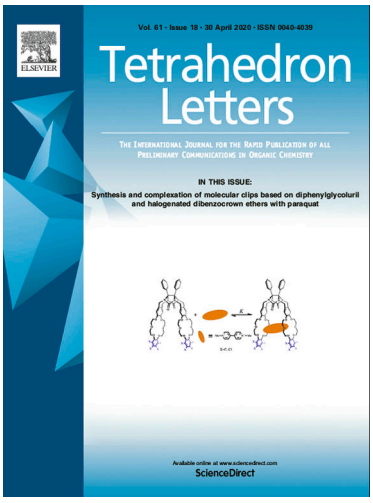

Concise and practical approach for the synthesis of honokiol, a neurotrophic agent

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PII: S0040-4039(20)30696-1
DOI: https://doi.org/10.1016/j.tetlet.2020.152229
Reference: TETL 152229

To appear in: *Tetrahedron Letters*

Received Date: 5 June 2020
Revised Date: 4 July 2020
Accepted Date: 8 July 2020

Please cite this article as: Rasvan Khan, P., Mujawar, T., Shekhar, P., Shankar, G., Subba Reddy, BV., Subramanyam, R., Concise and practical approach for the synthesis of honokiol, a neurotrophic agent, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152229

Graphical Abstract

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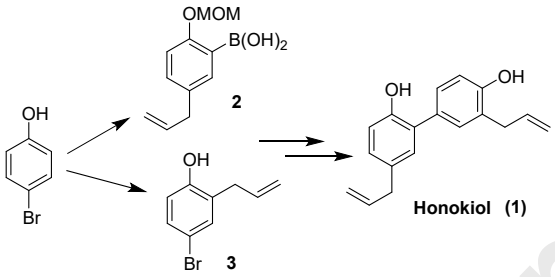

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Concise and practical approach for the synthesis of honokiol, a neurotrophic agent

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
ortho-Lithiation, Claisen rearrangement, Suzuki cross-coupling, honokiol

ABSTRACT

An improved method has been developed for the synthesis of honokiol using a readily available *p*-bromophenol as a precursor. The key step involved in this method is *ortho*-lithiation facilitated by methoxymethyl ether (MOM). Other important steps are *ortho*-allyl phenyl ether Claisen rearrangement and a Suzuki coupling for the construction of biaryls. This method does not require pre-functionalization of aromatic ring with bromide for the generation of arylboronic acid.

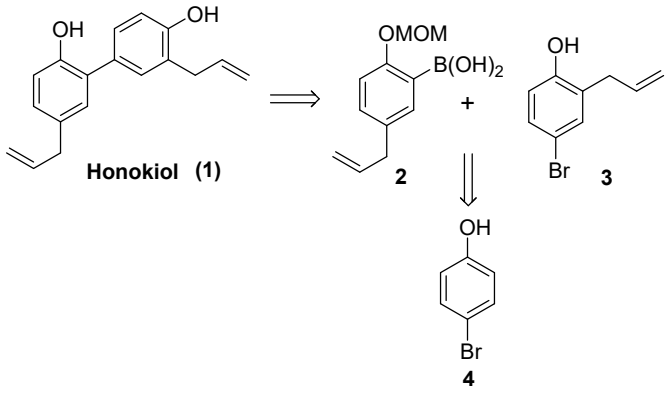
Introduction

The extracts of *Magnolia* have been used in Chinese traditional medicine for the treatment of gastrointestinal disorders, allergic diseases and anxiety.[1] Honokiol (**1**) was isolated originally from the stem and bark extracts of *Magnoliae officinalis* along with its structural isomer magnolol as two primary actives. Till date, honokiol was obtained from natural sources. However, the isolation of honokiol in pure form has become quite difficult due to its low concentration in the extract, the presence of closely related isomers and seasonal variations affecting its level.[2] Subsequently, honokiol was also isolated from *Magnoliae obovata*[3] and *Magnolia garrettii*.[4] Interest in honokiol stems from the fact that it exhibits a broad spectrum of biological activities such as anti-tumour,[5] anti-inflammatory,[6] anti-viral[7] and neurotrophic activity.[8] Honokiol can readily cross the blood brain barrier and blood-cerebrospinal fluid barrier.[9] The natural occurrence of honokiol is too low (2-3%).[10] Therefore, the synthesis of honokiol has attracted the attention of many synthetic chemists. As a result, numerous methods have been developed for the synthesis of honokiol.[11] However, most of these methods involve the use of BBr_3 or BCl_3 for demethylation or for Claisen rearrangement, which limit their use in large scale synthesis. Indeed, the formation of biaryls and the cross-coupling of allyl and aryl groups are the major challenges for the scale-up. Interestingly, there is a report on direct arylation of *ortho*-tert-butylphenol with *p*-bromoanisole to afford the biaryl ring using 10 mol% $[RhCl(COD)]_2$ and 30 mol% $P(NMe_2)_3$.[12] This method typically requires demethylation and de-*tert*-butylation from aromatic ring. Inspired by its inherent biological activity, we reported the synthesis of honokiol involving Grignard reaction and Claisen rearrangement as key steps.[13] However, we encountered some difficulties in the demethylation of aryl methyl ethers when performed in large scale. In addition, the honokiol was formed as a mixture of two regioisomers during the Claisen rearrangement, which limits its

us cal approach for the synthesis of honokiol owing to its potent biological activity and natural scarcity. Hence, we attempted a direct method for the *ortho*-lithiation of MOM protected phenyl ether to produce arylboronic acid, which is a precursor for Suzuki coupling.

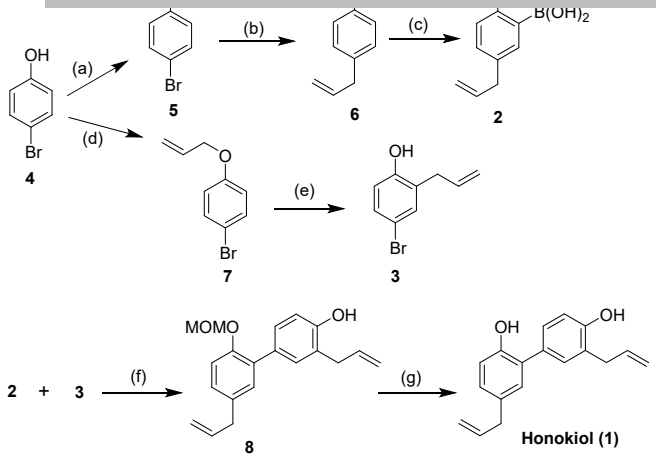
Results and Discussion

Following our interest on the large-scale synthesis, we herein report a concise and improved method for the synthesis of honokiol starting from a readily available 4-bromophenol. Retro-synthetically, honokiol (**1)** could be cleaved into two fragments aryl boronic acid **2** and 2-allyl-4-bromophenol **3**. Both compounds **2** and **3** could in turn be prepared from a common precursor, 4-bromophenol **4** (Scheme 1).



Scheme 1. Retrosynthetic analysis of honokiol (**1**)

Accordingly, we began the synthesis of honokiol from 4-bromophenol. Thus the protection of 4-bromophenol **4** with MOMCl using NaH in DMF at 0 °C afforded the MOM ether **5** in 96% yield. Further the cross-coupling of allyl bromide with arylmagnesium bromide, which is generated in situ from compound **5** and magnesium in THF gave the 4-allyl derivative **6**. *ortho*-Lithiation of compound **6** using *n*-BuLi followed by borylation with $B(OMe)_3$ at -78 °C furnished the desired aryl boronic acid **2** in 88% yield. On the other hand, the second key intermediate **3** was prepared in two steps from 4-bromophenol **4**. Treatment of compound **4** with allyl bromide using K_2CO_3 in acetone under reflux conditions gave the O-allyl derivative **7** in 96% yield. The Claisen rearrangement of allyl aryl ether **7** under thermal conditions afforded allyl derivative **3** in 97% yield. Finally, the cross-coupling of two key intermediates **2** and **3** followed by deprotection of MOM ether provided the desired honokiol (**1**). Accordingly, the Suzuki coupling of boronic acid **2** with aryl bromide **3** using $Pd(TPP)_4$ in the presence of K_2CO_3 in toluene:EtOH:H_2O under reflux conditions gave the unsymmetrical biaryl derivative **8** in 65% yield. Deprotection of MOM group from compound **8** using TMSCl in methanol at 25 °C afforded the honokiol (**1**) in 85% yield. The spectral data and physical properties of honokiol are consistent with a natural product (Scheme 2).



Scheme 2. Synthesis of honokiol: (a) NaH, MOMCl, DMF, 0 °C, N_2, 3h, 96%; (b) Mg, THF, rt then reflux, N_2, 0 °C, allyl bromide, then 70 °C, 2h, 91%; (c) *n*-BuLi, THF, N_2, $B(OMe)_3$, -78 °C, 2h, 88%; (d) K_2CO_3, acetone, N_2, allyl bromide, reflux, 4h, 95%; (e) 200-230 °C, 1h, 90%; (f) $Pd(PPh_3)_4$, N_2, toluene:EtOH:H_2O, K_2CO_3, reflux, 8h, 65%; (g) TMSCl, MeOH, 0 °C to rt, 6h, 85%.

In summary, we have successfully demonstrated the total synthesis of honokiol in seven steps involving the Suzuki coupling as a key step for the formation of biaryls. This method does not require pre-functionalization of aromatic ring with bromide for making arylboronic acid. The use of MOM protection does not require harsh conditions unlike demethylation for its removal. This method could be successfully applied for the large-scale synthesis of honokiol.

Acknowledgements: Funding for conducting this research was provided by Colgate Palmolive Technology Center, USA. The authors declare that there were no conflicts of interest. IICT/Pubs./2020/182.

Supplementary data

Characterization data, copies of ^1H and ^{13}C NMR spectrum of products are provided in supporting information.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Highlights

- It describes an improved synthesis of honokiol.
- This method is practical and operationally simple.
- It is a highly convergent and scalable process.
- It is a first report on ortho-lithiation for honokiol.

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