Synthetic Approach to the Chemical Isostere of *O*-Methyl Honokiol

Minghua Cui, Hak Sung Kim*

Institute of Pharmaceutical Research and Development, College of Pharmacy, Wonkwang University,
344-2 Shinyong-Dong, Iksan, Jeonbuk 570-749, South Korea
Fax +82(63)8431581; E-mail: hankidad@wku.ac.kr

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Abstract: We established a synthetic method for the chemical isostere of the structurally unique natural product, 4′-*O*-methyl honokiol by replacing two allyl groups with two different alkyl groups with the aim of developing synthetic analogues of the chemical isostere. The key steps in this synthetic route are the Suzuki–Miyaura coupling reaction for the formation of the phenylpyridine moiety and the Stille coupling reaction for the stepwise introduction of two allyl groups.

Key words: honokiol, 4′-*O*-methyl honokiol, chemical isostere, Suzuki–Miyaura coupling, Stille coupling

Structurally fascinating natural products may serve as subjects for new potential approaches in drug design. Honokiol, isolated from *Magnolia* sp., has been extensively studied because of its versatile bioactivities such as anticancer[1] and neurotrophic activity.[2] *O*-Methyl honokiol (Figure 1), a honokiol analogue found in the extract of *Magnolia virginiana* leaves[3] and *Magnolia officinalis* stem bark,[4] shows bioactivities similar to those of honokiol, including anti-inflammatory effects[5] and neuroprotective activity,[6] therefore, even this compound has gained interest in terms of its application in drug design. In 1985, Tobinaga and co-workers reported the first total synthesis of honokiol,[7] and recently Denton and co-workers presented a concise alternative synthetic method of honokiol[8] and *O*-methyl honokiol (**1**).[9] Also this group has accomplished the synthesis of the relevant compound dunnianol.[10] We were interested in synthesizing the chemical isostere of *O*-methyl honokiol by replacing the C-3 atom with a nitrogen atom. Herein we describe the synthesis of the chemical isostere of *O*-methyl honokiol with the stepwise introduction of two allyl groups.

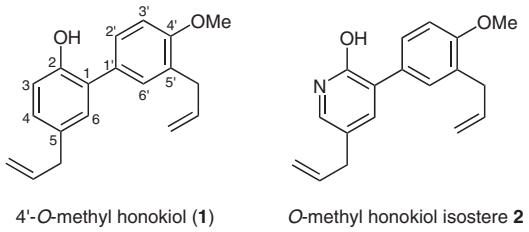
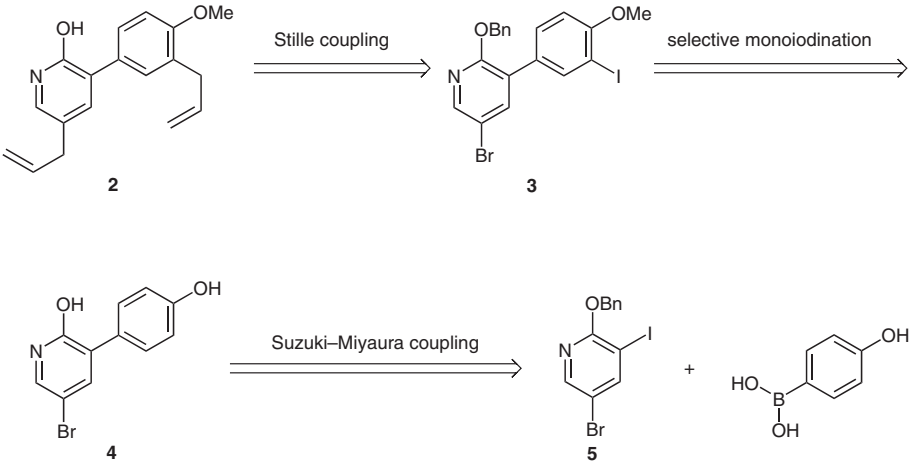


Figure 1 Structure of honokiol analogues

In the retrosynthetic analysis shown in Scheme 1, the target isostere **2** could be prepared by halogenative allylation on the key intermediate **3**, which may be prepared by a simple procedure like successive O-methylation and monoiodination from bromobiphenyl **4**. Coupling of pyridine moiety **5** with a commercially available phenylboronic acid via Suzuki–Miyaura reaction[11] could yield **4**.

Bromoiodopyridine **5** was synthesized from the commercially available bromopyridone **6** in five steps by using simple processes (Scheme 2). The bromoiodopyridone **7**[12] was obtained by iodination of bromopyridone **6** using *N*-



Scheme 1 Retrosynthetic analysis

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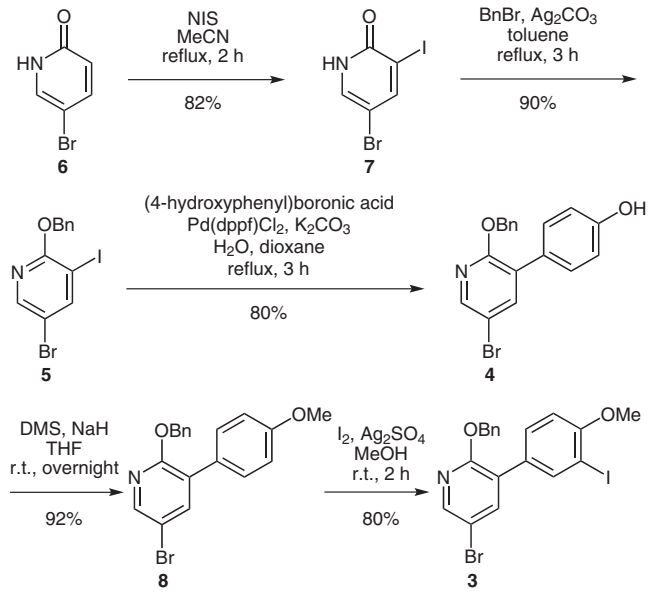


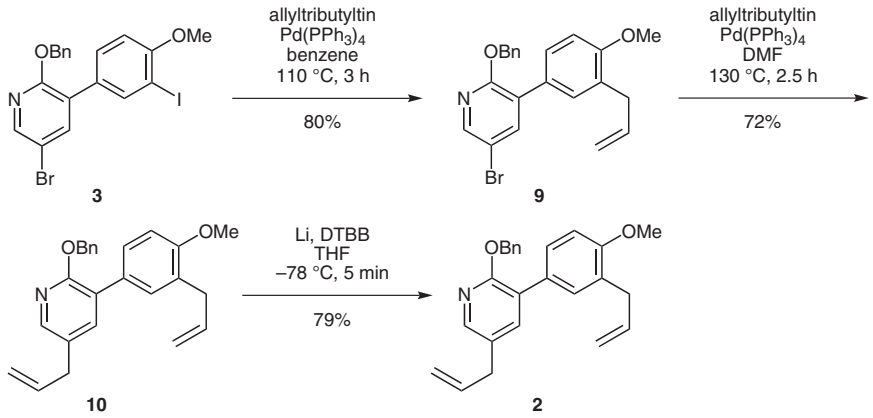
Scheme 2 Synthesis of the key intermediate **3**

iodosuccinimide. The pyridone moiety was converted into *O*-benzylpyridine **5** by O-benzylation of benzyl bromide in the presence of silver carbonate as a base. The coupling reaction of compound **5** with commercially available (4-hydroxyphenyl)boronic acid was accomplished by using the Suzuki–Miyaura coupling,[13] to readily obtain 3-phenylpyridine **4** in 80% yield. The successive O-methylation and monoiodination from 3-phenylpyridine **4** seemed to be simple, however, the monoiodination step was found to be problematic.

The main side reaction in the monoiodination process was the di-iodination at the two *ortho* positions of the methoxy group, for which various reaction conditions were attempted. As shown in Table 1,[14] the best selectivity and yield for C-5′ monoiodination were achieved by treatment with iodine in the presence of silver sulfate, a method patented by Sy.[15]

In the Stille coupling,[16] the more reactive iodo group yielded a faster allylation reaction speed (Scheme 3). Along with the successful one pot-allylation in moderate yield (60%), we were able to distinguish the iodo group from the bromo group for the stepwise introduction of two allyl groups, which gave the diallyl compound **10** from the monoallyl compound **9** in good yield. The final process, debenzylation, was not successful. Double-bond migration occurred under mild acidic conditions such as in the presence of trifluoroacetic acid (TFA)[17] and HBr/AcOH,[18] which were regular procedures for the O-debenzylation. Fortunately, reductive debenzylation using lithiated di-*tert*-butylbiphenyl(DTBB)[19,20] was successful in furnishing the final target **2**.

As shown in Scheme 2, two different halogen groups in 3-phenylpyridine **3** can exist as mechanistic attractive substituents for introducing two different alkyl groups on the basis of their unique differences in chemical reactivity, which may have great chemical merit for their synthetic application in the development of a variety of analogues.

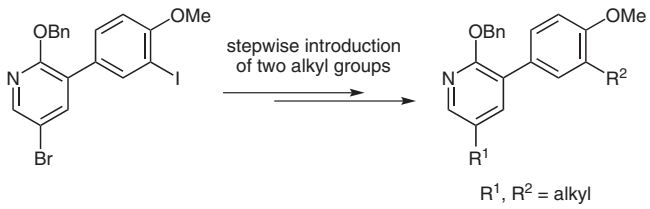


Scheme 3 Synthesis of *O*-methyl honokiol isostere **2**

Table 1 Iodination of 3-(4-Methoxyphenyl)pyridine **9**[a]

Entry	Reagents	Solvent	Time (h)	Product	Yield (%)
1	NaI, NaOCl, NaOH	MeOH	1	3′,5′-diiodo product	61
2	NaI, I_2, H_2O	NH_4OH	20	3′,5′-diiodo product	46
3	NIS, H_2SO_4	AcOH	20	3′,5′-diiodo product	70
4	NIS, I_2	MeOH	2	3′,5′-diiodo product	37
5	I_2, Ag_2SO_4	MeOH	1.5	5′-monoiodo product	80

[a] Reaction temperature: r.t.



Scheme 4 The applicability of the successive introduction of two different alkyl groups

In conclusion, we achieved the synthesis of a structurally unique isostere **2** of *O*-methyl honokiol in total eight steps with 19.8% overall yield. Evaluation of the biological activity of the target compound **2** is under way for developing the derivatives.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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